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Thesis Title

## Towards More Sustainable Organic Processes : Heterocyclizations in Non-Conventional Solvents

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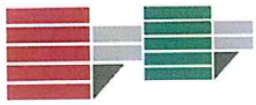

# UNIVERSITA' DELLA CALABRIA

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## Towards More Sustainable Organic Processes : Heterocyclizations in Non-Conventional Solvents

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## Abstract

This thesis reports the synthesis of important heterocyclic derivatives by iodocyclization, carbonylation and cycloisomerization reactions in Non-Conventionl solvents like deep eutectic solvents (DES) and Ionic Liquids (ILs).

In chapter one general aspects of green and sustainable chemistry and introduction to eco-friendly green solvents such as water, DES, $ScCO_2$ and ILs are described. Carbonylation processes, their advantages, types were described along with the application of transition metal catalysis in the carbonylation reactions with mechanistic approaches discussed.

In chapter two, we describe a convenient and general method for the synthesis of substituted thiophenes through heterocyclodehydration and iodocyclization of readily available 1-mercapto-3-alkyn-2-ols in DES as the solvents.

In chapter three we discuss a convenient carbonylative approach to 2-oxazolidinone derivatives carried out in an ionic liquid as the solvent ($EmimEtSO_4$) is presented. It is based on the sequential concatenation of two catalytic cycles, both catalyzed by the same metal species (auto-tandem catalysis).

In chapter four we present iodocyclization reactions to obtain iodinated isobenzofuranones and isochromenones by iodolactonization of 2-alkynyl benzoic acids in ionic liquids. In particular here we have developed divergent syntheses of (*E*)-3-(iodoalkylidene) isobenzofuran-1(3*H*)-ones and 4-iodo-1*H*-isochromen-1-ones by base-free Iodolactonization of 2-alkynylbenzoic acids in ionic liquids.

In chapter five we report the cycloisomerization of readily available 2-alkynylbenzoic acids using an ionic liquid as the reaction medium in the presence of $CuCl_2$ as a simple and inexpensive catalyst. Although in principle two different cyclization pathways can be followed, leading to either 5-exo-dig mode or 6-endo-dig mode, we have found that substrates bearing an aryl group on the triple bond or a terminal triple bond can be selectively converted into the isobenzofuranone derivatives, using N-ethyl-N-methylmorpholinium dicyanamide ($Mor_{1,2}N(CN)_2$) as the solvent. On the other hand, and in a complementary manner, substrates substituted with an alkyl or an alkenyl group on the triple bond selectively led to isochromenones when the reaction was carried out $EmimEtSO_4$ and with excellent recyclability of the catalyst/ionic liquid system.

**Abbreviations**

| | |
|---|---|
| ATP | Adenosine Tri Phosphate |
| $BmimBF_4$ | 1-Butyl-3-methyl-1H-imidazol-3-ium Tetrafluoroborate |
| Boc | *tert-butyloxycarbonyl* |
| CNS | Central Nervous System |
| ChCl | Choline Chloride |
| DMF | N' N'' Dimethylformamide |
| DNA | Deoxyribonucleic acid |
| DES | Deep Eutectic Solvents |
| HIV | Human Immunodeficiency Virus |
| IL | Ionic Liquid |
| IMDA | Intramolecular Diels Alder |
| MCF | Michigan Cancer Foundation |
| MWI | Microwave irradiation |
| MRSA | Meticillin resistant Staphylococcus aureus |
| RCM | Ring Closing Metathesis |
| RNA | Ribonucleic acid |
| RTIL | Room Temperature Ionic Liquid |
| SAR | structure–activity relationship |
| SCF | Supercritical fluids |
| SWNT | single-walled carbon nanotubes |
| TS | Transition State |
| TM | Transition metal |
| $Mor_{1,2}N(CN)_2$ | N-ethyl-N-methylmorpholinium dicyanamide |
| $BmimN(CN)_2$ | 3-butyl-1-methylimidazolium dicyanamide |
| $C_3CNmpyr)\ (NTf)_2$ | N-(cyanopropyl)-N-methyl pyrrolidinium triflimide |

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*To*

*My Beloved*

*Grand Maa*

# Chapter1

# Introduction

## 1.1 Green Chemistry

The term 'Green Chemistry' was first coined in the early 1990s by Anastas and colleagues of the US Environmental Protection Agency (EPA). The term green chemistry[1] defined as "the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances".

Solvents are used on a daily basis in numerous industrial processes, and it is estimated that they comprise almost 60% of all industrial emissions and 30% of all volatile organic compound emissions worldwide.[2] In 1991, chemist P.T. Anastas addressed the need for harmful solvents reduction through a specific program called *green chemistry*, and today this concept has surpassed academic circles, which is evident from the EU environmental policy and legislation for the period 2010–2050 where reduction of hazardous solvents in industry is one of the priorities.[3]

The main objective of green chemistry is to obtain safer, cleaner, and energy-efficient chemical processes and, to this end, twelve principles of Green Chemistry have been formulated by Anastas and Zimmerman[4] for benign by design of both products and processes.

**Table 1.1**

| | |
|---|---|
| 1.Waste prevention instead of remediation | 7. Preferably renewable raw materials |
| 2. Atom efficiency | 8. Shorter syntheses (avoid derivatization) |
| 3. Less hazardous/toxic chemicals | 9. Catalytic rather than stoichiometric reagents |
| 4. Safer products by design | 10. Design products for degradation |
| 5. Innocuous solvents and auxiliaries | 11.Analytical methodologies for pollution prevention |
| 6. Energy efficient by design | 12. Inherently safer processes |

More recently, a mnemonic, “PRODUCTIVELY” was proposed by Poliakoff [5] et al which captures the spirit of the twelve principles of green chemistry:

P – Prevent wastes;

R – Renewable materials

O – Omit derivatisation steps

D – Degradable chemical products

U – Use of safe synthetic methods

C – Catalytic reagents

T – Temperature, Pressure ambient

I – In-Process monitoring

V – Very few auxiliary substrates

E – E-factor, maximise feed in product

L – Low toxicity of chemical products

Y – Yes, it is safe

Alternatively, the green chemistry definition[6] reduced into a single sentence. “Green chemistry efficiently utilizes (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in them.

The most widely accepted measures of the environmental impact of chemical processes are the *E factor*[7], the mass ratio of waste produces to the desired product and the *atom economy*[8], “a percentage conversion of the molecular weights of all substances reacted to the molecular weight of the desired product.”

Having defined what green chemistry is we need to be able to compare processes (and products) on the basis of their greenness. There is no absolute greenness, one process is greener than another, and however considering green measurements is an essential task for the genuine examination of greenness. Green chemistry meshes with the important issues such as waste generation, and so in twelve principles it suggest use of less toxic/hazardous material and/or use them as in catalytic amount not in stoichiometric to avoid the waste generation. Although best catalyst is no catalyst and best solvent is no solvent. Use of toxic, volatile solvents in the synthesis is also an important issue in green chemistry.

Green chemistry is a very important tool of sustainable development, and its goal is to prevent or reduce environmental stress caused by technological processes, while simultaneously increasing the production. Green technology actively seeks new solvents to replace common organic solvents that present inherent toxicity and have

high volatility, leading to evaporation of volatile organic compounds to the atmosphere. The implementation of solvent-free processes would be ideal; however, solvents are almost unavoidable due to their crucial role in dissolving solids, mass and heat transfer, influencing viscosity and in separation and purification steps. Accordingly, two main strategies for green solvent development have been proposed, the substitution of solvents derived from petroleum with solvents from renewable resources, and the substitution of hazardous solvents with ones that show better environmental, health and safety properties. Regarding the aforesaid considerations, water is the first-choice solvent, and it has already been used on an industrial scale, mainly in emulsion polymerization processes and hydro distillations. Nevertheless, the negligible solubility of many organic and organo-metallic compounds in water, and also high energy demands for water removal upon completion of processes involving it, limits its applications.[9] Hence, various environment-friendly, tenable and smart solvents have been considered, among which room temperature ionic liquids, supercritical and subcritical fluids and solvents derived from natural or renewable sources stand out as the most promising approaches for current solvent innovation (Fig.1.1).

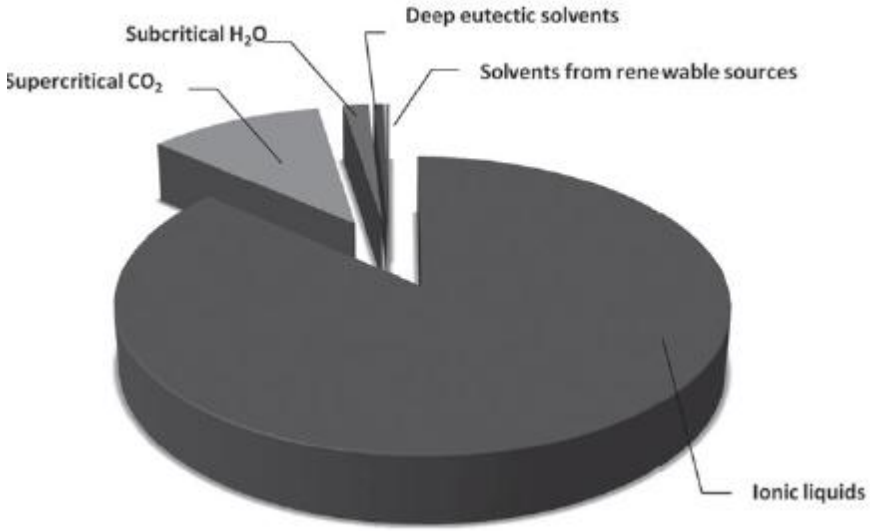



**Figure 1.1** Proportion of articles describing each class of solvents overviewed in 2010-2014

A comprehensive discussion regarding these new solvents is far beyond the scope of this review; however, a brief overview of the current knowledge regarding these solvents is presented herein, with special emphasis on their properties, applications and further perspectives as truly green industrial solvents.

Green technology actively seeks new solvents to replace common organic solvents that present inherent toxicity and have high volatility, leading to evaporation of volatile organic compounds to the atmosphere. Over the past two decades, ionic liquids (ILs) have gained much attention from the scientific community (Fig.1.2), and the number of reported articles in the literature has grown exponentially. Green Chemistry concerns environmentally benign solvents. In many research centers, solutions are developed to eliminate and limit the use of hazardous organic solvents and to replace them with new, milder and more environmentally benign solvents and reaction media. Such activities are aimed at achieving a balance between the development of technology, an increase in the production and a safe and clean environment.


**Figure 1.2** Presents characteristics of an ideally ‘green’ solvent and ionic liquids (ILs) life cycle.

So here we give a brief overview of the current knowledge regarding these solvents is presented herein, with special emphasis on their properties, applications and further perspectives as truly green industrial solvents

Over the last few years, there has been a noticeable progress in the field of green solvent development. New solutions have been found in the field of utilising

traditional solvents (such as water as a solvent or water and carbon dioxide) at supercritical state, but the biggest group of them still consists of organic solvents. Over the past two decades, ionic liquids (ILs) have gained much attention from the scientific community, and the number of reported articles in the literature has grown exponentially. Ionic liquids are molten salts, liquid at room temperature, whose enormous potential arises from particular characteristics of these liquids, namely, their physicochemical properties (viscosity, density, hydrophilicity, and solubility), which can be tuned by the combination of different cations and anions.1, 2 ILs have found applications in very diverse areas and serve very different purposes Ionic liquids (ILs) and deep eutectic solvents (DESs) constitute a very broad group of substances. Apart from many imperfections, ILs and DESs have been the most promising discoveries in the world of green chemistry in recent years. The main advantage of ILs is their unique physicochemical properties— they are very desirable from the technological point of view, but apart from these benefits, ILs appears to be highly toxic towards organisms from different tropic levels. DES areas of usage are very spread, because they cover organic synthesis, extraction processes, electrochemistry, enzymatic reactions and many others. Moreover, DESs seem to be a less toxic alternative to ionic liquids. New possibilities of applications and future development trends are sought and presented, including such important solutions of life branches as pharmaceuticals' production and medicine

### 1.2 Sustainability

In a world with a continuously increasing population and limited resources, the idea of the sustainable development is of major importance for the future in the 21$^{st}$ century. Chairman of "The World Commission for Environment and Development" founded by the United Nations defined the term sustainable development[139] as, "Meeting the needs of the present generation without compromising the ability of future generations to meet their own needs." Only research and innovation will allow the development of economic and social networks and processes that fulfil the requirements of sustainability. Sustainability in science and technology begins when we start thinking how to solve a problem or how to turn science into technology. The original concept of sustainability emphasized the needs to combine social objectives (health, quality of life, employment) to the management of scarce resources (energy and raw materials) and the preservation of the natural bases for life, for example, the

need to adopt all actions such as cleaner processes, recycle waste, reduce pollutant emissions necessary to preserve bio-diversification. Chemistry, as the science of matter and its transformation, plays a central role in this process and is the bridge between physics, material sciences and life sciences. Only chemical processes, which have reached a maximum in efficiency, will lead to more sustainable products and production. Sustainability through chemistry is thus an approach that starts from green chemistry concepts and goes on to a vision for the future sustainability of society

### 1.3 Solvents for sustainable chemical processes

Solvents are major issue in the production of chemicals. Glaxo-Smith-kline researchers[10] have pointed out that about 85% of the total mass of chemicals involved in pharmaceutical production is constituted by solvents. Although solvents are recovered after each step, the recovery efficiencies generally in range from 80%-50%, which clearly indicates that, the environmental impact of bulk and fine chemical processes is dramatically affected by the problem of solvents.

Green chemistry aims to change the use of toxic solvents with greener alternatives, with replacement and synthetic techniques, separation and purification which do not need the use of solvents. Green solvents can have been characterised for their low toxicity, higher low solubility in water (low miscibility), easily biodegradable under environmental conditions, high boiling point (not very volatile, low odour, health problems to workers) and easy to recycle after use.

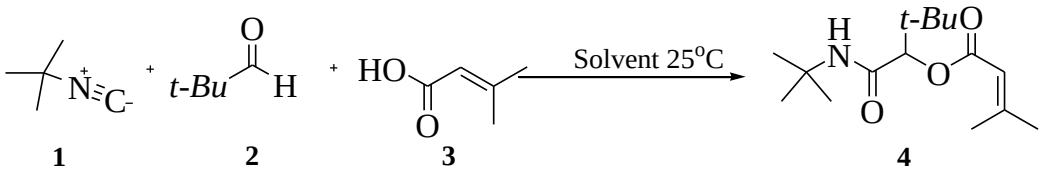
Various non-conventional reaction media have been intensely studied in recent years, including water[11], supercritical $CO_2$[12], fluorous biphasic[13] and ionic liquids[14] alone or in liquid–liquid biphasic combinations

#### 1.3.1 Water

In principle, water is the ideal green chemistry solvent. It is benign, non-toxic, and non-flammable; it has a very low odour & has a high specific heat capacity to absorb energy from reactions. It is available at a low cost, and is sustainable[16]. The use of water as solvent features many benefits such as, improving reactivities and selectivities, simplifying the workup procedures, enabling the recycling of the catalyst and allowing mild reaction conditions and protecting-group free synthesis in addition to being benign itself. In addition, exploring organic chemistry in water can

lead to uncommon reactivities and selectivities complementing the organic chemist synthetic toolbox in organic solvents. Studying chemistry in water also allows insight to be gained into nature's way of chemical synthesis[17].

The emergence of the use of water as a solvent for organic reactions was probably impulsed by the work of Breslow in the 1980s on the substantial rate enhancement of Diels–Alder reactions conducted in water compared to in other organic solvents[18]. In his studies, he observed that the cycloaddition of butenone and cyclopentadiene was 740 times faster in water than in isooctane and that an increased selectivity could be obtained with water (*endo/exo* = 21.4) compared to the same reaction in cyclopentadiene (*endo/exo* = 3.85). It was all the more remarkable that the use of protic polar solvents like methanol or ethanol led to similar results to those obtained with hydrocarbon solvents. These observations were rationalized by the hydrophobic effect[20]. This property of water comes from the repulsive interactions between hydrophobic molecules and water, which leads to the formation of hydrophobic aggregates that allow reducing the contact surface between them. To maintain the network of hydrogen bonds (related to its high cohesive energy density), water wraps itself around these aggregates, thus acting as an internal pressure, which accelerates reactions with negative activation volume, likes in Diels–Alder reactions. In some cases, the rate enhancements may also originate from interfacial interactions between the organic molecules (notably the transition states) and some free hydroxyl groups of water.[20] Ugi and Passerini reactions.[21] Indeed, as multicomponent reactions consist of the reaction of three or more starting materials to form a single product, they involve transition states resulting from the condensation of several molecules and are therefore predicted to have negative activation volumes. They initially studied the Passerini reaction of 3-methylbut-2-enoic acid 3, 3-methylbutanal 2 and 2-isocyano-2-ethylpropane 1 in several solvents (Eq. 1.1). They reported that dichloromethane allowed the formation of the product with a 50% yield after 18 h, whereas no product was obtained in methanol and only a 15% yield was observed in dimethylformamide. In contrast, the use of water furnished the expected product 4 quantitatively within 3.5 h.

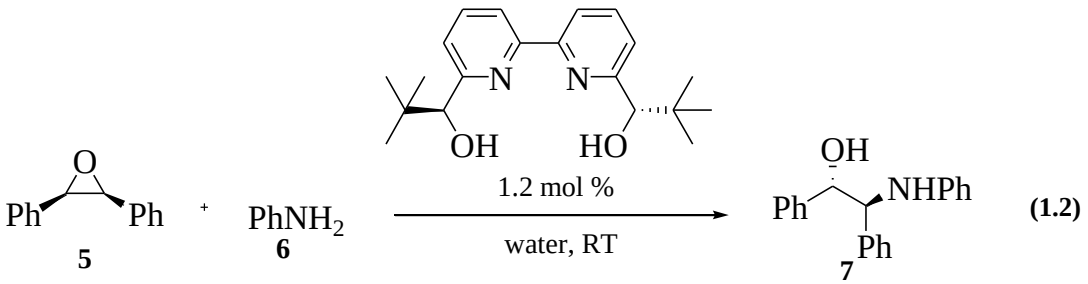



**1** **2** **3** **4** **(1.1)**

**Table 1.2**

| Solvent | Time (h) | Conversion |
|---|---|---|
| Dichloromethane | 18 | 50 |
| Dimethylformamide | 24 | 15 |
| Methanol | 24 | 0 |
| Water | 3.5 | 100 |

In 2005, the group of Kobayashi studied the asymmetric desymmetrization of meso-epoxides with amines catalyzed by a chiral scandium complex[22].They showed that the reaction of aromatic epoxides with anilines led to a higher enantiomeric excess in water compared to dichloromethane or THF/water mixtures (Eq. 1.2). In addition, the use of scandium tris(dodecylsulfate) instead of scandium triflate resulted in a better yield and enantiomeric excess, and these conditions were consequently successfully applied to a wide range of substrates, though the reaction is limited to aromatic amines.




**5** **6** **7** **(1.2)**

**Table 1.3**

| Solvent | Sc(III) | Yield (%) | ee (%) |
|---|---|---|---|
| Dichloromethane | $Sc(OTf)_3$ | 85 | 74 |
| THF/Water(9:1) | $Sc(OTf)_3$ | 5 | 71 |
| Water | $Sc(OTf)_3$ | 15 | 85 |
| Water | $Sc(OSO_3C_{12}H_{25})_3$ | 89 | 91 |

### 1.3.2 Supercritical Fluids

Supercritical fluids (SCFs) are also an attractive alternative to standard solvents. SCF is a fluid at conditions slightly above its critical temperature (Tc) and pressure (Pc). Fig. 3 shows a generalized temperature–pressure graph which illustrates the supercritical region.[23] As the temperature and accompanying pressure are increased the liquid becomes less dense and the vapour becomes denser. At the critical point they converge to ultimately become identical. The compressibility is the slope of the isotherm, and it is infinite at the critical point. In fact, all of the special properties of SCF's occur in the region of very high compressibility. Their main limitations are the technically challenging conditions required to reach the supercritical state for most compounds. Two well-known yet very different fluids are water (Tc 373 °C; Pc 22.1 MPa) and carbon dioxide (Tc 31 °C; Pc 7.4 MPa). Supercritical carbon dioxide (scCO2) has been found useful with extensive applications in green chemistry. Being a potential replacement for volatile organic compound, $scCO_2$ could be one aspect of a significant and necessary movement towards green chemistry. As a solvent, $ScCO_2$ is non-toxic, cheap, non-flammable; readily available, recyclable, and unrestricted by the US Environmental Protection Agency (EPA).[24] In addition, $scCO_2$ exhibits high selectivity as a result of low viscosity, high diffusivity and liquid-like density[25]

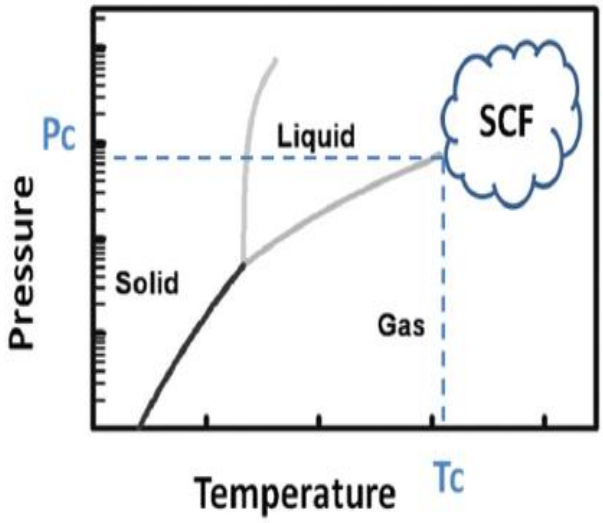



**Figure 1.3** General phase diagrame for supercritical fluids

As supercritical $CO_2$ ($scCO_2$) is non-toxic so could potentially be used for the production of consumable products, such as pharmaceutical and food products[26] as well as already being an established system for numerous processes, including

extractions,[27] extraction of heavy metals,[28] nanoparticle production and modification[29] and polymer processing[30]

Several researchers including Noyori[31a,] Jessop[31b] and Leitner[31c] have reported that reactions involving gas reagents have been found to be faster in supercritical media, probably because mass transfer problem between different phases can be avoided. In fact, reactions of gaseous with liquid reagents with homogeneous catalyst dissolved in a liquid phase are usually limited by the mass transport at the inter phase. The use of homogeneous catalyst systems in supercritical reaction media constitutes an elegant way to solve mass transport problem; in fact supercritical fluids are in several cases able to dissolve both the gas and liquid reagents thus forming a homogeneous mixture and then the reaction can be run with the fast kinetics typical of homogeneous catalysis. Moreover in some cases, such as oxidations or hydrogenation, the use of non flammable $scCO_2$ allows to reduce or avoid problems connected with flammability and explosion hazards.

Summarizing, SCFs allow potential advantages on several aspects of a catalytic reaction, including better yields and selectivities, easy recycle and longer lifetime of catalyst, enhanced ass and heat transfer.

### 1.3.4 Ionic Liquids

Ionic Liquids (ILs) are coordinated compounds composed of organic cations and inorganic or organic anions. In contrast to high-temperature molten salts ILs are liquid at room temperature, so they also termed as Room Temperature Ionic Liquids[32] (RTILs). ILs are made of positively and negatively charged ions (Fig. 1.4), whereas water and organic solvents, such as toluene and dichloromethane, are made of molecules.

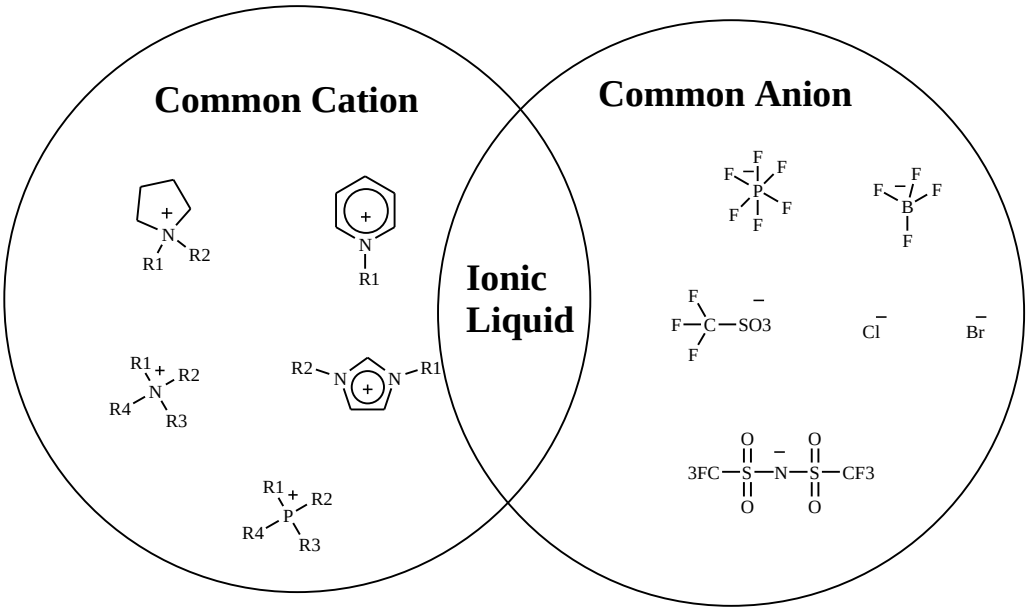



**Figure 1.4** Schematic Presentation Of Ionic Liquid

### a) Structure Of Ionic Liquid

The most commonly used cations in room-temperature ionic liquids are alkylammonium, alkylphosphonium, *N*,*N*′- dialkylimidazolium ([RR'IM]), and *N* alkylpyridinium ([RPy]) cations (Fig. 4). The most commonly utilized alkyl chains are methyl, ethyl, butyl, hexyl, octyl, and decyl. The most commonly investigated IL anions are shown in Table 1.4.

**Table 1.4** Common organic cations and inorganic anions

| Typical Cations | Typical anions |
|---|---|
| Imidazolium | Halides |
| Ammonium | Phosphates |
| Morpholinium | Sulphates |
| Phosphonium | Sulphonates |
| Piperidinium | Thiocyanates |
| Pyridinium | Borates |
| Pyrrolidinium | Sugar analogues |
| Quartenary ammonium salt | |
| Oxazolium | |
| Thiazolium | |

The development of Ionic liquids is given in short below. (Figure. 1.5)

First generation IL (1960–1992)- Creation of the first generation of ionic liquids, which were stable in contact with water and air, by J.S. Wilkes & R.A. Osteryoung, Ch. L. Hussey and J.S. Wilkesconducted research on the use of aluminium chloride liquids as electrolytes in batteries.

Second generation ionic liquids (1990s) - Creation of 2nd generation ionic liquids. In 1999 designing first low temperature ionic liquids for commercial purposes

Third generation of ionic liquids (2000-till now) creation of the 3rd generation of ionic liquids

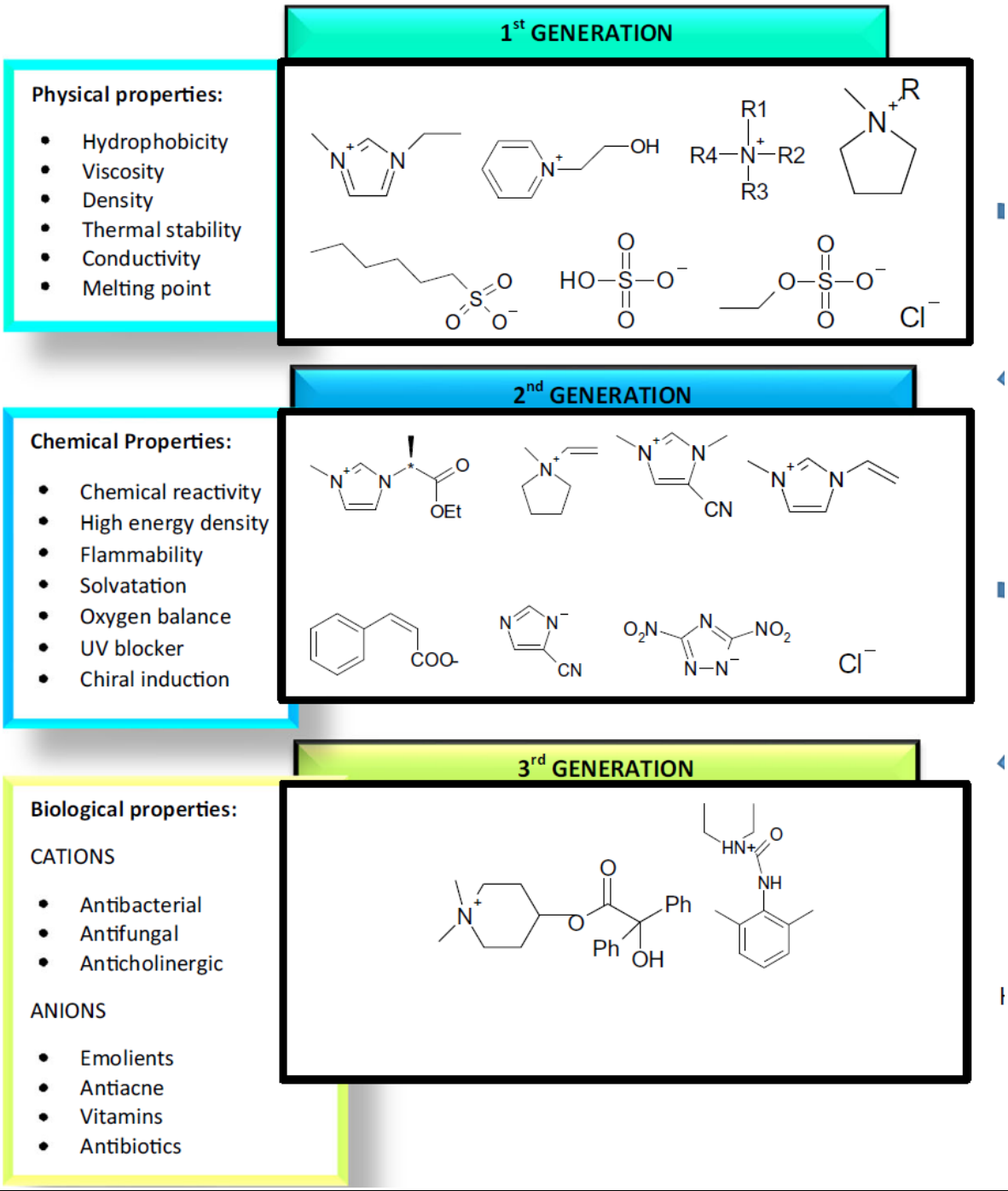



**Figure-1.5** The Development of Ionic liquids

The structure of ILs is similar to the table salt such as sodium chloride which contains crystals made of positive sodium ions and negative chlorine ions, not molecules. Since these conventional molten salts exhibit high melting points (400-800$^{o}$C), their use as solvents in applications is severely limited. Researchers explained that ILs remain liquid at room temperature due to the reason that their ions do not pack well.[33] The low melting points of ILs are a result of the chemical

composition. The combination of larger asymmetric organic cation and smaller inorganic counterparts (anion) lower the lattice energy and hence the melting points of the resulting ionic liquid medium are lower.[34].

Bearing characteristics as non volatile, non toxic, non flammable, high thermal stability, high re-use potential, miscible or immiscible in water (depending upon the nature of the anions), high viscosity, high conductivity, and high solvent power for organic and inorganic compounds has qualified ILs as green solvents which excited both the academic and the chemical industries.[35]

**c) Applications of Ionic Liquid**

As solvents, ILs posses following advantages over conventional organic solvents, which make them environmentally compatible[36]

• ILs have the ability to dissolve many different organic, inorganic and organometallic materials.

• ILs are highly polar.

• ILs consist of loosely coordinating bulky ions.

• ILs do not evaporate since they have very low vapour pressures.

• ILs are thermally stable, approximately up to 300$^{o}$C.

• Most of ILs has a liquid window of up to 200$^{o}$C which enables wide kinetic control.

• ILs have high thermal conductivity and a large electrochemical window.

• ILs are immiscible with many organic solvents.

• ILs are nonaqueous polar alternatives for phase transfer processes.

• The solvent properties of ILs can be tuned for a specific application by varying the anion cation combinations

The possibility to modify chemical and physical properties by changing the cationic moiety with a large choice of anions offers chemists a broad range of ILs. Thus the solvent properties can be changed significantly by changing the nature of the ions such as melting point, solubility, viscosity, density, conductivity, and refractivity. Due their unique properties, ILs considered being a relatively magical chemical; they have a large variety of applications in all areas of the chemical industries. The areas of application include electrolyte in batteries, lubricants, plasticizers, solvents and catalysis in synthesis, matrices for mass spectroscopy, solvents to manufacture nano-materials, extraction, gas absorption agents.[37]Another advantage of ILs in catalysis is the immobilization of the catalyst. Besides the tunable solubility to most organic chemicals, ILs are also able to dissolve a wide range of inorganic and organometallic

compounds, and therefore large numbers of catalysts having polar or ionic character can be immobilized in ILs, which can greatly facilitate the separation and subsequent reuse of the catalyst. In addition, the technological integration of ILs with other advanced technologies, including supercritical fluids, electrochemistry, biocatalysis, and nanotechnology, *etc.*, with great potential for growth, has received more and more attention in green catalysis. Ionic liquids have been widely applied as an alternative reaction medium benign catalysts of chemical transformations due to their favorable properties of excellent solubility, strong complexing activity, good thermal and chemical stability over a wide temperature range, modifiable, low corrosion and environment‑friendly ionic fluids also possess the advantages of both of them Homogenous and heterogeneous catalyst system, such as uniform catalytic active centers, easy separation and recyclability.

**d) Applications of Ionic Liquids in carbonylation Reactions**

The previous progress show that there are some merits for the application of ionic liquids in the carbonylation reactions, which not only improved the catalytic activity and selectivity of reaction, but also simplified the work, and facilitated the separation, reuse of traditional catalyst. After completion of the reaction , ionic liquid and the product is easy to separate and show heterogeneous catalysis and the ionic liquid catalyst system is likely to be recycled.[38] The carbonylation reaction consists of the "atomic economy" reaction with high selectivity and environmental friendly. Conventional carbonylation reactions are mostly catalyzed by noble metals. The process of reaction and separation involves a large amount of organic solvent and a catalyst. The active ingredient of the precious metal is expensive and easy to lose, resulting in a great wave and most organic solvents are volatile to cause environmental pollution. in order to better solve the above problems and can effectively improve the catalytic efficiency in recent years. The researchers applied ionic liquids to the carbonylation reaction. Ionic liquids, due to the good choice of solubility, coordination capacity, heat and chemical stability, low vapor pressure, adjustable structure and properties, has been widely used in organic synthesis, material preparation and biomass conversion field. The catalytic reaction process has a homogeneous catalytic characteristic of the reaction[38]. After completion of the reaction ionic liquid and the product is easy to separate and show heterogeneous catalysis and the ionic liquid catalyst system is likely to be recycled. Ionic liquid as a

"Green" reaction medium can effectively promote all kinds of carbonylation. The ionic liquid can be Used as a "Liquid carrier" for certain catalysts to facilitate product separation and reminder recycling agent, greatly simplifying the reaction of the post-treatment process, reducing the catalytic loss of agent.

**e) Ionic liquid recycle process**

IL was attached to vacuum pump for 5h in order to remove the traces of solvent and moisture. Then it was again introduced to stainless steel autoclave and used for next reaction cycles. Same process was repeated for next 6 cycles.

### 1.3.5 Deep Eutectic Solvents (DES)

A new solvent foundation was laid in 2003 reported by Abbott et al. and dubbed ‘‘Deep Eutectic Solvents’’ (DESs) [39]. Deep eutectic solvents are defined as[40] a mixture of two or more components, which may be solid or liquid and that at a particular composition present a high melting point depression becoming liquids at room temperature (**Fig. 1.6).** Deep eutectic solvents (DESs), a new generation of liquid salts based on ILs, are generally based on the mixtures obtained by the complexation between the two of the following.[40]

1. Hydrogen acceptor (HBA) such as nontoxic quaternary ammonium or phosphonium salt (e.g. cholinium chloride) and
2. A naturally derived uncharged hydrogen-bond donor (HBD) (e.g. amines, sugars, alcohols and carboxylic acids) in a certain molar ratio.

HBD and HBA can be associated with each other by means of hydrogen bond interactions. DESs usually have much lower melting point than the individual components mainly due to the formation of intermolecular hydrogen bonds. . In our opinion, this work definitely provides a new concept to widen the scope of DESs for chemical science[41]

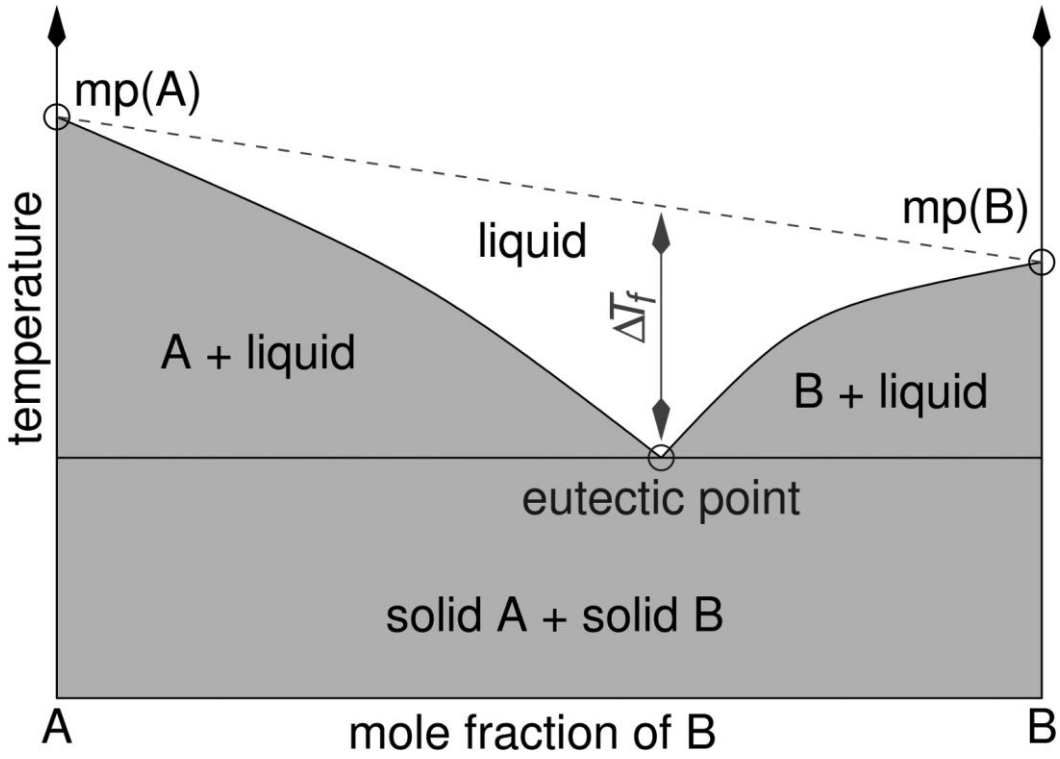



**Figure-1.6** Schematic representation of a eutectic point on a two component phase diagram.

The melting point of mixture is lower than the melting point of each of the organic compounds that comprises it. The charge delocalization occurring is hereafter responsible for the decreasing the lattice energy and the decrease in the melting point of the mixture relative to the melting points of the starting materials.[42-44] A classic example is the mixture of choline chloride (m.p. = $302^0$C, 2-hydroxyethyl trimethylammonium chloride) and urea (m.p. = $133^0$C) in a 1:2 molar ratio resulting in a room-temperature liquid (Tf =$12^0$C).[39] Due to the similarity between DESs and ILs (non-volatility, non-flammability, high viscosity, similarstarting materials),

DESs are sometimes referred to as the fourth-generation of ILs, even though they are not entirely composed of ionic species. The mixtures are sometimes referred to as low transition temperature mixtures (LTTMs),[45] because they may show a glass transition temperature instead of a eutectic melting point. DESs (or LTTMs) are regarded as promising alternative to ILs because they show many similar properties, but they are generally inexpensive and can be prepared in a easier way. Eutectic mixtures of salts have been extensively utilized to decrease the temperature for molten salt applications. An alternative to ILs are deep eutectic solvents (DES), which may also have an ionic character but consist of a mixture of organic compounds having a melting point significantly lower than that of either individual

component.[46] Figure 1.6 presents a schematic diagram of the solid−liquid boundaries of a mixture of two solids depending on the composition of the mixture. The most common DES are based on choline chloride (ChCl), carboxylic acids, and other hydrogen-bond donors, e.g., urea, citric acid, succinic acid and glycerol. DES have similar characteristics to ILs but are cheaper to produce (lower cost of the raw materials), less toxic, and often biodegradable.[47]

In addition, numerous structural possibilities encompassed by DESs and the possibility of designing their physicochemical properties for certain purpose makes them 'Designer solvents' as ILs are. DESs present many advantages, including low cost components, simple preparation, low or negligible toxicity profile and sustainability in view of environmental and economic benefits.[44-48] The first applications of choline-based eutectic solvents were in the electrodeposition and electropolishing of metals and in biodiesel production.[49] Subsequently, DESs have attracted attention as solvents in organic synthesis and biocatalysis, polymer production, electrochemistry, nanomaterials, biomedical applications and extraction of biologically active compounds from plant material.[43,44] The great interest in these new solvents is evident from 300 DES-related scientific papers in the period from 2009 to 2013. A lot of research is yet to be pursued; however, the potential contribution of DESs is foreseen not only from the technological perspective but also from the aspect of environmental safety and human health. Namely, they are a class of solvents based on compounds safe for human consumption (e.g. choline and sugars), giving great possibilities in the fields of drug delivery systems, bone therapy scaffolds, and other physical (negligible vapour pressure, stability under typical storage conditions) and chemical properties (high polarity, ability to form strong hydrogen bonds and to dissolve a variety of organic and inorganic compounds, as well as enzymes and transition metal complexes), in 2007 glycerol was proposed as a green solvent.[50–54]

Glycerol is very attractive in the field of organic chemistry due to its close similarity with water, however, application of glycerol enables working with substrates that are poorly miscible in water, such as hydrophobic molecules.[55] In addition, glycerol is able to facilitate dissolution of inorganic salts, acids, bases, enzymes and many transition metal complexes. Many hydrophobic solvents, such as ethers and hydrocarbons, are immiscible in glycerol, which enables the reaction products to be removed by simple liquid–liquid phase extraction. From the

technological point of view, the high boiling point (290 $^0$C) and the thermal stability of glycerol enable running of the processes at high temperatures and also make distillation of the reaction products a feasible separation technique (allowing re-usability of the solvent).[53]

**a) Preparation of DES**

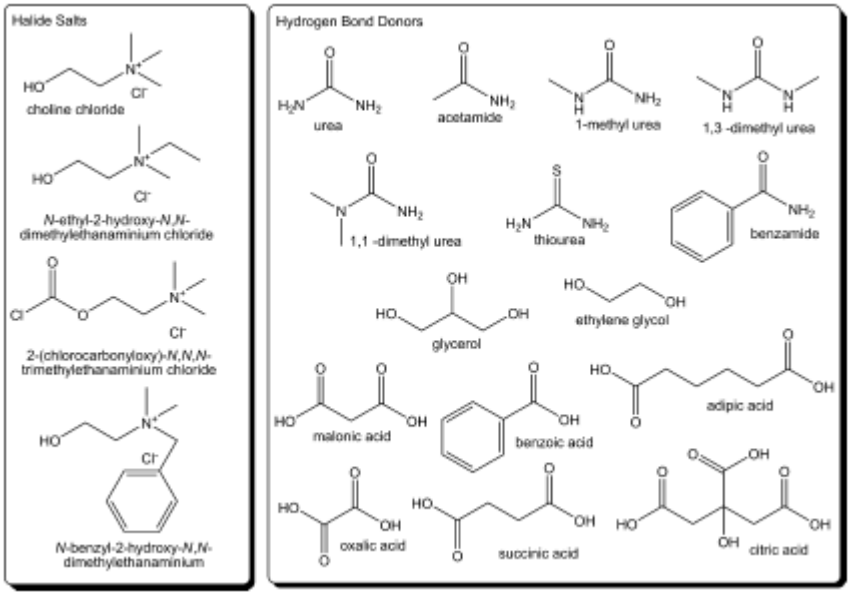



**Figure -1.7** Structures of some halide salts and hydrogen bond donors used in the formation of deep eutatic solvents

The DES can be prepared with 100% atom economy, through simple mixing of the two components, which are both inexpensive. In most occasions the eutectic mixture is achieved only by heating and mechanically stirring the individual components. Choline chloride (ChCl) is one of themost common components used since it is an inexpensive, biodegradable, and nontoxic quaternary ammonium salt.[56] If the ChCl is combined with hydrogen bond donors (such urea), renewable carboxylic acids or renewable polyols, ChCl is capable of forming a DES

**b) Charactricstics of DES**

DESs are characterized by high conductivities, viscosities, and surface tensions, they also have lower vapor pressure in comparison to other solvents.[57] Due to such beneficial properties, they have found plenty of various applications.The DES is renewable, because both glycerol and choline chloride are nontoxic and environment compatible

The first appearance of DES was as mixture of salt based on quaternary ammonium cation and a hydrogen donor (amine, imides, and carboxylic compounds). This eutectic phenomenon was first introduced through a mixture of urea and ChCl with a 2:1 molar ratio and melting points $133^0$C and $302^0$C respectively. The result was a eutectic mixture that melts at $12^0$C[58]. The most popular component among all DESs is choline chloride (ChCl) which is similar to B vitamins, and it is a biodegradable and nontoxic salt [59,60].

**c) Properties of DES**

The physical properties such as viscosity, conductivity, and surface tension of these DES are similar to ambient temperature ionic liquids therefore, exploiting them attracted other researchers[61]. And have been introduced as new alternative solvents to replace conventional ones for the use in synthetic processes[62] The refractive index is related to the electronic polarizability of the medium[16] and hence the DES with a phenyl moiety have the higher refractive indexes since the aromatic ring will be very polarizable. DESs present similar physical properties to ILs, with the advantage that they are more biodegradability and nontoxic;

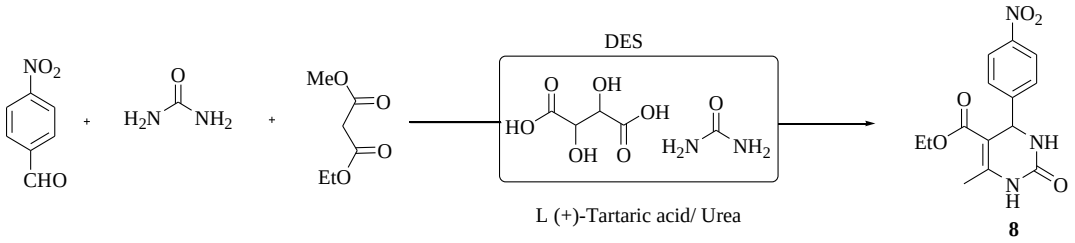
**d) Applications of DES**

They are increasingly being used in synthetic organic chemistry as well as in process technology, particularly for their unusual solvent properties. Emerging applications are in the field of biotransformations, organocatalysis, organometallic chemistry, and metal-catalyzed reactions. The use of DESs as possible alternative 'green' solvents for organic transformations, while of particular importance and attractiveness, has apparently to face the issue related with the chemical inertness of DESs, which are generally less chemically inert with respect to classical organic solvents and ionic liquids, so the success in using DESs in a particular chemical transformation cannot be taken for granted Copper(II) oxide and lithium chloride were successfully dissolved in this DES. Hence, DESs started to be used as solvents for metal cleaning prior to electroplating. Later, DESs were also utilized as a medium for electrochemical deposition and different metals were successfully electrodeposited such as Ag, Zn, Sn, Cr, and Cu [56,63] many potential applications in different fields of chemistry and electrochemistry. Main applications of DESs in nanotechnology The first combination of nanotechnology and ILs was published in 2001 [64,] however, the one related to DES was reported as late as 2008 introducing the use of the DES a solvent for the chemical synthesizing of gold nanoparticles. Later on, several

examples in nanotechnology fields were reported on the use of DESs. In addition, there are more than 500 patents studying various types of using ILs/DESs in nano-filed science.

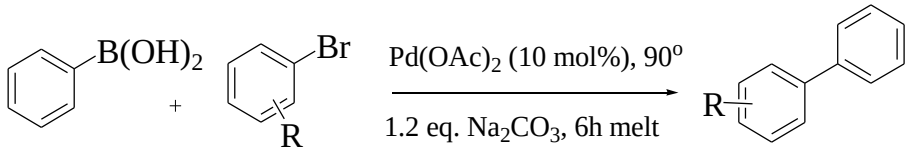
Solvents are undoubtedly substances indispensable in industry or an experimental branch of natural science. The technology of their production has evolved over the years, and its latest achievements are ionic liquids of 3rd generation and deep eutectic solvents. Each of these groups has great advantages over classical organic solvents, which usually are far from compliance with the requirements of Green Chemistry. The ease of synthesis, availability and biodegradability of the components makes these deep eutectic solvents versatile alternatives to ionic liquids. There are unlimited opportunities to prepare numerous DESs because of the high flexibility to choose their individual components as well as their composition. Thus, a plenty of room is available for the development of fundamental research in field of DESs. Different properties can be attained from DES production and envisaged applications can be achieved especially in high-tech production and processes that demand low costing materials [65]. Due to high polarity DES has wide application in the fields of in electrochemistry as electrolytes[66a] for electro deposition[66b] of metal, as solvents[66c] for electrochemistry reaction and for electro polishing (metal dissolution), etc. In the dissolution of several poorly soluble drugs including benzoic acid, griseofulvin, danazol, itraconazole and N-[4-[[6-[4-(trifluoromethyl)phenyl]- 4-pyrimidinyl]oxy]-2-benzothiazolyl]acetamide (AMG517) in ChCl/urea and ChCl/malonic acid DESs[66d].Moreover, it is noteworthy that recently the DESs have also been proven to be promising anhydrous solvents for nucleic acids. Hud and co-workers [107] showed that the nucleic acids can form several secondary structures that are reversibly denatured upon heating in DESs. In our opinion, this work definitely provides a new concept to widen the scope of DESs for life science[66e] In this context, Gore et al. reported the multicomponent synthesis of valuable biologically active dihydropyrimidinone (DHPM) [49] in acidic DESs[67]. This work aims at by-passing the traditional use of Bronsted and Lewis acids which dramatically impact the economical and ecological footprint of this reaction. DHPM was synthesized from urea, aldehyde and β-ketoesters (Biginelli reaction, (Scheme 1.1). Hence, urea was used in this example not only as a reactant but also as a component of the DES. For instance, in a citric acid/DMU (2:3) DES, *p*-4-nitrobenzaldehye, ethyl acetoacetate and DMU were selectively assembled at $65^0$C to the desired DHPM

which was obtained with 90% yield. An even higher yield (96%) was reported in a L-(+)-tartaric acid/DMU (3:7) DES.




**Scheme 1.1** Biginelli reaction in DES L (+)-Tartaric acid / Urea

In 2006, Konig and co-workers investigated the palladium-catalyzed Suzuki coupling[68] of phenyl boronic acid with aryl bromides in different carbohydrates–urea–inorganic salts eutectic mixtures. In all tested melts, quantitative conversion was observed and bi-arylated products were isolated with 78–98% yields. (Eq **1.3**) At the end of the reaction, products were isolated by liquid–liquid phase extraction with pentane (after dilution in water).




**9** **10** **11** **(1.3)**

## 1.4. Heterocyclic Compounds

The importance of heterocycles in many fields of science including organic, inorganic, bioorganic, agricultural, industrial, pharmaceutical, and medicinal chemistry, as well as material science can hardly be overemphasized and justifies a long-lasting effort to work out new synthetic protocols for their production[1]. Heterocyclic substances perform a very unique role in drug design and discovery. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are heterocyclic in nature.

Heterocycles form the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry. They have contributed to the development of society from a biological

and industrial point of view as well as to the understanding of life processes and to the efforts to improve the quality of life. Among the approximately 20 million chemical compounds identified by the end of the millennium, more than two thirds are fully or partially aromatics and approximately one half are heteroatomic. The presence of heterocycles in all kinds of organic compounds of interest in electronics, biology, optics, pharmacology, material sciences and so on is very well known. Between them, sulphur[2] and nitrogen-containing heterocyclic compounds[3] have maintained the interest of researchers through decades of historical development of organic synthesis. However, heterocycles with other heteroatoms such as oxygen[4], phosphorus[5] and selenium[6] also appears. Many natural drugs[7] such as papaverine, theobromine, quinine, emetine, theophylline, atropine, procaine, codeine, reserpine and morphine are heterocycles. Almost all the compounds we know as synthetic drugs such as diazepam, chlorpromazine, isoniazid, metronidazole, azidothymidine, barbiturates, antipyrine, captopril and methotrexate are also heterocycles. Some dyes (e.g. mauveine), luminophores, (e.g. acridine orange), pesticides (e.g. diazinon) and herbicides (e.g. paraquat) are also heterocyclic in nature. All these natural and synthetic heterocyclic compounds can and do participate in chemical reactions in the human body. Furthermore, all biological processes are chemical in nature. Such fundamental manifestations of life as the provision of energy, transmission of nerve impulses, sight, metabolism and the transfer of hereditary information are all based on chemical reactions involving the participation of many heterocyclic compounds, such as vitamins, enzymes, coenzymes, nucleic acids, ATP and serotonin.[8] why does nature utilize heterocycles? The answer to this question is provided by the fact that heterocycles are able to get involved in an extraordinarily wide range of reaction types. Depending on the pH of the medium, they may behave as acids or bases, forming anions or cations. Some interact readily with electrophilic reagents, others with nucleophiles, yet others with both. Some are easily oxidized, but resist reduction, while others can be readily hydrogenated but are stable toward the action of oxidizing agents. Certain amphoteric heterocyclic systems simultaneously demonstrate all of the above-mentioned properties. The ability of many heterocycles to produce stable complexes with metal ions has great biochemical significance. The presence of different heteroatoms makes tautomerism ubiquitous in the heterocyclic series. Such versatile reactivity is linked to the electronic distributions in heterocyclic molecules. Evidently, all the natural products and the synthetic drugs mentioned

above are good examples of nature's preference for heterocycles whose biological activity cannot be determined by one or a combination of two or three of the above mentioned properties. Synthetic heterocycles have widespread therapeutic uses[8] such as antibacterial, antifungal, antimycobacterial, trypanocidal, anti-HIV activity, antileishmanial agents, genotoxic, antitubercular, antimalarial, herbicidal, analgesic, anti-inflammatory, muscle relaxants anticonvulsant, anticancer and lipid peroxidation inhibitor, hypnotics, antidepressant, antitumoral, anthelmintic and insecticidal agents. There are larger number of synthetic heterocyclic compounds with other important applications such as fungicides, herbicides, anticorrosive agents, photostabilizers, agrochemicals, dyestuff, copolymer, photographic developers, fluorescent whiteners, sensitizers, booster agent, antioxidant in rubber and flavouring agent[9]. Pyrimidine (cytosine, thymine and uracil) and purine (adenine and guanine) derivatives are monocyclic and bicyclic heterocycles with two and four nitrogen atoms, respectively. They are key components of the deoxyribonucleic acid (DNA) molecules and participate directly in the encoding of genetic information. They also pass information to the related ribonucleic acid (RNA) molecules that control, in protein synthesis, the sequence of amino acids[10]. The need for minute quantities of accessory dietary factors, the vitamins is well-known. Vitamins in the B group thiamine, folic acid, riboflavin, cyanocobalamine, are nitrogen-containing heterocycles[10c] and function either as coenzymes or their precursors. Other vitamins such as ascorbic acid (vitamin C) and $\alpha$-tocopherol (vitamin E) are oxygen heterocycles.

The essential amino acid proline, histidine and tryptophan[11], photosynthesizing pigment chlorophyll; the oxygen transporting pigment haemoglobin[11b], the hormones kinetin, heteroauxin, cytokinins[11c], neurotransmitter serotonin, histamine respectively are successful application of heterocyclic compounds.

In conclusion, it can be questioned why it is specifically appropriate to emphasize the role of heterocycles, since analogies to the roles of other classes of organic compounds are easily found. In fact, dyes, luminophores, herbicides, pesticides and drugs do not necessarily have to be heterocyclic in structure. In a similar fashion there are many common features in chemistry and physics between such related compounds as pyrrole and aniline, or between pyridine and nitrobenzene. Nevertheless, nature selected the heterocycles pyrrole and pyridine and not the homocycles aniline and nitrobenzene, as the basis of most essential biological systems. We now know the reason for this: the introduction of a heteroatom into a

cyclic compound imparts new properties. Heterocycles are chemically more flexible and better able to respond to the many demands of biochemical systems. The constantly accelerating rate of research and development in heterocyclic chemistry suggested that, enormous numbers of heterocyclic systems are well known and this number is increasing very rapidly.

It is therefore easy to understand why both the development of new methods and strategic utilization of known methods for the synthesis of complex heterocyclic compounds continue to drive in the field of synthetic organic chemistry.

**1.5 Carbonylation reactions**

The term carbonylation[69a-j] can be described as the incorporation of CO molecule into an organic substrate either by the insertion of CO into an existing bond, e.g., C–X (X=Cl, Br, I), or by the addition of CO to unsaturated compounds, such as alkynes or olefins and alkylic, vinylic, arylic species in the presence of nucleophiles (NuH). Carbonylation is now widely recognized as a very important tool in industrial and organic chemistry. It allows the direct synthesis of carbonyl compounds starting from the simplest C-1 unit, which also meets the requirements of "atom economy"[70], step economy[71] and "green chemistry"[72]. The distinguishable advantages of carbonylation reactions are, the carbon chain can be easily increased after the insertion of carbon monoxide; carbonyl-containing compounds are important synthetic intermediates in organic synthesis, which hold imperative applications in advanced materials, agro-chemicals, dyes, pharmaceuticals, and so on; Being a fundamental and promising transformation, the carbonylation process introduces a new approach for constructing synthetically versatile cyclic-acyclic carbonylated derivatives with high efficiency and selectivity[73]. This growing importance of carbonylation methods in organic synthesis is attested to by the increasing number of publications dealing with this topic, including reviews[69a].

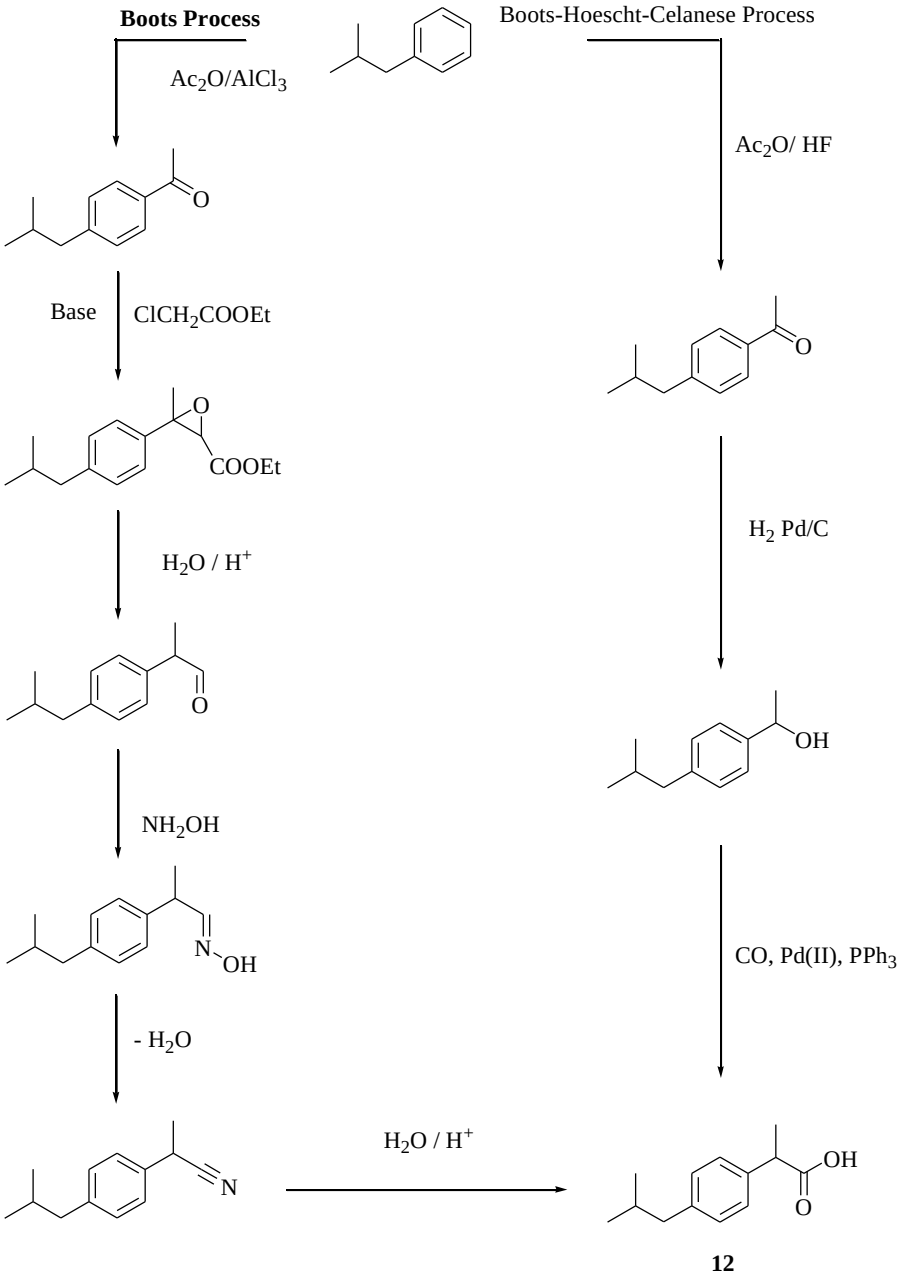
Carbon monoxide (CO) was discovered in the 18th century by de Lassone from the reaction of zinc oxide with coke. The initial work in the field of carbonylations was done by W. Reppe at BASF in the 1930s and 1940s; who coined the term ''carbonylation''74[b], since then, carbonylation reactions have gained great importance in Chemical industry. 80 years of research and development in the field of carbonylation, today made it possible to synthetic chemist to routinely employ CO as an inexpensive and easily available C1 source to synthesize all kinds of carbonyl

compounds. Now a day academic and industrial laboratories have broadly explored CO's use in chemical reactions[6]. Alcohols, amines, ethers, carboxylic acids and halides can be converted to acids, amides, esters, ketones, alkynones, alkenones, anhydrides and acid halides with the assistance of transition metal catalysts in the presence of a CO source. The CO sources used can be carbon monoxide gas, metal carbonyls such as $Mo(CO)_6$, $Co(CO)_6$, formic acid, aldehyde, etc.

Among the different catalytic reactions, carbonylation is of particular importance, which represents industrial core technologies for converting various bulk chemicals into a diverse set of useful products of our daily life. In fact, today the largest applications of homogeneous catalysis in bulk chemical industry (regarding scale) are carbonylation reactions, especially hydroformylations. The most successful example of industrial carbonylation process is the synthesis of acetic acid via carbonylation of methanol (by Rh catalysis Monsanto process or Ir catalysis Cativa process).[75] Not only carboxylic acids, esters and amides are accessible by carbonylation, but anhydrides, acid fluorides, aldehydes, and ketones can also be easily synthesized. Which of these products are obtained depends on the nucleophile: water (hydroxycarbonylation), alcohols (alkoxycarbonylation), amines (aminocarbonylation), carboxylate salts, fluorides, hydrides, or organometallic reagents can be used. A variety of carbonylation products can be prepared from the same aromatic substrate simply by changing the nucleophile, an advantage with respect to biologically active compound libraries. In addition to intermolecular carbonylations, intramolecular reactions are also possible, which allow for the synthesis of heterocycles. A prominent example is the intramolecular alkoxy- or aminocarbonylation (cyclocarbonylation) of hydroxy- or amino-substituted aryl/vinyl halides which enables the synthesis of lactones, lactams, oxazoles, thiazoles, imidazoles, and other heterocycles.[73]

An elegant example of carbonylative approach is the Hoechst-Celanese process for the synthesis of non-steroid anti-inflammatory drug, ibuprofen[76] 12 a common pharmaceutical product presently manufactured in over 8000t/y (Scheme 1.2)[76b]. Two routes for the production of ibuprofen, via the common intermediate, p-isobutylacetophenone, are compared. The classical route, developed by the Boots Pure Drug Company entails six steps with stoichiometric reagents, relatively low atom efficiency and substantial inorganic salt formation. In contrast, the elegant alternative, developed by the Boots Hoechst-Celanese (BHC) Company, involves

only three catalytic steps. Acetylation, hydrogenation and carbonylation, in which last two steps are 100% atom efficient. It represents a benchmark in environmental excellence in chemical processing technology that revolutionized bulk pharmaceutical production and became a source of inspiration for other pharmaceutical manufacturers for utilization of direct carbonylative protocols.




**Scheme 1.2** Synthesis of Ibuprofen 12, Classical route Vs carbonylative approach

Although, until the early sixties carbonylation chemistry was little considered as a synthetic method for the preparation of fine organic chemicals, but in recent years,

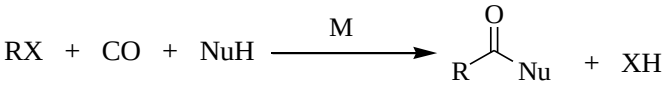
there has been a dramatic change in this picture, mostly brought about by the discovery of stable but extremely active catalysts based on organo-phosphine complexes of Palladium and Rhodium. Many carbonylations can now be carried out below 100°C at atmospheric pressure, using very small quantities of non-volatile, air-stable catalyst precursors, such as $[Pd(PPh3)_2CI_2]$ or $[RhCI(CO)(PPh_3)_2]$ and $K_2PdI_4$ [69a-e], which are converted to the active catalytic species *in situ.* Moreover, the scope and understanding of carbonylation has grown to such an extent that it can now be regarded, like catalytic hydrogenation, as one of the more generally useful techniques of synthetic organic chemistry, with a well-developed set of guidelines for choice of catalyst and reaction conditions. In most cases the functional group tolerances of catalysts and reaction conditions have been examined and selectivities between different functional groups established, so that reactions using new substrates can be carried out with a degree of confidence impossible a few years ago. Different kinds of carbonylation reactions can be defined; depending on the particular type of process under consideration four types of carbonylation processes are possible.

**Types of Carbonylation**

1) Substitutive Carbonylation
2) Additive Carbonylation
3) Reductive carbonylation
4) Oxidative Carbonylation

**1.5.1.1 Substitutive Carbonylation**

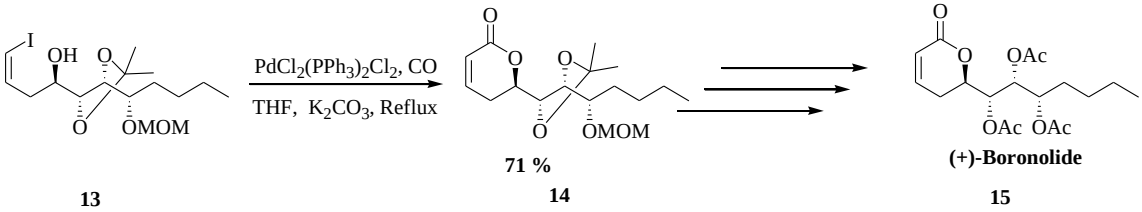
"Substitutive carbonylation" is a process in which a certain functional group (Generally aryl halides), such as a C–X bond (X = I, Br, Cl, OTf or another possible leaving group) is formally substituted with a NuH moiety (Eq. 1.4) [NuH usually corresponding to an OH, OR, NHR, or $R^1NHR^2$group.] This is a particularly versatile type of reaction providing a wide range of 'acyl anion equivalents', which allow the synthesis of many carboxylic acid derivatives from organic halides. Substitutive carbonylation of aliphatic halides is also possible, but generally requires more vigorous conditions[69e].




**(1.4)**

X = I, Br, Cl, O $SO_2R$,... NuH = $H_2O$, R'OH, $R^1NHR^2$,.....

Natural product (+)-Boronolide 15 isolated from Tetradenia fruticosa Benth having anti-malarial activity, was synthesized starting from 13 by intramolecular cyclization process to obtain 14 via substitutive carbonylative approach[77] (Scheme 1.3)

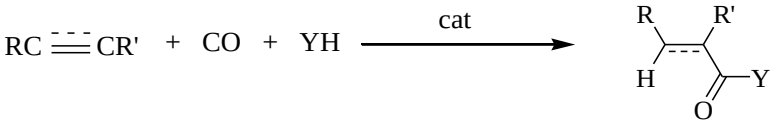



**13** **71 %** **14** **15**

**Scheme 1.3**

### 1.5.1.2 Additive Carbonylation

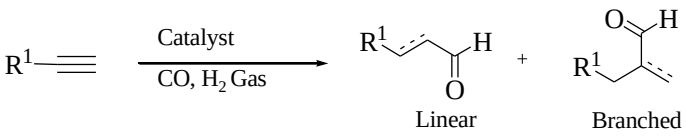
"Additive carbonylation" is a reaction in which a W–COY moiety (W usually corresponding to H; Y = H, OH, OR, NHR, $NR_2$, or some other nucleophilic group) formally adds to an unsaturated bond[1e] (Eq. 1.5)




**(1.5)**

Y = H,OH, OR', $NR^1R^2$,.....

This type of carbonylation reaction mainly includes hydroformylation reaction. Hydroformylation, also known as the oxo-process, refers to the addition of synthesis gas ("syngas"), a mixture of CO and $H_2$, to olefins in the presence of a catalyst under the formation of aldehydes. Hydrogen ("hydro") and a formyl group (H−C═O) are added in an atom-economical manner (Eq. 1.6).



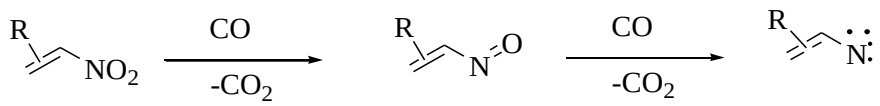

**(1.6)**

Today, this transformation represents one of the largest homogeneously catalyzed reactions in industry[74]. Formed aldehydes are valuable final products and intermediates in the synthesis of bulk chemicals like alcohols, esters, and amines which has end application in preparations of detergents, surfactants, solvents, lubricants and chemical intermediates[78].

**1.5.2.3 Reductive Carbonylation**

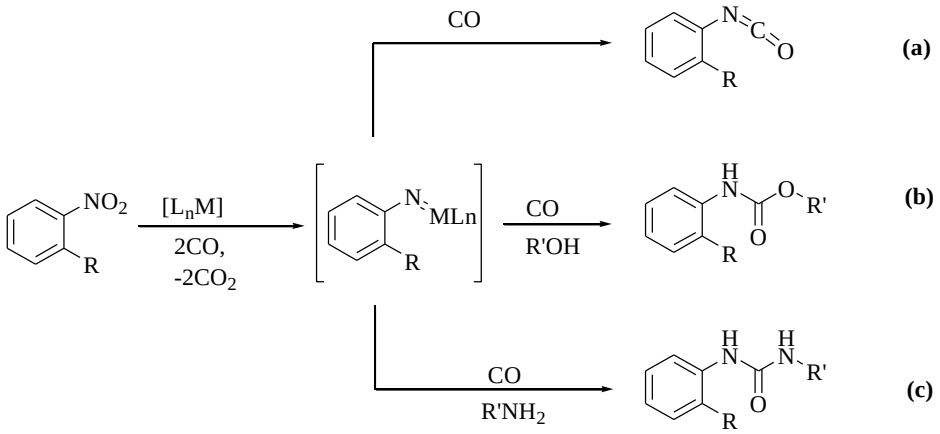
When carbonylation process takes place with reduction of the starting material(s), termed as reductive carbonylation[69e]. Metal catalyzed reductive carbonylation of nitroarenes to nitroso and/or nitrene is well known process of reductive carbonlylation[79] (Scheme 1.4) in

which CO is oxidized to $CO_2$. Conversion of aromatic halides to carbonyl derivatives is also a type of reductive carbonylation.




**Scheme-1.4**

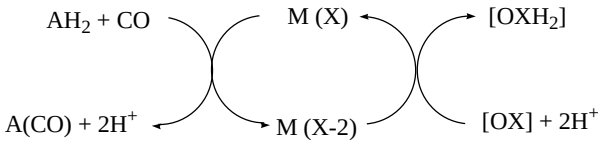
In recent year reductive carbonylation has been recognized as one of the important process for phosgene free direct conversion of nitroarene to phenylisocyanates (Scheme 1.5a) phenylcarbamate (Scheme.1.5b), and urease (Scheme.1.5c) derivatives1[88a-c]




**Scheme 1.5**

### 1.5.2.4 Oxidative Carbonylations

An oxidative carbonylation process can be defined as, "A process in which carbon monoxide is inserted into an organic substrate under the action of a suitable metal species undergoing a reduction of its oxidation state." [The reduction M(X) to M(X–2) being the most common case]. Usually an oxidative carbonylation process is promoted by a metal in a relatively high oxidation state, [most commonly M(II)], in the presence of an external oxidant. In order to achieve a catalytic process, the reduced metal must be reoxidized to its original oxidation state through the action of a suitable external oxidant (Scheme 1.6).




**Scheme1.6** The principle of oxidative carbonylation. M (X) = metal catalyst promoting the process; [$AH_2$] = organic substrate; [OX] = oxidant; [A(CO)] = carbonylated product; [$OXH_2$] = reduced oxidant.

Oxidative carbonylation is an important and powerful tool for the direct synthesis of carbonylated heterocycles[69a-e]. A wide variety of chemically and functionally distinct heterocyclic compounds were synthesized with the application of oxidative carbonylative approach by several research groups. Several oxidative carbonylative processes tends to undergo alkoxycarbonylation, aminocarbonylation and hydroxy carbonylation with respect to external nucleophile as Alcohol, amine and water. Synthesis of several heterocyclic compounds by Gabriele catalyst ($PdI_2$ in conjunction with KI) via Oxidative carbonylation will be discussed deeply in the next part.

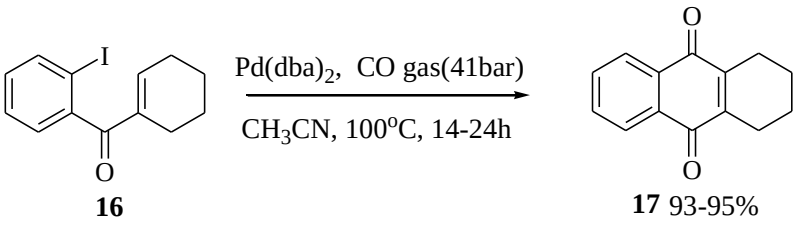
### 1.5.2 Carbonylative coupling reactions

C-C bond forming coupling reaction are routinely applied in the synthesis wide variety of organic compounds. Since Heck and co-worker reported the firstly the use of CO for heck coupling, new era of carbonylative cross coupling reactions started. Several examples of Heck coupling, Stille coupling, Suzuki coupling, Sonogashira coupling and so on has been published in last two decades. Cross-coupling reactions have become reliable transformations for all kinds of complex natural product syntheses. Moreover, the advancements in cross-coupling chemistry have made it

possible that some carbonylations of aryl halides are efficient enough to be run in industry on a ton scale. Carbonylative coupling reactions can works under mild conditions such as ambient or low pressure, which also increased their interest in academics too.

### 1.5.2.1 Carbonylative Heck Coupling Reaction

In 1974 Heck and co-workers described palladium-catalyzed alkoxy, hydroxy, and aminocarbonylation of aryl iodides and bromides, which is referred as 'Heck carbonylation Reaction[81]. Many carbonylative heck coupling reactions were reported of aryl halide[82b], vinyl halide[82c], aryl triflates[82d] with alkene and allenes[83a-c] to form cyclic acyclic derivatives. Negishi and his group reported first palladium catalyzed intramolecular synthesis of various quinines[82a] 17 from o-iodoaryl cyclohexenylketones (Eq. 1.7) as starting material 16 in good yields with 100% regioselectivity.

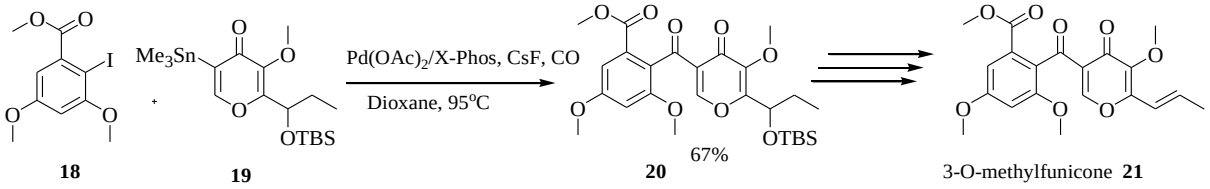



**16** **17** 93-95% **(1.7)**

### 1.5.2.2 Carbonylative Stille Coupling Reaction

The carbonylative Stille reaction between organic halides (or pseudohalides), carbon monoxide, and stannanes has been extensively studied in the past 20 years. In spite of the toxicity of the tin compounds, the Stille carbonylation has found many applications in organic synthesis because of its functional group tolerance and versatility.

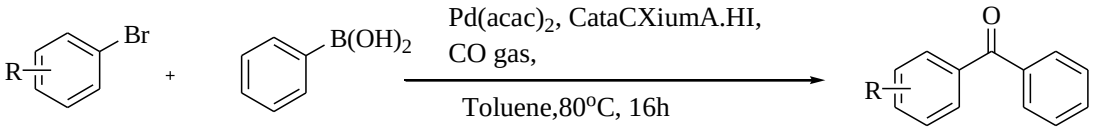
Antiproliferative and antifungal 3-O-methylfunicone 21 was synthesized by carbonylative stille cross coupling. Intermediate 20 was synthesized by Michel Ehrlich and Thomas Carell by carbonylative stlle cross coupling[84] of organohalide 18 with organostannate 19 under stille condition yielded coupling product 9 in moderate yield. (Scheme 1.7)




**Scheme 1.7**

### 1.5.2.3 Carbonylative Suzuki Coupling Reaction

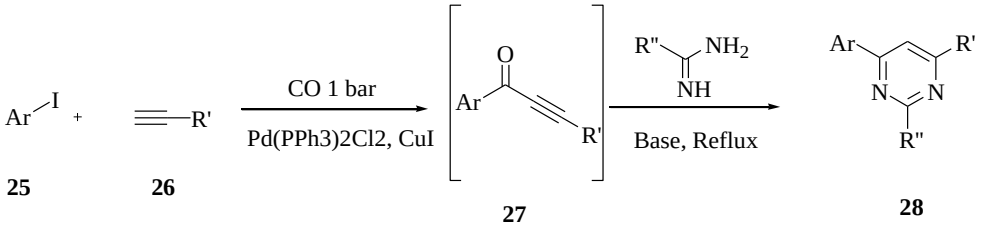
In 1993 first carbonylative Suzuki cross coupling was reported by A. Suzuki and co-workers[85]. Since then extensive work has been done to make the transformation more efficient and to widen its substrate scope[86]. Several diaryl and heteoaryl ketone[87] derivatives 21 unsymmetrical biaryl ketones[85] were synthesized by carbonylative cross coupling of aryl halide 22 with aryl boronic acids 23 (Eq.1.8)




**(1.8)**

### 1.5.2.4 Carbonylative Sonogashira Coupling Reactions

The carbonylative three-component cross-coupling of aryl halides with terminal alkynes in the presence of amines as the base to give alkynyl ketones is known as the carbonylative Sonogashira reaction. Carbonylative Sonogashira reactions have been successfully employed in natural product syntheses. For example Pawan J. Tambade, Yogesh P. Patil, Nitin S. Nandurkar, Bhalchandra M. Bhanageet reported the synthesis of 2,4,6-trisubstituted pyrimidines[88] 17 by a consecutive four- component carbonylative reaction sequence in one pot (Scheme 1.8). Starting from carbonylative Sonogashira coupling between (hetero) aryl iodides 25 and alkynes 26 to obtain in situ intermediate 27 which then underoes alkynylation/cyclocondensation with amidines to yield trisubstituted pyrimidine 28




**Scheme 1.8**

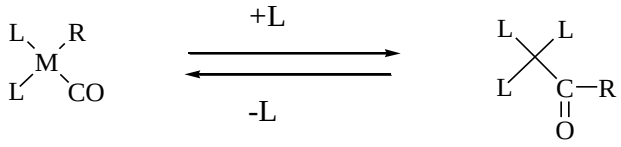
### 1.5.3 Transition metals in Carbonylation reactions

Transition metal catalysis dominates the organic synthesis and the fine chemical industry. Specifically, there are numerous procedures in industrial and fine chemical companies that require transition metals as their key catalysts[89]. Stoichiometric and catalytic transition-metal reactions have attracted great interest for their many applications in industrial and synthetic processes. Transition-metal reactions are critical in many thermodynamically feasible processes because they accelerate the reaction by opening a lower activation energy pathway, often one that was symmetry forbidden. These metal-centred reactions consists of one or more elementary reactions such as substitution, oxidative addition, reductive elimination, migratory insertion, hydrogen exchange, α-hydrogen transfer, σ-bond metathesis and nucleophilic addition.

First use of transition metal catalyst in carbonylation reaction as Cobalt ($HCo(CO)_4$) for hydroformylation of alkene with carbon monoxide and hydrogen gas was reported in 1938 (known as Roelen Reaction.[90]) and in 1953. Reppe's first catalytic carbonylation process converted acetylene, CO, and water to acrylic acid ( Hydroxycarbonylation) using $Ni(CO)_4$ as catalyst.[91] This was most fascinating examples of carbonylation reactions involving the interaction of a π-system with a transition metal. Since then carbonylation, "An insertion of carbon monoxide in organic substrate under the action of suitable metal catalyst (preferably transition metal) became an important synthetic tool for the synthesis of carbonylated derivatives. Continuous research progress in this area has led broader applications in the synthesis of a wide variety of simple carbonyl compounds to more complex organic molecules.

Synthetic organic reactions involving carbonylation of alkenes, alkynes such as hydroformylation and hydroesterification, amino and alkoxy carbonylation are catalyzed by the complexes of late transition metals such as Se[92], Tl[93], Hg[94], Mn[95], Fe[96], Co[97], Ni[98], Cu99, Ru[100], Rh[101], Pd[102], $PdI_2$[103], W[104], Pt[105], Ir[106] and Au[107]. In most cases metal carbonyl complexes have been used or assumed as catalyst. e.g. $HCo(CO)_4$, $HRh(CO)(PR_3)_3$ , $Ni(CO)_4$. In general these reactions involve activation of CO molecule by transition metal complexes as the key step. CO coordinates to the metal centre, giving the carbonyl-metal intermediates, and migratory insertion of the CO ligand into the M-C bond takes place as shown in (Eq. 1.9). Subsequent decomposition of the acyl-metal complex by reaction with a nucleophilic substances

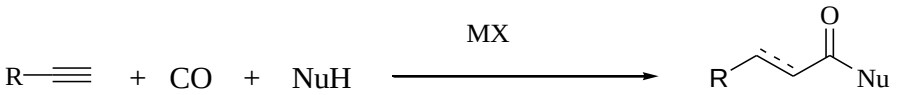
having active hydrogen (H-Y) results into final nucleophilic displacement to yield product respect to the nucleophile.




**(1.9)**

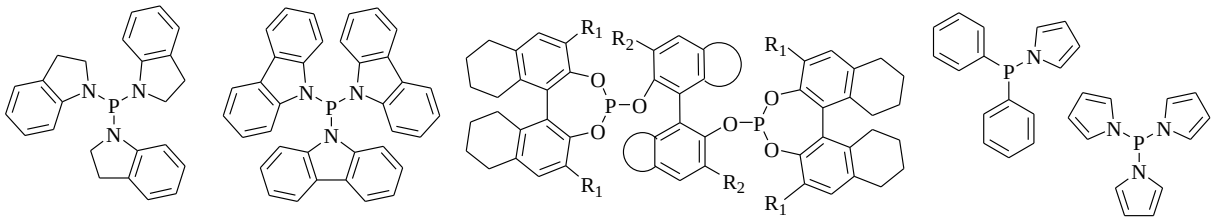
### 1.5.3.1Mechanistic Approach of Transition Metals in Carbonylation:

In general transition metal catalyzed carbonylation of olefins/acetylenes with nucleophiles such as alcohol, amine yields respected carbonylated derivatives (Eq. 1.10)




**(1.10)**

At the beginning of industrial homogeneous catalysis, nickel and cobalt catalysts prevailed in alkoxycarbonylations and hydroformylations. Later on there was tremendous increase in interest to develop less expensive and more selective catalysts based on transition metal for these reactions. Till date catalyst based on Rh, Pd, Ru, Pt, Ir, Fe, Ni, Mo, Cu has been discovered and developed by several research groups. Due to the improved activities and selectivities since the 1970s, catalyst developments focused especially on rhodium (for hydroformylation) and palladium (for alkoxycarbonylations) as base metals[74]. Due to the advancements in organometallic chemistry and organic ligand synthesis, now a days a plethora of ligands-N, -P and recently C-ligands is theoretically available (10.000 to 1000.000). These ligands are extremely important in determining the reactivity, productivity and selectivity of a homogeneous metal catalyst, In fact, "ligand-tailoring" constitutes an extremely powerful tool to control all kinds of selectivity in a given catalytic reaction and to influence catalyst stability and activity[110]. Some representative examples of –N, -P ligands are shown in Fig. 1.8



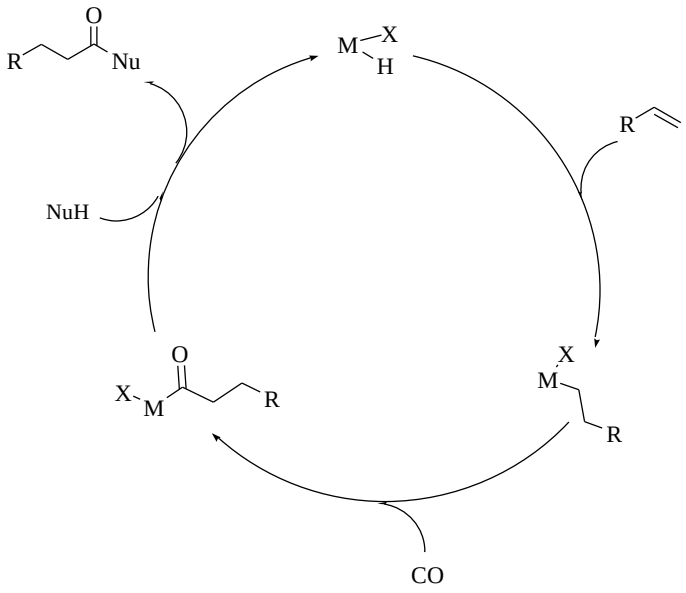
= Buta-1,3-dien-1,4-diyl, =butan-1,4-diyl

$R_1$ = H, Br, alkyl, aryl
$R_2$ = H, Br, alkyl, aryl

**Figure 1.8**

Despite the differences in the Organometallic catalyst, substrates or nucleophile carbonylation reaction follows general mechanism. (Scheme 1.9)

The reaction starts with the corresponding metal-hydride species, which is primarily formed by the reaction of the pre-catalyst with acid additives (TsOH, HBF4, etc.) or from the reaction of a suitable acyl metal complex with nucleophiles during the catalytic cycle. Subsequent coordination, insertion of the unsaturated substrates, followed by further insertion of carbon monoxide leads to the acyl metal complex. Finally, the catalytic cycle is finished by the nucleophilic attack of the nucleophile on the acyl-metal species and the metal-hydride is regenerated.



NuH = alcohol, amine, water

**Scheme 1.9**

As mentioned above due to the improved activities and selectivities since the 1970s, catalyst developments focused especially on rhodium (for hydroformylation) and

palladium (for alkoxycarbonylations) as base metals[74] and other metals used scarcely for these kinds of reactivities except cobalt considering as cost effective catalyst. Rhodium, Cobalt and Palladium catalyzed carbonylation will be discussed here.

**1.5.3.2 Rhodium Catalyzed Carbonylation Reaction**:

Rhodium (Rh) catalysts can be up to 1000 times more reactive than Co complexes. These features have also been recognized by the chemical industry. Thus, in 1980 less than 10% of hydroformylation was conducted with rhodium; by 1995 this had increased to ~80%. Rhodium catalyzed isomerization and hydroformylation reactions of internal olefins provide straightforward access to higher value aldehydes. Catalytic hydroaminomethylation offer an ideal way to synthesize substituted amines and even heterocycles directly.

Rh catalyzed hydroformylations can yields into formation of linear and branched aldehyde product. Linear aldehydes are of great interest in chemical industry and so mostly the research was focused on improvement of the regioselectivity. In order to obtain excellent regioselectivity, organometallic complex of Rh catalyst were designed and synthesized with chelating bulky phosphites or phosphines as ligands on the basis of conclusion made on the observations.

* Rate of isomerization of internal olefins must be faster than the hydroformylation reaction.

* Catalyst should be highly *n* selective for the hydroformylations.

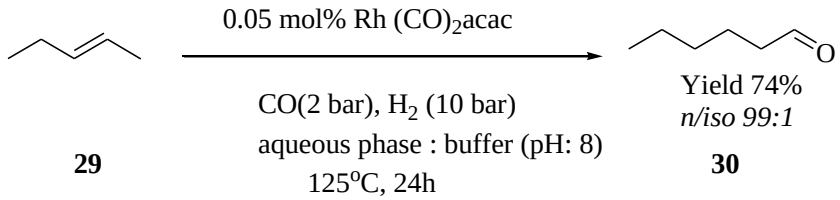
* Rhodium species coordinated with less electron-rich ligands exhibit significant activity toward isomerization of the substrate.

* Regioselectivity of the hydroformylation is influenced by π-acceptor and σ-donor properties of the respective ligand, so electronic properties of heterocyclic phosphine ligands can influence the *n / iso* regioselectivity.

Keeping in mind the above conclusions several group especially M. Beller and co-worker reported several bulky phosphine and phosphite based ligands for Rh catalysis. Such as pyrrolyl, indolyl, carbazoyl, Bisphosphite, BINAS, (Eq. 1.11).

Holger Klein, Ralf Jackstell and Matthias Beller reported the highly selective water-soluble rhodium-catalyzed hydroformylation of pentene[111] 29 by the use of Sulfonated Naphos (so-called BINAS). Apart from the ligand tailoring, also the pH value and CO partial pressure are important factors for the success of this reaction. The product was obtained n-selectivities exceeded in good yields and the catalyst

was easily reused several times without decrease of product yield and selectivities (Eq. 1.11).



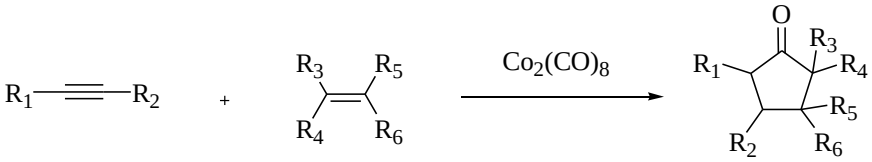

**29** **30** **(1.11)**

### 1.5.3.3 Cobalt catalyzed carbonylation reaction

As mentioned earlier in introduction, on apart from rhodium and palladium, other metals have only been scarcely applied in carbonylative transformations so far. The main reasons for this were the low activity of the corresponding metal carbonyl complexes as well as the tendency to undergo increased side reactions such as hydrogenations. On the other hand, the fact of the lower costs and toxicity of cobalt catalysts in comparison with other transition metals, ecological and economical cobalt-mediated transformations have received continuous ever-growing attention during the two last decades that leads to exciting and fruitful research. Moreover, cobalt has a high affinity to carbon−carbon $\pi$-bonds, carbon−nitrogen $\pi$-bonds, and carbonyl groups that was used to develop the Nicholas reaction [2+2+1] cycloaddition, Pauson-Khand reaction, [2+2+2] cycloadditions.[112] The cobalt carbonyls mainly $Co_2(CO)_8$ and cobalt hydrocarbonyl, $HCo(CO)_4$ play important roles in the catalysis[114].

**Pauson–Khand reactions [2 + 2 + 1] Cyclizations**

Pauson–Khand reactions are the most representative reactions with the organocobalt compounds used in organic synthesis[115]. These reactions involve the cyclization of one acetylene 31, one olefin 32 and a cobaltcarbonyl (as a carbon monoxide source, e.g. octacarbonyldicobalt) and yield cyclopentenone 33 by the [2 + 2 + 1] cyclization addition, as shown in (Eq. 1.12). In these reactions, $Co_2(CO)_8$ reacts with acetylene at room temperature for several hours to form a stable acetylene $\pi$-complex, then an olefin reacts with the complex under a nitrogen or carbon monoxide atmosphere with heating. Generally, a stoichiometric amount of the metal is required to achieve an acceptable yield because the cobalt carbonyl compound is used as the carbon monoxide source.[115]




(1.12)

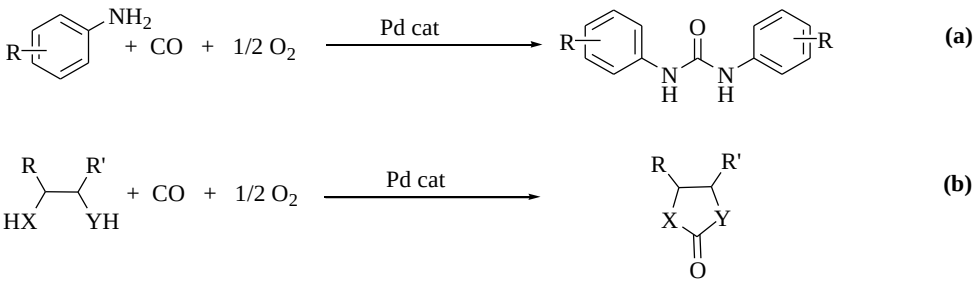
**31** **32** **33**

### 1.5.3.4 Palladium catalyzed carbonylation reaction

Palladium-catalyzed coupling reactions are well known; also carbonylation reactions have experienced impressive improvements since the first work of R. Heck and co-workers in 1974. Palladium catalyzed carbonylation reactions are now widely recognized as a very important tool in industrial and organic chemistry Palladium metal based catalytic system has been routinely employed in carbonylation reactions preferably for oxidative carbonylation and carbonylative coupling reactions than hydroformylation reactions. Palladium catalyzed oxidative carbonylation reactions require the coupling of organic nucleophiles or electrophiles in the presence of CO and an oxidant to prepare various carbonyl-containing compounds[117]. Under oxidative carbonylation conditions palladium can leads to the formation of mono and double carbonylated products[118]. Most commonly Pd(II) catalyst reacts with the organic substrates of electron-rich species, such as olefins, alkynes, and arenes[119]. Numerous Pd(II) complexes of the type $L_2PdX_2$ can be easily formed from $PdCl_2$ and the appropriate ligand L. The well known Pd(II) complexes[120] are $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, and $PdCl_2(RCN)_2$ and $PdI_2$[69a-e, 120]. Various carbonylation reactions catalyzed by palladium metal have been reported in literature.

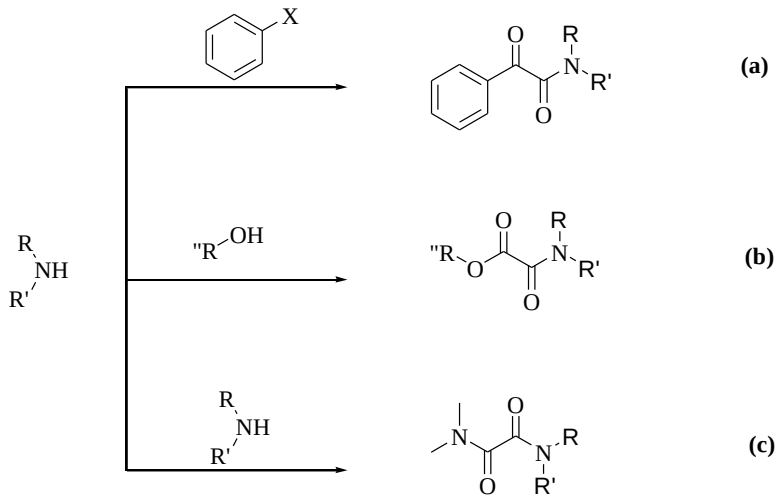
**Palladium catalyzed oxidative carbonylation**

Under palladium catalyzed oxidative carbonylation conditions amines (mostly primary), diols and amino alcohols undergoes mono-carbonylation process results into the formation of ureas[122] (Scheme 1.10, Eq. a), carbamate, cyclic carbonates[123] and Oxazolidinone[124] (Scheme 1.10, Eq. b) derivatives..




**Scheme 1.10**

Palladium catalyzed double carbonylation of amines and aryl halides is an important reaction for the synthesis of α-keto amides[125] (Scheme 1.11, Eq. a), oxamides[126] (Scheme 1.11, Eq. b) and oxamates[127] (Scheme 1.11, Eq. c)

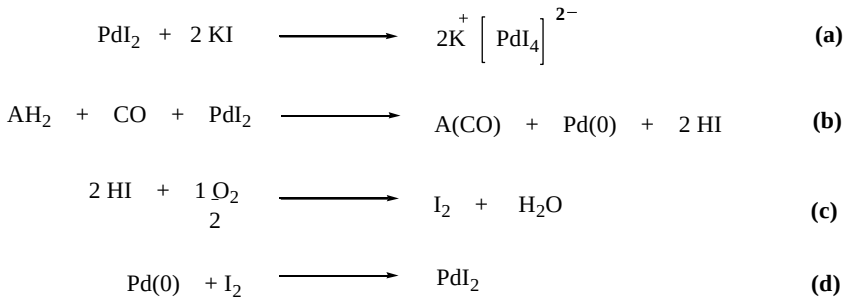



**Scheme 1.11**

### Gabriele Catalyst: $PdI_2$ in conjunction with KI

The Gabriele Catalyst i.e. $PdI_2$ in conjunction with KI was introduced by Prof. Gabriele about 20 years ago[121], now this catalytic system has been established as one of the most versatile and efficient catalysts for the oxidative carbonylation of simple and functionalized alkynes.[69a-e] Gabriele catalyst in conjunction with an excess of iodide anions from KI, constitutes an exceptionally efficient, selective and versatile catalyst for promoting a variety of oxidative carbonylation processes, leading to important acyclic as well as heterocyclic carbonyl compounds under mild conditions and with high selectivity. The main characteristics of this system are its simplicity, the only ligands for Pd(II) being electron rich iodide anions which also provides efficient mechanism of re-oxidation of Pd(0) to Pd(II) by the use of oxygen directly as the external oxidant. $PdI_4^{2-}$ formed in situ (Scheme 1.12, Eq. a) from the reaction between $PdI_2$ and KI is an active species to carry out the effective carbonylation process, also responsible for solubility of catalyst in the solvent which tends to perform carbonylation under homogeneous catalytic conditions. General mechanism for $PdI_2$/KI catalyzed carbonylation can be described as (in the following scheme anionic iodide ligands are omitted for clarity), Carbonylation of organic substrate ($AH_2$) results into formation of carbonylated product and reduced Pd(0) species

along with liberated two moles of HI (Scheme 1.12, Eq. b). Reaction of HI with oxygen present in gas mixture occurs along with production of water as product (Scheme 1.12, Eq. c). Pd(0) reoxidation occurs through oxidative addition of $I_2$ (Scheme 1.12, Eq. d)



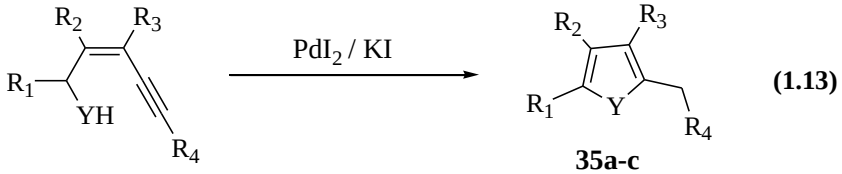

**Scheme 1.12**. Mechanism of Pd(0) reoxidation in $PdI_2$/KI-catalysed oxidative carbonylation reactions. Anionic iodide ligands are omitted for clarity. $AH_2$ = organic substrate; A (CO) = carbonylated product.

$PdI_4^{2-}$ is generally a more active catalyst species than $PdCl_4^{2-}$, which was, in turn, more active than neutral complexes, such as $(PhCN)_2PdCl_2$ or $Pd(OAc)_2$. These results indicates that the active catalytic species is stabilized by halide ligands. Moreover, the better results obtained with iodide rather than chloride can be interpreted in view of the higher electron-releasing power of $I^-$ compared with $Cl^-$, which tends to favour the final protonolysis step leading to the heterocyclic ring. Gabriele catalytic system is able to promote different heterocyclization reactions under mild conditions and with high selectivity. The synthetic protocols leading to heterocycles mainly grouped into two classes of reactions: (a) cycloisomerization; and (b) oxidative carbonylations. Cycloisomerization and oxidative carbonylations will be discussed and explained below.

**$PdI_2$-Catalyzed Cycloisomerization Reactions**:

The synthesis of substituted furans (Oxygen heterocycles), thiophenes (sulphur heterocycles), and pyrroles (nitrogen heterocycles) by transition metal-catalyzed heterocyclization reactions has recently attracted great interest in view of the possibility of constructing the heterocyclic ring with the desired substitution pattern in a one-step procedure[128]. From the point of view of atom economy[70], the ideal approach is clearly represented by a simple cycloisomerization process[129]. $PdI_2$ is an excellent catalyst for carrying out the cycloisomerization (Eq. 1.13) of (*Z*)-2-en-4-yn-

1-ols 34a, (*Z*)-2-en-4-yne-1-thiols 34b, and (*Z*)-(2-en-4-ynyl)amines 34c into the corresponding furans,[130] thiophenes,[131] and pyrroles[132] 35a–c, respectively has been reported by Gabriele research group.



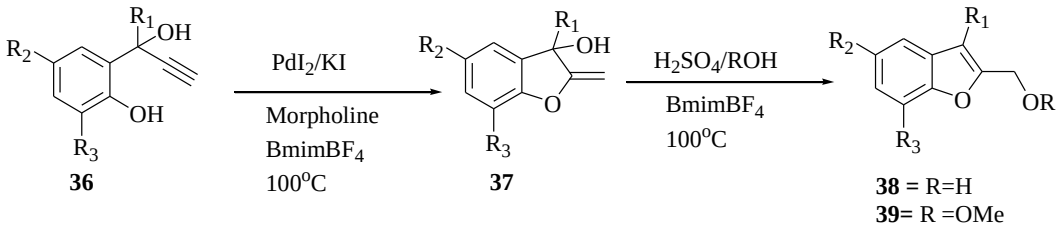

**(1.13)**

**35a-c**

**34a = Y = O**
**34b = Y = S**
**34c = Y= NR**

Cycloisomerization reactions leading to furans, thiophenes, and pyrrols have been performed under mild conditions in classical organic solvents, either dipolar aprotic (such as *N', N''*- dimethylacetamide (DMA), dimethylsulfoxide (DMSO), or MeCN), apolar or slightly polar (such as toluene, THF, or $CH_2Cl_2$), or protic ones (such as MeOH). However, recently these processes were carried out successfully in unconventional solvents, such as ionic liquids (ILs). This has allowed the easy and convenient recycling of the reaction medium and/or of the catalyst[131b].

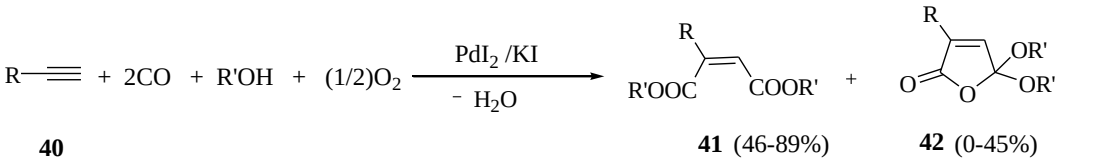
Recyclable approach for $PdI_2$ catalyzed synthesis of 2-methylene-2,3-dihydrobenzofuran-3-ols 37 by cycloisomerization of 2-(1-hydroxyprop-2-ynyl)phenols 36 in an ionic liquid medium ($BmimBF_4$)[133] (Scheme 1.13) published recently by Gabriele research group. The recyclable process takes place under relatively mild conditions (100 °C, 5 h) in the presence of catalytic amounts (2 mol %) of $PdI_2$ in conjunction with KI (5 equiv with respect to $PdI_2$) and an organic base, such as morpholine (one equiv. with respect to 36), to give 37 in high yields (70%–86%), and catalytic system was recycled up to six times. Moreover, conversion of products 37 into 2-hydroxymethylbenzofurans 38 (52%–71%) and 2-methoxymethylbenzofurans 39 (52%–80%) based on 36 was achieved in a one-pot fashion via acid-catalyzed allylic isomerization or allylic nucleophilic substitution.




**Scheme 1.13**

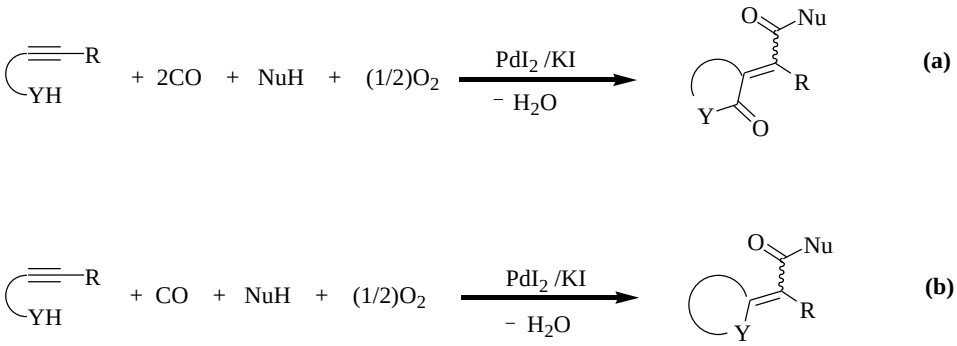
**$PdI_2$ Catalyzed Oxidative Carbonylation Reactions**

$PdI_2$/KI-catalyzed oxidative carbonylation of simple/substituted alkyl- or arylacetylenes, as well as of propynyl alcohol and propynyl acetate 40, carried out in alcoholic solvents under mild conditions (15–25 atm of CO, 4–9 atm of air, 25–80 ◦C), led to the formation of maleic derivatives 41(together with small amounts of fumaric derivatives) and 5,5-dialkoxyfuran-2(5*H*)-ones 42, in high yields and with unprecedented catalytic efficiencies for this kind of reaction (up to ca. 4000 mol of product per mol of Pd) (Eq. 1.14).[69d] The furanone derivatives were easily converted into maleic esters by acid-promoted alcoholysis. The process could also be applied to the synthesis of maleic acids or maleic anhydrides[134]working in DME-$H_2O$ or water-containg dioxane, respectively, under appropriate conditions.




**40** **41** (46-89%) **42** (0-45%) **(1.14)**

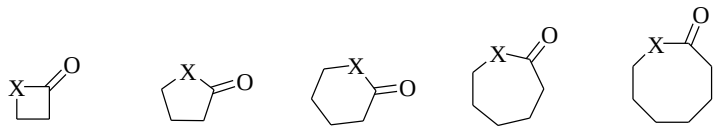
Alkynes bearing a nucleophilic group in suitable position for cyclization are excellent substrates for different kinds of oxidative carbonylation reactions leading to functionalized heterocyclic derivatives. $PdI_2$ catalyzed oxidative carbonylation process can leads to two different pathways a) oxidative Cyclocarbonylation (with incorporation of CO in the cycle) (Scheme 1.14, Eq. a) and oxidative cyclization–carbonylation (without incorporation of CO in the cycle) are possible (Scheme 1.14 Eq. b).




**Scheme 1.14**

**Oxidative Cyclocarbonylation**

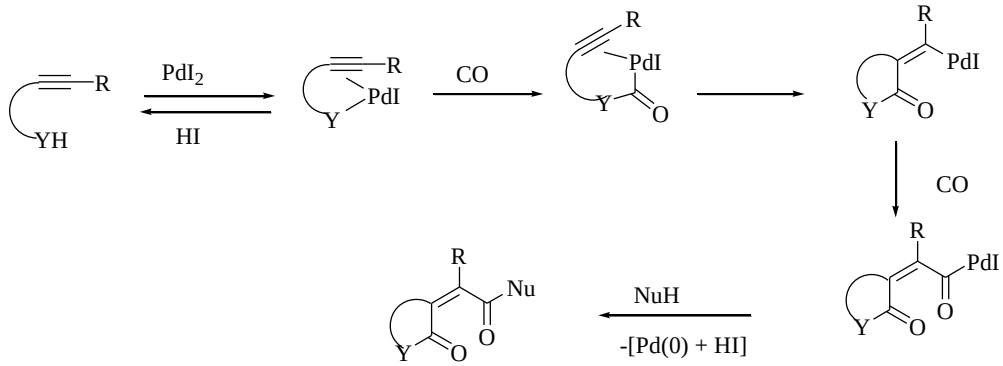
Synthesis of saturated or unsaturated heterocyclic compounds consisting carbonyl group in the ring such as lactones, lactams, and pyrrolidinones from small to large size can be achieved by direct oxidative cyclocarbonylation approach (Fig. 1.9) in single step[73].



X = O, -NH, -NR

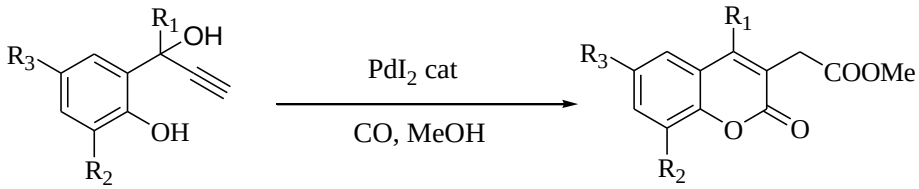
**Figure 1.9** lactones and lactams of different size

Cyclocarbonylative pathway (Scheme 1.15) proceeds via formation of an alkoxycarbonylpalladium (or carbamoylpalladium) intermediate[69e] through the reaction between the nucleophilic function of the substrate –YH (Y = O, NR), CO and $PdI_2$, followed by intramolecular *syn* insertion of the triple bond, CO insertion and nucleophilic displacement by an external nucleophile (NuH).



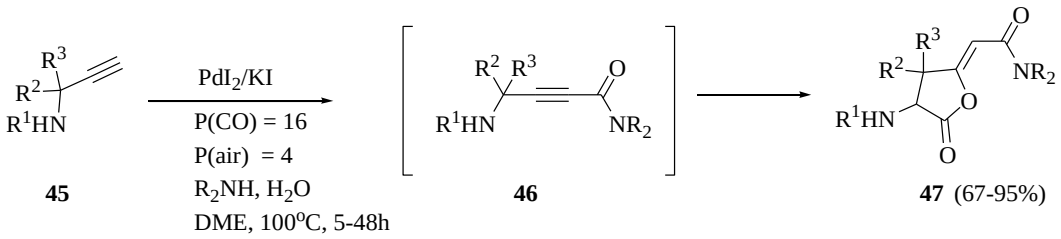
**Scheme 1.15**

Synthesis of coumarin starting from readily available 2-(1-hydroxyprop-2-ynyl) phenols, under oxidative carbonylation conditions catalyzed by $PdI_2$/KI catalytic system[135] follows the cyclocarbonylative pathway (Eq. 1.15). Starting from readily available 2-(1-hydroxyprop-2- ynyl) phenols 43, palladium-catalyzed cyclocarbonylative-dicarbonylation process in MeOH as the solvent in the presence of catalytic amounts of $PdI_2$ in conjunction with an excess of KI at room temperature and under 90 atm of CO to give 3-[(methoxycarbonyl)- methyl coumarins 44 in good to high isolated yields (62-87%).




**43** **44** (62-87 %) **(1.15)**

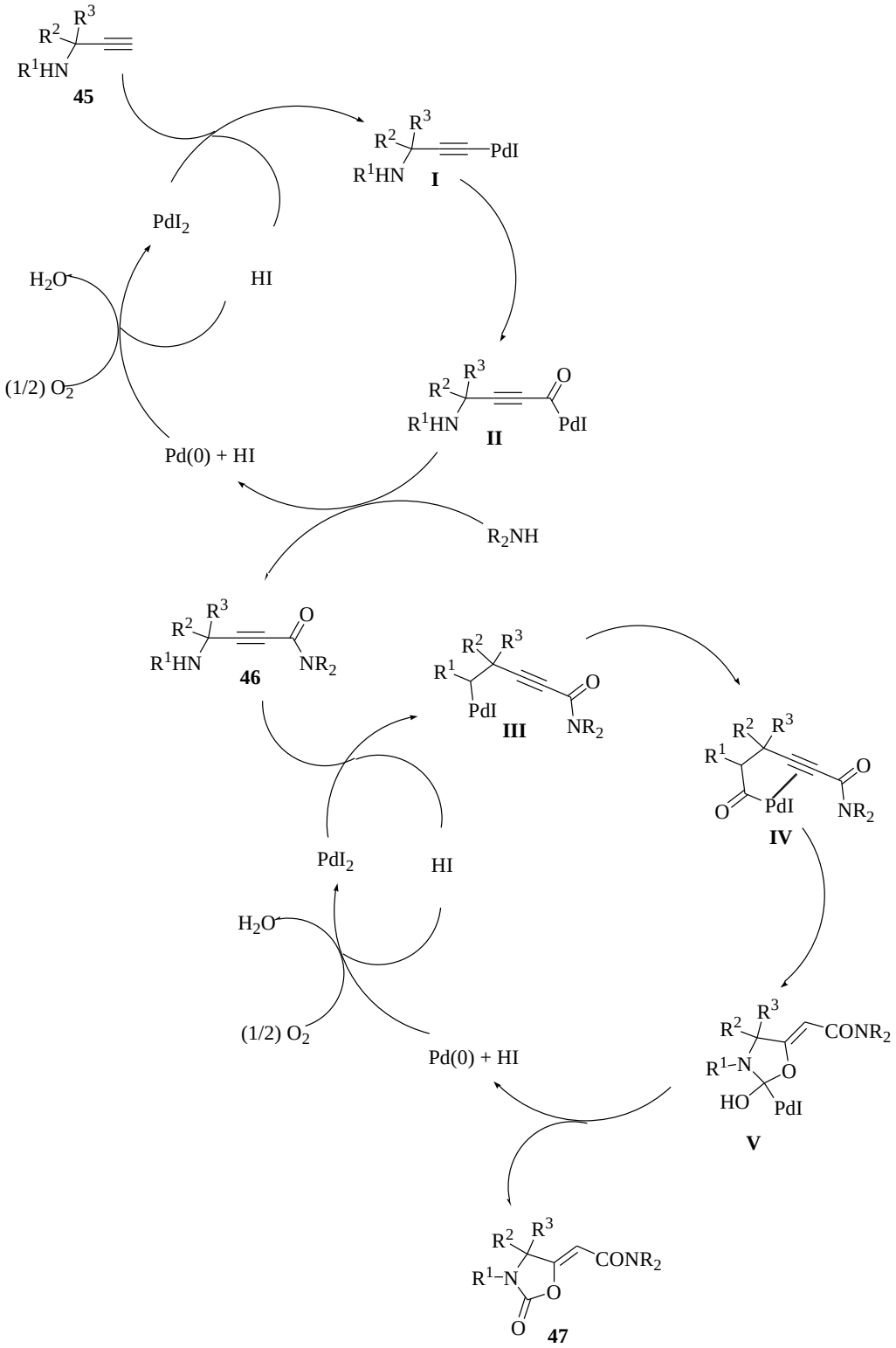
Bartolo Gabriele, Pierluigi Plastina, Giuseppe Salerno, Raffaella Mancuso, and Mirco Costa, reported water and secondary amine mediated sequential oxidative aminocarbonylation/cyclocarbonylation process of α,α-disubstituted 2-ynylamines 45 (Scheme 1.16), leading to oxazolidin-2-ones 47, Via two sequential catalytic processes[136], both catalyzed by $PdI_2$.




**45** **46** **47** (67-95%)

**Scheme 1.16**

The first process corresponds to oxidative aminocarbonylation of the triple bond of 45 to give the 2-ynamide intermediate 46 (Scheme 1.17) via initial reaction $PdI_2$ to form intermediate I, which is then followed by carbonyl insertion to form carbamoyl intermediate II and then nucleophilic displacement with secondary amine to form 46 Intermediate 46 is converted into the carbamoylpalladium complex IV through the reaction of the amino group with $PdI_2$ followed by CO insertion on complex III. Attack by water to the carbonyl of IV followed by intramolecular conjugate addition then gives intermediate V. Elimination of [Pd(0) + HI] from the H-O-C-Pd-I unit of V. Reductive elimination eventually leads to the final product 47 and Pd- (0). Reoxidation of Pd(0) to $PdI_2$ takes as explained above.

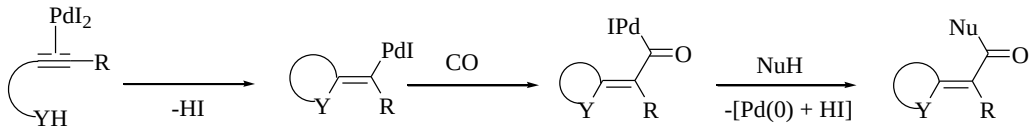



**Scheme 1.17**

Thus, formation of 47 from 45 takes place through the concatenation of two catalytic cycles, both promoted by $PdI_2$ oxidative aminocarbonylation of the triple bond to give 45 followed by oxidative water-driven cyclocarbonylation (Scheme 1.17).

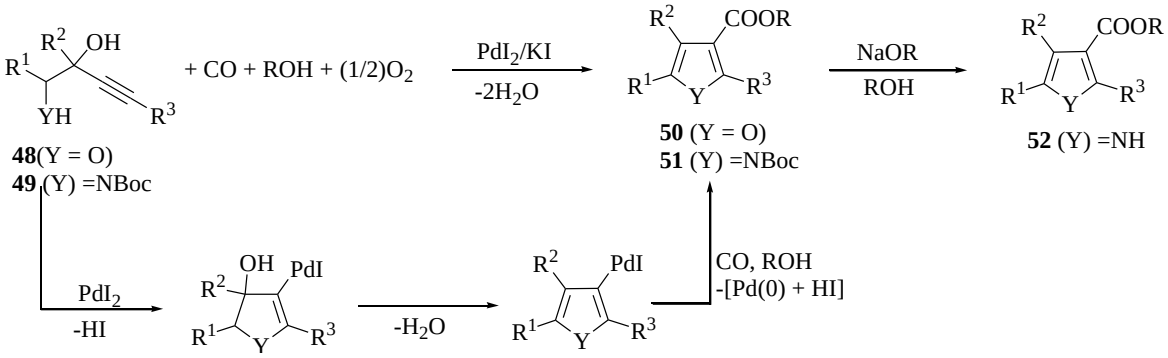
B-Oxidative cyclization–carbonylation

This reaction pathway is also known as oxidative heterocyclization-carbonylation, In this reaction pathway *anti* intramolecular nucleophilic attack[1e] by the –YH (Y= -O, -NH, -NR) group on the triple bond coordinated to $PdI_2$ occurs. Depending upon the substituted group on the nucleophile or the carbon chain, the cyclization mode either *exo* or *endo (*only the *exo* mode is shown in Scheme 1.18), followed by CO insertion and nucleophilic displacement by an external nucleophile (NuH).




**Scheme 1.18**

Gabriele catalyst catalyzed hetero-cyclization-carbonylation of 3-alkyne-1,2-diols 48 or N-Boc-1-amino-3-alkyn-2-ols 49 leading to Furan-3-carboxylic Esters[137] 50 and Pyrrole-3-carboxylic Esters[70] 51 respectively has been reported (Scheme 1.19). Both the process undergoes $PdI_2$/KI-catalyzed *5-endo-dig* heterocyclodehydration-alkoxycarbonylation approach. Reactions were carried out in alcoholic solvents at 80−100 °C and under 20 atm of a 4:1 mixture of CO−air, in the presence of the $PdI_2$−KI catalytic system (2−5 mol % of $PdI_2$, KI/$PdI_2$ molar ratio = 10) resulted into formation furan-3-carboxylic acid ester derivatives 50 in 56-72% yield, while Pyrrole-3-carboxylic acid esters 52 in 55-75% yields.




**Scheme 1.19**

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# Chapter 2

## 2.1 Synthesis of substituted thiophenes by iodo & heterocyclization of 1-mercapto-3-alkyn-2-ols in DES as a solvent.

### 2.1.1 Pharmacological importance of thiophenes

Organic compounds containing five-membered heteroaromatic rings are very common in nature and play important biological roles. The thiophene core, in particular, is a structural motif present in many pharmaceutical compounds.

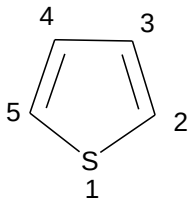



**Figure 2.1**

Different thiophene derivatives are biologically active , [1] such as ticlopidine and clopidogrel, platelet anti-aggregating drugs.

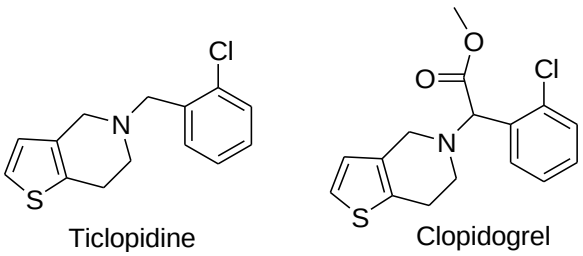



**Figure 2.2**

Both of them are thienopyridine derivatives and they are used in the treatment of cardiovascular diseases, such as acute coronaryc syndromes (heart attack, instable angina). [2] Olanzapine is an atypical anti-psychotic drug, delivered for schizophrenia treatment and bipolar disturb. [3]

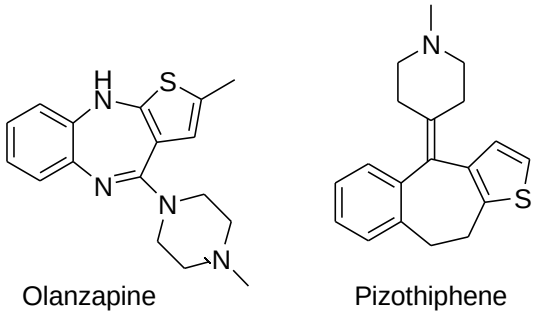



**Figure 2.3**

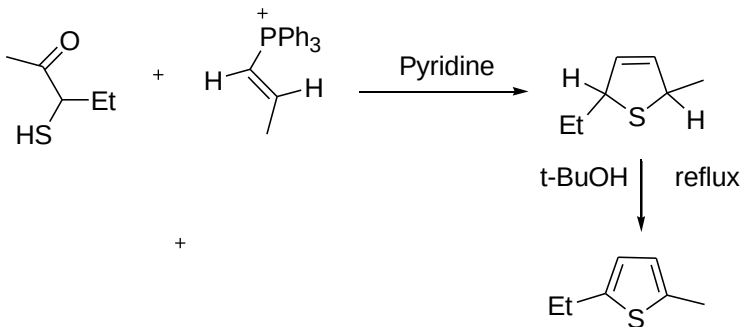
Olanzapine presents a thiophene ring condensed with a 1,5-benzodiazepine ring, which is responsible, according to a number of hypothesis, for the antagonistic

activity towards $D_2$ dopaminergic receptors. Pizothiphene shows a good efficacy in the prevention of some migraine conditions.[4] From recent pharmacological studies, it was clear that thiophene derivatives have also anti-inflammatory activity[5] In all the studies it was demonstrated that acetylenic thiophene derivatives produce a powerful anti-inflammatory effect by reducing an edema burned out by carragenin, a vegetable gelatin used in food processing industry.

**2.1.2. Synthesis of thiophene derivatives.**

**1) From thiocarbonylic compounds**

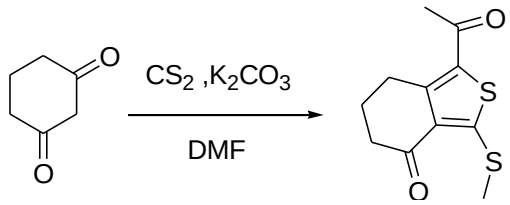
2-Ketothiol derivatives, when reacted with alkenylphosphonium ions, lead to 2,5-dihydrothiophenes after ring closure through Wittig reaction. The corresponding thiophene is obtained by de-hydrogenation.




**Scheme 2.1**

**2) With carbon disulfide**

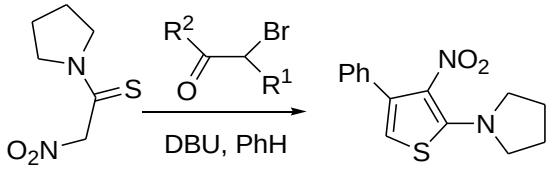
2-Alkylthiophenes can be synthesized from addition of a carbanion to carbon disulfide, followed by S-alkylation.




**(2.1)**

**3) From thionitroacetamides**

S-alkylation of thionitroacetamides with 2-bromoketones leads to the formation of 2-amino-3-nitrothiophenes.




**(2.2)**

**A] Classical methods**

Thiophenes and their derivatives can be obtained through different synthetic approaches. Thiophene ring can be built from non-heterocyclic precursors following two different paths.

1. Ring building from open chained suitable precursors:

This method involves the introduction of the sulfur atom in the starting material bearing the entire carbon skeleton.

2. α and β position functionalization towards the S-atom with right precursors:

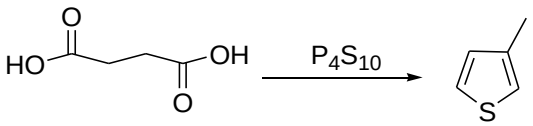
In this method the authors carried out the reaction between a mercaptoacetate and a 1,3-dicarbonylic compound or the reaction between a thiodiacetate and a 1,2-dicarbonylic compound.

The most known classical procedures in organic synthesis are

(a) Paal-Knorr (b) Fiesselmann (c) Gewald and (d) Hinsberg syntheses.

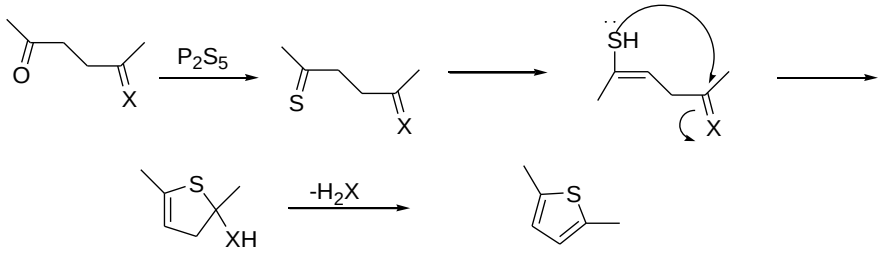
**a) Paal-Knorr synthesis of thiophenes**.

This reaction is better known as Paal synthesis. 1,4-dicarbonylic compounds react with a sulfur atoms source, to give thiophenes




**(2.3)**

Phosphorus pentasulfide ($P_2S_5$), Lawesson reagent and bis(trimethylsilyl)sulfide are the commonly used sulfur sources. The reaction mechanism involves the initial formation of a thione, followed by tautomerization and cyclization. The consequent aromaticity leads to $H_2O$ or $H_2S$ elimination.

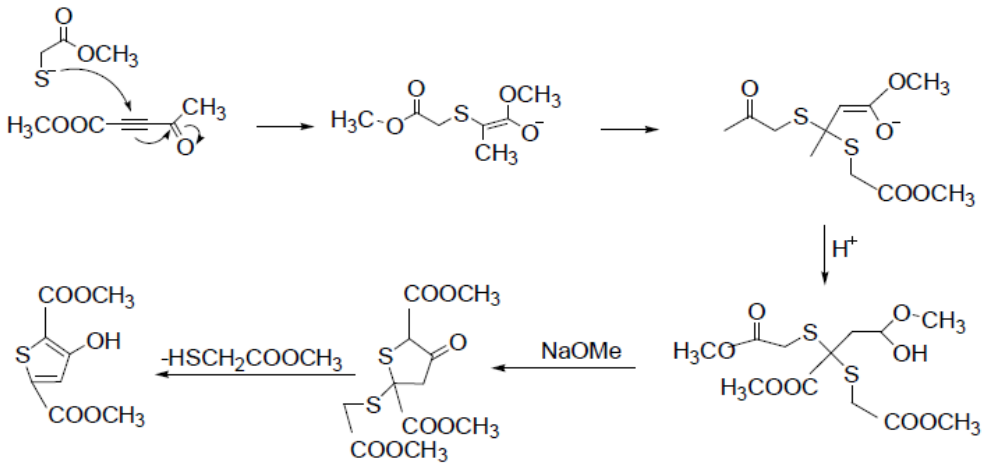



**Scheme 2.2** Reaction mechanism of the Paal synthesis.

**(b) Fiesselmann**

In this synthesis there is a condensation between thioglicolic acid (or its derivatives) with α,β-acetylenic esters which, after base treatment, leads to 3-hydroxy-2-thiophenecarboxylic acids (or their derivatives). The reaction works through a base-

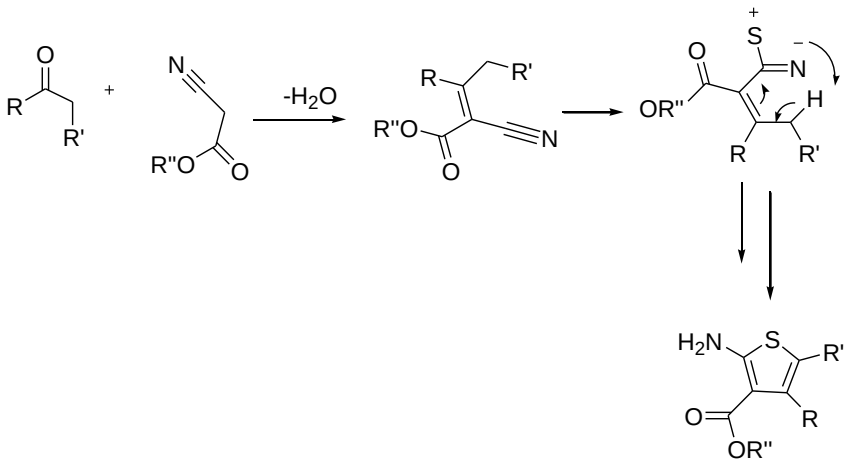
catalyzed 1,4-addition to form a thioacetal derivative. Treatment with a stronger base allows the formation of an enolate, while intramolecolar reaction (a Dieckman condensation), leads to a ketone. The final product is obtained after thioglicolate elimination, followed by aromatization.




**Scheme 2.3** Reaction mechanism of the Fiesselmann synthesis.

**c) Gewald synthesis**.

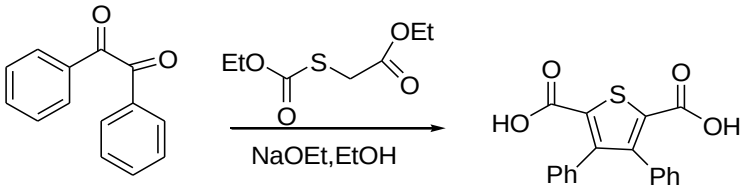
The Gewald synthesis is a useful method for the synthesis of 2-aminothiophenes. It consists in the base-catalyzed condensation of a ketone bearing a $–CH_2$ group with a β-ketonitrile, able to form an olefin, following by elemental sulfur cyclization. In the first step occurs a Knoevenagel condensation between an activated nitrile and a ketone (or an aldehyde) to form an acrylonitrile. This condensation product is sulfurated on the nitrilic carbon atom. After the sulfuration, this compound converts into a mercaptide, which undergoes cyclization through an intramolecular attack.




**Scheme 2.4** Reaction mechanism of the Gewald synthesis.

**d) Hinsberg synthesis.**

Two consecutive aldolic condensations between a 1,2-dicarbonylic compound and diethyldithioacetate lead to thiophene formation.

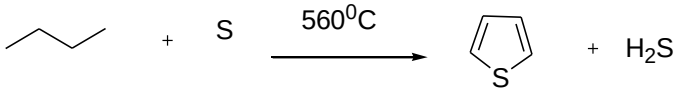



**(2.4)**

Hinsberg synthesis

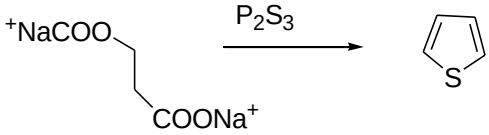
**B] Industrial scale synthesis.**

i) At elevated temperatures thiophene can be synthesized thanks to the reaction between butane and elemental sulfur.



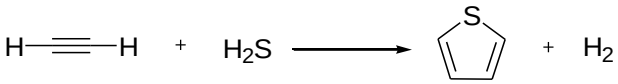

**(2.5)**

ii) Another method includes the reaction between sodium succinate and phosphorous trisulfide under heating.




**(2.6)**

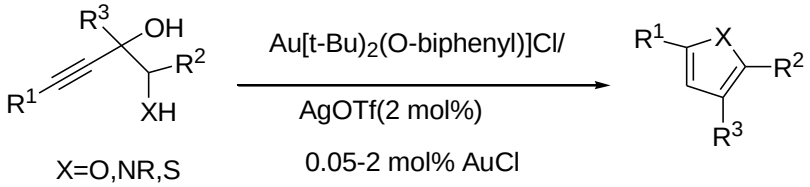
iii) Thiophene can be synthesized by passing in acetylene and sulfidric acid through a tube containing alumina at 400°C.




**(2.7)**

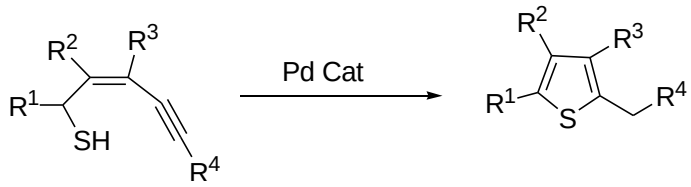
Metal-catalyzed syntheses of substituted thiophenes.

In the following Scheme is reported a synthetic strategy for the synthesis of heterocyclic derivatives through an Au-catalyzed heterocyclodehydration starting from a propargylic alcohol (one step reaction).[6]



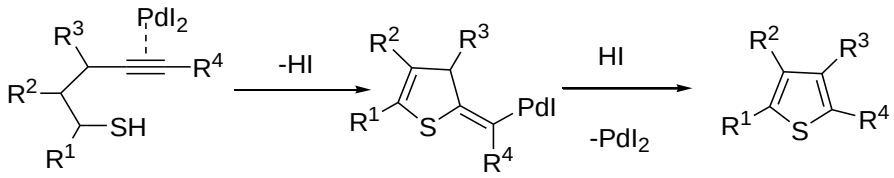

**(2.8)**

Another method occurs through a Pd-catalyzed cycloisomerization mechanism of (Z)-2-en-4-yne-1-thiols , to obtain thiophene derivatives[7]



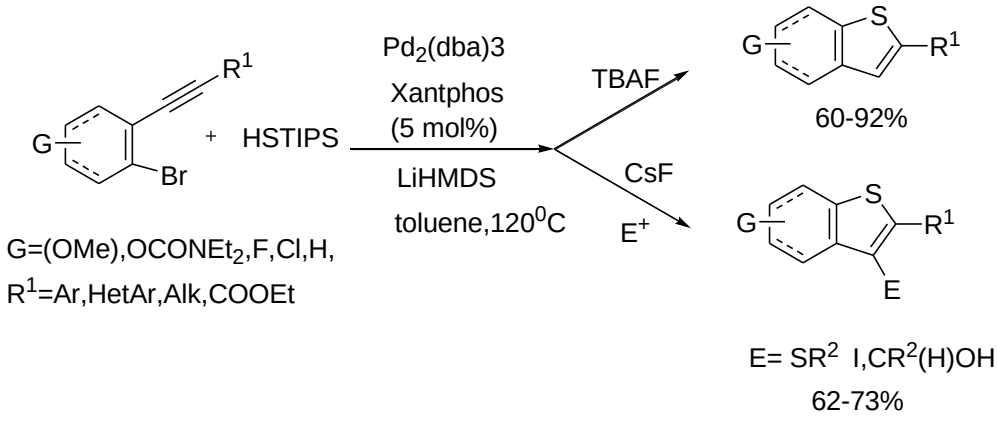

**(2.9)**

The reaction mechanism starts with the electrophilic activation of the triple bond by Pd(II), followed by an intramolecular nucleophilic attack of –SH group, protonolysis and aromatization (Scheme 2.5)



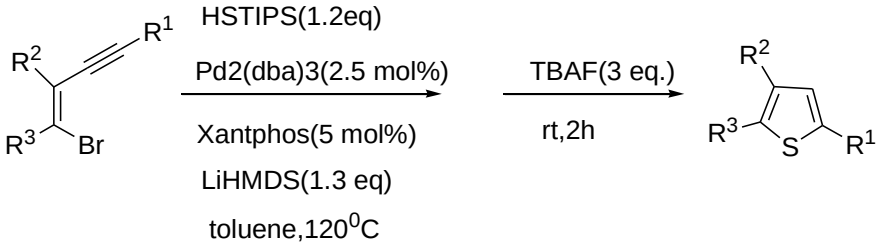

**Scheme 2.5**

An efficient synthesis of thiophenes and benzothiophenes was developed starting from available molecules, such as bromoenynes and o-alkynylbromobenzine derivatives (Scheme 1.4). This innovative one-pot procedure involves the formation of a C-S bond Pd-catalyzed by a HS surrogate, followed by an hetercyclization. Furthermore, the successive functionalization with suitable electrophilic species expands the potential of this methodology.[43]




**Scheme 2.6**

By using this synthetic strategy it is possible to synthesize 2,3,5-trisubstituted thiophenes, starting from bromoenyne derivatives.



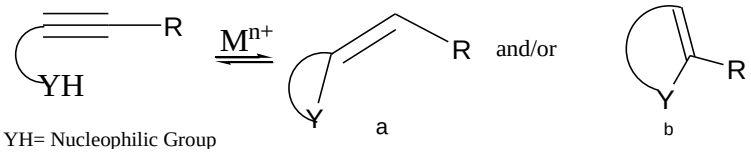

**Scheme 2.7**

## 2.2. Present Work

Synthesis of thiophenes derivatives through

i) Heterocyclization ii) Iodocyclization reaction

### 2.2.1. Heterocyclization Reaction




YH= Nucleophilic Group

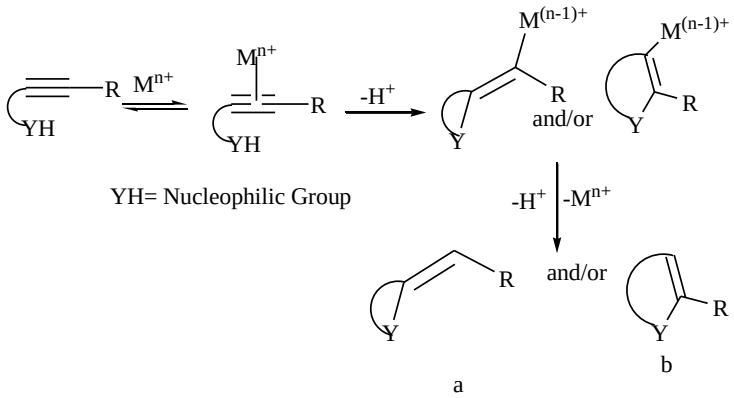
**(2.10)**

Metal-catalyzed heterocyclodehydration of unsaturated substrates bearing a suitably placed nucleophilic group (**Eq.2.10**) is a powerful methodology for the direct and atom-economical synthesis of heterocycles starting from readily available starting materials under essentially neutral conditions.[8-9] The general interest for metal-catalyzed reactions in organic synthesis is increasing year by year. In particular, the preparation, starting from simple and available substrates, of substituted heterocyclic compounds is acquiring an increasing importance. These compounds could be prepared by functionalization of the ring, through classical reactions, such as α- metalation o β-alogenation. Anyway, heterocyclization reactions from acyclic precursors are an alternative methodology which directly allows obtaining the desired molecule in a regioselective way. Recently different methods were developed: all of them show the utility of this approach.

### 2.2.1.1Mechanism Of Heterocyclization Reaction

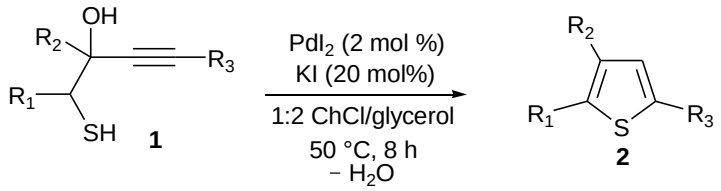
**General Mechanism**

Metal (M=Pd) catalyzed heterocyclization of acetylenes bearing a suitably placed nucleophile group leading to heterocycles through activation of the triple bond by the metal species followed by intramolecular nucleophilic attack and protonolysis.




**Scheme 2.8**

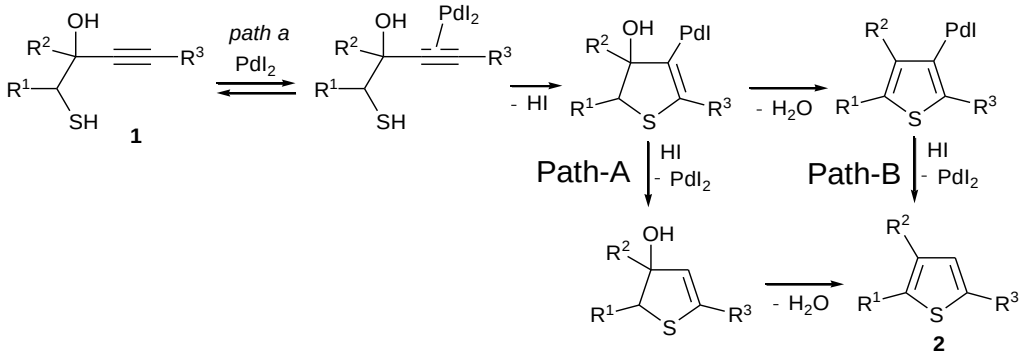
In the present thesis, we report the heterocyclization reaction of 1- mercapto-3-yn-2-ol derivatives in DES (deep eutectic solvent ) as a reaction medium, to obtain substituted thiophenes **2** (eq. 2.11).




**(2.11)**

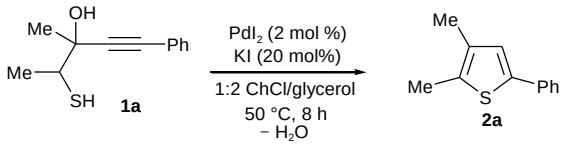
This strategy is very interesting because it allows the one-step synthesis of useful substituted thiophenes molecules, under mild conditions and starting from simple starting materials and using a non conventional atoxic solvent. So we report here the Synthesis of substituted thiophenes **2** (Eq.2.11) by $PdI_2$/KI-catalyzed heterocyclization of 1-mercapto-3-alkyn-2-ols **1** in ChCl/Gly (1:2) as the solvent and the recycling experiments.

**Proposed Mechanism for the $PdI_2$/KI-Catalyzed Heterocyclodehydration of 1-Mercapto-3-alkyn-2-ols 1 to Substituted Thiophenes 2. in ChCl/Gly (1:2) as the solvent and recycling experiments.**




**Scheme 2.9**

The heterocyclodehydration of readily available 1-mercapto-3-alkyn-2-ols **1** has been conveniently performed for the first time in a deep eutectic solvent (DES), such as ChCl/Gly (1:2 molar ratio; ChCl = choline chloride, Gly = glycerine), as a non-conventional green solvent. The process, carried out at $50^0$C for 8 h in the presence of a simple catalytic system ($PdI_2$/KI), led to the formation of the corresponding thiophenes.



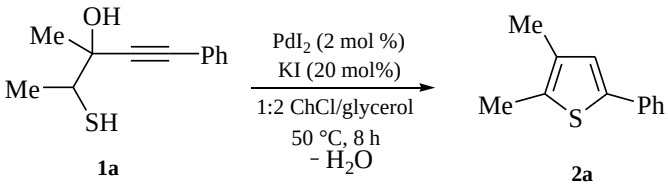

**(2.12)**

The mechanism of this reaction takes place through 5-endo-dig intramolecular attack of the mercapto group to the triple bond coordinated to the metal centre, followed by dehydration and protonolysis or vice versa. **(Scheme 2.9**) The DES/catalytic system could be easily recycled several times without appreciable loss of activity, after extraction of the thiophene product with hexane. Such a 1:2 ChCl/glycerol mixture proved also to be an excellent green solvent for realizing the iodocyclization of the same substrates carried out under particularly mild conditions ($25^0$C, 5 h Eq.2.14). Also in this case, the DES mixture could be successfully recycled several times. The alkynylation reaction of α-mercapto ketones, necessary for the preparation of the alkynylthiols, has also been successfully accomplished in the above protic eutectic mixture in spite of the potentially competitive protonolysis.

### 2.2.1.2 Optimization of reaction parameters of Heterocyclization reaction

The first heterocyclization experiments was carried out using 4-mercapto-3-methyl-1phenylpent-1-yn-3-ol, **1a** as the substrate, which was allowed to react in the presence of $PdI_2$ (2 mol %) and KI/(20 mol %) in 1:2 ChCl/urea as the solvent at 50 $^0$C for 8 h. After cooling, the reaction mixture was extracted with hexane and analyzed by GLC and TLC, which showed the presence of the substrate almost unreacted (7% conversion). We next changed the nature of one of the component of the eutectic mixture, and conducted the same experiment in a 1:2 ChCl/Gly mixture.

The next experiment was carried out with using ChCl/Glycerol(1:2) (Eq. 2.1.4) with 1:2:20 eqivalent of **1**:$PdI_2$:KI at $25^0$C for 3 hrs. Substance conversion was 20% (Table 2.1 entry 2) and the yield of the 2**a** was 12%. Starting from this initial result, a brief optimization study was then carried out in which we made a screening of the reaction parameters by changing temperature and reaction time, and the best result was obtained when (Table 2.1, entry 7) the reaction time was 8 h and the temperature at $50^0$C the yield remained unchanged, suggesting that product is rather stable at 100°C (Table 2.1, entry 12)




**1a** **2a** **(2.12)**

**Table 2.1** Reaction was optimised by changing the temperature and time parameters

| Run | 1:$PdI_2$:KI | DES | T($^0$c) | t( h) | Conv(%) | Yield 2a(%) |
|---|---|---|---|---|---|---|
| 1 | 1:2.20 | ChCl/urea | 50 | 8 | 7 | - |
| 2 | 1:2.20 | Gly:ChCl | 25 | 3 | 31 | 22 |
| 3 | 1:2.20 | Gly:ChCl | 25 | 5 | 35 | 26 |
| 4 | 1:2.20 | Gly:ChCl | 25 | 8 | 55 | 44 |
| 5 | 1:2.20 | Gly:ChCl | 50 | 3 | 74 | 59 |
| 6 | 1:2.20 | Gly:ChCl | 50 | 5 | 80 | 62 |
| 7 | 1:2.20 | Gly:ChCl | 50 | 8 | 100 | 80 |
| 8 | 1:2.20 | Gly:ChCl | 80 | 3 | 81 | 58 |
| 9 | 1:2.20 | Gly:ChCl | 80 | 5 | 100 | 65 |
| 10 | 1:2.20 | Gly:ChCl | 80 | 8 | 100 | 77 |
| 11 | 1:2.20 | Gly:ChCl | 100 | 5 | 90 | 72 |
| 12 | 1:2.20 | Gly:ChCl | 100 | 8 | 100 | 79 |

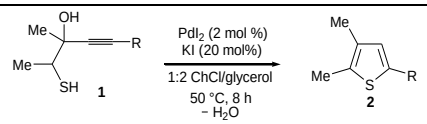
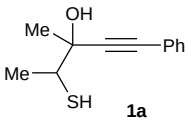
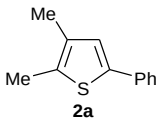
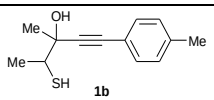
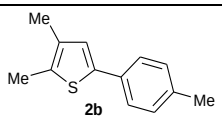
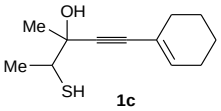
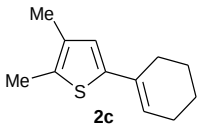
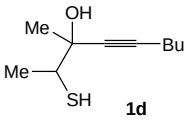
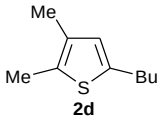
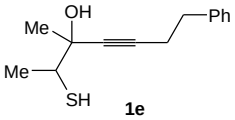
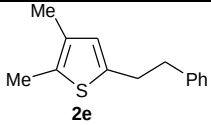
Conversion of 1 was quantitative in all cases.

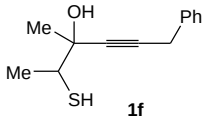
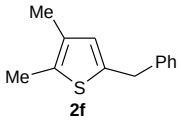
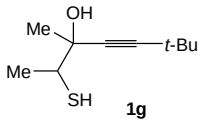
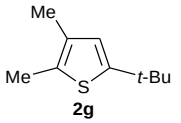
### 2.2.1.3 Generalization of the process

We were pleased to find that, using this DES, the formation of the desired thiophene **2a** now occurred in 80% yield after 8 h at 50 $^0$C (Table 2.2, entry 1, run 1). This result testifies that DESs are not interchangeable with each other and that their nature can have a profound and unpredictable influence on the outcome of a particular reaction. The process leading to **2a** may be interpreted as occurring through 5-endo-dig intramolecular attack of the mercapto group to the triple bond coordinated to the metal centre, followed by protonolysis and dehydrative aromatization or vice versa (Scheme 2.9; anionic iodide ligands are omitted for clarity). We next verified the possibility of recycling the catalyst/solvent system, by adding fresh substrate to the residue obtained after extraction

of the thiophene product with hexane and repeating the catalytic procedure. After 8 h, **2a** was formed again with the same yield as that of the first experiment (Table 2.2, entry 1, run 2). The recycling procedure was repeated for additional four runs, with **2a** being consistently obtained in 78 to 80% yields (Table 2.2, entry 1, runs 3 to 6). The generality of the process was then assessed, by varying the nature of the substituent on the triple bond. As can be seen from the results reported in Table 2.2 entries 2 to 7), satisfactory yields were obtained with all the substrates tested, bearing a p-tolyl (entry 2), a cyclohexen-1-yl (entry 3), or an alkyl substituent (entries 4to7) on the triple bond (including a sterically demanding tertbutyl group, entry 7). In all cases, the recyclability of the DES/catalyst system could be successfully achieved.

**Table 2.2** shows the yields obtained in each experiment with recycling

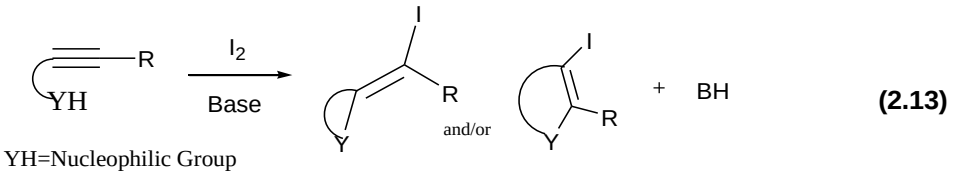
| n° |  | | Yield of **2**[b] (%) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Run 1 | Run 2 | Run 3 | Run 4 | Run 5 | Run 6 |
| 1 |  |  | 80 | 80 | 79 | 80 | 79 | 78 |
| 2 |  |  | 80 | 79 | 79 | 78 | 78 | 79 |
| 3 |  |  | 69 | 68 | 68 | 67 | 69 | 67 |
| 4 |  |  | 78 | 77 | 76 | 76 | 75 | 77 |
| 5 |  |  | 83 | 82 | 82 | 83 | 82 | 82 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 6 |  **1f** |  **2f** | 73 | 73 | 72 | 73 | 73 | 72 |
| 7 |  **1g** |  **2g** | 65 | 63 | 64 | 64 | 63 | 64 |

[a] All reactions were carried out at 50 °C for 8 h in 1:2 ChCl/Gly mixture as the solvent (0.20 mmol of starting **1** per mL of DES) in the presence of $PdI_2$ (2 mol %) in conjunction with KI (20 mol %). Conversion of **1** was quantitative in all cases. [b] Isolated yield based on starting **1**. [c] Run 1 corresponds to the 1st experiment, the next runs to recycles.

### 2.2.2 Iodocyclization Reaction

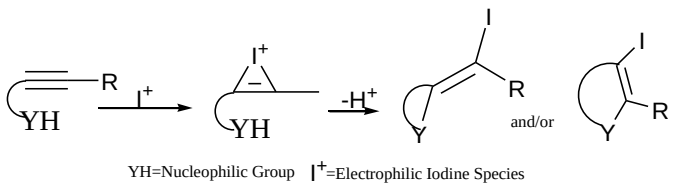
Iodocyclization reactions are acquiring an increasing importance in organic synthesis, in view of the possibility to obtain iodine- containing heterocycles starting from readily available acyclic substrates under mild reaction conditions. Various aspects of these iodocyclization reactions have been recently reviewed[10], including the application of iodocyclization processes to the synthesis of natural products, heterocyclic derivatives, and carbocyclic derivatives, as well as the construction of heterocyclic libraries.




**(2.13)**

The iodo heterocyclization of acetylenic substrates bearing a suitably placed nucleophilic group is a powerful method for the direct synthesis of unsaturated iodine containing heterocycles. The products obtained can be further elaborated through various cross-coupling reactions (such as Heck, Suzuki- Miyaura, and Sonogashira reactions), making the process of particular synthetic interest. Moreover, the iodocyclization reaction is carried out under very mild reaction conditions (generally at room temperature), using a simple source of electrophilic iodine, such as $I_2$, ICl, or NIS (N-iodo-succinimide), usually in the presence of a base to help buffer the acid produced by deprotonation of the nucleophilic functional group present in the substrate. usually. iodocyclizations show high functional group compatibility, the halogen, carbonyl, nitro and cyano groups being usually very well tolerated.

#### 2.2.2.1 Mechanism of Iodocyclization Reaction of Functionalised Alkynes.



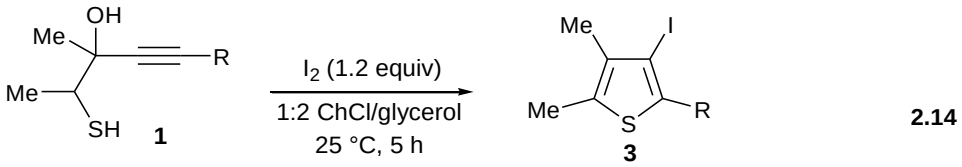

**Scheme 2.10** Iodocyclization of acetylenes beaing a sutably placed nucleophilic groupleading to iodine-containing carbo and heterocycles.

The iodocyclization of functionalized alkynes takes place through the formation of an iodonium species from the interaction between the carbon-carbon triple bond and an

electrophilic iodine species (indicated by I+), followed by intramolecular exo or endo nucleophilic attack. The reaction is usually carried out in the presence of a base to trap the acid generated during the process, so the overall stoichiometry corresponds to that shown in Equation 2.13.

### 2.2.2.2 Present Work

In this work, we have studied the iodocyclization reaction of 1- mercapto-3-alkyn-2-ol derivatives in DES (deep eutectic solvent) as a reaction medium, to obtain substituted thiophenes **2** (eq. 2.14)



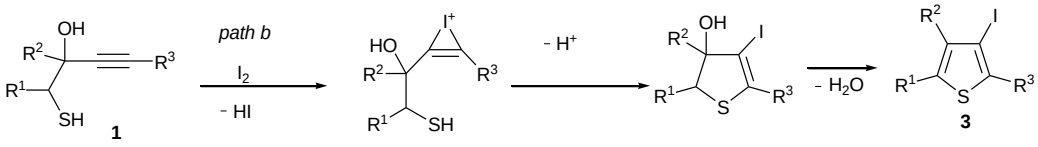

**2.14**

Considering the good results obtained in the Pd-catalyzed heterocyclization of 1-mercapto-3-alkyn-2-ols 1(Eq.2.12), we next studied the reactivity of the same substrates under iodocyclization conditions in 1:2 ChCl/Gly as the reaction medium. With 1.2 equiv of $I_2$ and in the absence of base, the iodocyclization of 1 proceeded smoothly under mild conditions (room temperature) to afford the corresponding 3-iodothiophenes in good yields (up to 80%) and with an excellent recyclability of the solvent (up to 5 additional runs, Table 2.4). As far as we know, this reaction represents the first example in the literature of an iodocyclization reaction carried out in a DES as the reaction medium.

### 2.2.2.3 Mechanicum Of Iodocyclization Reaction

The iodocyclization of readily available 1-mercapto-3-alkyn-2-ols **1**(Scheme 2.11**)** has been conveniently performed for the first time in a deep eutectic solvent (DES), such as ChCl/Gly (1:2 molar ratio; ChCl = choline chloride, Gly = glycerine), as a non-conventional green solvent. The process, carried out at $50^0$C for 8 h in the presence of a simple catalytic system ($PdI_2$/KI), led to the formation of the corresponding thiophenes through 5-endo-dig intramolecular attack of the mercapto group to the triple bond coordinated to the metal centre, followed by dehydration and protonolysis or vice versa. The DES/catalytic system could be easily recycled several times without appreciable loss of activity, after extraction of the thiophene product with hexane.The ChCl/glycerol mixture also proved to be an excellent green solvent for realizing the iodocyclization of

the same substrates , carried out under particularly mild conditions ($25^0$C, 5 h). Also in this case, the DES mixture could be successfully recycled several times.

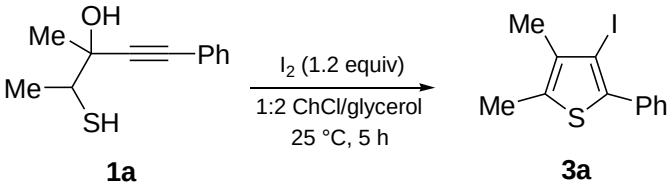



**Scheme 2.11**

This innovative methodology is of great interest also in view of the availability of the starting substrates, whose precursor α-mercaptoketones are commercially available and unexpensive.

### 2.2.2.4 Optimization of reaction parameters of Iodocyclization reaction

The first experiment was carried out with using ChCl/Glycerol(1:2) with 1.2 eqivalent of $I_2$ at $25^0$C for 3 hrs. Substance conversion was 80% and the yield of the **3a** (Eq. 2.1.4) was 64%. Starting from this initial result, A brief optimization study was then carried out in which we made a screening of the reaction parameters by changing temperature and reaction time. and the best result was obtained when (Table 2.3, entry 2). the reaction time was 5 h and the temperature at $25^0$C. The yield remained unchanged, suggesting that product is rather stable at higher temperatures (Table 2.3, entry 8).




**(2.14)**

**Table 2.3** Reaction was optimised by changing the temperature and time parameters

| Run | Sub:$I_2$ | DES | Temperature ($^0$C) | Time t(hrs) | Conversion | Yields (%)[b] |
|---|---|---|---|---|---|---|
| 1 | 1:1.2 | Gly:ChCl | 25 | 3 | 80 | 64 |
| **2** | **1:1.2** | Gly:ChCl | **25** | **5** | **100** | **79** |
| 3 | 1:1.2 | Gly:ChCl | 25 | 8 | 100 | 79 |
| 4 | 1:1.2 | Gly:ChCl | 50 | 3 | 80 | 65 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 5 | 1:1.2 | Gly:ChCl | 50 | 5 | 100 | 78 |
| 6 | 1:1.2 | Gly:ChCl | 50 | 8 | 100 | 78 |
| 7 | 1:1.2 | Gly:ChCl | 80 | 3 | 85 | 65 |
| 8 | 1:1.2 | Gly:ChCl | 80 | 5 | 100 | 78 |

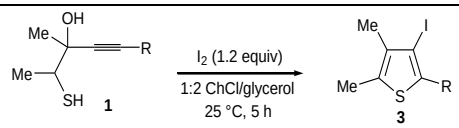
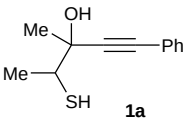
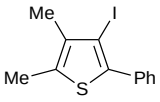
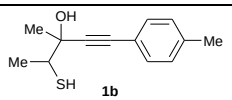
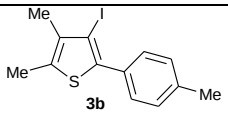
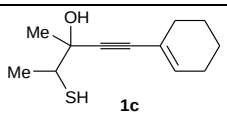
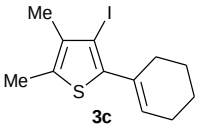
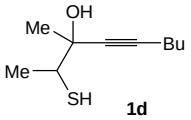
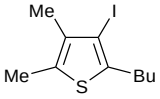
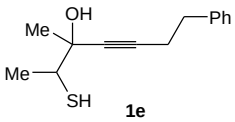
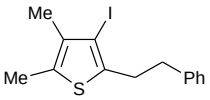
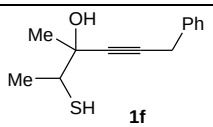
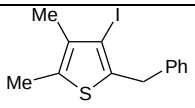
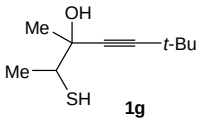
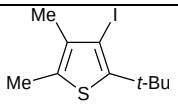
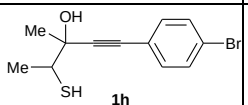
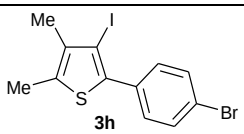
Conversion of 1 was quantitative in all cases. b Isolated yield based on starting 1

**2.2.2.5 Generalization of the process**

Based on the first iodocyclization experiments were carried out using 4-mercapto-3-methyl-1phenylpent-1-yn-3-ol **1a** as the substrate (Table 2.3 entry 2), which was allowed to reactwith $\mathbf{I_2}$in the in 1:2 ChCl/Gly mixture at 25 $^0$C for 5 h. After cooling, the reaction mixture was extracted with hexane and analyzed by GLC and TLC, We were pleased to find that, using this DES, the formation of the desired thiophene **2a** occurred in 79% yield after 5 h at 25 $^0$C (Table 2.4, entry 1, run 1. We next verified the possibility of recycling the catalyst/solvent system, by adding fresh substrate to the residue obtained after extraction of the iodo thiophene product with hexane and repeating the catalytic procedure. After 5 h, **3a** was formed again with the same yield as that of the first experiment (Table 2.4, entry 1, run 2). The recycling procedure was repeated for additional four runs, with **3a** being consistently obtained in 78 to 80% yields (Table 2.4, entry 1, runs 3 to 6). The generality of the process was then assessed, by varying the nature of the substituent on the triple bond. As can be seen from the results reported in Table 2.4 entries 2 to 7), satisfactory yields were obtained with all the substrates tested, bearing a p-tolyl (entry 2), a cyclohexen-1-yl (entry 3), or an alkyl substituent (entries 4 to7) on the triple bond (including a sterically demanding tertbutyl group, entry 7). In all cases, the recyclability of the DES/catalyst system could be successfully achieved.

Table 2.4 shows the results obtained with different kind of starting materials **1** in 1:2 ChCl/glycerol as the solvent, at 25$^0$C for 5 hrs. As can be seen from the table the process was general and the compounds iodo thiophenes were obtained in good yields. Thus DES medium could be successfully recyclized several times.

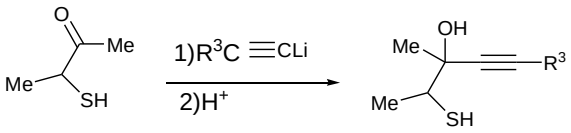
**Table 2.4** yields obtained in each recycling experiments

| n° |  | | Yield of **3**[b] (%) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Run 1 | Run 2 | Run 3 | Run 4 | Run 5 | Run 6 |
| 1 |  **1a** |  **3a** | 79 | 80 | 80 | 79 | 79 | 79 |
| 2 |  **1b** |  **3b** | 78 | 77 | 75 | 75 | 74 | 76 |
| 3 |  **1c** |  **3c** | 69 | 68 | 68 | 67 | 69 | 67 |
| 4 |  **1d** |  **3d** | 72 | 72 | 71 | 73 | 71 | 72 |
| 5 |  **1e** |  **3e** | 76 | 74 | 75 | 74 | 76 | 76 |
| 6 |  **1f** |  **3f** | 76 | 74 | 75 | 74 | 76 | 75 |
| 7 |  **1g** |  **3g** | 65 | 63 | 64 | 63 | 62 | 63 |
| 8 |  **1h** |  **3h** | 62 | 62 | 60 | 61 | 60 | 61 |

[a] All reactions were carried out with $I_2$ (1.2 equiv) at 25 °C for 5 h in 1:2 Chl/glycerol as the solvent (0.20 mmol of starting **1** per mL of DES). Conversion of **1** was quantitative in all cases. [b] Isolated yield based on starting **1**. [c] Run 1 corresponds to the 1st experiment, the next runs to recycles. See text for details.

## 2.3 Experimental Procedures

### 2.3.1 Synthesis of Starting Materials [Preparation of 1-Mercapto-3-alkyn-2-ols [1a−h.]




(2.15)

**1a**

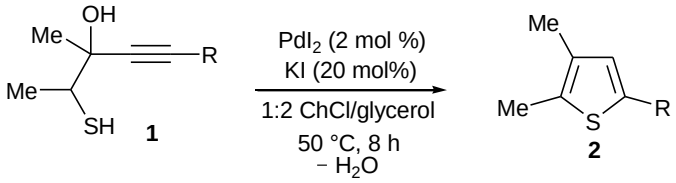
To a cooled (−78 °C), stirred solution of BuLi (1.6 M in hexane) (28 mL, 44.8 mmol) in anhydrous THF (16 mL), maintained under nitrogen, was added dropwise a solution of the 1-alkyne (44.5 mmol) (phenyl-acetylene, 4.55 g; p-methylphenylacetylene, 5.17 g; p-bromophenylace-tylene, 8.05 g; 3-ethynylthiophene, 4.81 g; 1-ethynylcyclohex-1-ene, 4.72 g; 1-hexyne, 3.66 g; 4-phenyl-1-butyne, 5.79 g; 3-phenyl-1-propyne, 5.17 g; tert-butylacetylene, 3.66 g) in anhydrous THF (6 mL). To the resulting mixture was added, at the same temperature under nitrogen, a solution of LiBr (1.56 g, 18 mmol) in anhydrous THF (6 mL). After additional stirring for 0.5 h, was added, at the same temperature under nitrogen, a solution of 3-mercapto-2-butanone (1.77 g, 17.0 mmol) in anhydrous THF (5 mL). The resulting mixture was stirred for an additional 2 h at −78 °C and then allowed to warm up to room temperature. Saturated $NH_4Cl$ (20 mL) and 1 N HCl (10 mL) were added, and the mixture was extracted with $Et_2O$ (3 × 50 mL). The collected organic phases were washed with brine (40 mL) and dried over $Na_2SO_4$. After filtration and evaporation of the solvent, the crude products were purified by column chromatography using 95:5 hexane-AcOEt as eluent.

**Table 2.5** Isoleted Yields in the the synthesis of starting material

| n° | **1** | **$R^3$** | **%Yield** |
|---|---|---|---|
| 1 | 1a | Ph | 90 |
| 2 | 1b | p-MeC6H4 | 80 |
| 3 | 1c | 1-Cyclohexeynyl | Crude Product |
| 4 | 1d | -Bu | 91 |
| 5 | 1e | -CH2CH2Ph | 87 |
| 6 | 1f | -CH2Ph | 85 |
| 7 | 1g | -tBu | 40 |
| 8 | 1h | -pBrC6H4 | 51 |

For the prepareation of all the starting material from 1a to 1h litterature reported procedure [9] is followed.

**2.3.2 General procedure for the synthesis of thiophenes 2 by heterocylization of 1-mercapto-3-alkyn-2-ols 1 in ChCl/Gly (1:2) as the solvent (Table 2.2).**




**(2.16)**

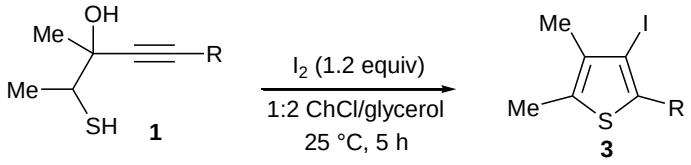
To a solution of **1** (0.42 mmol) (**1a**, 87 mg; **1b**, 93 mg; **1c**, 88 mg; **1d**, 78 mg; **1e,** 99 mg; **1f,** 93 mg; **1g,** 78 mg) in ChCl/Gly (1:2; 2 mL) were added $PdI_2$ (3.0 mg, $8.3\times10^{-3}$ mmol) and KI (13.8 mg, $8.3\times10^{-2}$ mmol) in this order under nitrogen in a Schlenk flask. The mixture was allowed to stir at $50^0$C for 8 h. After cooling, the product was extracted with hexane (6×5 mL), and the residue (still containing the catalyst dissolved in the DES) was used as such for the next recycle (see below). The hexane phases were collected and, after evaporation of the solvent, products **2a**-g were purified by column chromatography on silica gel using 99: 1 hexane-AcOEt as the eluent: 2,3-dimethyl-5-phenylthiophene **2a** was a yellowish solid, mp 49-$50^0$C (yield: 63 mg, 80%); 2,3-dimethyl-5-p-tolylthiophene **2b** was a yellow solid, mp 47-49 $^0$C (68 mg, 80%); 5- cyclohexenyl-2,3-dimethylthiophene **2c** was a yellow oil (56 mg, 69%); 5-butyl-2,3-dimethylthiophene **2d** was a yellow oil (55 mg, 78%); 2,3-dimethyl-5-phenethylthiophene **2e** was a yellow solid, mp=28-30 $^0$C (75 mg, 83%); 5-benzyl-2,3-dimethylthiophene **2f** was a yellow solid, mp 38-39 $^0$C (62 mg, 73%); 5-tert-butyl-2,3- dimethylthiophene **2g** was a yellow oil (46 mg, 65%). $R_f$ values were as follows (pure hexane): **2a**, 0.54; 2b, 0.51; **2c**, 0.75; **2d**, 0.75; **2e**, 0.43; **2f**, 0.52; **2g,** 0.72.

**2.3.3 Recycling procedure**

To the DES residue obtained as described above was added a solution of 1 (0.42 mmol) in Et2O (3 mL). The Et2O was removed under vacuum and then the same procedure described above was followed.

### 2.3.4 For Iodocyclization Reaction.

**General procedure for the synthesis of 3-iodothiophenes 3 by iodocylization of 1-mercapto-3-alkyn-2-ols 1 in ChCl/Gly (1:2) as the solvent (Table 2.4).**




**(2.16)**

To a solution of **1** (0.50 mmol) (**1a**, 103 mg; **1b**, 110 mg; **1c**, 105 mg; **1d**, 93 mg; **1e**, 117 mg; **1f**, 110 mg; **1g**, 93 mg; **1h**, 143 mg;) in ChCl/Gly(1:2; 2.5 mL) was added $I_2$ (140 mg, 0.55 mmol) under nitrogen. The mixture was allowed to stir at 25 °C for 5 h and then extracted with hexane (6 × 5 mL). After evaporation of the solvent, the products **2a–h** were purified by column chromatography on silica gel using 99 : 1 hexane–AcOEt as the eluent: 3-iodo-4,5-dimethyl-2-phenylthiophene **3a** was a yellow oil (124 mg, 79%); 3-iodo-4,5-dimethyl-2-p-tolylthiophene **3b** was a yellow solid, mp 54-55 °C (128 mg, 78%); 2-cyclohex-1-enyl-3-iodo-4,5-dimethylthiophene **3c** was a yellowish solid, mp 25-26 °C (110 mg, 69 %); 2-butyl-3-iodo-4,5-dimethylthiophene **3d** was a yellow solid, mp 115-117 °C (106 mg, 72%); 3-iodo-4,5-dimethyl-2-phenethylthiophene **3e** was a yellow oil (130 mg, 76%); 2-benzyl-3-iodo-4,5-dimethylthiophene **3f** was a yellow oil (125 mg, 76%); 2-tert-butyl-3-iodo-4,5-dimethylthiophene **3g** was a yellow solid, mp 114-115 °C (96 mg, 65%); 2-(4-bromophenyl)-3-iodo-4,5-dimethylthiophene **3h** was a colorless solid, mp 104-105 °C (122 mg, 62%).

## 2.4. Conclusion

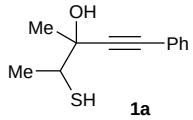
In conclusion, we have reported a convenient and general method for the synthesis of substituted thiophenes through heterocyclodehydration and Iodocyclization from readily available 1-mercapto-3-alkyn-2-ols in ChCl/Gly (1:2) as the solvent and its recycling experiments without majour impact on the yield on the the reactivity of the substrate on the final product.

For Heterocyclization reactions the process is catalyzed by a simple catalytic system, consisting of $PdI_2$ in conjunction with an excess of KI, under mild reaction conditions (DES as the solvent at 50°C) and can be applied to a variety of substrates, including 1-mercapto-2,2- dialkynyl-2-ols. The latter were converted into the corresponding thiophene derivatives without affecting the additional alkynyl substituent, which would allow further functionalization at the thiophene ring.

For Iodocyclization reactions the process is proceed without any catalyst, under mild reaction conditions (DES as the solvent at 25°C) and can be applied to a variety of substrates, including 1-mercapto-2,2- dialkynyl-2-ols **(1a to 1h).**

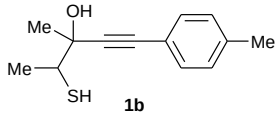
## 2.5 Characterization Data

**starting Materials (1a to 1h)** All starting materials and thiophene derivatives were fully characterized by MS spectrometry, IR, $^{1}H$ NMR and $^{13}C$, NMR spectroscopies, and elemental analysis, as reported below.



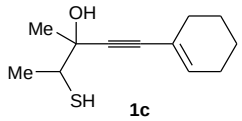

**1a**

4-Mercapto-3-methyl-1-phenylpent-1-yn-3-ol **(1a).**Yield: 2.98 g, starting from 1.77 g of 3-mercaptobutan-2-one (90%). Mixture of diastereomers A+B, A:B ratio ca. 6:4, determined by GLC. Yellow oil; $C_{12}H_{14}OS$ (206.30). IR (film): ν = 3448 (s, br), 2974 (m), 2932 (m), 2557 (m), 2230 (w), 1598 (m), 1489 (m), 1372 (m), 1262 (w), 1106 (m), 1070 (m), 756 (s) $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$): δ = 7.47-7.40 (m, 4H arom, A+B), 7.37-7.28 (m, 6H arom, A+B), 3.37 (s, 1H, OH, B), 3.3 (q, J = 6.9, 1H, $CHCH_3$, A), 3.0-2.92 (m, 1H, $CHCH_3$, B), 2.81 (s, 1H, OH, A), 1.96 (d, J = 10.9, 3H, $CHCH_3$, B), 1.77 (dd, J = 0.8, 6.5, 1H, SH, B), 1.65 (s, 3H, $CH_3COH$, B), 1.63 (s, 3H, $CH_3COH$, A), 1.66 (d, J = 6.9, 3H, $CHCH_3$, A), 1.43 (dd, J = 0.8, 6.9, 1H, SH, A); $^{13}C$ NMR (75 MHz, $CDCl_3$ ): δ = 131.7 (B), 131.68 (A), 128.5 (B+A), 128.3 (B+A), 122.3 (B), 122.28 (A), 91.3 (A), 89.4 (B), 85.0 (B), 84.4 ( A), 72.0 (B), 71.2 (A), 40.5 (B), 46.3 (A), 26.8 (B), 25.5 (A); 22.0 (B), 18.4 (A). GC-MS (EI, 70 eV) A : m/z = 206 (0.5) $[M^{+}]$; 146 (11); 145 (100); 129 (14); 115 (10); 77 (8); 75 (5); 43 (72); B : m/z = 207 (0.14) $[M^{+1}]$; 137 (0.6) $[M^{+}]$; 188 (14); 173 (10); 145 (100); 129 (15); 115 (12); 77 (11); 43 (80).




**1b**

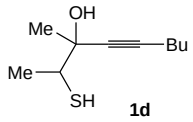
4-Mercapto-3-methyl-1-p-tolylpent-1-yn-3-ol **(1b).** Mixture of diastereoisomers A+B, A:B ratio = 1.5, determined by $^{1}H$ NMR. Yield: 2.99 g, starting from 1.77 g of 3-mercapto-2-butanone (80%). Yellow oil. IR (film): ν = 3434 (m, br), 2566 (vw), 2229 (w), 816 (s) $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$): δ = 7.36−7.27 [A (m, 2 H), + B (m, 2 H)], 7.13−7.06 [A (m, 2 H) + B (m, 2 H)], 3.43 [B, (s, br, 1 H)], 3.27 [A (quintuplet, J = 6.6, 1 H)], 3.00−2.87 [A (m, 1 H) + B (m, 1 H)], 2.33 [A (s, 3 H) + B (s, 3 H)], 1.96 [A (d, J = 6.6, 1 H)], 1.78 [B (d, J = 10.3, 1 H)], 1.64 [B (s, 3 H)], 1.62 [A (s, 3 H)], 1.53 [B (d, J = 6.6, 3 H)], 1.42 [A (d, J = 6.6, 3 H)]; $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 138.6, 131.7, 131.6, 129.0, 119.2, 90.6, 88.7, 85.1, 84.5, 72.0, 71.3, 48.5, 46.3, 26.8, 25.6, 21.9, 21.5, 18.6; GC-MS: diastereomer A: m/z = 220 ($M^{+}$, <0.5%), 159 (100); diastereomer B: m/z = 220 ($M^{+}$, <0.5%), 159 (100); anal. calcd for $C_{13}H_{16}OS$ (220.33): C, 70.87; H, 7.32; S, 14.55; found C, 70.95; H, 7.31; S, 14.64.




**1c**

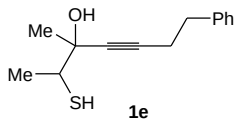
1-Cyclohex-1-enyl-4-mercapto-3-methyl-pent-1-yn-3-ol **(1c**).

Mixture of diastereomers A+B, A:B ratio = 2.0, determined by $^{1}$H NMR. Yield: 3.11 g, starting from 1.77 g of 3-mercapto-2-butanone (87%). Yellow oil. IR (film): ν = 3434 (m, br), 2570 (vw), 2216 (m), 919(s) cm$^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$): δ = 6.16−6.06 [A (m, 1 H) + B (m, 1 H)], 3.30 [B (s, br, 1 H)], 3.19 [A (quintuplet, J = 6.6, 1 H)], 2.95−2.83 [B (m, 1 H)], 2.82 [A (s, br, 1 H)], 2.15−2.03 [A (m, 4 H) + B (m, 4 H)], 1.92 [A (d, J = 6.6, 1 H)], 1.73 [B (d, J = 10.3, 1 H)], 1.68− 1.53 [A (m, 4 H) + B (m, 4 H)], 1.61 [B (s, 3 H)], 1.59 [A (s, 3 H)], 1.48 [B (d, J = 7.3, 1 H)], 1.37 [A (d, J = 6.6, 1 H)]; $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 135.5, 119.9, 88.6, 86.8, 86.6, 86.2, 71.9, 71.2, 48.5, 46.3, 29.2, 29.1, 26.8 25.63, 25.58, 22.2, 21.9, 21.4, 18.5; GC-MS: diastereomer A: m/z = 210 (<0.5) [M$^{+}$], 192 (23), 149 (100), 91 (21); diastereomer B: m/z = 210 (<0.5) [M$^{+}$], 149 (100); anal. calcd for $C_{12}H_{18}OS$ (210.34): C, 68.52; H, 8.63; S, 15.25; found C, 68.63; H, 8.61; S, 15.23




**1d**

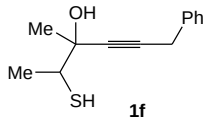
2-Mercapto-3-methylnon-4-yn-3-ol **(1d**). Mixture of diastereomers A+B, A:B ratio = 1.4, determined by $^{1}$H NMR. Yield: 2.69 g, starting from 1.77 g of 3-mercapto-2-butanone (85%). Yellow oil. IR (film): ν = 3447 (m, br), 2567 (vw), 2240 (vw), 917 (m) cm$^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$): δ = 3.22 [B (s, br, 1 H)], 3.14 [A (quintuplet, J = 6.9, 1 H)], 2.86 [B (dq, J = 10.5, 6.9, 1 H)], 2.75 [A (s, br, 1 H)], 2.26−2.16 [A (m, 2 H), + B (m, 2 H)], 1.89 [A (d, J = 10.5, 1 H), 1.71 [B (d, J = 6.9, 1 H)], 1.53−1.38 [A (m, 4 H) + B (m, 4 H)], 1.52 [B (s, 3 H)], 1.51 [A (s, 3H)], 1.46 [B (d, J = 6.9, 1 H)], 1.36 [A (d, J = 10.5, 1 H)], 0.92 [B (t, J = 7.3, 3 H)], 0.91 [A (t, J = 7.3, 3 H)]; $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 85.6, 85.1, 82.6, 80.6, 71.6, 70.9, 48.4, 46.4, 30.8, 30.7, 27.0, 25.9, 22.0, 21.8, 18.6, 18.3, 13.6; GC-MS: diastereomer A: m/z = 186 (<0.5) [M$^{+}$], 125 (95), 43 (100); diastereomer B: m/z = 186 (<0.5) [M$^{+}$], 125 (98), 43 (100); anal. calcd for $C_{10}H_{18}OS$ (186.32): C, 64.46; H, 9.74; S, 17.21; found C, 64.53; H, 9.72; S, 17.20.




**1e**

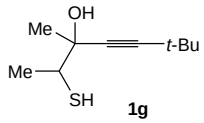
2-Mercapto-3-methyl-7-phenylhept-4-yn-3-ol **(1e).** Mixture of diastereomers A+B, A:B ratio = 1.5, determined by $^{1}$H NMR. Yield: 1.59 g, starting from 1.77 g of 3-mercapto-2-

butanone (40%). Yellow oil. IR (film): ν = 3439 (m, br), 2559 (vw), 2237 (w), 698 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.32−7.03 [A (m, 5 H) + B (m, 5 H)], 3.09−2.92 [A (m, 1 H) + B (m, 1 H)], 2.83−2.70 [A (m, 2 H) + B (m, 2 H)], 2.54−2.42 [A (m, 2 H) + B (m, 2 H)], 1.75 [A (d, J = 6.7, 1 H)], 1.52 [B (d, J = 10.3, 1 H)], 1.45 [A (s, 3 H) + B (s, 3 H)], 1.31 [B (d, J = 6.7, 3 H)], 1.26 [A (d, J = 6.7, 3 H)] (Note: the OH signals were too broad to be detected); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 140.3, 128.4, 128.3, 126.3, 84.5, 84.1, 83.4, 81.7, 71.5, 70.9, 48.0, 46.0, 34.8, 26.8, 25.9, 21.4, 20.6, 20.5, 18.7; GC-MS: diastereomer A: m/z = 234 (1) [$M^+$], 173 (74), 91 (100); diastereomer B: m/z = 234 (1) [$M^+$], 173 (65), 125 (47), 91 (100); anal. calcd for $C_{14}H_{18}OS$ (234.36): C, 71.75; H, 7.74; S, 13.68; found C, 71.82; H, 7.72; S, 13.67.



**1f**

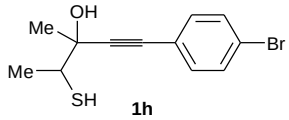
2-Mercapto-3-methyl-6-phenyl-hex-4-yn-3-ol (**1f**). Mixture of diastereomers A+B, A:B ratio = 2.0, determined by $^1H$ NMR. Yield: 1.91 g, starting from 1.77 g of 3-mercapto-2-butanone (51%). Yellow oil. IR (film): ν = 3432 (s, br), 2567 (vw), 2243 (w), 697 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.34−7.18 [A (m, 5 H) + B (m, 5 H)], 3.63 [B (s, 2 H)], 3.62 [B (s, 2 H)], 3.16 [A (quintuplet, J = 6.7, 1 H)], 2.94−2.79 [B (m, 1 H)], 1.86 [A (d, J = 6.7, 1 H)], 1.70 [B (d, J = 10.3, 1 H)], 1.56 [B (s, 3 H)], 1.54 [A (s, 3 H)], 1.46 [B (d, J = 6.7, 3 H)], 1.37 [A (d, J = 6.7, 3 H)] (Note: the OH signals were too broad to be detected);$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 136.5, 136.4, 128.51, 127.84, 127.77, 126.6, 84.8, 83.1, 83.0, 82.5, 71.7, 71.0, 48.2, 46.2, 27.0, 25.8, 24.9, 21.7, 18.7; GC-MS: diastereomer A: m/z = 220 (1) [$M^+$], 159 (100), 115 (57); diastereomer B: m/z = 220 (2) [$M^+$], 202 (26), 187 (34), 159 (100), 116 (29), 115 (69); anal. calcd for $C_{13}H_{16}OS$ (220.33): C, 70.87; H, 7.32; S, 14.55; found C, 70.93; H, 7.31; S, 14.54.



**1g**

2-Mercapto-3,6,6-trimethyl-hept-4-yn-3-ol **(1g)**. Mixture of diaster-eomers A+B, A:B ratio = 1.1, determined by $^1H$ NMR. Yield: 2.91 g, starting from 1.77 g of 3-mercapto-2-butanone (92%). Yellow oil. IR (film): ν = 3436 (m, br), 2570 (vw), 2220 (w), 915 (m), $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 3.23 [B (s, br, 1 H)], 3.20−3.07 [A (m, 1 H)], 2.91−2.79 [B (m, 1 H)], 2.72 [A (s, br, 1 H)], 1.89 [A (d, J = 6.6, 1 H)], 1.68 [B (d, J = 10.6, 1 H)], 1.51 [B (s, 3 H), 1.50 [A (s, 3 H)], 1.46 [B (d, J = 6.6, 3 H)], 1.36 [A (d, J = 6.6, 3 H)], 1.24 [B (s, 9 H)], 1.22

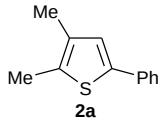
[A (s, 9 H)]; $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 93.8, 93.2, 80.9, 78.9, 73.6, 70.7, 48.6, 46.5, 30.9, 26.9, 25.7, 23.2, 22.0, 20.5, 18.5; GC-MS: diastereomer A: m/z = 186 (absent) [$M^+$], 125 (40), 43 (100); diastereomer B: m/z = 186 (absent) [$M^+$], 125 (38), 43 (100); anal. calcd for $C_{10}H_{18}OS$ (186.32): C, 64.46; H, 9.74; S, 17.21; found C, 64.52; H, 9.72; S, 17.19.



**1h**

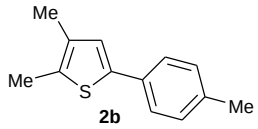
1-(4-Bromophenyl)-4-mercapto-3-methylpent-1-yn-3-ol **(1h)** could not be obtained in a pure state even after repeated purification by column chromatography, so it was used crude for the next iodocyclization step.

## Characterization of thiophenes (2a-2g)



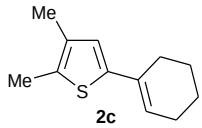
**2a**

5-phenyl-2,3-dimethylthiophene **(2a)**. Yield: 167.6 mg, starting from 206.3 mg of 1b (89%) (Table 2.3, entry 2). Yellow solid; m.p. = 46-47 °C; lit. 46-47°C; $C_{12}H_{12}S$ (188.29). IR (KBr): ν = 2914 (m), 2855 (m), 1665 (w), 1597 (m), 1443 (m), 1202 (w), 1072 (w), 832 (m), 754 (s) 689 (s) $cm^{-1}$H NMR (300 MHz, $CDCl_3$): δ = 7.54-7.47 (m, 2H, on phenyl ring), 7.35-7.25 (m, 3H, on phenyl ring), 7.23-7.15 (m, 2H, on phenyl ring), 6.99 (s, 1H, H-4), 2.33 (s, 3H, Me at C-2), 2.12 (s, 3H, Me at C-3). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 139.1, 134.7, 134.1, 131.4, 128.7, 126.8, 126.0, 125.3, 13.6, 13.1.GC-MS (EI, 70 eV): m/z = 189 (16) [$M^{+1}$], 188 (100) [$M^+$], 187 (54), 173 (69), 128 (15), 77 (18) 59 (13), 51 (16).



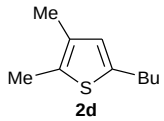
**2b**

2,3-dimethyl-5-p-tolylthiophene (**2b**).Yield: 151.7 mg, starting from 220.3 mg of 1d (75%) (Table 2.3, entry 4). Yellow amorphous solid; m.p. = 46-47°C; $C_{13}H_{14}S$ (202.32). IR (KBr): ν = 2918 (m), 2857 (m), 1638 (w), 1516 (m), 1446 (w), 1215 (w), 944 (w), 811 (s), 757 (m), 484 (w) $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.40 (d, J = 8.1, 2 H, H-2 + H-6 on thiophene ring ), 7.12 (d, J = 8.1, 2 H, H-3 + H-5 on phenyl ring), 6.94 (s, 1 H, H-4), 2.33 (s, 3 H, Me at C-2), 2.12 (s, 3 H, Me at C-3). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 139.3, 136.6, 133.9, 132.0, 131.3, 129.4, 125.5, 125.3, 21.1, 13.6, 13.1. GC-MS (EI, 70 eV): m/z = 203 (17) [$M^{+1}$], 202 (100) [$M^+$], 201 (54), 187 (50), 153 (5), 128 (6) 115 (6).



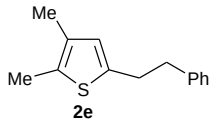
**2c**

5-Cyclohex-1-enyl-2,3-dimethylthiophene (**2c**).Yield: 96 mg, starting from 210.3 mg of 1f (50%) . Yellow oil; $C_{12}H_{16}S$ (192.32). IR (KBr): ν = 2927 (m), 2857 (m), 1660 (w), 1567 (w), 1446 (m), 1435 (m), 1348 (w), 1135 (w), 819 (m), 797 (m) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 6.60 (s, 1 H, on thienyl ring), 6.06-5.96 (m, 1 H, H-2 on cyclohexenyl ring), 2.28 (s, 3 H, Me at C-5), 2.31-2.11 (m, 4 H, $CH_2C{=}CCHCH_2$), 2.06 (s, 3 H, Me at C-4), 1.77-1.68 (m, 2 H, $=CHCH_2CH_2CH_2$ or $=CHCH_2CH_2CH_2$), 1.68-1.55 (m, 2 H, $=CHCH_2CH_2CH_2$ or $=CHCH_2CH_2CH_2$). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 134.0, 132.9, 131.2, 130.0, 124.2, 122.6, 27.2, 25.6, 25.5, 22.4, 22.2. GC-MS (EI, 70 eV): m/z = 193 (14) [$M^{+1}$], 192 (100) [$M^+$], 177 (86), 164 (40), 163 (26), 149 (68) 135 (17), 125 (14), 115 (14), 91 (17), 79 (14), 77 (17), 59 (18).



**2d**

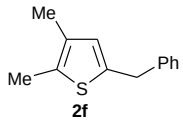
5-butyl-2,3-dimethylthiophene (**2d**). Yield: 795.3 mg, starting from 1 g of 1a (81%) (Table 2.3, entry 1). Colorless oil; $C_{10}H_{16}S$ (168.30). IR (film):ν = 2948 (m), 2834 (m), 1653 (w), 1449 (w), 1086 (w), 1028 (s), 875 (w), 758 (m) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 6.44, (s, 1 H, H-4), 2.69 (t,J = 7.7, 2 H), 2.27 (s, 3 H, Me), 2.06 (s, 3 H, Me), 1.66-1.53 (m, 2 H), 1.45-1.30 (m, 2 H), 0.92 (t, J = 7.3, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 140.9, 132.3, 129.8, 126.9, 33.9, 29.6, 22.2, 13.9, 13.5, 12.9. GC-MS (EI, 70 eV): m/z = 168 (26) [$M^+$], 126 (12), 125 (100), 91 (13), 59 (9), 41 (9).



**2e**

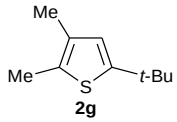
2,3-Dimethyl-5-phenethylthiophene (**2e**). Yellow solid, mp 28-30 °C. IR (KBr): ν = 2939 (m), 2916 (m), 2855 (m), 1492 (m), 1450 (m), 1151 (w), 1069 (w), 848 (m), 824 (m), 749 (s), 702 (s) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.31-7.23 (m, 2 H, aromatic), 7.22-7.13 (m, 3 H, aromatic), 6.45 (s, 1 H, =CH), 3.05-2.85 (m, 4 H, $CH_2CH_2Ph$), 2.27 (s, 3 H, Me), 2.05 (s, 3 H, Me); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ =141.3, 139.6, 132.4, 130.1, 128.4, 128.3, 127.2, 126.0, 38.1, 31.9, 13.5, 12.9 ; GC-MS: m/z = 216 (28) [$M^+$], 127 (7), 126 (11), 125 (100), 110 (2), 97

(3), 91 (16), 79 (2); anal. calcd for $C_{14}H_{16}S$ (216.34): C, 77.72; H, 7.45; S, 14.82; found C, 77.69; H, 7.48; S, 14.81.



**2f**

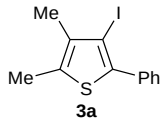
5-Benzyl-2,3-dimethylthiophene (**2f**). Yellow solid, mp 38-39 °C. IR (KBr): ν = 2914 (w), 2854 (w), 1498 (m), 1462 (m), 1442 (w), 1203 (w), 1072 (w), 1029 (w), 831 (m), 754 (s), 687 (s) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.40-7.30 (m, 5 H, aromatic), 6.45 (s, 1 H, =CH), 4.01 (s, 2 H, $CH_2Ph$), 2.25 (s, 3 H, Me), 2.04 (s, 3 H, Me); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 140.6, 139.0, 132.6, 131.1, 128.6, 128.5, 128.0, 126.3, 36.1, 13.5, 12.9; GC-MS: m/z = 202 (95) [$M^+$], 201 (39), 188 (16), 187 (100), 172 (8), 171 (6), 153 (8), 152 (6), 141 (4), 125 (32), 115 (7), 111 (4), 91 (10), 77 (4); anal. calcd for $C_{13}H_{14}S$ (202.32): C, 77.18; H, 6.97; S, 15.85; found C, 77.23; H, 6.99; S, 15.88.



**2g**

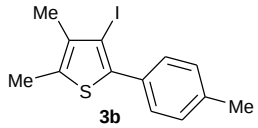
5-tert-Butyl-2,3-dimethylthiophene (**2g**). Yellow oil. IR (film): ν = 2923 (s), 2851 (m), 1642 (m), 1464 (m), 1215 (w), 760 (s) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 6.48 (s, 1 H, =CH), 2.27 (s, 3 H, Me), 2.06 (s, 3 H, Me), 1.33 (s, 9 H, t-Bu); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 152.4, 132.0, 129.4, 124.2, 34.1, 32.4, 13.6, 12.9; GC-MS: m/z = 168 (31) [$M^+$], 154 (13), 153 (10), 137 (6), 125 (8), 113 (8), 105 (2), 97 (2), 91 (4), 77 (3); anal. calcd for $C_{10}H_{16}S$ (168.30): C, 71.36; H, 9.58; S, 19.05; found C, 71.33; H, 9.55; S, 19.10.

## IODOCYCLIZATION PRODUCT (3a-3h)



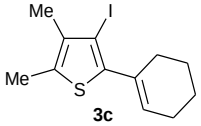
**3a**

3-Iodo-4,5-dimethyl-2-phenylthiophene **(3a**). Yield: 67 mg, start-ing from 62 mg of 5a (71%) (Table 1, entry 1). Yellow oil. IR (film): ν = 1598 (m), 1501 (m), 1441 (m), 1167 (m), 1012 (m), 749 (s), 695 (s) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.56−7.47 (m, 2 H), 7.43−7.28 (m, 3 H), 2.42 (s, 3 H), 2.21 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 137.6, 136.1, 132.4, 131.4, 129.5, 128.2, 127.9, 86.0, 17.3, 14.2; GC-MS: m/z = 314 (100) [$M^+$], 187 (36); anal. calcd for $C_{12}H_{11}IS$ (314.19): C, 45.87; H, 3.53; S, 10.21; found C, 45.95; H, 3.51; S, 10.23.



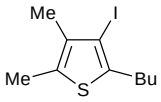
**3b**

3-Iodo-4,5-dimethyl-2-p-tolylthiophene (**3b**). Yield: 82 mg, starting from 66 mg of 5b (83%) (Table 1, entry 2). Yellow solid, mp = 54−55 °C. IR (KBr): ν = 1519 (m), 1436 (m), 1164 (m), 1025 (m), 947 (m), 814 (s), 796 (s), 767 (s) $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$): δ = 7.47− 7.39 (m, 2 H), 7.24−7.16 (m, 2 H), 2.43 (s, 3 H), 2.37 (s, 3 H), 2.21 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 137.8, 137.7, 135.9, 132.3, 131.3, 129.4, 129.0, 85.8, 21.3, 17.3, 14.2; GC-MS: m/z = 328 (100) [$M^+$], 201 (26), 115 (24); anal. calcd for $C_{13}H_{13}IS$ (328.21): C, 47.57; H, 3.99; S, 9.77; found C, 47.65; H, 4.01; S, 9.75



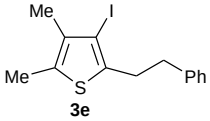
**3c**

2-Cyclohex-1-enyl-3-iodo-4,5-dimethylthiophene **(3c**). Yield: 68 mg, starting from 63 mg of 5e (71%) (Table 1, entry 5). Yellow solid, mp = 25−26 °C. IR (KBr): ν = 1435 (s), 758 (s) $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$): δ = 6.02−5.95 (m, 1 H), 2.38−2.31 (m, 2 H), 2.36 (s, 3 H), 2.21−2.12 (m, 2 H), 2.14 (s, 3 H), 1.80−1.59 (m, 4 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 140.4, 135.1, 132.3, 130.2, 130.1, 84.2, 30.0, 25.5, 22.9, 21.8, 17.0, 14.1; GC-MS: m/z = 318 (100) [$M^+$], 163 (64), 148 (25), 79 (47); anal. calcd for $C_{12}H_{15}IS$ (318.22): C, 45.29; H, 4.75; S, 10.08; found C, 45.33; H, 4.76; S, 10.12.



**3d**

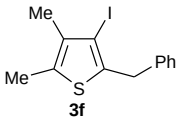
2-Butyl-3-iodo-4,5-dimethylthiophene (**3d**). Yield: 59 mg, starting from 56 mg of 5f (67%) (Table 1, entry 6). Yellow solid, mp = 115−117 °C. IR (KBr): ν = 1456 (s), 1375 (m) $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$): δ = 2.73 (t, J = 7.7, 2 H), 2.37 (s, 3 H), 2.12 (s, 3 H), 1.68−1.52 (m, 2 H), 1.50−1.33 (m, 2 H), 0.94 (t, J = 7.3, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 139.0, 134.4, 129.5, 86.8, 32.9, 32.3, 22.2, 16.8, 14.1, 13.9; GC-MS: m/z = 294 (32) [$M^+$], 251 (100), 125 (33); anal. calcd for $C_{10}H_{15}IS$ (294.20): C, 40.83; H, 5.14; S, 10.90; found C, 40.81; H, 5.15; S, 10.89.



**3e**

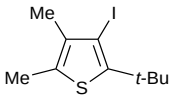
3-Iodo-4,5-dimethyl-2-phenethylthiophene (**3e**). Yield: 72 mg, starting from 70 mg of 5g (70%) (Table 1, entry 7). Yellow oil. IR (film): ν = 1603 (m), 1495 (m), 1453 (s), 1164 (m), 749 (s),

698 (s) $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$): δ = 7.35−6.95 (m, 5 H, Ph), 3.07−2.82 (m, 4 H, $CH_2CH_2Ph$), 2.36 (s, 3 H, Me), 2.13 (s, 3 H, Me); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 140.9, 137.6, 131.0, 130.0, 128.5, 128.4, 126.2, 87.2, 36.9, 34.6, 16.7, 14.1; GC-MS: m/z = 342 (19) [$M^+$], 251 (100); anal. calcd for $C_{14}H_{15}IS$ (342.24): C, 49.13; H, 4.42; S, 9.37; found C, 49.20; H, 4.41; S, 9.35.



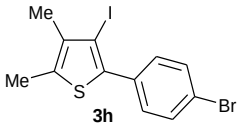
**3f**

2-Benzyl-3-iodo-4,5-dimethylthiophene (**3f**). Yield: 67 mg, starting from 66 mg of 5h (68%). (Table 1, entry 8). Yellow oil. IR (film): ν = 1494 (m), 1452 (s), 1432 (m), 1073 (m), 1029 (m), 763 (m), 697 (s), $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$): δ = 7.35−7.05 (m, 5 H), 4.00 (s, 2 H), 2.26 (s, 3 H), 2.06 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 139.2, 137.5, 134.5, 130.7, 128.5, 128.3, 126.4, 87.6, 38.4, 16.6, 13.9; GC-MS: m/z = 328 (100) [$M^+$], 201 (58), 186 (26); anal. calcd for $C_{13}H_{13}IS$ (328.21): C, 47.57; H, 3.99; S, 9.77; found C, 47.62; H, 3.98; S, 9.80.



**3g**

2-tert-Butyl-3-iodo-4,5-dimethylthiophene (**3g**). Yield: 57 mg, starting from 56 mg of 5i (65%) (Table 1, entry 9). Yellow solid, mp = 114−115 °C. IR (KBr): ν = 1463 (m), 1363 (m), 1214 (m), 1168 (m), 760 (s) $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 2.14 (s, 3 H), 1.50 (s, 9 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 146.0, 136.5, 127.6, 81.4, 35.1, 30.1, 17.5, 14.0; GC-MS: m/z = 294 (36) [$M^+$], 279 (100), 152 (22); anal. calcd for $C_{10}H_{15}IS$ (294.20): C, 40.83; H, 5.14; S, 10.90; found C, 40.86; H, 5.15; S, 10.88.



**3h**

2-(4-Bromophenyl)-3-iodo-4,5-dimethylthiophene (**3h**). Yield: 77 mg, starting from 86 mg of crude 5c (65%) (Table 1, entry 3). White solid, mp = 104−105 °C. IR (KBr): ν = 1500 (m), 1384 (m), 1072 (s), 1009 (s), 826 (s), 782 (s) $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$): δ = 7.56−7.47 (m, 2 H), 7.45−7.36 (m, 2 H), 2.44 (s, 3 H), 2.21 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 136.4, 136.2, 134.1, 132.8, 131.5, 131.1, 122.2, 86.4, 17.3, 14.2; GC-MS: m/z = 394 (100) [$(M+2)^+$], 392 (98) [$M^+$], 185 (23); anal. calcd for $C_{12}H_{10}BrIS$ (393.08): C, 36.67; H, 2.56; Br, 20.33; S, 8.16; found C, 36.75; H, 2.54; Br, 20.31; S, 8.14.

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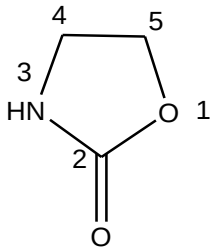
# Chapter 3

## 3.1 Synthesis of 2-Oxazolidinones by Palladium-Catalyzed Oxidative Carbonylation of Propargylic Amines in $EmimEtSO_4$

### 3.1.1 Introduction




**1,3-Oxazolidin-2-one**

2-Oxazolidinones are a very important class of heterocyclic compounds. containing both nitrogen and oxygen in a 5-membered ring. Oxazolidinones are a class of compounds containing 2-oxazolidone in the structure. Chiral 2-oxazolidinones are widely used as chiral auxiliaries in many important asymmetric syntheses[1], Usually, the acid chloride substrate reacts with the oxazolidinone to form an imide. Substituents at the 4 and 5 position of the oxazolidinone direct any aldol reaction to the alpha position of the carbonyl of the substrate.

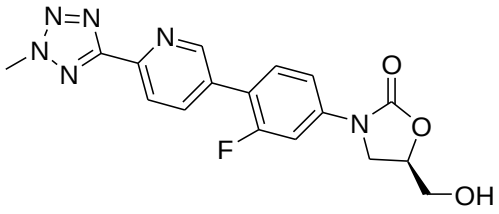
moreover, oxazolidinone derivatives have shown important pharmacological properties, in particular as antibacterial agents.[2] The importance of these heterocyclic derivatives justifies the continuous efforts for developing novel approaches to their synthesis.

### 3.1.2 Pharmaceutical Applications

Oxazolidinones are mainly used as antimicrobials. The antibacterial effect of oxazolidinones is by working as pr synthesis inhibitors, targeting an early step involving the binding of N-formylmethionyl-tRNA to the ribosome.[3] Some of the most important oxazolidinones are the last generation of antibiotics used against gram-positive pathogens, including superbugs such as methicillin-resistant Staphylococcus aureus. These antibiotics are considered as a choice of last resort where every other antibiotic therapy has failed

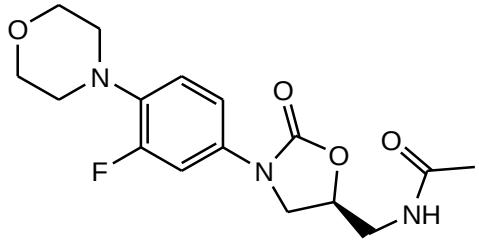
### 3.1.3 Examples of antibiotic oxazolidinones

**a)Tedizolid,**



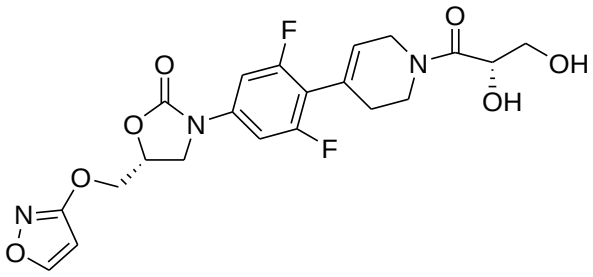

Tedizolid, (Sivextro) which is approved for acute skin infections

**b)Linezolid**



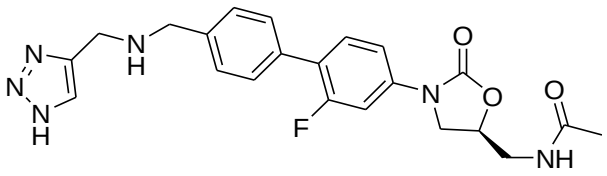

Linezolid is an antibiotic used for the treatment of infections caused by Gram-positive bacteria that are resistant to other antibiotics Linezolid (Zyvox), which is available for intravenous administration and also has the advantage of having excellent oral bioavailability.

**c) Posizolid**



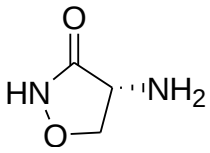

Posizolid, which appears to have excellent, targeted bactericidal activity against all common gram-positive bacteria, regardless of resistance to other classes of antibiotics.[4]Posizolid is an oxazolidinone antibiotic under investigation by AstraZeneca for the treatment of bacterial infections. At a concentration of 2 mg/L it inhibited 98% of all Gram-positive bacteria tested in vitro.[4]

**d) Radezolid**



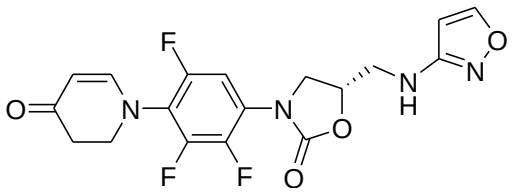
Radezolid (RX-1741) has completed some phase-II clinical trials.[5]Radezolid (INN, codenamed RX-1741) is a novel oxazolidinone antibiotic being developed by Melinta Therapeutics, Inc. for the treatment of serious multi-drug–resistant infections. Radezolid has completed two phase-II clinical trials. One of these clinical trials was for uncomplicated skin and skin-structure infections (uSSSI) and the other clinical trial was for community acquired pneumonia (CAP).

**e) Cycloserine**



Cycloserine is a second line drug against tuberculosis. Note that cycloserine, while technically an oxazolidone, has a different mechanism of action and substantially different properties from the aforementioned compounds. Cycloserine, sold under the brand name Seromycin, is an antibiotic used to treat tuberculosis. Specifically it is used, along with other antituberculosis medications, for active drug resistant tuberculosis. It is given by mouth.[6]

**f) MRX-I**

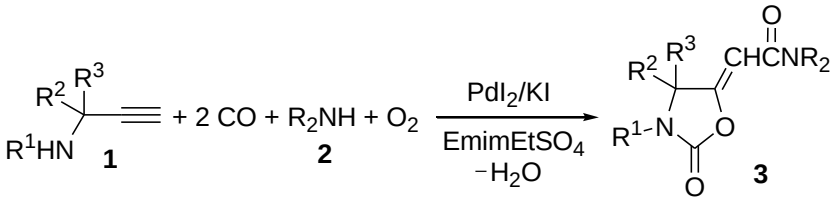


(S)-5-((isoxazol-3-ylamino)methyl)-3-(2,3,5-trifluoro-4-(4-oxo-3,4-dihydropyridin-1(2H)-yl)phenyl)oxazolidin-2-one (MRX-I) has reported phase 1 data[7] and completed phase II trials in 2015, and is starting a phase 3 trial in 2016.[8]An oxazolidinone derivative used for other

purposes is rivaroxaban, which is approved by the FDA for venous thromboembolism prophylaxis.

### 3.2. Present Work

#### 3.2.1 Synthesis of Oxazolidinones in Ionic Liquid




**(3.1)**

In this thesis we present a convenient carbonylative approach to 2-oxazolidinone derivatives **3** (Eq.3.1) carried out in an ionic liquid $EmimEtSO_4$ as unconventional solvent (1-ethyl-3-methyl-1H-imidazol-3-ium ethyl sulfate,[9]) Reactions are carried out using a simple catalytic system consisting of $PdI_2$ in conjunction with an excess of KI, and the catalyst/solvent system could be recycled several times without appreciable loss of activity after extraction of the organic product with $Et_2O$.This is an attractive route to the formation of the 2-oxazolidinone core is based on annulation of a suitable acyclic precursor, which can allow the regioselective preparation of the final heterocycle with the desired substitution pattern[10].

#### 3.2.2. Mechanism

Cascade catalysis, in which a catalytic cycle is concatenated to another eventually leading to the final product, is one of the most exciting areas of modern catalysis [20-29]. Although rather frequent in biological systems [30], where processes may be sequentially catalyzed by different enzymes, it is still relatively rare in chemical transformations, where usually involves two concatenated cycles. A particularly interesting case, commonly referred as "auto-tandem catalysis" [28], occurs when the same catalytic system is able to catalyze both the concatenated cycles, as shown in Scheme 1.

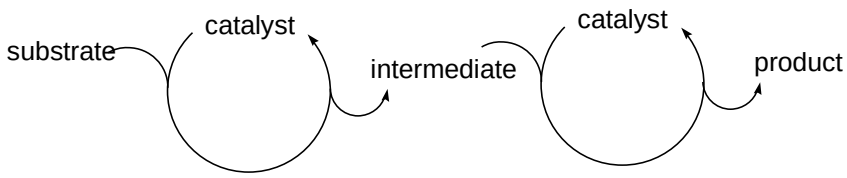


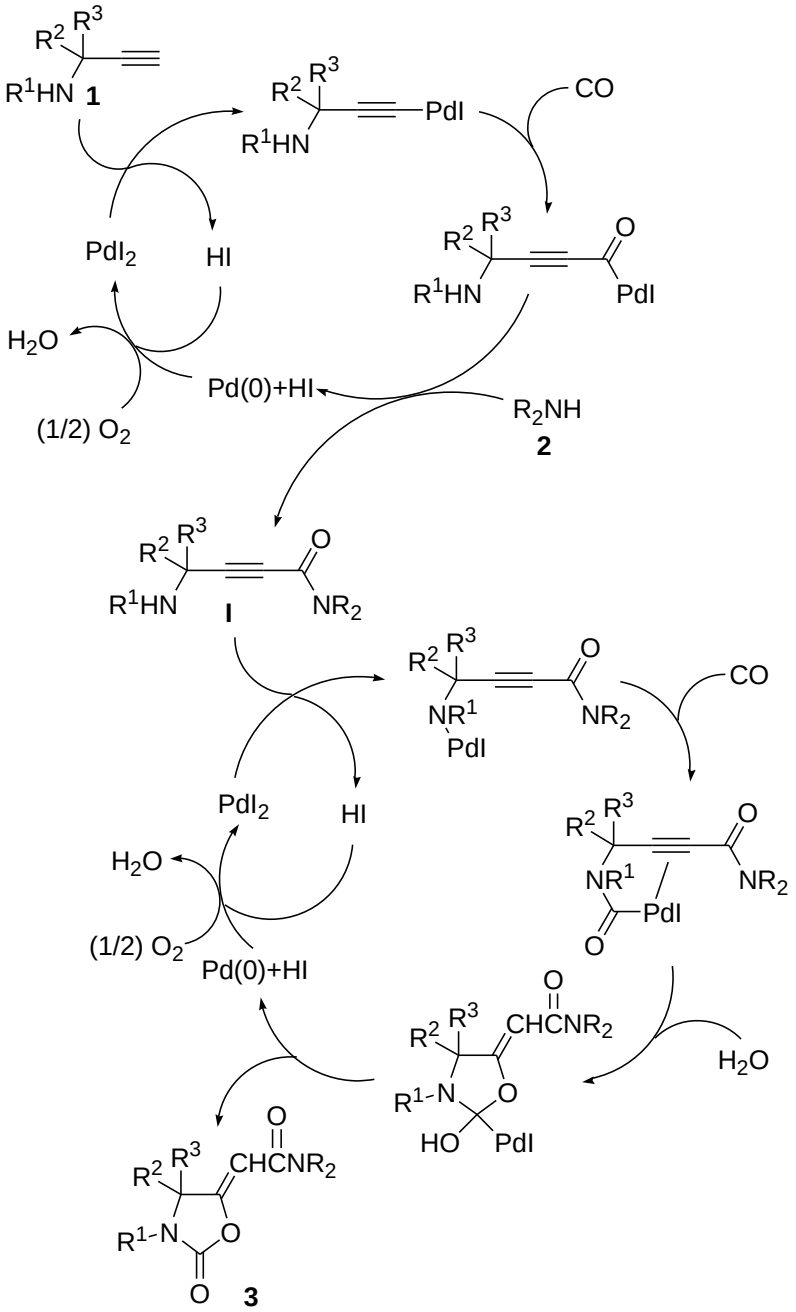

**Figure-1**

In this work, we report on the direct synthesis of 2-oxazolidinone derivatives through an auto-tandem catalysis process consisting of the concatenation of two carbonylative catalytic cycles,

both catalyzed by the same catalytic system ($PdI_2$ in conjunction with an excess of KI), performed in the ionic liquid 1-ethyl-3-methyl-1H-imidazol-3-ium ethyl sulfate ($EmimEtSO_4$) as unconventional solvent.

i) The first cycle corresponds to the oxidative mono amino carbonylation of the triple bond of propargylic amines to give the corresponding 2-alkynamide intermediates,

ii) The second one to the cyclocarbonylation of the latter to yield 2-(2-oxooxazolidin-5-ylidene) acetamides.




**Scheme 3.1**

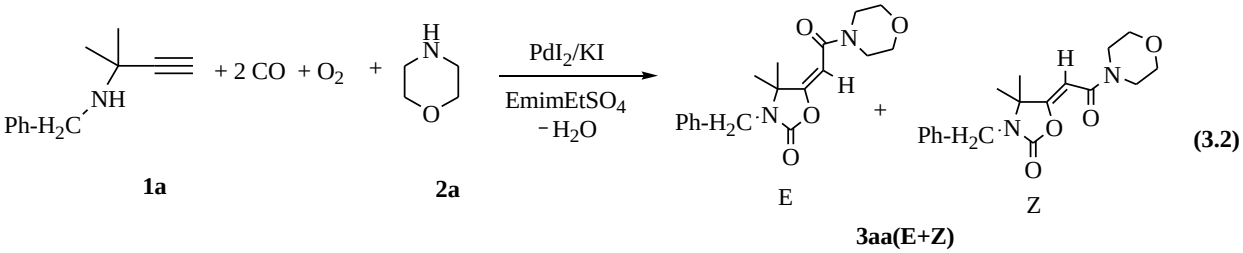
The synthesis of 2-(2-oxooxazolidin-5-ylidene)acetamides **3** is based on the $PdI_2$/KI-catalyzed oxidative carbonylation [11-18] of substituted propargylic amines **1**, carried out in the presence of a secondary amine **2** as external nucleophile, water as a promoter, and molecular oxygen as oxidant [19]. The process, carried out at 100 °C in in the ionic liquid 1-ethyl-3-methyl-1H-imidazol-3-ium ethyl sulfate ($EmimEtSO_4$) as unconventional solvent. under 20 atm (at 25 °C) of a 4:1 mixture of CO/air, led to the formation of a Z/E mixture of **3.**

Considering the importance of the class of products obtained, which are known to possess important pharmacological activities [31-34], and the current attention devoted to the possibility to carry out catalytic processes in ionic liquids (ILs) as safer and more environmentally friendly solvents with respect to classical VOCs 35-39, coupled to the possibility to recycle the catalytic system, we have herein explored the possibility to perform our process in the ionic liquid $EmimEtSO_4$.

### 3.3.1 First Experiment and Optimization Studies

Our first experiment was carried out using N-benzyl-2-methylbut-3-yn-2-amine **1a** as the substrate. This compound was allowed to react with CO, morpholine(**2a**), $O_2$, and water in the presence of the catalytic system $PdI_2$/KI under the same conditions: $PdI_2$/KI/**1a**/**2a**/$H_2O$ molar ratio = 1:10:50:250:250, T = 80 °C, P(CO) = 16 atm, P(air) = 4 atm, $BmimBF_4$ as the solvent (0.5 mmol of **1a** per mL of solvent) After 15 hrs ,the reaction mixture was extracted several times with diethyl ether and the collected ethereal phases analyzed by TLC, GLC and GC-MS, GLC shows the percentage conversion was 8 (Table 3.1 , entry 1),

Our next experiment was carried out using N-benzyl-2-methylbut-3-yn-2-amine **1a** as the substrate. This compound was allowed to react with CO, morpholine(**2a**), $O_2$, and water in the presence of the catalytic system $PdI_2$/KI under the same conditions: $PdI_2$/KI/**1a**/**2a**/$H_2O$ molar ratio = 1:10:50:250:250, T = 80 °C, P(CO) = 16 atm, P(air) = 4 atm, $EmimEtSO_4$ as the solvent (0.5 mmol of **1a** per mL of solvent) (Table 3.1,entry 2). After 8 hrs, the reaction mixture was extracted several times with diethyl ether and the collected ethereal phases analyzed by TLC, GLC and GC-MS, GLC shows the percentage conversion was 40 and formation of the two products whose MS spectra were compatible with the expected isomeric oxazolidinone products **3aa**-Z and **3aa**-E (**Eq.3.2**) The two isomers were isolated by column chromatography and their structure confirmed by IR, $^1$HNMR and $^{13}$CNMR spectroscopies (Z/E ratio = 3.1:1). This result confirmed the possibility to carry out the auto-tandem catalysis process leading to oxazolidinones **3** in an ionic liquid (IL) as unconventional solvent.



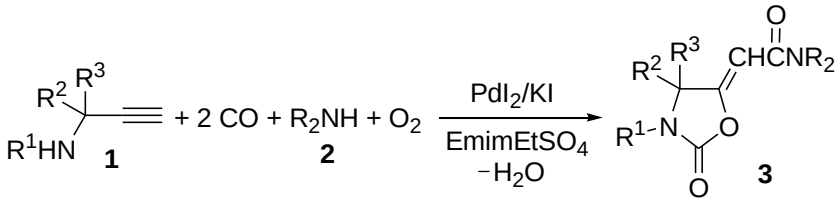

Starting from this encouraging initial result, we made a screening of the reaction parameters by changing time gas pressure, substrate concentration, catalyst amount, solvent/dehydrating agent ratio, temperature and reaction time. We observed that either decreasing time or increasing substrate concentration the yield of desired product decreased We also verified how the amount of KI influences the catalyst activity (Table 3.1, entries 5-6) and the best result was obtained when the amount of KI was equal to 10 times the amount of $PdI_2$ . Decreasing the temperature, we obtained the desired products in a lower yield (Table 3.1, entry 2.) When the reaction time was increased to 24 h reaction was carried out with a reaction conditions no. 6, complete substrate conversion was achieved and the yield was good. (Table 3.1, entry 6); on the other hand, unsatisfactory results were obtained with higher time. Increasing the reaction time from 24 h to 48 h the yield decreased suggesting that product is unstable at higher temperature formore time. (Table 3.1, entry 8). We accordingly verified the possibility to recycle the catalyst/solvent system. Thus, the residue obtained after product extraction (still containing the catalyst dissolved in the IL), after drying under vacuum (to eliminate the residual diethyl ether), was used again by adding to it fresh propargylamine **1a** and morpholine **2a** (1:5 ratio). After stirring at 100 °C for 24 h, **3aa** was obtained again as a 3.2:1 Z/E mixture in 71% total isolated yield (Table 3.2, entry 1, run 2), after extraction with diethyl ether. The recycling procedure was then successfully repeated up to 6 times

**Table-3.1**

| n° | Ionic Liquid | $PdI_2$/KI/1a/2/H2O molar ratio | PCO | Pair | T(°C) | t(h) | conv (%) | Yield %(E+Z) |
|---|---|---|---|---|---|---|---|---|
| 1 | $BmimBF_4$ | 1:10:50:250:250 | 16 | 4 | 80 | 15 | 8 | - |
| 2 | $EmimEtSO_4$ | 1:10:50:250:250 | 16 | 4 | 80 | 8 | 40 | 32 |
| 3 | $EmimEtSO_4$ | 1:10:100:250:250 | 16 | 4 | 100 | 12 | 51 | 38 |
| 4 | $EmimEtSO_4$ | 1:10:100:250:250 | 16 | 4 | 100 | 15 | 60 | 43 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 5 | $EmimEtSO_4$ | 1:5:50:250:250 | 16 | 4 | 100 | 18 | 80 | 49 |
| **6** | $EmimEtSO_4$ | **1:10:50:250:250** | **16** | **4** | **100** | **24** | **100** | **71** |
| 7 | $EmimEtSO_4$ | 1:10:50:250:250 | 32 | 8 | 100 | 24 | 100 | 71 |
| 8 | $EmimEtSO_4$ | 1:10:50:250:250 | 16 | 4 | 100 | 48 | 100 | 63 |
| 9 | $EmimEtSO_4$ | 1:10:50:500:500 | 16 | 4 | 100 | 24 | 100 | 62 |
| 10 | $EmimEtSO_4$ | 1:10:50:300:1500 | 16 | 4 | 100 | 24 | 100 | 59 |

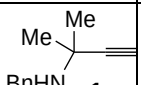
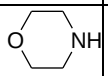
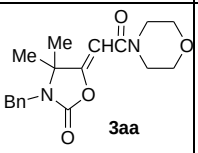
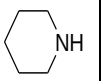
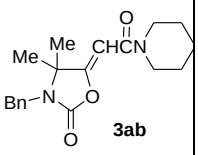
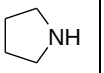
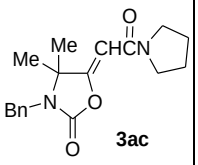
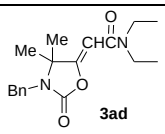
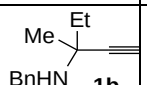
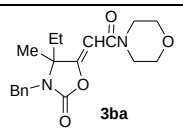
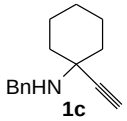
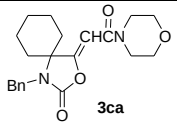
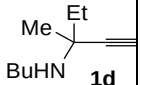
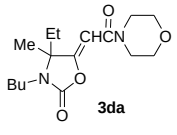
### 3.3.2 Generalization of the process

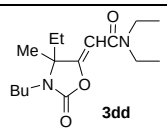
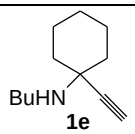
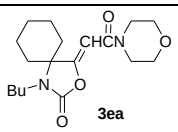



**(3.1)**

In order to assess the generality of the method, the reaction was then performed using different combinations of propargylic amines **1a-e** and secondary amines **2a-d**; the results obtained are shown in Table 3.2, entries 1-9. As can be seen from Table 3.2, the method could be successfully applied to propargylic amines bearing various alkyl groups α to the triple bond, including simple alkyl groups [such as methyl and ethyl (**1a**, **1b**, and **1d**) and a cyclic chain[such as $–(CH_2)_4$, (**1c**)], different groups on nitrogen [such as benzyl (**1a-c**) and butyl (**1e**, **1f**)], and different nucleophilic secondary amines, both cyclic [as in the case of morpholine (**2a**), piperidine (**2b**), and pyrrolidine (**2c**)] and acyclic (as in the case of diethylamine, **2d**). In all cases, good yields of the corresponding 2-(2-oxooxazolidin-5-ylidene)acetamides **3** were obtained (69-76%), and the $PdI_2$/KI/$EmimEtSO_4$ system could be conveniently recycled up to 6 times without loss of activity.

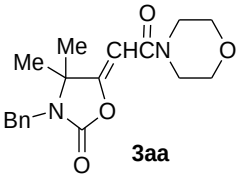
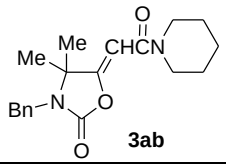
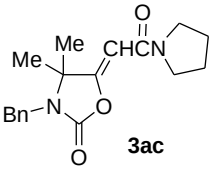
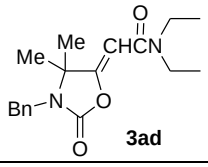
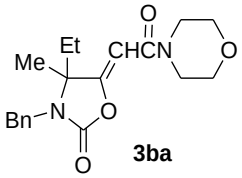
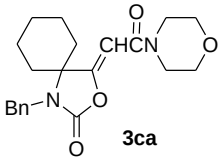
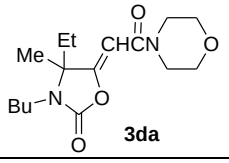
**Table 3.2.** Synthesis of 2-(2-oxooxazolidin-5-ylidene)acetamides (3) by $PdI_2$/KI-catalyzed oxidative carbonylation of propargylic amines (1) with CO, $O_2$, and secondary amines (2) in $EmimEtSO_4$ and recycling experiments[a] Conversion of 1 was quantitative in all cases

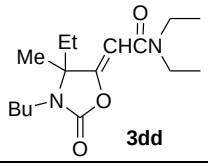
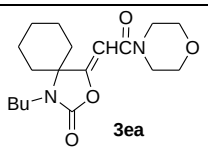
| n[0] | 1 | 2 | 3 | Yield of **3** (%)[b] (Z/E ratio)[c] | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Run 1 | Run 2 | Run 3 | Run 4 | Run 5 | Run 6 | Run 7[d] |
| 1 |  **1a** |  **2a** |  **3aa** | 70 (3.1) | 71 (3.2) | 74 (2.9) | 74 (3.4) | 71 (3.2) | 70 (3.4) | 70 (3.2) |
| 2 | **1a** |  **2b** |  **3ab** | 74 (3.1) | 75 (3.4) | 73 (3.2) | 75 (3.0) | 74 (3.3) | 73 (3.2) | 74 (3.3) |
| 3 | **1a** |  **2c** |  **3ac** | 75 (4.0) | 75 (3.9) | 74 (3.9) | 76 (4.0) | 76 (3.9) | 75 (3.7) | 75 (3.8) |
| 4 | **1a** | $Et_2NH$ **2d** |  **3ad** | 70 (3.2) | 71 (2.9) | 71 (3.1) | 70 (3.4) | 70 (3.4) | 69 (3.0) | 71 (3.1) |
| 5 |  **1b** | **2a** |  **3ba** | 75 (2.9) | 75 (3.4) | 74 (3.3) | 75 (3.0) | 76 (3.1) | 74 (3.1) | 74 (3.2) |
| 6 |  **1c** | **2a** |  **3ca** | 72 (6.1) | 74 (7.2) | 72 (6.9) | 74 (6.4) | 73 (7.1) | 75 (7.3) | 74 (7.3) |
| 7 |  **1d** | **2a** |  **3da** | 69 (5.3) | 70 (5.4) | 70 (6.0) | 71 (5.5) | 72 (5.0) | 69 (5.9) | 72 (5.6) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 8 | **1d** | **2d** |  **3dd** | 74 (6.4) e | 76 (5.9) e | 76 (6.0) e | 75 (6.3) e | 74 (6.2) e | 75 (6.1) e | 74 (6.0) e |
| 9 |  **1e** | **2a** |  **3ea** | 69 (4.3) | 72 (4.5) | 71 (4.5) | 71 (4.9) | 72 (4.5) | 72 (4.5) | 70 (4.8) |

[a] All reactions were carried out in the presence of $PdI_2$, KI, and $H_2O$ at 100 °C under 20 atm (at 25 °C) of a 4:1 mixture CO/air, in $EmimEtSO_4$ for 24 h with a substrate concentration of 0.5 mmol of **1** per mL of ionic liquid. The $H_2O$:**2**:**1**:KI:$PdI_2$ molar ratio was 250:250:50:10:1.

**Table-3.3** Isolated yields of 2-Oxazolidinones with each E and Z isomer

| n0 | Product 3 | E-Isomer(%) | Z-Isomer(%) | Total % Yield(E+Z) |
|---|---|---|---|---|
| 1 |  **3aa** | 17 | 53 | 70 |
| 2 |  **3ab** | 18 | 56 | 74 |
| 3 |  **3ac** | 15 | 60 | 75 |
| 4 |  **3ad** | 17 | 53 | 70 |
| 5 |  **3ba** | 19 | 56 | 75 |
| 6 |  **3ca** | 10 | 61 | 71 |
| 7 |  **3da** | 11 | 57 | 68 |

| | | | | |
|---|---|---|---|---|
| 8 |  **3dd** | 10 | 13 | 23 |
| 9 |  **3ea** | 13 | 56 | 69 |

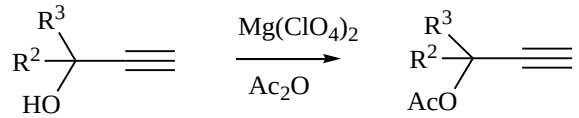
Note: Product **3dd**-Z could not be isolated at the pure state by column chromatography, and the GLC analysis evidenced a purity of ca. 60%. The GLC-MS analysis was compatible with the proposed structure and $^{1}$H NMR spectrum of the crude product evidenced a peak at 5.19, compatible with a Z stereochemistry

### 3.4. General Experimental Section

General Information:- Chemicals were purchased from Sigma-Aldrich Italia (Milano, Italy) and were used as such without further purification. Melting points were taken on a Reichert Thermovar apparatus and are uncorrected. $^{1}$H-NMR and $^{13}$C-NMR spectra were recorded at 25 °C in $CDCl_3$ solutions with a Bruker DPX Avance 300 spectrometer (Bruker Italia, Milano, Italy) operating at 300 MHz and 75 MHz, respectively, with $Me_4Si$ as internal standard. IR spectra were taken with a JASCO FT-IR 4200 spectrometer (Jasco Europe s.r.l., Cremella, Lecco, Italy). Mass spectra were obtained using a Shimadzu QP-2010 GC-MS apparatus (Shimadzu Italia, Milano, Italy) at 70 eV ionization voltage. Microanalyses were carried out with a Thermo-Fischer Elemental Analyzer Flash 2000 (Fischer Scientific Italia, Rodani, Milano, Italy). All reactions were analyzed by TLC (Merck Italy, Vimodrone, Milano, Italy) on silica gel 60 F254 (Merck Italy, Vimodrone, Milano, Italy) or on neutral alumina (Merck) and by GLC using a Shimadzu GC-2010 gas chromatograph (Shimadzu Italia, Milano, Italy) and capillary columns with polymethylsilicone + 5% polyphenylsilicone as the stationary phase (HP-5). Column chromatography was performed on neutral alumina 90 (Merck, 70–230 mesh). Evaporation refers to the removal of solvent under reduced pressure.

#### 3.4.1. Preparation of Substrates

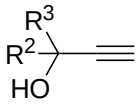
All starting 2-alkynylamines **1a-g** were prepared by amination of the corresponding 2-alkyn-1-ol acetates,obtained in their turn by acetylation of 2-alkyn-1-ols, according to the following Scheme 2.




**(3.3)**

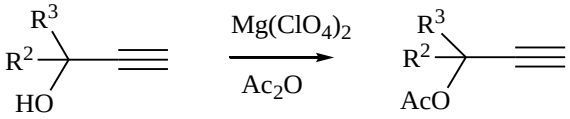
**Scheme 2**

**a) Preparation of 2-alkyn-1-ols.**



2-Methylbut-3-yn-2-ol (R2 = R3 = Me), 3-methylpent-1-yn-3-ol(R2 =Et, R3 = Me), 1-ethynylcyclohexanol [R2-R3 = _(CH2)5_], and 2-phenylbut-3-yn-2-ol (R2 = Me, R3= Ph) were commercially available and were used without further purification.

**b) Preparation of 2-alkyn-1-ol Acetates.**



**(3.3)**

Acetic acid 1-methyl-1-phenylprop-2-ynyl ester was prepared according to a literature procedure.[2] The method of Bartoli and co-workers[40] was used for acetylation of 2-methylbut-3-yn-2-ol (R2 = R3 = Me), 3-methylpent-1-yn-3-ol (R2 = Et, R3 = Me), 1-ethynylcyclohexanol [R2-R3 = _(CH2)5_], and 4-ethylhex-1-yn-3-ol (R2 = CHEt2, R3 = H). Thus, the 2-yn-1-ol (50.0 mmol in the case of 2-methylbut-3-yn-2-ol, 3-methylpent-1-yn-3-ol, and 1-ethynylcyclohexanol; 83.2 mmol in the case of 4-ethylhex-1-yn-3-ol) was slowly added (dropwise, when liquid, or in small portions, when solid) to a solution of Mg(ClO4)2 (112.0 mg, 0.50 mmol, in the case of 2-methylbut-3-yn-2-ol, 3-methylpent-1-yn-3-ol, and 1-ethynylcyclohexanol; 92.8 mg, 0.42 mmol in the case of 4-ethylhex-1-yn-3-ol) in Ac2O (5.2 mL in the case of 2-methylbut-3-yn-2-ol, 3-methylpent-1-yn-3-ol, and 1-ethynylcyclohexanol; 4.3 mL in the case of 4-ethylhex-1-yn-3-ol) at room temperature with stirring. After additional stirring for 1 h (in the case of 2-methylbut-3-yn-2-ol, 3-methylpent-1-yn-3-ol, and 1-ethynylcyclohexanol) or 3 h (in the case of 4-ethylhex-1-yn-3-ol) the mixture was diluted with a 0.1 M solution of NaHCO3, and extracted several times with Et2O. After drying over Na2SO4 and filtration, the solvent was evaporated to give the product,which was used as such for the next step. Acetic acid 1,1-dimethylprop-2-ynyl ester was a colorless oil (6.18 g, 98%); acetic acid 1-ethyl-1-methylprop-2-ynyl ester was a colorless oil (6.66 g, 95%); acetic acid 1-ethynylcyclohexyl ester was a colorless oil (7.89 g, 95%); acetic acid 1-(1- ethylpropyl)prop-2-ynyl ester was a pale yellow oil (13.0 g, 93%).

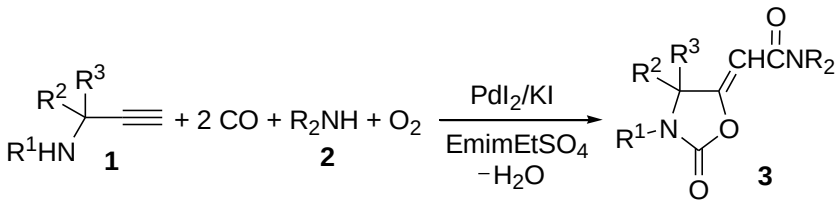
**c) Preparation of 2-alkynylamines (1a-e)**


**(3.4)**

**(1)**

The method of Murahashi and co-workers [41] was employed for amination of 2-alkyn-1-ol acetates. A solution of the 2-alkyn-1-ol acetate (10 mmol), the primary amine $R_1NH_2$ (R1 = Bn or Bu, 20 mmol) and CuCl (50.0 mg, 0.5 mmol) in anhydrous THF (20.0 mL) was allowed to reflux with stirring for 2 h. After cooling, the mixture was acidified with 2 N HCl and phases were separated. The aqueous phase was cautiously basified with 2 N NaOH and extracted with CH2Cl2 (4×25 mL). After drying over Na2SO4, the solvent was evaporated and the crude product was purified by column chromatography on silica gel using $CH_2Cl_2$ as the eluent.The yields obtained in each case are given below in Characterization Data for Substrates.

### 3.4.2 General Procedure for the $PdI_2$/KI-catalyzed oxidative carbonylation of propargylic amines (1) with CO, $O_2$, and secondary amines (2) in $EmimEtSO_4$ and recycling experiments




**(3.1)**

A 35 mL stainless steel autoclave was charged with $PdI_2$ (8.3 mg, 0.023 mmol), KI (38.3 mg, 0.23 mmol), the starting propargyl amine **1** (**1a**, 199.0 mg; **1b**, 215.0 mg; **1c**, 245.0 mg; **1d**, 176.0 mg; **1e**, 206.0 mg; 1.15 mmol) and the amine **2** (**2a**, 501.0 mg; **2b**, 490.0 mg; **2c**, 409.0 mg; **2d**, 420.5 mg; 5.75 mmol) in $EmimEtSO_4$ (2.3 mL). Water (103.5□L , 5.75 mmol) was then added and the autoclave was sealed, and pressurized at 20 atm (16 atm CO and 4 atm Air). After stirring at 100 °C for 24 h, the autoclave was cooled and degassed. The mixture was then extracted with $Et_2O$ (6x4 mL), and the residue (still containing the catalyst and water dissolved in the ionic liquid) was used as such for the next recycle (see below). The collected ethereal phases were concentrated and the products purified by column chromatography on neutral alumina using as the eluent hexane:AcOEt from 95:5 to 6:4 (the E isomers were eluted first in all cases).

### 3.4.5. Preparation of Ionic Liquids

**1) $BmimBF_4$**

$NaBF_4$ (5.7 g, 51.9 mmol) was added to 9.0 g (51.8 mmol) of BmimCl maintained at 80°C under vigorous stirring. The mixture was allowed to stir at 80°C for 8 h and then at room temperature for 15 h. $CH_2Cl_2$ (ca. 30 mL) was added with stirring, and the solution was cooled to -20°C and allowed to stand at this temperature overnight. The precipitate (NaCl) was removed by filtration, and the solvent was removed under vacuum to give pure $BmimBF_4$, which was stored under nitrogen at room temperature (9.3 g, 80%).

**2) Preparation of $EmimEtSO_4$**

Diethyl sulfate (29 mL, 0.221 mol) was added dropwise to a solution of 1-methylimidazole (18.146 g, 0.221 mol) in toluene (100 mL) cooled in an ice-bath under dinitrogen at a rate to maintain the reaction temperature below 40 °C. CAUTION! The reaction is highly exothermic. Formation of the IL product was immediate and caused the initially clear solution to become opaque, followed by biphasic separation of the toluene solution and formation of a denser IL phase. After addition of the diethyl sulfate, the reaction mixture was stirred at room temperature for 1 h. The upper, organic phase was decanted and the lower, IL phase was washed with toluene (50 mL), dried with heating at 75 °C under reduced pressure to remove residual organic solvents, and finally in vacuo to yield the resulting 1-ethyl-3-methyl-1H-imidazol-3-ium ethyl sulfate IL as a colorless hydroscopic liquid (48.2 g, 92%), free from starting materials.

**Recyclic procedure.**

After removal of $Et_2O$ under vacuum, the residue obtained as described above, still containing the catalyst dissolved in the ionic liquid, was transferred into the autoclave. The starting material **1** (1.15 mmol), the amine **2** (5.75 mmol) and $H_2O$ (103.5 µL , 5.75 mmol) was added, and then the same procedure described above was followed.

**3.5.Conclusion**

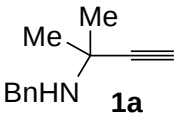
In general we can say that we have given a convenient carbonylative approach to 2-oxazolidinone derivatives carried out in an ionic liquid as the solvent (1-ethyl-3-methyl-1H-imidazol-3-ium ethyl sulfate, $EmimEtSO_4$) is presented. It is based on the sequential concatenation of two catalytic cycles, both catalyzed by the same metal species (auto-tandem catalysis): the first cycle corresponds to the oxidative monoaminocarbonylation of the triple bond of propargylic amines to give the corresponding 2-alkynamide intermediates, the second one to the cyclocarbonylation of the latter to yield 2-(2-oxooxazolidin-5-ylidene)acetamides. Reactions are carried out using a simple catalytic system consisting of $PdI_2$ in conjunction with an excess of KI, and the catalyst/solvent system could be recycled several times without appreciable loss of activity after extraction of the organic product with $Et_2O$.

### 3.6. Characterization Data

**A] EmimEtSO$_4$**

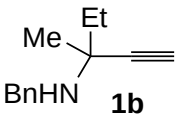
1H NMR, dH (360 MHz, $CDCl_3$) 1.279 (3H, t, $NCH_2CH_3$), 1.566 (3H, t, $OCH_2CH_3$), 4.028 (3H, s, $NCH_3$), 4.067 (2H, q, $OCH_2$), 4.333 (2H, q, $NCH_2$), 7.617 (2H, s, C(4,5)H), 9.441 (1H, s, C(2)H). 13C NMR, dC (360 MHz, $CDCl_3$) 13.7 ($NCH_2CH_3$), 14.0 ($OCH_2CH_3$), 34.6 ($_{NCH3)}$, 43.4 ($NCH_2CH_3$), 61.5 ($OCH_2CH_3$), 120.9, 122.4 (C(5)H, C(4)H), 135.0 (C(2)H). IR (liquid film) vmax/cm21; 3149, 3106, 2933, 2861, 1678, 1574, 1467, 1380, 1339, 1227, 1170, 1060, 1019, 916, 852, 740.

**B] Starting Materials 1(a-e ).**



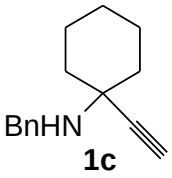

**1a**

Benzyl-(1,1-dimethylprop-2-ynyl)amine (1a). Yield: 1.07 g, starting from 1.26 g of acetic acid 1,1-dimethylprop-2-ynyl ester (62%). Yellow solid, 42-43 °C. IR (KBr):  = 3302 (m), 2078 (w), 1458 (m), 1189 (m), 1066 (w), 791 (m), 754 (s), 705 (s) cm-1 ; 1 H NMR (300 MHz, $CDCl_3$): = 7.38-7.19 (m, 5 H, Ph), 3.86 (s, 2 H, $CH_2Ph$), 2.34 (s, 1 H, CH), 1.41 (s, 6 H, 2 Me), 1.33 (s, br, 1 H, NH); 13C NMR (75 MHz, $CDCl_3$):δ = 140.9, 128.4, 126.9, 89.2, 69.8, 50.1, 49.0, 29.7; GC-MS: m/z = 173 (M+ , 2), 159 (28), 158 (100), 106 (14), 104 (9), 92 (31), 91 (79), 89 (7), 79 (27), 77 (21), 71 (12); anal. calcd for $C_{12}H_{15}N$ (173.25): C, 83.19; H, 8.73; N, 8.08; found C, 83.23; H, 8.71; N, 8.06.



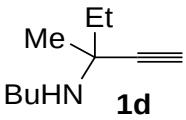

**1b**

Benzyl-(1-ethyl-1-methylprop-2-ynyl)amine (1b). Yield: 1.18 g, starting from 1.40 g of acetic acid 1-ethyl-1-methylprop-2-ynyl ester (63%). Yellow oil. IR (film):  = 3299 (s), 1496 (w), 1454 (s), 1371 (m), 1177 (m), 1153 (m), 1029 (w), 736 (m), 702 (m), 636 (s) cm-1 ; 1 H NMR (300 MHz, $CDCl_3$): = 7.39-7.18 (m, 5 H, Ph), 3.87 (distorted d, J = 11.7, 1 H, CHHPh), 3.82 (distorted d, J = 11.7, 1 H, CHHPh), 2.35 (s, 1 H, CH), 1.73-1.58 (m, 2 H, $CH_2CH_3$), 1.35 (s, 3 H, $CH_3CCH_2CH_3$), 1.29 (s, br, 1 H, NH), 1.02 (t, J = 7.3, 3 H, $CH_2CH_3$); 13C NMR (75 MHz, $CDCl_3$):δ = 141.1, 128.5, 128.4, 126.9, 88.4, 70.8, 54.1, 48.6, 34.7, 26.5, 8.6; GC-MS: m/z = 187 (M+ , 2), 145 (19), 144 (99), 115 (4), 106 (5), 92 (13), 91 (100), 65 (15); anal. calcd for $C_{13}H_{17}N$ (187.28): C, 83.37; H, 9.15; N, 7.48; found C, 83.42; H, 9.13; N, 7.45.



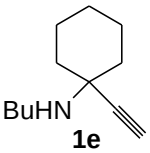

**1c**

Benzyl-(1-ethynylcyclohexyl)amine (1c). Yield: 1.21 g, starting from 1.66 g of acetic acid 1-ethynylcyclohexyl ester (57%). Yellow oil. IR (film):  = 3297 (s), 1604 (w), 1494 (w), 1453 (s), 1349 (w), 1277 (m), 1118 (m), 940 (m), 741 (s), 702 (s) cm-1 ; 1 H NMR (300 MHz, $CDCl_3$): = 7.39-7.17 (m, 5 H, Ph), 3.88 (s, 2 H, $CH_2Ph$), 2.39 (s, 1 H, CH), 1.94-1.13 [m, 11 H, $(CH_2)5$ + NH]; 13C NMR (75 MHz, $CDCl_3$): δ= 141.0, 128.44, 128.37, 126.8, 88.1, 71.9, 54.6, 47.8, 38.0, 25.8, 22.7; GC-MS: m/z = 213 (M+ , 13), 212 (21), 198 (20), 184 (16), 171 (12), 170 (74), 156 (16), 106 (11), 92 (11), 91 (100); anal. calcd for $C_{15}H_{19}N$ (213.32): C, 84.46; H, 8.98; N, 6.57; found C, 84.50; H, 8.95; N, 6.55.




**1d**

Butyl-(1-ethyl-1-methylprop-2-ynyl)amine (1d). Yield: 0.92 g, starting from 1.40 g of acetic acid 1-ethyl-1-methylprop-2-ynyl ester (60%). Yellow oil. IR (film):  = 3308 (s), 1460 (s), 1378 (m), 1288 (m), 1156 (m), 890 (w), 792 (w), 736 (m), 634 (s) cm-1 ; 1 H NMR (300 MHz, $CDCl_3$): = 2.76-2.60 (m, 2 H, $NCH_2$), 2.27 (s, 1 H, CH), 1.70-1.31 (m, 7 H, $CH_3CCH_2CH_3$ + $CH_2CH_2CH_3$ + NH), 1.29 (s, 3 H, $CH_3CCH_2CH_3$), 1.00 (t, J = 7.4, 3 H, $CH_2CH_3$), 0.93 (t, J = 7.1, 3 H, $CH_2CH_3$); 13C NMR (75 MHz, $CDCl_3$):δ = 88.3, 70.5, 53.6, 43.5, 34.6, 32.7, 26.3, 20.6, 14.0, 8.7; GC-MS: m/z = 153 (M+ , < 0.5), 138 (31), 125 (70), 124 (99), 110 (17), 94 (18), 82 (46), 80 (28), 79 (27), 68 (100), 57 (23), 53 (35); anal. calcd for $C_{10}H_{19}N$ (153.26): C, 78.37; H, 12.50; N, 9.14; found C, 78.42; H, 12.46; N, 9.12

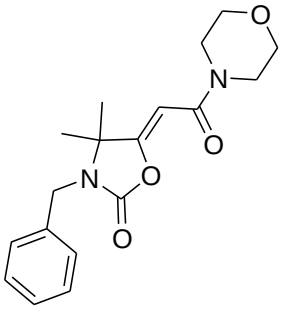



**1e**

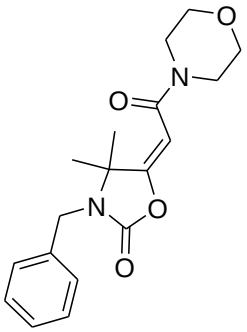
**Butyl-(1-ethynylcyclohexyl)amine** (**1e**). Yield: 0.98 g, starting from 1.66 g of 2-acetic acid 1-ethynylcyclohexyl ester (55%). Yellow solid, mp 37-38 °C. IR (KBr):  = 3295 (m), 1479 (m), 1450 (m), 1347 (w), 1282 (w), 1261 (w), 1128 (s), 938 (m), 818 (m), 780 (w) cm-1 ; 1 H NMR (300 MHz, $CDCl_3$): = 2.72 (t, J = 7.1, 2 H, $NCH_2$), 2.33 (s, 1 H, CH), 1.90-1.07 [m, 15 H,

($CH_2$)5 + $CH_2CH_2CH_3$ + NH], 0.93 (t, J = 7.1, 3 H, $CH_3$); 13C NMR (75 MHz, $CDCl_3$): δ= 88.1, 71.7, 54.4, 42.8, 38.0, 32.8, 25.9, 22.8, 20.6, 14.0; GC-MS: m/z = 179 (M+ , 8), 164 (23), 150 (21), 137 (18), 136 (100), 122 (14), 108 (16), 94 (15), 80 (24), 79 (12); anal. calcd for $C_{12}H_{21}N$ (179.30): C, 80.38; H, 11.81; N, 7.81; found C, 80.33; H, 11.84; N, 7.83.

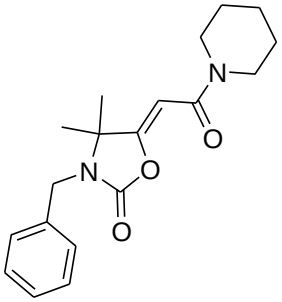
**[B]Characterization of Oxazolidinones ( 3aa-*Z*, 3aa-*E*, 3ab-*Z*, 3ab-*E*, 3ad-*Z*, 3ad-*E*, 3ba-*Z*, 3ba-*E*, 3ca-*Z*, 3ca-*E*, 3da-*Z*, 3da-*E*, 3ea-*Z*, 3ea-*E*,)**



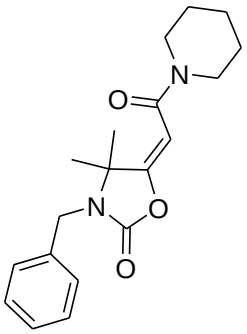
(Z)-3-Benzyl-4,4-dimethyl-5-(2-morpholin-4-yl-2-oxoethylidene)-oxazolidin-2-one (**3aa-Z**).
Yield: 957.5 mg, starting from 730.0 mg of 1a (69%) (Table 1, entry 1). Yellow solid, mp 161-162 °C. IR (KBr): = 1772 (s), 1680 (s), 1607 (m), 1456 (m), 1409 (m), 1360 (m), 1271 (m), 1232 (m), 1110 (m), 1031 (s), 955 (m), 812 (w), 756 (w), 710 (m) cm-1 ; 1 H NMR (500 MHz, $CDCl_3$):δ = 7.36-7.25 (m, 5 H, Ph), 5.19 (s, 1 H, =CH), 4.46 (s, 2 H, $CH_2Ph$), 3.76-3.61 (m, 6 H, $CH_2OCH_2$ + CHHNCHH), 3.52-3.44 (m, 2 H, CHHNCHH), 1.35 (s, 6 H, 2 Me); 13C NMR (126 MHz, $CDCl_3$):δ = 163.2, 159.2, 153.5, 137.0, 128.7, 127.9, 127.8, 93.3, 66.8, 66.6, 62.2, 47.2, 44.2, 42.0, 27.3. GCMS: m/z = 330 (M+ , 5), 315 (4), 244 (6), 197 (4), 92 (8), 91 (100), 86 (11), 65 (5); anal. calcd for $C_{18}H_{22}N_2O_4$ (330.38) C, 65.44; H, 6.71; N, 8.48; found C, 65.36; H, 6.70; N, 8.49.



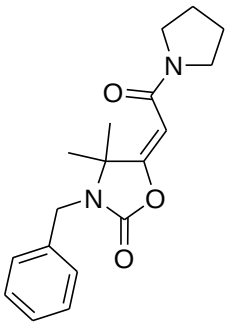
(E)-3-Benzyl-4,4-dimethyl-5-(2-morpholin-4-yl-2-oxoethylidene)-oxazolidin-2-one (**3aa-E**).
Yield: 347.0 mg, starting from 730.0 mg of 1a (25%) (Table 1, entry 1). Yellow solid, mp 124-125 °C. IR (KBr):  = 1768 (s), 1669 (s), 1619 (m), 1439 (m), 1409 (s), 1366 (m), 1253 (w), 1189 (w), S 8 1033 (s), 956 (w), 705 (m) cm-1; 1 H NMR (300 MHz, $CDCl_3$): δ= 7.37-7.23 (m, 5 H, Ph), 5.86 (s, 1 H, =CH), 4.46 (s, 2 H, $CH_2Ph$), 3.68-3.44 (m, 8 H, $NCH_2CH_2OCH_2CH_2$), 1.59 (s, 6 H, 2 Me); 13C NMR (75 MHz, $CDCl_3$): = 165.7, 163.9, 153.5, 137.4, 128.8, 127.86, 127.84, 95.4, 66.8 (br), 64.1, 47.1 (br), 44.0, 42.3 (br), 24.4; GC-MS: m/z = 330 (M+ , 7), 315 (5), 244 (6), 197 (4), 92 (8), 91 (100), 86 (13); anal. calcd for $C_{18}H_{22}N_2O_4$ (330.38): C, 65.44; H, 6.71; N, 8.48; found C, 65.51; H, 6.69; N, 8.46



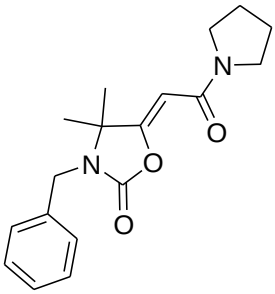

(Z)-3-Benzyl-4,4-dimethyl-5-(2-oxo-2-piperidin-1-ylethylidene)-oxazolidin-2-one (**3ab-Z**).
Yield: 800.0 mg, starting from 725.0 mg of 1a (58%) (Table 1, entry 7). Yellow solid, mp 137-138 °C. IR (KBr):  = 1770 (s), 1682 (s), 1606 (m), 1446 (m), 1404 (m), 1310 (w), 1213 (m), 1045 (m), 954 (m), 805 (w), 705 (m) cm-1 ; 1 H NMR (300 MHz, $CDCl_3$): δ= 7.35-7.25 (m, 5 H, Ph), 5.18 (s, 1 H, =CH), 4.46 (s, 2 H, $CH_2Ph$), 3.63-3.55 (m, 2 H, CHHNCHH), 3.44-3.36 (m, 2 H, CHHNCHH), 1.70-1.50 (m, 6 H, $NCH_2CH_2CH_2CH_2$), 1.35 (s, 6 H, 2 $CH_3$); 13C NMR (75 MHz, $CDCl_3$):δ = 162.9, 157.9, 153.8, 137.1, 128.7, 127.9, 127.8, 94.3, 62.0, 47.8, 44.2, 42.5, 27.4, 26.5, 25.4, 24.5; GC-MS: m/z = 328 (M+ , 14), 313 (3), 193 (4), 154 (8), 147 (5), 112 (9), 92 (8), 91 (100), 84 (68), 83 (6); anal. calcd for $C_{19}H_{24}N_2O_3$ (328.41): C, 69.49; H, 7.37; N, 8.53; found C, 69.56; H, 7.38; N, 8.55.



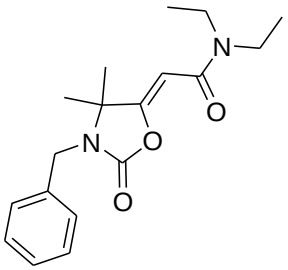
(E)-3-Benzyl-4,4-dimethyl-5-(2-oxo-2-piperidin-1-ylethylidene)-oxazolidin-2-one (**3ab**-**E**).
Yield: 303.5 mg, starting from 725.0 mg of 1a (22%) (Table 1, entry 7). Yellow solid, mp 119-120 °C. IR (KBr):  = 1775 (s), 1669 (m), 1617 (m), 1440 (m), 1403 (m), 1309 (m), 1262 (m), 1067 (s), 1010 (m), 840 (m), 743 (m), 703 (m) cm-1 ; 1 H NMR (500 MHz, $CDCl_3$): δ= 7.37-7.24 (m, 5 H, Ph), 5.89 (s, 1 H, =CH), 4.45 (s, 2 H, $CH_2Ph$), 3.56-3.50 (m, 2 H, CHHNCHH), 3.46-3.40 (m, 2 H, CHHNCHH), 1.67-1.49 (m, 6 H, $NCH_2CH_2CH_2CH_2$), 1.57 (s, 6 H, 2 $CH_3$); 13C NMR (126 MHz, $CDCl_3$):δ = 163.8, 163.4, 153.8, 137.4, 128.7, 127.8, 127.7, 96.7, 63.8, 47.7, 43.7, 42.8, 26.6, 25.6, 24.5; GC-MS: m/z = 328 (M+ , 18), 313 (3), 180 (4), 154 (10), 147 (5), 112 (11), 92 (8), 91 (100), 85 (6), 84 (72); anal. calcd for $C_{19}H_{24}N_2O_3$ (328.41): C, 69.49; H, 7.37; N, 8.53; found C, 69.55; H, 7.38; N, 8.53.



(E)-3-Benzyl-4,4-dimethyl-5-(2-oxo-2-pyrrolidin-1-ylethylidene)-oxazolidin-2-one (**3ac**-E).
White solid, mp = 124-125 °C. IR (KBr): ν = 1779 (s), 1664 (m), 1611 (m), 1404 (m), 1346 (w), 1194 (w), 709 (w) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.38-7.26 (m, 5 H, aromatic), 5.83 (s, 1 H, =CH), 4.47 (s, 2 H, $CH_2Ph$), 3.51-3.40 (m, 4 H, pyrrolidin ring), 2.02-1.82 (m, 4 H, pyrrolidin ring), 1.64 (s, 6 H, 2 Me); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 165.4, 162.9, 153.6, 137.3, 128.7, 127.8, 96.8, 64.4, 47.2, 45.7, 43.8, 26.2, 24.4, 23.9; GC-MS m/z = 314 (11) [$M^+$], 299 (5), 286 (2), 255 (1), 244 (2), 223 (13), 216 (2), 181 (2), 166 (4), 146 (2), 140 (8), 132 (2), 112 (2), 98 (9), 91 (100); anal. calcd for $C_{18}H_{22}N_2O_3$ (314.38): C, 68.77; H, 7.05; N, 8.91; found C, 68.75; H, 7.04; N, 8.89.

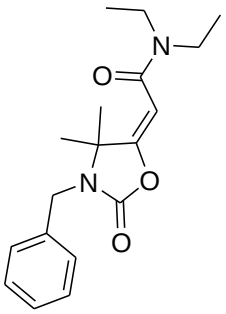


(Z)-3-Benzyl-4,4-dimethyl-5-(2-oxo-2-pyrrolidin-1-ylethylidene)-oxazolidin-2-one (**3ac**-Z). Yellow solid, mp = 105-106 °C. IR (KBr): ν = 1780 (s), 1685 (s), 1616 (m), 1438 (m), 1401 (m), 1225 (w), 1036 (m), 754 (w) $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$): δ = 7.48-7.22 (m, 5 H, aromatic), 5.21 (s, 1 H, =CH), 4.48 (s, 2 H, $CH_2Ph$), 3.59-3.43 (m, 4 H, pyrrolidin ring), 2.03-1.84 (m, 4 H, pyrrolidin ring), 1.35 (s, 6 H, 2 Me); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 162.7, 160.5, 153.8, 137.1, 128.8, 128.0, 127.8, 94.6, 62.4, 47.1, 45.7, 44.2, 27.5, 25.9, 24.4; GC-MS m/z = 314 (8) [$M^+$], 299 (4), 286 (1), 255 (1), 243 (3), 223 (11), 216 (1), 181 (2), 166 (2), 147 (4), 140 (6), 132 (1), 112 (2), 98 (7), 91 (100); anal. calcd for $C_{18}H_{22}N_2O_3$ (314.38): C, 68.77; H, 7.05; N, 8.91; found C, 68.78; H, 7.03; N, 8.92.

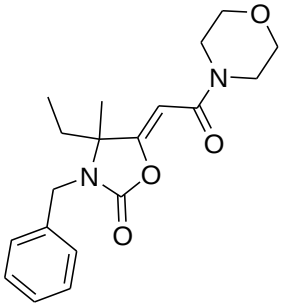


(Z)-2-(3-Benzyl-4,4-dimethyl-2-oxo-2-oxazolidin-5-ylidene)-N,N-diethylacetamide (**3ad**-Z).Yield: 785.0 mg, starting from 725.0 mg of 1a (59%) (Table 1, entry 11). Yellow solid, mp 103-104 °C. IR (KBr):  = 1774 (s), 1678 (s), 1613 (m), 1448 (m), 1413 (m), 1267 (m), 1205 (m), 1045 (s), 949 (m), 815 (m), 754 (m), 699 (m) cm-1 ; 1 H NMR (300 MHz, $CDCl_3$): = 7.36-7.26 (m, 5 H, Ph), 5.23 (s, 1 H, =CH), 4.47 (s, 2 H, $CH_2Ph$), 3.43 (q, J = 7.1, 2 H, $CH_2NCH_2$), 3.33 (q, J = 7.1, 2 H, $CH_2NCH_2$), 1.34 (s, 6 H, $CH_3CCH_3$), 1.18 (t, J = 7.1, 3 H, $CH_3CH_2NCH_2CH_3$), 1.15 (t, J = 7.1, 3 H, $CH_3CH2NCH_2CH_3$); 13C NMR (75 MHz, $CDCl_3$):δ = 163.6, 159.6, 153.9, 137.2, 128.7, 127.9, 127.8, 94.0, 62.1, 44.1, 42.8, 39.8, 27.4, 14.5, 13.1; GC-MS: m/z = 316 (M+ , 9), 244 (5), 183 (6), 142 (4), 112 (4), 92 (8), 91 (100), 73 (5), 72 (30);

anal. calcd for $C_{18}H_{24}N_2O_3$ (316.39): C, 68.33; H, 7.65; N, 8.85; found C, 68.44; H, 7.64; N, 8.86.

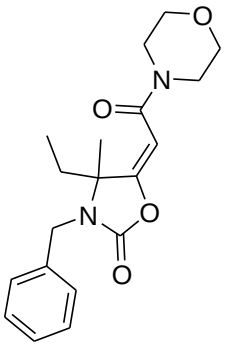


(E)-2-(3-Benzyl-4,4-dimethyl-2-oxo-oxazolidin-5-ylidene)-N,N-diethylacetamide (**3ad**-E). Yield: 265.8 mg, starting from 725.0 mg of 1a (20%) (Table 1, entry 11). Yellow solid, mp 87-89 °C. IR (KBr): = 1789 (s), 1666 (m), 1615 (m), 1407 (m), 1314 (m), 1267 (w), 1192 (m), 1059 (m), 954 (w), 842 (m), 747 (m), 705 (m) cm-1 ; 1 H NMR (300 MHz, $CDCl_3$):δ = 7.37-7.23 (m, 5 H, Ph), 5.89 (s, 1 H, =CH), 4.46 (s, 2 H, $CH_2Ph$), 3.42-3.27 (m, 4 H, $CH_2NCH_2$), 1.60 (s, 6 H, $CH_3CCH_3$), 1.17 (t, J = 7.1, 3 H, $CH_3CH_2NCH_2CH_3$), 1.11 (t, J = 7.1, 3 H, $CH_3CH_2NCH_2CH_3$); 13C NMR (75 MHz, $CDCl_3$): = 164.6, 163.9, 153.7, 137.4, 128.7, 127.72, 127.69, 96.5, 64.1, 43.7, 42.9, 40.5, 24.2, 14.4, 13.0; GC-MS: m/z = 316 (M+ , 14), 301 (3), 244 (7), 183 (8), 142 (6), 112 (7), 100 (7), 92 (11), 91 (100), 72 (45); anal. calcd for $C_{18}H_{24}N_2O_3$ (316.39): C, 68.33; H, 7.65; N, 8.85; found C, 68.26; H, 7.66; N, 8.86.

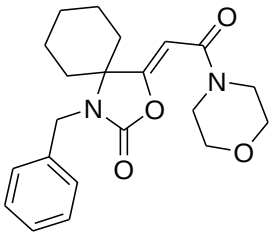


(Z)-3-Benzyl-4-ethyl-4-methyl-5-(2-morpholin-4-yl-2-oxoethylidene)-oxazolidin-2-one (**3ba**-Z). Yield: 926.0 mg, starting from 783.0 mg of 1b (64%) (Table 1, entry 2). Yellow solid, mp 137-138 °C. IR (KBr): = 1777 (s), 1680 (s), 1627 (s), 1431 (m), 1271 (m), 1110 (m), 1025 (s), 930 (w), 818 (w), 754 (w) cm-1 ; 1 H NMR (500 MHz, $CDCl_3$): = 7.39-7.25 (m, 5 H, Ph), 5.13 (s, 1 H, =CH), 4.60 (distorted d, J = 15.9, 1 H, CHHPh), 4.22 (distorted d, J = 15.9, 1 H, CHHPh), 3.75- 3.62 (m, 6 H, $CH2OCH_2$ + CHHNCHH), 3.52-3.42 (m, 2 H, CHHNCHH), 1.90-1.78 (m, 1 H, $CHHCH_3$), 1.62-1.50 (m, 1 H, $CHHCH_3$), 1.30 (s, 3 H, $CH_3CCH_2CH_3$), 0.72 (t, J = 7.1, 3 H, $CH_2CH_3$); 13C NMR (126 MHz, $CDCl_3$):δ = 163.3, 157.4, 154.1, 136.8, 128.7,

128.2, 128.0, 93.8, 66.8, 66.7, 66.1, 47.3, 44.2, 42.1, 32.2, 27.0, 7.8; GC-MS: m/z = 344 (M+ , 2), 329 (2), 316 (5), 315 (28), 182 (4), 92 (8), 91 (100), 73 (6), 69 (6); anal. calcd for $C_{19}H_{24}N_2O_4$ (344.40): C, 66.26; H, 7.02; N, 8.13; found C, 66.33; H, 7.01; N, 8.12.

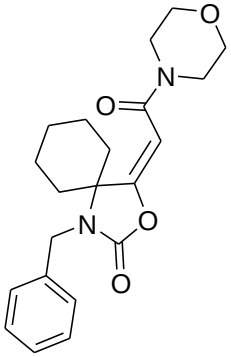


(E)-3-Benzyl-4-ethyl-4-methyl-5-(2-morpholin-4-yl-2-oxoethylidene)-oxazolidin-2-one (**3ba**-E).Yield: 376.0 mg, starting from 783.0 mg of 1b (26%) (Table 1, entry 2). Yellow solid, mp 84-85 °C. IR (KBr): = 1767 (s), 1669 (s), 1612 (s), 1458 (m), 1351 (m), 1173 (m), 1101 (s), 1023 (s), 853 (m), 751 (m), 703 (m) cm-1 ; 1 H NMR (300 MHz, $CDCl_3$):δ = 7.40-7.23 (m, 5 H, Ph), 5.93 (s, 1 H, =CH), 4.58 (distorted d, J = 15.7, 1 H, CHHPh), 4.22 (distorted d, J = 15.7, 1 H, CHHPh), 3.70- 3.40 (m, 8 H, $NCH_2CH_2OCH_2CH_2$), 2.66-2.51 (m, 1 H, $CHHCH_3$), 1.73-1.58 (m 1 H, $CHHCH_3$), 1.51 (s, 3 H, $CH_3CCH_2CH_3$), 0.69 (t, J = 7.3, 3 H, $CH_2CH_3$); 13C NMR (75 MHz, $CDCl_3$): = 164.0, 163.6, 154.2, 137.1, 128.6, 128.1, 127.8, 95.9, 68.2, 66.73, 66.68, 46.9, 43.7, 41.9, 28.5, 24.0, 7.9; GC-MS: m/z = 344 (M+ , 3), 329 (3), 316 (7), 315 (33), 182 (8), 92 (8), 91 (100), 86 (5); anal. calcd for $C_{19}H_{24}N_2O_4$ (344.40): C, 66.26; H, 7.02; N, 8.13; found C, 66.15; H, 7.04; N, 8.15.

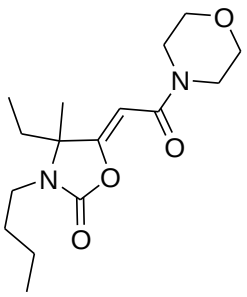


(Z)-1-Benzyl-4-(2-morpholin-4-yl-2-oxoethylidene)-3-oxa-1-azaspiro[4.5]decan-2-one (**3ca**-Z).Yield: 1.01 g, starting from 898.0 mg of 1c (65%) (Table 1, entry 3). Yellow solid, mp 138-139 °C. IR (KBr): = 1794 (m), 1777 (m), 1639 (s), 1433 (m), 1366 (w), 1267 (m), 1231 (m), 1115 (s), 1066 (m), 957 (w), 758 (m) cm-1 ; 1 H NMR (300 MHz, $CDCl_3$):δ = 7.47-7.21 (m, 5

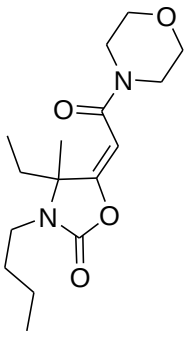
H, Ph), 5.45 (s, 1 H, =CH), 4.48 (s, 2 H, $CH_2Ph$), 3.93-3.36 (m, 8 H, $NCH_2CH_2OCH_2CH_2$), 1.86-1.48 [m, 10 H, $(CH_2)_5$]; 13C NMR (126 MHz, $CDCl_3$): = 163.4, 156.2, 153.8, 137.3, 128.8, 127.7, 127.2, 97.2, 66.9, 66.7, 64.1, 47.3, 43.7, 42.1, 33.8, 23.8, 21.5; GC-MS: m/z = 370 (M+ , 5), 279 (12), 256 (13), 114 (5), 92 (8), 91 (100), 88 (7), 86 (9), 73 (9); anal. calcd for $C_{21}H_{26}N_2O_4$ (370.44): C, 68.09; H, 7.07; N, 7.56; found C, 68.10; H, 7.06; N, 7.58.



(E)-1-Benzyl-4-(2-morpholin-4-yl-2-oxoethylidene)-3-oxa-1-azaspiro[4.5]decan-2-one (**3ca**-E).Yield: 467.0 mg, starting from 898.0 mg of 1c (30%) (Table 1, entry 3). Yellow solid, mp 124-126 °C. IR (KBr):  = 1781 (s), 1679 (s), 1632 (s), 1435 (m), 1270 (m), 1114 (m), 1056 (m), 951 (w), 754 (m) cm-1; 1 H NMR (500 MHz, $CDCl_3$):δ = 7.35-7.30 (m, 2 H on phenyl ring), 7.29-7.24 (m, 3 H on phenyl ring), 5.84 (s, 1 H, =CH), 4.85 (s, 2 H, $CH_2Ph$), 3.69-3.59 (m, 6 H, $CH_2OCH_2$ + CHHNCHH), 3.55-3.49 (m, 2 H, CHHNCHH), 2.71 (td, J = 14.3, 5.5, 2 H, $CHHCCHHCH_2CH_2CH_2$), 1.85-1.78 (m, 2 H on cyclohexyl ring), 1.70-1.59 (m, 3 H on cyclohexyl ring), 1.55-1.33 (m, 3 H on cyclohexyl ring); 13C NMR (75 MHz, $CDCl_3$): = 166.3, 163.8, 154.4, 137.2, 128.7, 127.4, 126.5, 95.0, 66.8 (br), 65.4, 47.3, 46.9, 42.0, 33.4, 22.8, 22.2; GC-MS: m/z = 370 (M+ , 6), 279 (14), 256 (16), 237 (7), 114 (7), 91 (100), 88 (11), 86 (10), 69 (13); anal. calcd for $C_{21}H_{26}N_2O_4$ (370.44): C, 68.09; H, 7.07; N, 7.56; found C, 68.12; H, 7.05; N, 7.57.

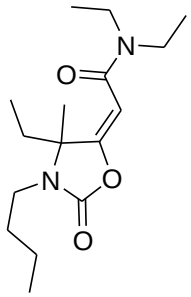


(Z)-3-Butyl-4-ethyl-4-methyl-5-(2-morpholin-4-yl-2-oxoethylidene)-oxazolidin-2-one (**3da**-Z).Yield: 847.5 mg, starting from 640.0 mg of 1d (65%) (Table 1, entry 4). Yellow solid, mp 89-90 °C. IR (KBr):  = 1773 (s), 1679 (s), 1625 (m), 1435 (m), 1332 (m), 1271 (m), 1242 (m), 1115 (m), 1032 (m), 829 (m), 790 (w), 759 (m) cm-1 ; 1 H NMR (300 MHz, $CDCl_3$):δ = 5.14 (s, 1 H, =CH), 3.76-3.45 (m, 8 H, $NCH_2CH_2OCH_2CH_2$), 3.33-3.20 (m, 1 H, $NCHHCH_2CH_2$), 3.05-2.92 (m, 1 H, $NCHHCH_2CH_2$), 1.93-1.79 (m, 1 H, $CH_3CCHHCH_3$), 1.74-1.53 (m, 3 H, $CH_3CCHHCH3$ + $CH_2CH_2CH_3$), 1.48 (s, 3 H, $CH_3CCH_2CH_3$), 1.43-1.29 (m, 2 H, $CH_2CH_2CH_3$), 0.95 (t, J = 7.3, 3 H, $CH_2CH_3$), 0.83 (t, J = 7.3, 3 H, $CH_2CH_3$); 13C NMR (75 MHz, $CDCl_3$): = 163.4, 157.5, 153.5, 93.5, 66.8, 66.7, 65.8, 47.3, 42.1, 40.4, 32.3, 31.1, 26.9, 20.2, 13.7, 8.0; GC-MS: m/z = 310 (M+ , 6), 282 (20), 281 (100), 182 (30), 180 (33), 124 (35), 114 (16), 86 (19), 70 (18), 69 (88); anal. calcd for $C_{16}H_{26}N_2O_4$ (310.39): C, 61.91; H, 8.44; N, 9.03; found C, 62.03; H, 8.46; N, 9.01

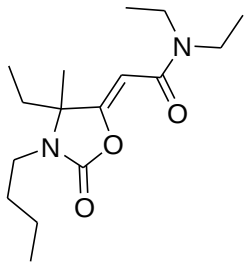



(E)-3-Butyl-4-ethyl-4-methyl-5-(2-morpholin-4-yl-2-oxoethylidene)-oxazolidin-2-one (**3da**-E).Yield: 300.0 mg, starting from 640.0 mg of 1d (23%) (Table 1, entry 4). Yellow solid, mp 67-68 °C. IR (KBr): = 1783 (s), 1679 (m), 1664 (m), 1625 (m), 1438 (m), 1377 (m), 1272 (m), 1248 (m), 1189 (m), 1090 (m), 1030 (m), 831 (m), 781 (w), 758 (m) cm-1 ; 1 H NMR (500 MHz, $CDCl_3$):δ = 5.94 (s, 1 H, =CH), 3.73-3.51 (m, 8 H, $NCH_2CH_2OCH_2CH_2$), 3.27-3.19 (m, 1 H, $NCHHCH_2CH_2$), 3.04-2.96 (m, 1 H, $NCHHCH_2CH_2$), 2.66-2.57 (m, 1 H, $CH_3CCHHCH_3$), 1.74-1.56 (m, 3 H, $CH_3CCHHCH_3$ + $CH_2CH_2CH_3$), 1.65 (s, 3 H, $CH_3CCH_2CH_3$), 1.36 (sextuplet, J = 7.4, 2 H, $CH_2CH_2CH_3$), 0.95 (t, J = 7.4, 3 H, $CH_2CH_2CH_3$), 0.79 (t, J = 7.4, 3 H,$CH_3CCH_2CH_3$) (Note: All assignments were confirmed by a 2D COSY experiment); 13C NMR (75 MHz, $CDCl_3$):δ = 164.4, 163.8, 153.5, 95.5, 67.9, 66.8, 66.7, 46.9, 41.9, 39.9, 31.1, 28.6, 23.7, 20.3, 13.7, 8.2; GC-MS: m/z = 310 (M+ , 6), 282 (19), 281 (100), 194 (21), 182 (66), 180 (21), 124 (25), 114 (35), 86 (17), 70 (20), 69 (70); anal. calcd for $C_{16}H_{26}N_2O_4$ (310.39): C, 61.91; H, 8.44; N, 9.03; found C, 61.82; H, 8.46; N, 9.05

(E)-2-(3-Butyl-4-ethyl-4-methyl-2-oxooxazolidin-5-ylidene)-N,N-diethylacetamide (**3dd**-E).

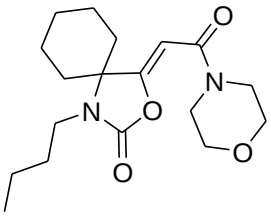


Yellow oil. IR (film): ν = 1786 (s), 1687 (m), 1618 (m), 1401 (w), 1052 (m), 1082 (m) $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$): δ = 5.92 (s, 1 H, =CH), 3.46-3.30 (m, 4 H, 2 $NCH_2$), 3.29-3.16 (m, 1 H, CHH), 3.06-2.93 (m, 1 H, CHH), 2.76-2.60 (m, 1 H, CHH), 1.70.-1.53 (m, 3 H, $CH_2$ + CHH), 1.42-1.30 (m, 2 H, $CH_2$), 1.66 (s, 3 H, Me), 1.19 (t, J = 7.2, 3 H, Me), 1.14 (t, J = 7.1, 3 H, Me), 0.95 (t, J = 7.4, 3 H, Me), 0.79 (t, J = 7.4, 3 H, Me); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 164.1, 163.5, 153.8, 96.7, 68.0, 43.0, 40.5, 40.0, 31.1, 28.5, 23.7, 20.3, 14.5, 13.7, 13.1, 8.2; GC-MS m/z = 296 (25) [$M^+$], 281 (15), 267 (100), 224 (8), 180 (15), 168 (98), 140 (15), 124 (19), 112 (9), 100 (54), 72 (71); anal. calcd for $C_{16}H_{28}N_2O_3$ (296.41): C, 64.83; H, 9.52; N, 9.45; found C, 64.80; H, 9.54; N, 9.42.

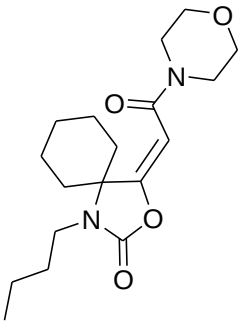


(Z)-2-(3-Butyl-4-ethyl-4-methyl-2-oxooxazolidin-5-ylidene)-N,N-diethylacetamide (**3dd**-Z).

Yellow oil, purity: ca. 60% (by GLC). GC-MS m/z =296 (26) [$M^+$], 281 (11), 267 (100), 224 (13), 197 (8), 180 (26), 168 (74), 138 (13), 124 (33), 112 (14), 100 (37), 72 (89).



(Z)-1-Butyl-4-(2-morpholin-4-yl-2-oxoethylidene)-3-oxa-1-azaspiro[4.5]decan-2-one (**3ea**-Z).Yield: 947.0 mg, starting from 755.0 mg of 1e (67%) (Table 1, entry 5). Yellow solid, mp 78-79 °C. IR (KBr):  = 1784 (s), 1676 (m), 1631 (m), 1463 (m), 1406 (m), 1265 (w), 1243 (w), 1113 (m), 1069 (m), 1038 (w), 971 (w), 808 (w), 750 (w) cm-1 ; 1 H NMR (300 MHz, CDCl3):δ = 5.42 (s, 1 H, =CH), 3.78-3.44 (m, 8 H, $NCH_2CH_2OCH_2CH_2$), 3.19-3.09 (m, 2 H, $NCH_2CH_2CH_2$), 1.88-1.55 [m, 12 H, $(CH_2)_5$ + $CH_2CH_2CH_3$], 1.42-1.28 (m, 2 H, $CH_2CH_2CH_3$), 0.94 (t, J = 7.3, 3 H, $CH_3$); 13C NMR (75 MHz, $CDCl_3$): = 163.5, 156.4, 152.9, 96.7, 66.8, 66.7, 63.6, 47.3, 42.0, 40.2, 33.7, 31.5, 23.8, 21.4, 20.2, 13.7; GC-MS: m/z = 336 (M+ , 52), 223 (16), 222 (100), 207 (23), 206 (57), 178 (15), 152 (21), 151 (52), 114 (16), 87 (16), 86 (37), 81 (20), 70 (18), 69 (88); anal. calcd for $C_{18}H_{28}N_2O_4$ (336.43): C, 64.26; H, 8.39; N, 8.33; found C, 64.17; H, 8.40; N, 8.35.




(E)-1-Butyl-4-(2-morpholin-4-yl-2-oxoethylidene)-3-oxa-1-azaspiro[4.5]decan-2-one (**3ea**-E).Yield: 311.0 mg, starting from 755.0 mg of 1e (22%) (Table 1, entry 5). Yellow oil. IR (film):  = 1782 (s), 1655 (m), 1622 (m), 1433 (m), 1401 (m), 1357 (w), 1250 (m), 1181 (m), 1113 (m), 1023 (m), 921 (w), 838 (m) cm-1; 1 H NMR (500 MHz, $CDCl_3$): = 5.77 (s, 1 H, =CH), 3.71-3.61 (m, 6 H, $CH_2OCH_2$ + CHHNCHH), 3.59-3.54 (m, 2 H, $NCH_2CH_2CH_2$), 3.54-3.49 (m, 2 H, CHHNCHH), 2.81-2.73 (m, 2 H, $CHHCCHHCH_2CH_2CH_2$), 1.87-1.76 (m, 5 H on cyclohexyl ring), 1.72-1.57 (m, 5 H, 3 H on cyclohexyl ring + $NCH_2CH_2CH_2$), 1.35 (sextuplet, J = 7.4, 2 H, $CH_2CH_3$), 0.95 (t, J = 7.4, 3 H, $CH_3$); 13C NMR (75 MHz, $CDCl_3$):δ = 166.3, 163.9, 153.0, 94.6, 66.7 (br), 64.7, 46.9, 44.2, 42.0, 33.6, 31.1, 23.0, 22.1, 20.2, 13.7; GC-MS: m/z = 336 (M+ , 56), 237 (18), 222 (100), 207 (23), 206 (46), 178 (18), 152 (22), 151 (42), 114 (20), 87 (21), 86 (41), 81 (19), 70 (20), 69 (73); anal. calcd for $C_{18}H_{28}N_2O_4$ (336.43): C, 64.26; H, 8.39; N, 8.33; found C, 64.33; H, 8.37; N, 8.32.

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[41] We have recently reported the synthesis of 4,4-dialkyl-5-[(methoxycarbonyl) methylene]oxazolidin-2-ones by Pd-catalyzed sequential oxidative carboxylation-methoxycarbonylation of R,R-dialkyl substituted 2-ynylamines: (a) Bacchi, A.; Chiusoli, G. P.; Costa, M.; Gabriele, B.; Righi, C.; Salerno, G. *Chem. Commun*. 19 97, 1209-1210. (b) Chiusoli, G. P.; Costa, M.; Gabriele, B.; Salerno, G. *J. Mol. Catal. A: Chem*. **1999**, 143, 297- 310. In that reaction, carbon dioxide was incorporated into the cycle, while carbon monoxide was

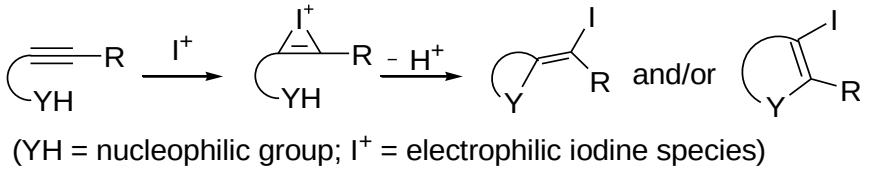
incorporated into the (methoxycarbonyl)methylene moiety, so the process was completely different from that described in the present work, in which both the carbonyl groups present in the final product derive from carbon monoxide. The direct formation of 5-methylene-2-oxazolidinones by carboxylation of 2-ynylamines has also been reported; see, for example: (c) Costa, M.; Chiusoli, G. P.; Taffurelli, D.; Dalmonego, G. *J. Chem. Soc., Perkin Trans*. 1 **1998,** 1541-1546. (d) Maggi, R.; Bertolotti, C.; Orlandini, E.; Oro, C.; Sartori, G.; Selva, M. *Tetrahedron Lett.* **2007**, 48, 2131-2134.

# Chapter 4

## 4.1 Iodocyclizations in Ionic Liquids Divergent Syntheses of (*E*)-3-(Iodoalkylidene)isobenzofuran-1(3*H*)-ones and 4-Iodo-1*H*-isochromen-1-ones by Base-Free Iodolactonization of 2-Alkynylbenzoic Acids in $Mor_{1,2}N(CN)_2$ and $EmimEtSO_4$

### 4.1.1 Synthesis of Iodinated Isobenzofuranones and isochromenones by iodolactonization of 2-alkynyl benzoic acids in ionic liquids

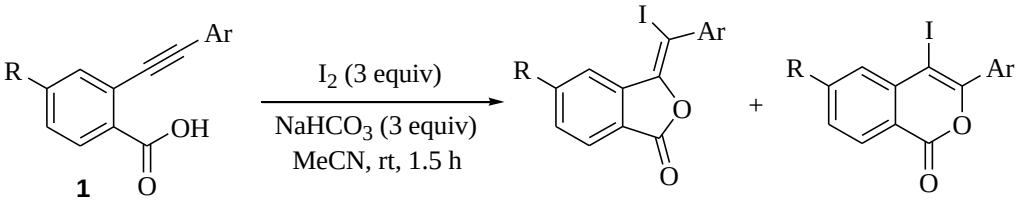
The iodocyclization of acetylenic substrates bearing a suitably placed nucleophilic group is an excellent method for the direct synthesis of iodine-containing carbo- and heterocycles.[1,2] The importance of this process is further demonstrated by the possibility to functionalize the iodocyclized product through cross-coupling techniques.[3] Iodocyclizations are usually carried out in a classical organic solvent, such as methylene chloride or MeCN, in the presence of a base necessary to trap the acid generated during the process, which occurs through the formation of a iodirenium intermediate followed by *exo* or *endo* intramolecular nucleophilic attack (Scheme 1).[1-3]




**Scheme 1.** Iodocyclization of alkynes bearing a suitably placed nucleophilic group, leading to iodine-containing hetero- or carbocycles (both the *exo* and the *endo* possible cyclization modes are shown).[1,2]

In this work we have studied the possibility to synthesize iodinated isobenzofuranones and isochromenones starting from 2-alkynyl benzoic acids using ionic liquids as unconventional solvents.

In spite of their availability, the iodolactonization of some 2-alkynylbenzoic acids **1** has been scantily studied in the literature. The formation of 3-(2-hydroxy-1-iodo-2-methylpropylidene)isobenzofuran-1(3*H*)-one (*E*/*Z* mixture) was briefly mentioned to occur by treatment of crude 2-(3-hydroxy-3-methylbut-1-alkynyl)benzoic acid which is obtained in situ by Sonogashira coupling between 2-iodobenzoic acid and 2-methylbut-3-yn-2-ol) with ICl.[4] More recently, the reaction between 2-(2-phenylethynyl)benzoic acid or 4-methoxy-2-(2-(4-methoxyphenyl)ethynyl)benzoic acid with $I_2$ (3 equiv), carried out in MeCN at rt for 1.5 h in the presence of $NaHCO_3$ as the base (3 equiv), was reported to afford a mixture of the corresponding (*E*)-3-(iodomethylene)isobenzofuran-1(3*H*)-ones (from *anti* 5-*exo* cyclization) and 4-iodo-1*H*-isochromen-1-ones (from 6-*endo* cyclization) (5/95 and 15/85, respectively), the latter being formed preferentially (88% and 18% yield) (Eq 4.1).

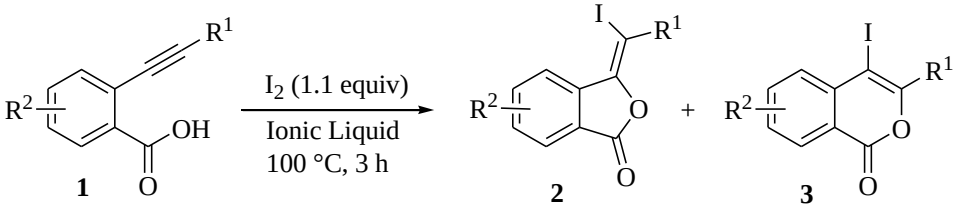



**(4.1)**

R = H, Ar = Ph: isobenzofuranone/isochromenone = 5/95, yield of isochromenone: 88%
R = OMe, Ar = 4-$MeOC_6H_4$: isobenzofuranone/isochromenone = 15/85, yield of isochromenone: 18%

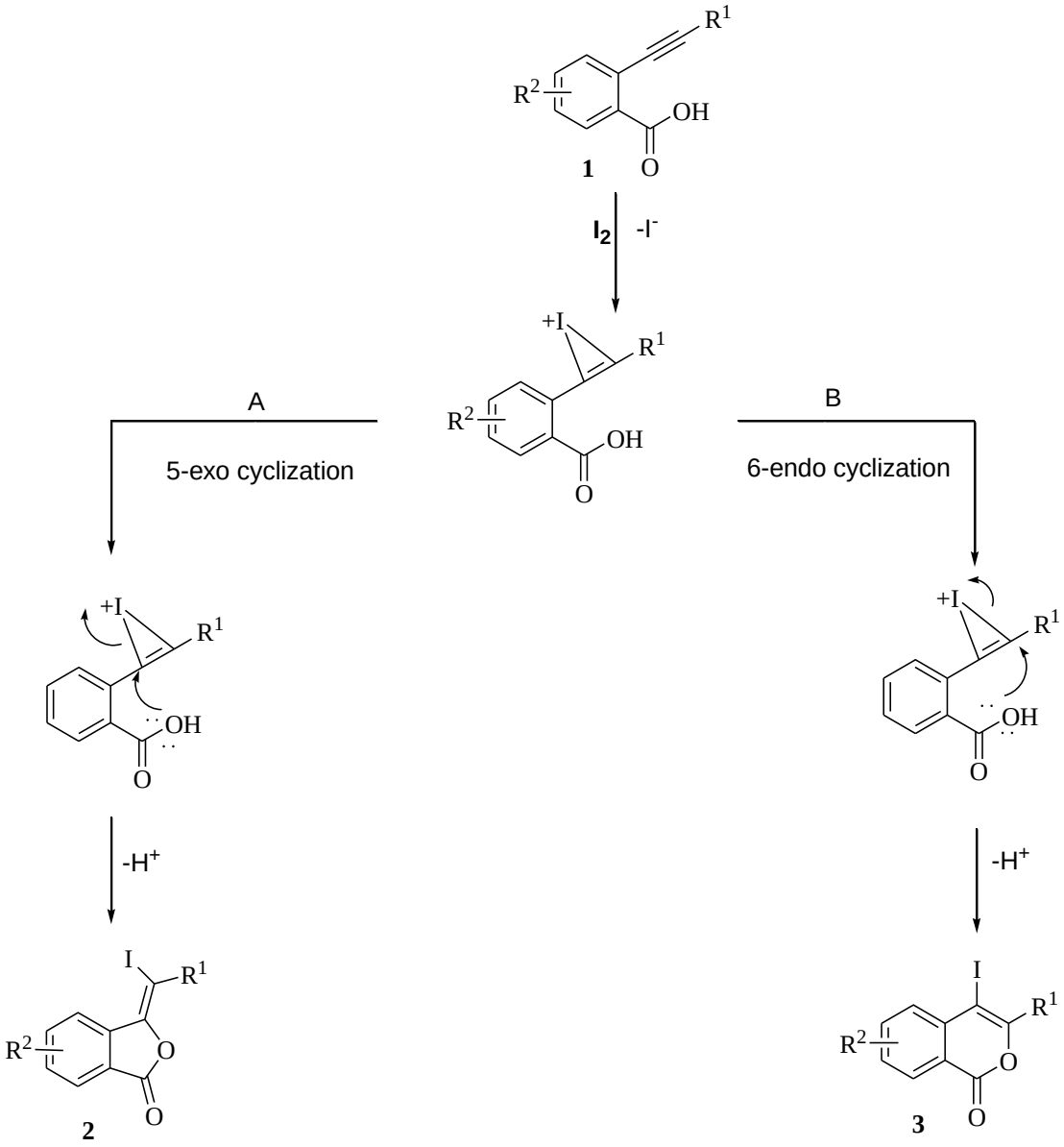
## 4.2 Present Work

In this work, we have studied the iodocylization of several 2-alkynylbenzoic acids **1** in ionic liquids (ILs) as unconventional and recyclable solvents,[6,7] using $I_2$ as the iodine source and in the absence of external bases, with the aim of realizing an efficient, general, and regioselective method for the direct synthesis of **2**(iodoalkylidene)isobenzofuran-1(3*H*)-ones and 4-iodo-1*H*-isochromen-1-ones **3** (**Eq.4.2**) Density functional calculations have been carried out in order to elucidate the specific role of the IL ions on the reaction course.




**(4.2)**

**Mechanism**

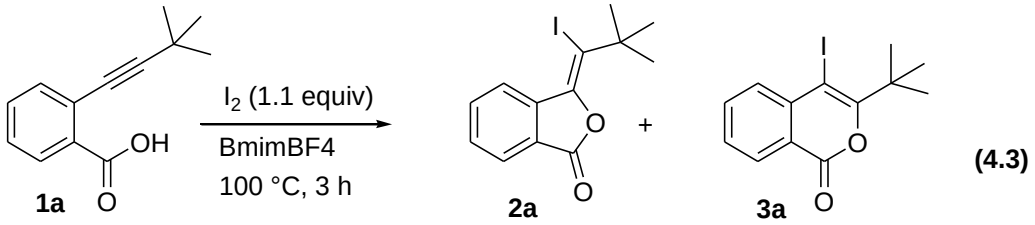



**Scheme 2** Schematic presentation of product formation 2 and 3

As shown in scheme 2 the formation of product **2** and **3** follows path A and path B respectively in which the first step is coordination of iodide to the triple bond. In path a, the second step is 5-exo-dig cyclization to form **2** while in path b, 6-endo-dig cyclization takes place to from **3** takes.

### 4.2.2 Results and Discussion

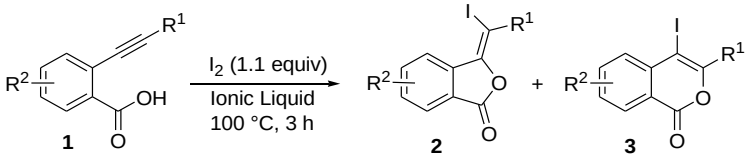
Our initial experiment was carried out (Eq. 4.3) using 2-(3, 3-dimethylbut-1-ynyl) benzoic acid **1a**. The reaction of **1a** with $I_2$ (1.1 equiv), carried out at 100 °C for 3 h in 3-butyl-1-methylimidazolium tetrafluoroborate ($BmimBF_4$) as the solvent, led to the formation of a mixture of (*E*)-3-(1-iodo-2,2-dimethylpropylidene)isobenzofuran-1(3*H*)-one **2a** and 3-*tert*-butyl-4-iodo-1*H*-isochromen-1-one **3a** (5.7:1 molar ratio) in 49% total isolated yield at 67% substrate conversion (Table 4.1, entry 1).



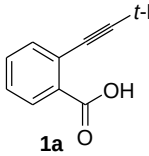
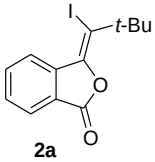
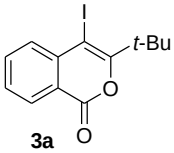
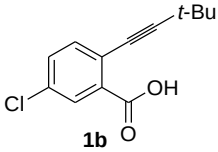
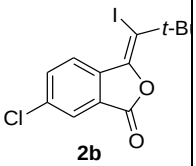
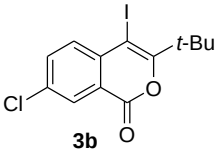
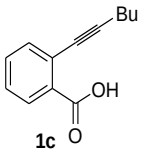
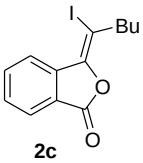
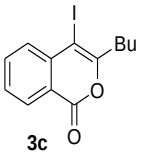

**(4.3)**

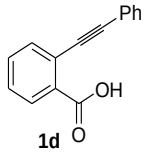
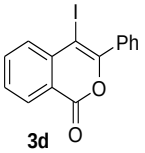
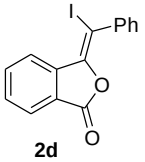
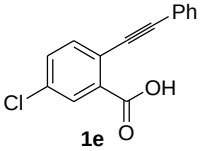
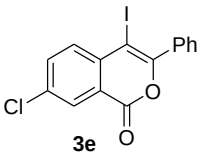
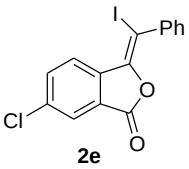
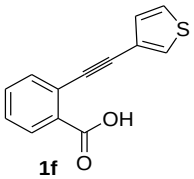
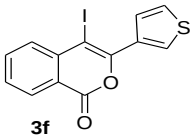
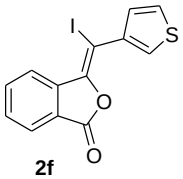
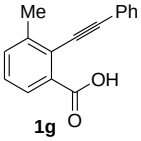
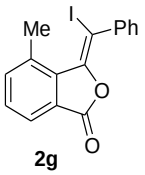
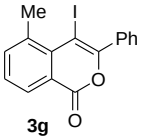
A brief optimization study was then carried in order to verify if the process was general, with different kind of ionic liquids With the aim of improving this initial result both in terms of yield and regioselectivity, we then changed the nature of the IL medium; the results obtained are shown in Table 4.1, entries 2-5. Only partial substrate degradation was obtained using 3-butyl-1-methylimidazolium acetate (BmimOAc, Table 4.1, entry 2). On the other hand, an inversion of the regioselectivity of the process in favor of **3a** (**3a**/**2a** molar ratio = 1.4, total yield = 95%) was observed in 1-ethyl-3-methyl-1H-imidazol-3-ium ethyl sulfate ($EmimEtSO_4$, Table 4.1, entry 3). Very interestingly, the process turned out to be completely regioselective toward the formation of the 5-membered product **2a** (whose structure was confirmed by X-ray diffraction analysis, see the Supporting Information for details) when using as solvent 3-butyl-1-methylimidazolium dicyanamide ($BmimN(CN)_2$; 77% yield, Table 4.1, entry 4) or *N*-ethyl-*N*-methylmorpholinium dicyanamide ($Mor_{1,2}N(CN)_2$; 85% yield, Table 4.1, entry 5). Similar results were obtained with 5-chloro-2-(3,3-dimethylbut-1-ynyl)benzoic acid **1b**: in $EmimEtSO_4$, the reaction was more selective toward the formation of 3-*tert*-butyl-7-chloro-4-iodo-1*H*-isochromen-1-one **3b** (**3b**/**2b** molar ratio = 2.2, total yield = 83%; Table 4.1, entry 6), while only (*E*)-6-chloro-3-(1-iodo-2,2-dimethylpropylidene)isobenzofuran-1(3*H*)-one **2b** was obtained in $Mor_{1,2}N(CN)_2$ (85 % yield; Table 4.1, entry 7).

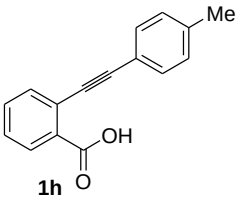
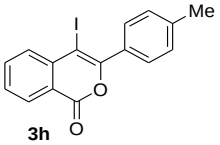
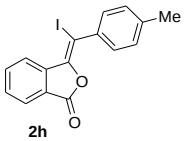
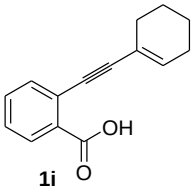
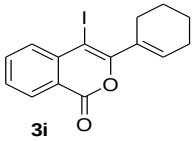
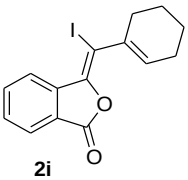
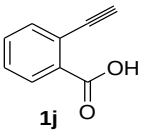
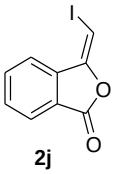
**Table 4.1.** Divergent Syntheses of (*E*)-3-(Iodoalkylidene)isobenzofuran-1(3*H*)-ones **2** and 4-Iodo-1*H*-isochromen-1-ones **3** by Base-Free Iodolactonization of 2-Alkynylbenzoic Acids **1** in $Mor_{1,2}N(CN)_2$ and $EmimEtSO_4$, respectively.[a]




**(4.3)**

| Entry | **1** | IL | **2** | **3** | **2 / 3** molar ratio[b] | Total Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 |  **1a** | $BmimBF_4$ |  **2a** |  **3a** | 5.70 | 49[c] |
| 2 | **1a** | BmimOAc | | | | NR[d] |
| 3 | **1a** | $EmimEtSO_4$ | **2a** | **3a** | 0.71 | 95 |
| 4 | **1a** | $BmimN(CN)_2$ | **2a** | | **2a** only | 77 |
| 5 | **1a** | $Mor_{1,2}N(CN)_2$ | **2a** | | **2a** only | 85 (84-83-85-83-82-83) |
| 6 |  **1b** | $EmimEtSO_4$ |  **2b** |  **3b** | 0.45 | 83 |
| 7 | **1b** | $Mor_{1,2}N(CN)_2$ | **2b** | | **2b** only | 85 (84-85-83-85-83) |
| 8 |  **1c** | $EmimEtSO_4$ |  **2c** |  **3c** | 0.57 | 72 |
| 9 | **1c** | $Mor_{1,2}N(CN)_2$ | **2c** | **3c** | 2.13 | 74 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 10 |  **1d** | $EmimEtSO_4$ | |  **3d** | **3d** only | 80 (79-78-80-80-79-79) |
| 11 | **1d** | $Mor_{1,2}N(CN)_2$ |  **2d** | | **2d** only | 73 (72-73-72-72-71-72) |
| 12 |  **1e** | $EmimEtSO_4$ | |  **3e** | **3e** only | 88 (87-88-86-87-88) |
| 13 | **1e** | $Mor_{1,2}N(CN)_2$ |  **2e** | | **2e** only | 72 (72-71-72-72-71) |
| 14 |  **1f** | $EmimEtSO_4$ | |  **3f** | **3f** only | 91 (89-90-91-89-90) |
| 15 | **1f** | $Mor_{1,2}N(CN)_2$ |  **2f** | | **2f** only | 75 (72-74-74-75-74) |
| 16 |  **1g** | $EmimEtSO_4$ |  **2g** |  **3g** | 0.78 | 87<br>31% (2g)<br>56%(3g) |
| 17 | **1g** | $Mor_{1,2}N(CN)_2$ | **2g** | | **2g** only | 75 (73-74-75-73-75) |

| | | | | | | |
|---|---|---|---|---|---|---|
| 18 |  **1h** | $EmimEtSO_4$ | |  **3h** | **3h** only | 94 (90-93-90-91-90-90) |
| 19 | **1h** | $Mor_{1,2}N(CN)_2$ |  **2h** | **3h** | 2.32 | 73 |
| 20 |  **1i** | $EmimEtSO_4$ | |  **3i** | **3i** only | 80 (77-79-80-78-78) |
| 21 | **1i** | $Mor_{1,2}N(CN)_2$ |  **2i** | **3i** | 1.63 | 71<br>60%(2i)<br>11%(3i) |
| 22 |  **1j** | $EmimEtSO_4$ |  **2j** | | **2j** only | 83 (82-82-81-83-829 |
| 23 | **1j** | $Mor_{1,2}N(CN)_2$ | **2j** | | **2j** only | 76 (75-76-74-76-75) |

[a] Unless otherwise noted, all reactions were carried out at 100 °C under nitrogen for 3 h with a substrate concentration of 0.2 mmol of **1** per mL of ionic liquid, in the presence of 1 equiv of $I_2$. [b] Determined by GLC [c] Isolated yield based on starting **1**. In parentheses are given the yields obtained in the recycling experiments (see text for details). [c] Substrate conversion was 67% (determined by GLC). [d] Partial substrate degradation occurred (substrate conversion was 38%, by GLC).

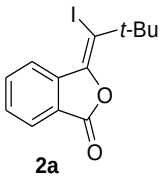
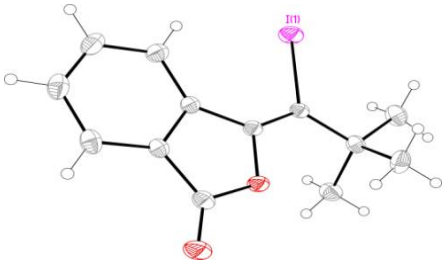
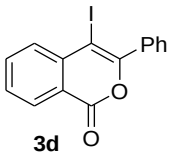
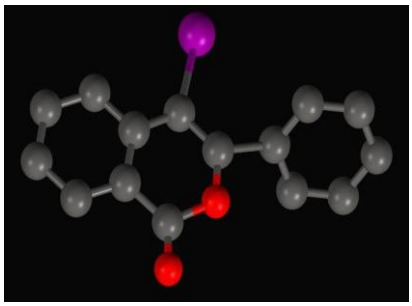
Encouraged by these initial results, we then studied the reactivity of other differently substituted substrates in the most performing ILs found for the iodocyclization of **1a** and **1b** ($EmimEtSO_4$ and $Mor_{1,2}N(CN)_2$). The reactions of 2-(hex-1-alkynyl)benzoic acid **1c**, bearing a linear rather than a branched alkyl group on the triple bond, turned out to be less selective when compared to the analogous reactions of **1a** and **1b**, and mixtures of the corresponding isobenzofuranone **2c** and isochromenone **3c** were consistently obtained. However, in agreement with the trend

already observed in the case of **1a** and **1b**, the 6-membered product **3c** turned out to be the major isomer in $EmimEtSO_4$ (Table 4.1, entry 8), while the 5-membered product **2c** predominated in $Mor_{1,2}N(CN)_2$ (Table 4.1, entry 9).

On the other hand, the divergent selective formation of either the isochromenone or the isobenzofuranone product in the two ILs was observed with 2-(2-phenylethynyl)benzoic acid **1d** (Table 4.1, entries 10 and 11) and 5-chloro-2-(2-phenylethynyl)benzoic acid **1e** (Table 4.1, entries 12 and 13), bearing a phenyl group on the triple bond, as well as with 2-[2-(thiophen-3-yl)ethynyl]benzoic acid **1f**, bearing a 3-thienyl substituent on the triple bond (Table 4.1, entries 14 and 15). The structure of 4-iodo-3-phenyl-1*H*-isochromen-1-one **3d** was confirmed by X-ray diffraction analysis (see the experimental section for details). With an *o*-methyl-substituted substrate, such as **1g**, a selective reaction toward the formation of the corresponding isobenzofuranone **2g** was obtained in $Mor_{1,2}N(CN)_2$ (Table 4.1, entry 17), while isochromenones **3h** and **3i** were selectively formed in $EmimEtSO_4$ from 2-(2-*p*-tolylethynyl)benzoic acid **1h** and 2-(2-cyclohexenylethynyl)benzoic acid **1i**, respectively (Table 4.1, entries 18 and 20, respectively). Finally, in the case of 2-ethynylbenzoic acid **1j**, bearing a terminal triple bond, only the 5-membered product, (*E*)-3-(iodomethylene)isobenzofuran-1(3*H*)-one **2j**, was produced in both $EmimEtSO_4$ and $Mor_{1,2}N(CN)_2$ media (Table 4.1, entries 22 and 23, respectively).

For the most selective reactions, we also assessed the possibility to recycle the IL medium, by extracting the product from the reaction mixture with diethyl ether and adding fresh substrate and iodine to the ionic liquid residue. As can be seen from the results reported in Table 4.1, entries 5, 7, 10-15, 17, 18, 20, 22, and 23, the solvent could be successfully recycled for several additional runs in all cases.

**Table 4.2 Structures of some isolated products confirmed by the X-ray diffraction**

| | | |
|---|---|---|
| 1 |  **2a** |  |
| 2 |  **3d** |  |

X-ray diffraction patter confirms the structure of the isolated product

### 4.3 Computational Details.

All the calculation has been performed using the Terachem Package, version 1.5k[11] on a Linux workstation equipped with four NVIDA GTX Titan GPUs. The level of calculation was B3LYP/6-311++G(d,p). Nudged elastic band (NEB) algorithm with six sample points and a climbing image has been used to investigate the reaction path between optimized encounter and product complexes[12]. Default optimization and convergence parameters has been used. Grimme D3 dispersion correction[13] has been used. Optimized geometries and absolute energies are reported in the Supporting Information.

### DFT Calculations

The calculations were carried out in collaboration with Dr.Christian Pomelli (University of Pisa) In order to rationalize the effect exerted by the nature of the IL on the regioselectivity of the process, we have performed a DFT study. The products of the reaction presented in this paper depend strongly on the ionic liquid used as solvent. Thus, initially we have defined the model system to study that contains one or more explicit ions in order to take into account of the above mentioned specific effects. The scheme that we have adopted is the supermolecular one. This scheme has been proved to be very effective in the description of organic reactivity in ionic

liquids[8] and we have assumed successfully this scheme in a previous paper on a similar reaction[6a]. In this case, the model system consisted on the iodonium complex of the substrate complemented by two ionic liquid anions: one near the iodonium center acting as counterion and the other, near the proton of a thiolic moiety, acting as proton acceptor. In the present investigation, we can consider a very similar model system where the second anion is localized near the carboxylic proton. However, since this study involves two different ionic liquids that differ both in anion and in cation (while in the previous paper the systems considered share the cation) we decided to include also a cation, localized near the second anion. Thus the resulting system does not present a neat charge. The model system is schematized in Scheme 3.

The two anions involved in the above defined model system play a role on two different subreactions, that take place synchronously in different portions of the space. The first subreaction is the iodirenium opening. The nature of the anion should be able to modulate the reactivity and the symmetry/asymmetry of the iodirenium ring. Since there is not sterical hindering on this side of the encounter complex and the subsystem idoirenium-anion is uncharged there is not necessity to include a cation here. In the second subreaction the anion, acting as a proton acceptor triggers the polarity inversion of the carboxylic group. The cation here has been included to neutralize the anion charge and furthermore it gives a more realistic picture of eventually sterical hindering phenomena that probably depend also on the nature of the R group on the triple bond. We will analyze the effect of the IL ions on these two different subreaction.

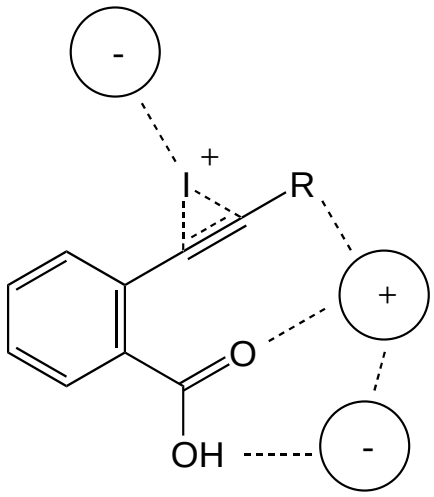



**Figure 4.1.** Model system as defined in the text. The ions are represented generically by charged spheres. The spatial arrangement leads the cation present in the model system to interact simultaneously with an anion, the carboxylic group and the sidechain R.

The supermolecular system, depicted in Scheme 3, has been used as starting point of the reaction. It is an encounter complex (ec): a system where all actors are in place, practically immediately before the reaction takes place. The same model system after the reaction will be called product complex (pc). For every choice of anion/cation and sidechain R we will have two different product complexes: the one where a five-membered ring has been closed (pc5) and the other one where a six membered ring is obtained (pc6). Therefore, the two complexes correspond to the two different possible reaction products. While the encounter complex is shared there are, obviously, two different product complexes. Any ec will be connected to pc5 and pc6 by two reaction paths. The geometry and energetic profile of these two paths will rationalize and elucidate the experimental evidences presented in this paper. A Nudged Elastic Band (NEB) method has been used. The details are reported in the experimental part. We have studied the two possible paths for the two ionic liquids considered in this paper with selected sidechains: two aromatic sidechains, phenyl and thiophene, and two aliphatic sidechains, hydrogen and *tert*-butyl. These choices will permit us to evaluate the effects of conjugation and of sterical hindering on this reaction along with the solvent specific effect.

Some selected energetic and geometric quantities are reported in Table 2. We found two very different behaviors. In the cases in which the solvent is $Mor_{1,2}N(CN)_2$, we have a reaction with barrier (Figure 4.1): between ec and pc5/pc6 there is an energetic barrier summoned by a transition state structure. For all the four investigated sidechains, the barrier that leads to pc6 is higher than the one leading to pc5, while the product stability is inverted: the six-membered isomers are thermodynamically more stable than the five-membered one. Since in these cases the barrier height determines the reaction path that is effectively followed, there is a full concordance with experimental evidences. When the solvent is $EmimEtSO_4$ the behavior is very different. Except the case with $R=(CH_3)_3C$, having a behavior similar to the cases in which the solvent is $Mor_{1,2}N(CN)_2$ , the reaction paths are barrierless (Figure 4.2) or present very small barriers easily overwhelmed by zero-point energy. From the thermodynamical point of view, also in this case, the six-membered isomers are more thermodynamically stable than the five-membered one.

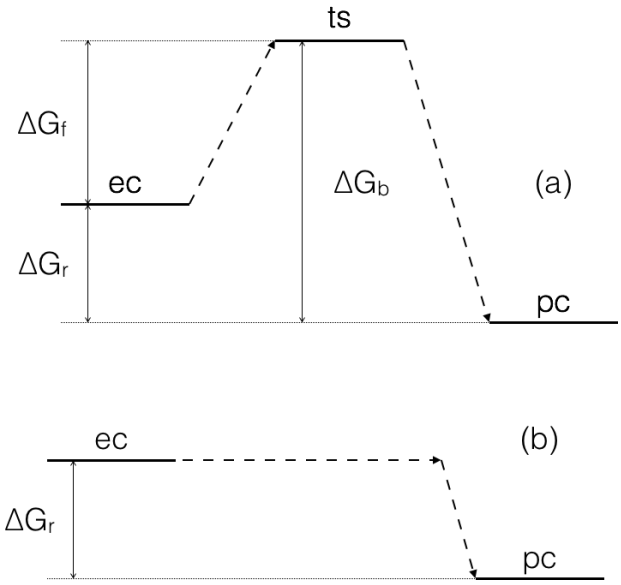



**Figure 4.2.** The reaction paths investigated show two different behaviors: (a) reaction with barrier. (b) barrierless reaction. The energetic quantities here defined are reported in Table. 5.3.

**Table 4.3** Energetic and geometric quantities obtained by the DFT calculations. Geometrical parameters are related to the encounter complexes (ec). For definition of $\Delta G_f$, $\Delta G_b$ and $\Delta G_r$ see Figure 1. For definition of θ see Figure 2.

| Solvent | R | path | $\Delta G_f$ | $\Delta G_b$ | $\Delta G_r$ | $r_{C5-I}$ | $r_{C6-I}$ | $r_{A-I}$ | θ |
|---|---|---|---|---|---|---|---|---|---|
| | | | (KJ/mol) | | | | (Å) | | (˚) |
| $Mor_{1,2}N(CN)_2$ | Ph | 5 | 23.98 | 88.74 | -64.76 | 3.02 | 2.83 | 2.19 | 26.8 |
| | | 6 | 37.38 | 118.62 | -87.01 | | | | |
| | H | 5 | 22.34 | 87.84 | -110.12 | 3.09 | 2.82 | 2.19 | 30.2 |
| | | 6 | 46.61 | 106.43 | -148.63 | | | | |
| | $C_4H_3S$ | 5 | 26.32 | 100.26 | -73.93 | 2.79 | 3.16 | 2.20 | 25.8 |
| | | 6 | 40.34 | 121.1 | -80.76 | | | | |
| | $C(CH_3)_3$ | 5 | 36.55 | 81.10 | -44.55 | 2.97 | 2.86 | 2.21 | 38.9 |
| | | 6 | 54.06 | 116.55 | -62.49 | | | | |
| $EmimEtSO_4$ | Ph | 5 | - | - | -72.63 | 2.89 | 2.65 | 2.19 | 6.3 |
| | | 6 | - | - | -116.79 | | | | |
| | H | 5 | - | - | -99.06 | 2.98 | 2.47 | 2.21 | 9.3 |
| | | 6 | - | - | -109.98 | | | | |
| | $C_4H_3S$ | 5 | - | - | -63.70 | 2.96 | 2.46 | 2.25 | 9.8 |
| | | 6 | - | - | -72.08 | | | | |
| | $C(CH_3)_3$ | 5 | 18.19 | 49.70 | -31.51 | 2.78 | 2.62 | 2.20 | 23.5 |
| | | 6 | 28.67 | 73.03 | -44.43 | | | | |

An exhaustive analysis of the various geometrical and electronic structures and related parameters of the encounter complexes leads to the following results:

1. The anion that acts as counteranion of the iodirenium species strongly affects the nature of this intermediate. When the anion is $[N(CN)_2]^-$ the two distances between the iodine atoms and the two sp carbon atoms (reported in Table 4.2) are larger, the complex is more symmetric and the trigonalization of the two sp carbon atoms is less pronounced than when the anion is $[EtSO_4]^-$, with the sole remarkable exception is represented by $R=C(CH_3)_3$, where the steric hindering of *tert*-butyl force the iodine atom far from the triple bond. Speaking in reaction terms: the complex formation is more advanced when the sulfate based anion is involved (in absence of sterical hindering). A more activated triple bond corresponds to a lower or even to a no barrier and a lower selectivity.
2. On the other side of the activated triple bond there is a relevant sterical effect exerted by the IL cation, which interacts both with the anion and with the carboxyl/carboxylate group. Furthermore, the steric interactions with the R sidechain are also significant.

In the case of $EmimEtSO_4$ with $R=C_6H_5$, H, $C_4H_3S$ the R group is nearly collinear with the two sp carbon atoms. The torsion between the two groups is lower than $10^o$ (the structure with R=H is reported in Figure 2, along with the definition of the torsion angle. Related values are reported in Table 4.2). In this condition, the positions and orientations of all atoms participating to the reaction are favorable to a six ring closure that corresponds also to the energetically more stable product. Different is the situation for $Mor_{1,2}N(CN)_2$, in the presence of this IL there is a relevant torsion between the two groups. The torsion angle values for this set of reactions are between $23^o$ and $38^o$. The reason of this torsion is the steric hindering: morpholinium cation is bigger than imidazolium (this latter presents a smaller ring and is nearly flat). Furthermore, the presence of three terminal oxygen atoms on the ethylsulfate anion allows a more flexible organization of the cation around the anion than in the case of $[N(CN)_2]^-$. For a more detailed description see Figure 2 caption. On the other hand, in the presence of the *tert*-butyl group even the smaller and more tunable ion pair ($Emim^+$ $EtSO_4^-$) is not able to compensate the sterical hindering of the sidechain that is forced between the cation and the iodine atom.

In agreement with theoretical calculation, the reaction of 2-(3,3-dimethylbut-1-ynyl)benzoic acid **1a** with $I_2$ in $EmimEtSO_{44}$ leads to the formation of a mixture of (*E*)-3-(1-iodo-2,2-dimethylpropylidene)isobenzofuran-1(3*H*)-one **2a** and 3-*tert*-butyl-4-iodo-1*H*-isochromen-1-one **3a,** with **3a**/**2a** molar ratio = 1.4 (Table 4.1, entry 3). Similar results have been obtained in

the iodocyclization reaction of 5-chloro-2-(3,3-dimethylbut-1-ynyl)benzoic acid (**1b**) in $EmimEtSO_4$. A mixture of (*E*)-6-chloro-3-(1-iodo-2,2-dimethylpropylidene)-3*H*-isobenzofuran-1-one (**2b**) and 3-*tert*-butyl-7-chloro-4-iodo-1-isochromen-1-one (**3b**) was formed, with **3b**/**2b** molar ratio = 2.22 (Table 4.1, entry 6). In all cases, the 6-membered product **3** is the major isomer in $EmimEtSO_4$.

On the other hand, the use of $Mor_{1,2}N(CN)_2$ as reaction medium in the iodolactonation reaction of 2-alkynyl benzoic acids **1** promotes the *anti* 5-*exo* cyclization pathway, with preferential or sole formation of the 5-membered product **2.** The reaction of 2-(3,3-dimethylbut-1-ynyl)benzoic acid **1a**, for example, with $I_2$ in $Mor_{1,2}N(CN)_2$ leads to the exclusive formation of (*E*)-3-(1-iodo-2,2-dimethylpropylidene)isobenzofuran-1(3*H*)-one **2a** (Table 4.1, entry 5) and 4-iodo-3-phenylisochromen-1-one **2d** was formed, in the some IL, when 2-(2-phenylethynyl)benzoic acid **1d** was used (Table 4.1, entry 11). These two different scenarios are therefore induced by the solvent ions: $[N(CN)_2]^-$ leads to a less pronounced trigonalization of the triple bond (*i.e.* to a lower iodirenium character) than $[EtSO_4]^-$ being the negative charge less delocalized and consequently having a higher electrostatic attraction toward the iodine atom. On the contrary, the larger sterical hindering of $[Mor_{1,2}]^+$ w.r.t. $[Emim]^+$ and the delocalization of the charge on $[EtSO_4]^-$ modify the geometry of the encounter complex leading to a different selectivity.

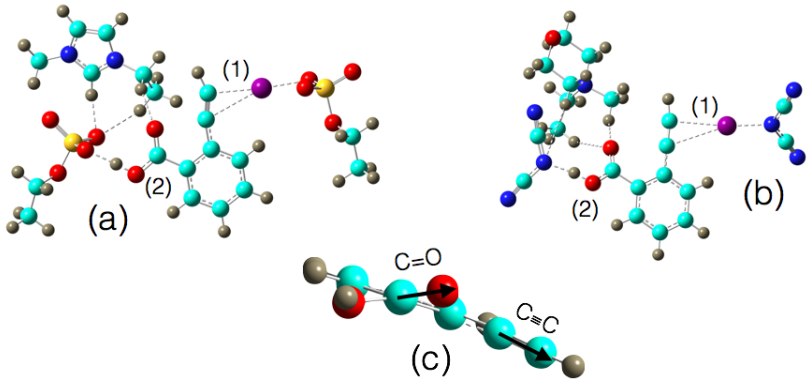



**Figure 4.3**. The two encounter complexes with R=H. We decided to report these structures since the reduced dimension of the sidechain leads to clearer pictures. (a) $EmimEtSO_4$ case. (b) $Mor_{12}N(CN)_2$ case. (c) The torsion angle is defined by the four atoms reported or, alternatively by the two bond axes. (1). Different symmetry of the iodirenium group and the different degree of trigonalization of the two sp carbon atoms in the two cases. (2) In the left (a) case the carboxyl group is coplanar with iodirenium while in the right (b) is bent

## 4.4 Experimental Section

**General Experimental Methods.** Solvent and chemicals were reagent grade and were used without further purification. All reactions were analyzed by TLC on silica gel 60 F254 and by GLC using capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase. Column chromatography was performed on silica gel 60 (70-230 mesh). Evaporation refers to the removal of solvent under reduced pressure. Melting points are uncorrected. $^{1}$H NMR and $^{13}$C NMR spectra were recorded at 25 °C on a 300 or Spectrometer in $CDCl_3$ with $Me_4Si$ as internal standard. Chemical shifts ($\delta$) and coupling constants ($J$) are given in ppm and in Hz, respectively. IR spectra were taken with an FT-IR spectrometer. Mass spectra were obtained using a GC-MS apparatus at 70 eV ionization voltage and by electrospray ionization mass spectrometry (ESI-MS). The LC-MS was operated in the positive ion mode. The experimental conditions were as follows: $N_2$ was employed as desolvation gas at 300°C and a flow rate of 8 L/min. The nebulizer was set to 45psig. The Sheat gas temperature was set at 400°C and a flow of 12 L/min. A potential of 3.5 kV was used on the capillary for positive ion mode. The fragmentor was set to 175 V. MS spectra were recorded in the 150–1000 m/z range. Microanalyses were carried out in our analytical laboratory.

**Preparation of ILs.**

3-Butyl-1-methylimidazolium acetate (BmimOAc) was prepared by dropwise addition of a stoichiometric amount of acetic acid to a methanolic solution of 3-buthyl-1-methylimidazolium methylcarbonate (Proionic).

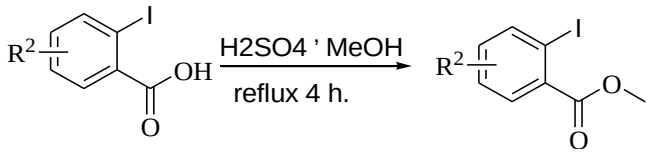
Ionic liquids 3-butyl-1-methylimidazolium tetrafluoroborate ($BmimBF_4$), 1-ethyl-3-methyl-1H-imidazol-3-ium ethyl sulfate ($EmimEtSO_4$), 3-butyl-1-methylimidazolium dicyanamide ($BmimN(CN)_2$), and *N*-ethyl-*N*-methylmorpholinium dicyanamide ($Mor_{1,2}N(CN)_2$) were prepared according to literature procedures. Structure and purity of all ILs were confirmed by $^{1}$H and $^{13}$C NMR spectroscopy.[14]

### 4.4.1Preparation of Substrates.

2-Alkynylbenzoic acids **1** were prepared by Sonogashira coupling between the corresponding methyl 2-halobenzoates and terminal alkynes followed by hydrolysis,[15] as described below.

### 4.4.2 1st step Preparation of Methyl 2-Halobenzoates.

Methyl 2-bromo-5-chlorobenzoate and methyl 3-methyl-2-iodobenzoate were prepared by Fischer esterification, according to the following procedure:

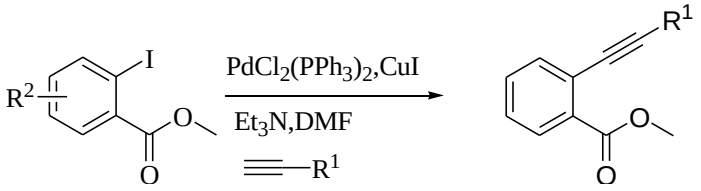



**(4.4)**

To a stirred solution of the 2-halobenzoic acid [10.0 mmol; 2-bromo-5-chlorobenzoic acid (commercially available), 2.35 g; 3-methyl-2-iodobenzoic acid,[16] 2.62 g) in MeOH (4.1 mL) was added, dropwise, concentrated $H_2SO_4$ (0.8 mL). The resulting mixture was allowed to reflux under stirring for 4 h. After cooling, water (10 mL) was added, and the mixture was extracted with $CH_2Cl_2$ (10 × 3 mL). The combined organic layers were washed with saturated $NaHCO_3$ to neutral pH and then dried over $Na_2SO_4$. After evaporation of the solvent, the crude methyl esters were sufficiently pure to be used as such for the next step without further purification.

### 2nd Step preparation of Methyl 2-Alkynyl Benzoates.

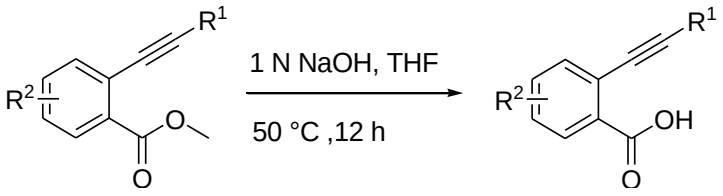
Is prepaired by Sonogashira Coupling Between Methyl 2-Halobenzoates and Terminal Alkynes




**(4.5)**

The method of Kundu[20] was adapted. A solution of the methyl 2-halobenzoate derivative (4.0 mmol; methyl 2-iodobenzoate, 1.05 g; methyl 2-bromo-5-chlorobenzoate, 1.00 g; methyl 2-iodo-3-methylbenzoate, 1.10 g), $PdCl_2(PPh_3)_2$ (99.2 mg, 0.14 mmol), CuI (61.0 mg, 0.32 mmol) and $Et_3N$ (1.9 mL) in anhydrous DMF (10 mL) was allowed to stir under nitrogen for 1 h. The terminal alkyne (3,3-dimethyl-1-butyne, 395 g; 1-hexyne, 395 mg; phenylacetylene, 490 mg; 3-ethynylthiophene, 520 mg; 1-ethynyl-4-methylbenzene, 558 mg; 1-ehtynylcyclohexene, 510 mg; trimethylsilylacetylene, 470 mg) (4.8 mmol) was then added under nitrogen, and the resulting mixture was heated at 80-85 °C (oil bath) for 15 h. After cooling, $CH_2Cl_2$ (100 mL) was added, and the mixture washed with water (3 × 100 mL). After drying over $Na_2SO_4$, the solvent was evaporated, and the residue purified by column chromatography on silica gel using hexane-AcOEt from 99:1 to 95:5 as eluent.

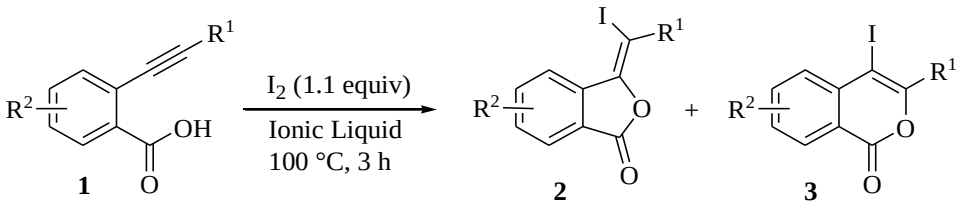
**3rd Step Hydrolysis of Methyl 2-Alkynylbenzoates to Give 2-Alkynylbenzoic Acids 1.**




**(4.6)**

The method of Kundu[20] was adapted. A stirred solution of the methyl 2-alkynylbenzoate [2.5 mmol; methyl 2-(3,3-dimethylbut-1-ynyl)benzoate, 541 mg; methyl 5-chloro-2-(3,3-dimethylbut-1-ynyl)benzoate, 627 mg; methyl 2-(hex-1-ynyl)benzoate, 541 mg; methyl 2-(2-phenylethynyl)benzoate, 591 mg; methyl 5-chloro-2-(2-phenylethynyl)benzoate, 677 mg; methyl 2-[2-(thiophen-3-yl)ethynyl]benzoate, 606 mg; methyl 3-methyl-2-(2-phenylethynyl)benzoate, 626 mg; methyl 2-(2-*p*-tolylethynyl)benzoate, 626 mg; methyl 2-[(1-cyclohexenyl)ethynyl]benzoate, 601 mg; methyl 2-[2-(trimethylsilyl)ethynyl]benzoate, 581 mg and 1 N NaOH (14.0 mL) in THF (3.0 mL) was heated at 50 °C for 12 h. After cooling to room temperature, the mixture was washed with $Et_2O$ (3 × 15 mL), further cooled with the aid of an ice bath, and neutralized with 1 N HCl. The resulting mixture was extracted at room temperature with $CH_2Cl_2$ (3 × 50 mL), and the collected organic layers dried over $Na_2SO_4$. Filtration and evaporation of the solvent afforded the crude 2-alkynylbenzoic acid derivatives (in the case of methyl 2-[2-(trimethylsilyl)ethynyl]benzoate, triple bond deprotection also occurred together with ester hydrolysis to give 2-ethynylbenzoic acid). 2-(Hex-1-ynyl)benzoic acid **1c** was a low melting yellowish solid, and was sufficiently pure to be used as such in the iodocyclization reactions. All other 2-alkynylbenzoic acids **1a,b** and **1d-i** and 2-ethynylbenzoic acid **1j** were further purified by crystallization with $Et_2O$/hexane.

### 4.4.3 General Procedure for the Iodolactonization of 2-Alkynylbenzoic Acids in Ionic Liquids




**(4.3)**

In a Schlenk flask containing the ionic liquid was added, under nitrogen, the pure substrate (for **1a**, **1b**, and **1d-j**) or a solution of the substrate in $Et_2O$ (2 mL; for **1c**) (0.40 mmol; **1a**, 81.0 mg; **1b**, 95.0 mg; **1c**, 81.0 mg; **1d**, 89.0 mg; **1e**, 103.0 mg; **1f**, 91.0 mg; **1g**, 94.3 mg; **1h**, 94.3 mg; **1i**,

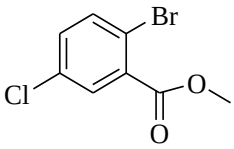
90.5 mg; **1j**, 59.0 mg). In the case of **1c**, the excess $Et_2O$ was then eliminated under vacuum for 10 min. To the solution of the substrate in the IL, was added, under nitrogen, $I_2$ (112.0 mg, 0.44 mmol), and the resulting mixture was heated with stirring at 100 °C (oil bath) for 3 h. After cooling, the product was extracted with diethyl ether (2 mL, followed by 6 × 5 mL), and the IL residue, after elimination of the traces of $Et_2O$ under vacuum, was used as such for the next recycle (see below). The collected ethereal phases were concentrated. After evaporation of the solvent, products were purified by column chromatography on silica gel using 95:5 hexane–AcOEt as the eluent.

**Recycling Procedure.** To the residue obtained as described above, was added the fresh substrate **1** (0.40 mmol) and $I_2$ (111.7 mg, 0.44 mmol) in $Et_2O$ (3 mL), and then the same procedure described above was followed.

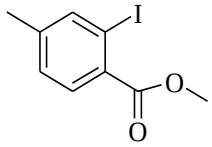
## 4.5 Conclusion

In conclusion, we have found that the iodolactonization of 2-alkynylbenzoic acids **1** can be conveniently performed in ionic liquids as reaction media, in the absence of an external base and with the possibility to recycle several times the IL solvent. We have found that the regiochemical output of the process may be modulated by the nature of the IL employed: in particular, *N*-ethyl-*N*-methylmorpholinium dicyanamide ($Mor_{1,2}N(CN)_2$) promoted the *anti* 5-*exo* cyclization mode, with preferential or sole formation of (*E*)-3-(iodomethylene)isobenzofuran-1(3*H*)-ones **2**, while 1-ethyl-3-methyl-1H-imidazol-3-ium ethyl sulfate ($EmimEtSO_4$) tended to favor the 6-*endo* cyclization mode, with selective or exclusive formation of 4-iodo-1*H*-isochromen-1-ones **3**. The structure of representative products (isobenzofuranone **2a** and isochromenone **3d**) was confirmed by XRD analysis, and DFT calculations have been performed to clarify the role of the nature of the IL medium on the regioselectivity of the process. The heterocyclic derivatives synthesized in this work belong to particularly important classes of heterocycles, known to possess a wide range of biological activities.[9,10]

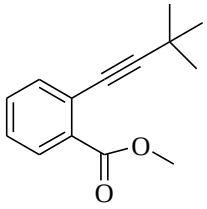
### 4.6 Characterization Data




Methyl 2-bromo-5-chlorobenzoate. Yield: 2.35 mg, starting from 2.35 g of 5-chloro-2-iodobenzoic acid (94 %). Colorless solid, mp = 37-38 °C (lit.,[17] 37-38 °C). IR (KBr): $\nu$ = 1734 (s), 1461 (w), 1434 (w), 1295 (m), 1251 (m), 1119 (m), 1101 (m), 1034 (m), 962 (w), 814 (m), 779 (w), 753 (w) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.78 (distorted dd, $J$ = 2.6, 0.8, 1 H), 7.58 (distorted dd, $J$ = 8.5, 0.8, 1 H), 7.30 (distorted ddd, $J$ = 8.5, 2.6, 0.8, 1 H), 3.94 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 165.3, 135.5, 133.4, 133.3, 132.6, 131.3, 119.7, 52.8; GC-MS: $m/z$ = 250 (60) [$(M+2)^+$], 248 (50) ($M^+$), 219 (100), 217 (89), 191 (24), 189 (23), 110 (18), 75 (24); anal. calcd for $C_8H_6BrClO_2$ (249.49): C, 38.51; H, 2.42; Br, 32.03; Cl, 14.21; found C, 38.54; H, 2.40; Br, 32.00; Cl, 14.24. The spectroscopic data were in good agreement with those reported.[18]

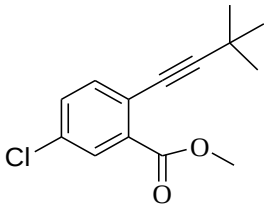



Methyl 3-methyl-2-iodobenzoate. Yield: 2.35 mg, starting from 2.62 g of 3-methyl-2-iodobenzoic acid (85 %). Yellow oil. IR (KBr): $\nu$ = 1733 (s), 1572 (w), 1433 (m), 1399 (w), 1294 (m), 1265 (w), 1242 (w), 1194 (m), 1177 (w), 1143 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.37-7.18 (m, 3 H), 3.91 (s, 3 H), 2.47 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 168.6, 143.2, 138.3, 131.7, 127.7, 127.0, 99.9, 52.5, 29.6; GC-MS $m/z$ = 276 (89) [$M^+$], 245 (100), 217 (17), 149 (14), 134 (3), 119 (8), 90 (53); anal. calcd for $C_9H_9BrO_2$ (229.07): C, 47.19; H, 3.96; Br, 34.88; found C, 47.17; H, 3.99; Br, 34.85.[19] The spectroscopic data agreed with those reported.

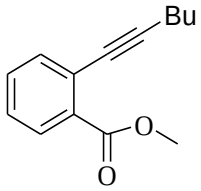



Methyl 2-(3,3-dimethylbut-1-ynyl)benzoate. Yield: 720 mg, starting from 1.05 g of methyl 2-iodobenzoate (83 %). Yellow oil. IR (film): $\nu$ = 2239 (w), 1720 (s), 1597 (w), 1447 (w), 1290 (m), 1250 (m), 1128 (m), 1081 (m), 757 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.91-7.83 (m, 1 H), 7.52-7.45 (m, 1 H), 7.22 (td, $J$ = 7.6, 1.5, 1 H), 7.29 (td, $J$ = 7.6, 1.5, 1 H), 3.91 (s, 3 H), 1.34 (s, 9 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 167.3, 133.9, 132.2, 131.4, 130.2, 127.1,

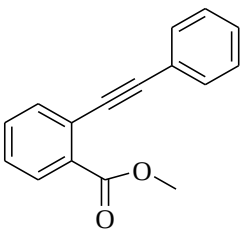
124.2, 103.6, 77.9, 51.9, 30.9, 28.2; GC-MS: *m/z* = 216 (39) [$M^+$], 201 (100), 185 (14), 157 (87), 141 (42), 115 (55); anal. calcd for $C_{14}H_{16}O_2$ (216.28): C, 77.75; H, 7.46; found C, 77.73; H, 7.49.



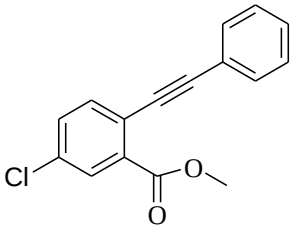

Methyl 5-chloro-2-(3,3-dimethylbut-1-ynyl)benzoate. Yield: 800 mg, starting from 1.00 g of methyl 2-bromo-5-chlorobenzoate (80 %). Yellow oil. IR (film): *v* = 2239 (w), 1720 (s), 1473 (m), 1435 (m), 1287 (s), 1239 (s), 1142 (w), 1077 (w), 974 (w), 829 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.85 (d, *J* = 2.2, 1 H), 7.40 (distorted d, *J* = 8.4, 1 H), 7.35 (distorted dd, *J* = 8.4, 2.2, 1 H), 3.91 (s, 3 H), 1.34 (s, 9 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 165.9, 135.1, 133.5, 133.0, 131.5, 130.2, 122.8, 104.7, 77.0, 52.1, 30.8, 28.3; GC-MS: *m/z* = 252 (11) [$(M+2)^+$], 250 (33) [$M^+$], 235 (100), 215 (47), 203 (41), 191 (30), 156 (71), 149 (14), 139 (21), 128 (14), 115 (17); anal. calcd for $C_{14}H_{15}ClO$ (250.72): C, 67.07; H, 6.03; Cl, 14.14; found C, 67.09; H, 6.06; Cl, 14.11.



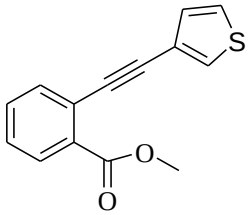

Methyl 2-(hex-1-ynyl) benzoate. Yield: 615 mg, starting from 1.05 g of methyl 2-iodobenzoate (80 %). Yellow oil. IR (film): *v* = 2229 (m), 1733 (s), 1597 (w), 1567 (w), 1485 (m), 1433 (m), 1294 (m), 1250 (m), 1128 (m), 1083 (m), 964 (w), 758 (m), 702 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.87 (dd, J = 7.6, 1.2, 1 H), 7.50 (distorted d, J = 7.6, 1 H), 7.40 (td, J = 7.6, 1.2, 1 H), 7.29 (td, J = 7.6, 1.2, 1 H), 3.91 (s, 3 H), 2.48 (t, J = 7.0, 2 H), 1.69-1.43 (m, 4 H), 0.95 (t, J = 7.2, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 167.0, 134.2, 132.0, 131.5, 130.1, 127.1, 124.5, 96.0, 79.2, 52.0, 30.8, 22.0, 19.5, 13.7; GC-MS: *m/z* = 216 (14) [$M^+$], 201 (20), 183 (12), 174 (100), 159 (44), 143 (23), 131 (27), 115 (36); anal. calcd for $C_{14}H_{16}O_2$ (216.28): C, 77.75; H, 7.46; found C, 77.76; H, 7.48. The spectroscopic data agreed with those reported.



Methyl 2-(2-phenylethynyl) benzoate. Yield: 830 mg, starting from 1.05 g of methyl 2-iodobenzoate (88 %). Yellow oil. IR (film): $\nu$ = 2218 (w), 1730 (s), 1599 (w), 1568 (w), 1494 (m), 1433 (w), 1293 (m), 1252 (m), 1128 (m), 1078 (m), 964 (w), 756 (m), 690 (m) $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.98-7.93 (m, 1 H), 7.65-7.55 (m, 3 H), 7.45 (td, $J$ = 7.6, 1.4, 1 H), 7.38-7.30 (m, 4 H), 3.94 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 166.7, 134.0, 131.9, 131.73, 131.68, 130.5, 128.5, 128.4, 127.9, 123.7, 123.3, 94.4, 88.3, 52.2; GC-MS: *m/z* = 236 (100) [$M^+$], 221 (76), 205 (24), 193 (36), 165 (38), 151 (17), 126 (4), 102 (10); anal. calcd for $C_{16}H_{12}O_2$ (236.27): C, 81.34; H, 5.12; found C, 81.32; H, 5.15. The spectroscopic data agreed with those reported.[21,22]

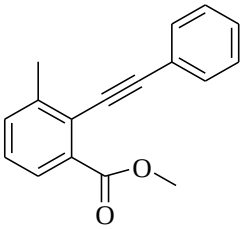



Methyl 5-chloro-2-(2-phenylethynyl) benzoate. Yield: 848 mg, starting from 1.00 g of methyl 2-bromo-5-chlorobenzoate (78 %). Yellow solid, mp = 53-54 °C. IR (KBr): $\nu$ = 2216 (w), 1734 (s), 1493 (m), 1435 (w), 1289 (s), 1242 (s), 1109 (m), 1073 (m), 827 (w), 755 (m), 689 (m) $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.94 (d, $J$ = 2.3, 1 H), 7.60-7.49 (m, 2 H), 7.42 (distorted dd, J = 8.4, 2.2, 1 H), 7.38-7.29 (m, 4 H), 3.95 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 165.4, 135.1, 133.8, 133.1, 131.8, 131.7, 130.6, 128.7, 128.4, 95.4, 87.3, 52.4; GC-MS *m/z* = 270 (100) [$M^+$], 255 (73), 239 (18), 227 (34), 199 (25), 176 (53), 150 (13), 119 (8), 88 (30); anal. calcd for $C_{16}H_{11}ClO_2$ (270.71): C, 70.99; H, 4.10; Cl, 13.10; found C, 70.97; H, 4.13; Cl, 13.11.

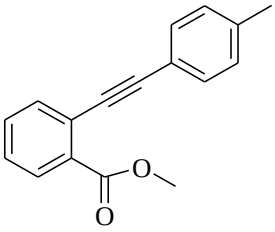



Methyl 2-[2-(thiophen-3-yl) ethynyl] benzoate. Yield: 795 mg, starting from 1.05 g of methyl 2-iodobenzoate (82 %). Yellow solid, mp = 36-38 °C. IR (KBr): $\nu$ = 2216 (w), 1728 (s), 1595 (w), 1566 (w), 1481 (w), 1432 (w), 1292 (m), 1283 (m), 1253 (m), 1126 (m), 1076 (m), 940 (w), 870 (w), 783 (m), 756 (m), 698 (m), 623 (m) $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.96 (dd, $J$ = 7.6, 1.4, 1 H), 7.62 (distorted dd, $J$ = 7.6, 1.3, 1 H), 7.59-7.54 (m, 1 H), 7.46 (td, $J$ = 7.6, 1.4, 1 H), 7.34 (distorted td, $J$ = 7.6, 1.3, 1 H), 7.29 (distorted dd, $J$ = 5.0, 2.9, 1 H), 7.23 (distorted dd, $J$ = 5.0, 1.1, 1 H), 3.94 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 166.6, 133.9, 131.7, 130.5,

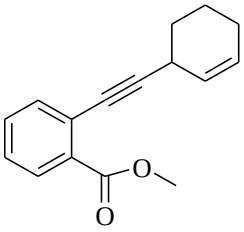
129.9, 129.1, 127.8, 125.4, 123.7, 122.4, 89.6, 87.8, 52.1; GC-MS *m/z* = 242 (100) [$M^+$], 227 (65), 211 (21), 199 (57), 183 (12), 171 (26), 139 (54), 105 (12), 91 (24); anal. calcd for $C_{14}H_{10}O_2S$ (242.29): C, 69.40; H, 4.16; S, 13.23; found C, 69.38; H, 4.13; S, 13.24. The spectroscopic data agreed with those reported.[23]



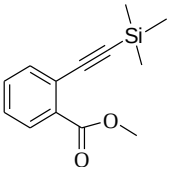
Methyl 3-methyl-2-(2-phenylethynyl) benzoate. Yield: 760 mg, starting from 1.10 g of methyl 2-iodo-3-methylbenzoate, 1.10 g (76 %). Yellow oil. IR (KBr): *v* = 2213 (w), 1730 (s), 1597 (w), 1491 (m), 1436 (m), 1291 (m), 1268 (m), 1193 (m), 1137 (m), 1017 (m), 876 (w), 756 (s), 691 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.79-7.73 (m, 1 H), 7.61-7.35 (m, 2 H), 7.40-7.30 (m, 4 H), 7.23 (t, *J* = 7.7, 1 H), 3.93 (s, 3 H), 2.55 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 167.2, 141.8, 132.9, 132.5, 131.6, 128.5, 128.4, 127.7, 127.4, 123.5, 122.9, 99.3, 86.6, 52.1, 21.3; GC-MS *m/z* = 250 (77) [$M^+$], 235 (100), 219 (29), 207 (47), 191 (45), 189 (72), 179 (46), 178 (26), 165 (19), 95 (27); anal. calcd for $C_{17}H_{14}O_2$ (250.29): C, 81.58; H, 5.64; found C, 81.56; H, 5.65.



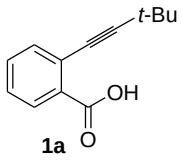
Methyl 2-(2-p-tolylethynyl) benzoate. Yield: 842 mg, starting from 1.05 g of methyl 2-iodobenzoate (84 %). Yellow oil. IR (film): *v* = 2216 (m), 1731 (s), 1595 (w), 1566 (w), 1510 (m), 1433 (m), 1293 (m), 1252 (m), 1189 (w), 1127 (m), 1078 (m), 1040 (w), 965 (w), 818 (m), 757 (m), 700 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.98-7.91 (m, 1 H), 7.65-7.58 (m, 1 H), 7.51-7.40 (m, 3 H), 7.37-7.28 (m, 1 H), 7.14 (distorted dd, *J* = 7.9, 2 H), 3.94 (s, 3 H), 2.34 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 166.7, 138.7, 133.9, 131.8, 131.6, 130.4, 129.1, 127.7, 123.9, 120.2, 94.6, 87.7, 52.1, 21.5; GC-MS *m/z* = 250 (100) [$M^+$], 235 (91), 219 (20), 207 (56), 189 (39), 165 (9), 125 (6), 109 (12), 95 (21); anal. calcd for $C_{17}H_{14}O_2$ (250.29): C, 81.58; H, 5.64; found C, 81.60; H, 5.63. The spectroscopic data were in good agreement with those reported.[24]



Methyl 2-(2-cyclohexenylethynyl) benzoate. Yield: 823 mg, starting from 1.05 g of methyl 2-iodobenzoate (86 %). Yellow oil, IR (film): $\nu$ = 2201 (m), 1718 (s), 1595 (w), 1566 (w), 1483 (m), 1434 (m), 1290 (m), 1251 (m), 1129 (m), 1077 (m), 758 (m), 700 (w) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.95-7.88 (m, 1 H), 7.54-7.49 (m, 1 H), 7.42 (td, $J$ = 7.5, 1.4, 1H), 7.30 (td, $J$ = 7.7, 1.4, 1H), 6.30-6.24 (m, 1 H), 3.91 (s, 3 H), 2.32-2.10 (m, 4 H), 1.74-1.53 (m, 4 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 166.8, 136.0, 133.8, 131.61, 131.57, 130.3, 127.3, 124.2, 121.0, 96.4, 85.8, 52.0, 29.1, 25.8, 22.3, 21.5; GC-MS *m/z* = 240 (100) [$M^+$], 225 (47), 207 (20), 197 (20), 179 (25), 165 (27), 159 (21), 147 (18), 133 (17), 115 (16); anal. calcd for $C_{16}H_{16}O_2$ (240.30): C, 79.97; H, 6.71; found C, 79.99; H, 6.68. The spectroscopic data agreed with those reported.[25]



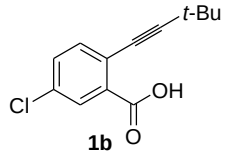
Methyl 2-[2-(trimethylsilyl) ethynyl] benzoate. Yield: 748 mg, starting from 1.05 g of methyl 2-iodobenzoate (88 %). Yellow oil. IR (film): $\nu$ = 2106 (w), 1729 (s), 1595 (w), 1568 (w), 1484 (w), 1434 (m), 1298 (m), 1258 (m), 1133 (m), 1080 (m), 963 (w), 830 (w), 759 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.93-7.87 (m, 1 H), 7.61-7.54 (m, 1 H), 7.43 (td, $J$ = 7.5, 1.6, 1H), 7.35 (td, J = 7.6, 1.4), 3.92 (s, 3 H), 0.28 (s, 9 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 167.0, 134.6, 132.7, 131.6, 130.4, 128.3, 123.3, 103.4, 99.8, 52.1, 0.09; GC-MS *m/z* = 232 (5) [$M^+$], 248 (7), 217 (34), 187 (100), 158 (9), 143 (9), 131 (5), 129 (5), 115 (6), 101 (7), 93 (6); anal. calcd for $C_{13}H_{16}O_2Si$ (232.35): C, 67.20; H, 6.94; Si, 12.09; found C, 67.23; H, 6.93; Si, 12.07. The spectroscopic data agreed with those reported.[26]



**1a**

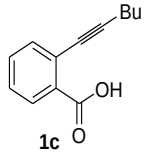
2-(3,3-Dimethylbut-1-ynyl)benzoic acid ***(1a)***. Yield: 420 mg, starting from 541 mg of methyl 2-(3,3-dimethylbut-1-ynyl)benzoate (83%). White solid, mp = 116-118 °C, lit.,[27] 118-122 °C. IR (KBr): $\nu$ = 3074 (w), 2966 (m), 2243 (w), 1695 (s), 1566 (w), 1486 (m), 1412 (m), 1297 (m), 1267 (s), 1087 (w), 938 (m), 756 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 12.57 (s, br, 1 H),

8.06 (dd, *J* = 7.9, 1.2, 1 H), 7.52 (distorted dd, *J* = 7.9, 1.2, 1 H), 7.46 (td, *J* = 7.3, 1.2, 1 H), 7.34 (td, *J* = 7.3, 1.2, 1 H), 1.36 (s, 9 H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ = 171.7, 134.1, 132.3, 131.1, 130.9, 127.3, 124.9, 105.1, 77.8, 30.7, 28.3; LC-MS: *m/z* =225.09 [$(M+Na)^+$]; anal. calcd for $C_{13}H_{14}O_2$ (202.25): C, 77.20; H, 6.98; found C, 77.22; H, 6.96. The spectroscopic data were in good agreement with those reported.[27]



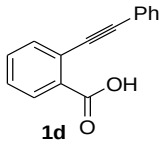
**1b**

5-Chloro-2-(3,3-dimethylbut-1-ynyl)benzoic acid ***(1b)***. Yield: 472 mg, starting from 627 mg of methyl 5-chloro-2-(3,3-dimethylbut-1-ynyl)benzoate (80%). White solid, mp = 112-113 °C. IR (KBr): *v* = 3075 (w), 2964 (m), 2240 (w), 1705 (s), 1480 (w), 1438 (m), 1415 (m), 1298 (s), 1252 (s), 1112 (m), 830 (m), 718 (m) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 11.35 (s, br, 1 H, OH), 8.05-8.01 (m, 1 H), 7.46-7.42 (m, 2 H), 1.35 (s, 9 H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 170.4, 135.3, 133.2, 132.5, 132.0, 131.1, 123.5, 106.2, 76.9, 30.6, 28.4; LC-MS: *m/z* = 275.01 [$(M+K)^+$]; anal. calcd for $C_{13}H_{13}ClO_2$ (236.69): C, 65.97; H, 5.54; Cl, 14.98; found C, 65.95; H, 5.55; Cl, 14.96.



**1c**

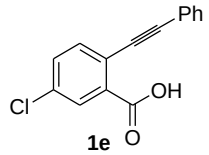
2-(Hex-1-ynyl) benzoic acid ***(1c)***. Yield: 320 mg, starting from 541 mg of methyl 2-(hex-1-ynyl)benzoate (63%). Low-melting yellowish solid. IR (film): *v* = 1691 (s), 1575 (w), 1411 (m), 1271 (s), 920 (m), 740 (m), 664 (w) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 11.96 (s, br, 1 H, OH), 8.06 (distorted dd, *J* = 7.8, 1.0, 1H), 7.54 (distorted dd, *J* = 7.7, 1.1, 1 H), 7.47 (td, *J* = 7.7, 1.2, 1 H), 7.35 (td, *J* = 7.7, 1.1, 1 H), 2.50 (t, *J* = 6.8, 2 H), 1.70 -1.45 (m, 4 H), 0.96 (t, *J* = 7.2, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 171.6, 134.4, 132.4, 131.1, 130.7, 127.3, 125.0, 97.4, 79.1, 30.6, 22.0, 19.5, 13.6.; LC-MS *m/z* = 225.09 [$(M+Na)^+$]; anal. calcd for $C_{13}H_{14}O_2$ (202.25): C, 77.20; H, 6.98; found C, 77.17; H, 6.95. The spectroscopic data agreed with those reported.[24]



**1d**

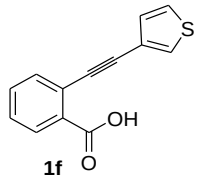
2-(2-Phenylethynyl) benzoic acid ***(1d)***. Yield: 497 mg, starting from 591 mg of methyl 2-(2-phenylethynyl)benzoate (89%). Yellow solid, mp = 126-127 °C, lit. 127-129 °C[28] 126-127 °C.

IR (KBr): $\nu$ = 2216 (w), 1694 (s), 1564 (m), 1494 (m), 1480 (m), 1419 (m), 1298 (m), 1271 (s), 1159 (w), 1079 (w), 917 (m), 751 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 11.26 (s, br, 1H, OH), 8.13 (dd, $J$ = 7.9, 1.2, 1H), 7.68 (distorted dd, $J$ = 7.8, 1.1, 1 H), 7.61-7.50 (m, 3 H), 7.40 (td, $J$ = 7.6, 1.2, 1 H), 7.33-7.25 (m, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 171.8, 134.2, 132.6, 131.8, 131.4, 130.5, 128.6, 128.4, 127.9, 124.5, 123.2, 95.3, 88.1; LC-MS *m/z* = 245.06 [$(M+Na)^+$]; anal. calcd for $C_{15}H_{10}O_2$ (222.24): C, 81.07; H, 4.54; found C, 81.09; H, 4.53. The spectroscopic data were in good agreement with those reported.[28]



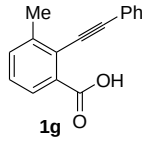
**1e**

5-Chloro-2-(2-phenylethynyl) benzoic acid ***(1e)***. Yield: 526 mg, starting from 677 mg of methyl 5-chloro-2-(2-phenylethynyl)benzoate (82%). White solid, mp = 138-139 °C. IR (KBr): $\nu$ = 3083 (m, br), 2218 (w), 1697 (s), 1494 (w), 1475 (w), 1302 (m), 1252 (m), 1107 (m), 835 (w), 751 (m), 685 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 11.03 (s, br, 1 H), 8.12-8.06 (m, 1 H), 7.66-7.46 (m, 4 H), 7.37-7.25 (m, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 170.4, 135.3, 134.0, 132.8, 131.8, 131.4, 130.2, 128.8, 128.5, 123.1, 122.9, 96.4, 87.1; LC-MS *m/z* = 257.04 [$(M+H)^+$]; anal. calcd for $C_{15}H_9ClO_2$ (256.68): C, 70.19; H, 3.53; Cl, 13.81; found C, 70.21; H, 3.52; Cl, 13.80.



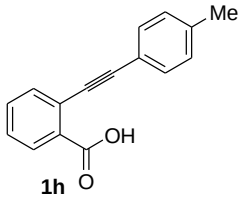
**1f**

2-(2-Thiophen-3-yl) ethynyl]benzoic acid ***(1f)***. Yield: 526 mg, starting from 606 mg of methyl 2-[2-(thiophen-3-yl)ethynyl]benzoate (82%). Yellow solid, mp = 53-54 °C. IR (KBr): $\nu$ = 2828 (w, br), 2212 (vw), 1678 (s), 1567 (w), 1408 (w), 1307 (m), 1284 (m), 1262 (m), 1077 (w) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 10.18 (s, br, 1 H), 8.12 (distorted d, $J$ = 7.8, 1 H), 7.65 (distorted d, $J$ = 7.7, 1 H), 7.59-7.48 (m, 2 H), 7.40 (td, $J$ = 7.8, 1.1, 1 H), 7.29-7.19 (m, 2 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 171.4, 134.1, 132.6, 131.4, 130.5, 129.9, 129.3, 127.9, 125.4, 124.5, 122.3, 90.5, 87.7; LC-MS: *m/z* = 251.01 [$(M+Na)^+$]; anal. calcd for $C_{13}H_8O_2S$ (228.27): C, 68.40; H, 3.53; S, 14.05; found C, 68.41; H, 3.55; S, 14.03.



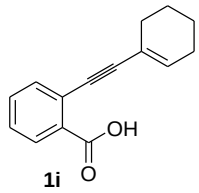
**1g**

3-Methyl-2-(2-phenylethynyl)benzoic acid (***1g***). Yield: 498 mg, starting from 626 mg of methyl 3-methyl-2-(2-phenylethynyl)benzoate (84%). White solid, mp = 72-73 °C. IR (KBr): $\nu$ = 2969 (m, br), 2209 (w), 1683 (s), 1441 (w), 1412 (w), 1295 (m), 1267 (m), 759 (m), 691 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 11.60 (s, br, 1 H), 7.98-7-91 (m, 1 H), 7.61-7.53 (m, 2 H), 7.48-7.42 (m, 1 H), 7.33-7-23 (m, 4 H), 2.59 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ =172.3, 142.1, 133.8, 131.6, 131.1, 128.7, 128.5, 128.4, 127.4, 123.7, 123.4, 100.4, 86.5, 21.3; LC-MS *m/z* = 237.09 $[(M+H)^+]$; anal. calcd for $C_{16}H_{12}O_2$ (236.27): C, 81.34; H, 5.12; found C, 81.32; H, 5.14.



**1h**

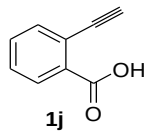
2-p-Tolylethynylbenzoic acid ***(1h)***. Yield: 504 mg, starting from 626 mg of methyl 2-(2-*p*-tolylethynyl)benzoate (85%). White solid, mp = 117-118 °C, lit.,[24] 98-100 °C. IR (KBr): $\nu$ = 3417 (w, br), 2216 (w), 1696 (s), 1511 (w), 1412 (w), 1003 (m), 1268 (m), 816 (m), 756 (m) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 11.64 (s, br, 1 H), 8.12 (d, *J* = 7.3, 1 H), 7.66 (distorted d, *J* = 7.9, 1 H), 7.52 (td, *J* = 7.3, 1.2, 1 H), 7.46 (d, *J* = 7.9, 2 H), 7.39 (td, *J* = 7.9, 1.2, 1 H), 7.08 (d, *J* = 7.9, 2 H), 2.32 (s, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ = 171.7, 138.8, 134.1, 132.6, 131.7, 131.4, 130.5, 129.2, 127.7, 124.7, 120.2, 95.7, 87.6, 21.5; LC-MS *m/z* = 259.08 $[(M+Na)^+]$; anal. calcd for $C_{16}H_{12}O_2$ (236.27): C, 81.34; H, 5.12; found C, 81.37; H, 5.10. The spectroscopic data agreed with those reported.[24,29]



**1i**

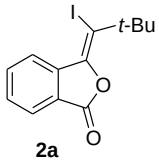
2-[(1-Cyclohexenyl)ethynyl]benzoic acid ***(1i)***. Yield: 480 mg, starting from 601 mg of methyl 2-[(1-cyclohexenyl)ethynyl]benzoate (85%). Yellow solid, mp = 75-76 °C. IR (KBr):$\nu$ = 2935 (m, br), 2197 (w), 1698 (s), 1592 (w), 1435 (w), 1414 (m), 1315 (m), 1287 (m), 1078 (w), 920 (m), 752 (m), 656 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 11.71 (s, br, 1 H), 8.08 (dd, *J* = 7.9, 0.8, 1 H), 7.56 (distorted dd, *J* = 7.7, 0.8, 1 H), 7.53-7.45 (m, 1 H), 7.41-7.32 (m, 1 H), 6.34-6.26 (m, 1 H), 2.33-2.22 (m, 2 H), 2.22-2.11 (m, 2 H), 1.76-1.56 (m, 4 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 171.6, 147,5, 136.4, 134.0, 132.4, 131.2, 130.3, 127.4, 124.8, 120.9, 97.5, 85.5, 28.8, 25.9, 22.3, 21.5; LC-MS *m/z* = 249.09 $[(M+Na)^+]$; anal. calcd for $C_{15}H_{12}O_2$ (226.27):

C, 79.62; H, 6.24; found C, 79.64; H, 6.21. The spectroscopic properties agreed with those previously reported.[25]



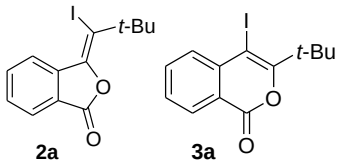
**1j**

2-Ethynylbenzoic acid ***(1j)***. Yield: 220 mg, starting from 581 mg of methyl 2-[2-(trimethylsilyl)ethynyl]benzoate (60%). Yellow solid, mp = 120-122 °C lit.,[28] 121-123 °C. IR (KBr): $\nu$ = 3291 (w), 1696 (s), 1595 (w), 1569 (w), 1489 (m), 1406 (m), 1279 (s), 1080 (w), 919 (m), 828 (w), 757 (s) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 11.62 (s, br, 1 H), 8.09 (distorted d, $J$ = 7.9, 1 H), 7.66 (distorted d, $J$ = 7.7, 1 H), 7.53 (t, $J$ = 7.6, 1 H), 7.44 (distorted t, $J$ = 7.6, 1 H), 3.46 (s, 1 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 171.4, 135.2, 132.6, 131.3, 131.2, 128.6, 123.2, 83.3, 81.8; LC-MS $m/z$ = 169.02 [$(M+Na)^+$]; anal. calcd for $C_9H_6O_2$ (146.14): C, 73.97; H, 4.14; found C, 73.99; H, 4.16. The spectroscopic properties agreed with those previously reported.[28]



**2a**

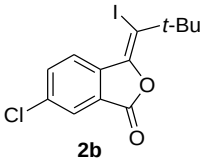
(E)-3-(1-Iodo-2,2-dimethylpropylidene)-3H-isobenzofuran-1-one ***(2a)***. Yield: 112 mg, starting from 81 mg of **1a** (85%; Table 1, entry 5). White solid, mp = 109-110 °C. IR (KBr): $\nu$ = 1768 (s), 1469 (m), 1251 (w), 1223 (w), 1105 (m), 1003 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 9.1 (d, $J$ = 8.2, 1 H), 7.92 (d, $J$ = 7.7, 1 H), 7.73 (td, $J$ = 7.4, 1.2, 1 H), 7.58 (td, $J$ = 7.4, 0.4, 1 H), 1.51 (s, 9 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 165.0, 143.8, 140.2, 133.8, 130.1, 126.3, 126.0, 125.7, 102.5, 41.0, 32.6; GC-MS: $m/z$ =328 ($M^+$) (39), 313 (7), 272 (54), 201 (100), 186 (98), 159 (25), 145 (16), 129 (22), 115 (27); anal. calcd for $C_{13}H_3IO_2$ (328.15): C, 47.58; H, 3.99; I, 38.67; found C, 47.55; H, 4.01; I, 38.69.



**2a** **3a**

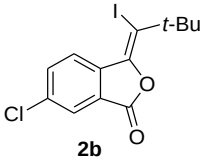
Mixture of (E)-3-(1-Iodo-2,2-dimethylpropylidene)-3H-isobenzofuran-1-one ***(2a)*** + *3-tert-Butyl-4-iodo-1-isochromen-1-one* ***(3a)*** Total yield: 125 mg, starting from 81 mg of **1a** (95%; **3a** / **2a** = 1.41, determined by GLC; Table 1, entry 3). White solid. IR (KBr): $\nu$ = 1771 (s), 1733 (s), 1371 (w), 1251 (w), 1106 (m), 1002 (m), 962 (w), 762 (s), 688 (s) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 9.01 (d, $J$ = 8.2, 1 H, **2a**), 8.21 (d, $J$ = 7.6, 1 H, **3a**), 8.02-7.87 [m, 1 H (**2a**) +

1 H (**3a**)], 7.82-7.68 [m, 1 H (**2a**) + 1 H (**3a**)], 7.63-7.46 [m, 1 H (**2a**) + 1 H (**3a**)], 1.62 (s, 9 H, **3a**), 1.50 (s, 9 H, **2a**); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 165.0 (**2a**), 162.4 (**3a**), 161.1 (**3a**), 143.8 (**2a**), 140.2 (**2a**), 139.5 (**3a**), 135.2 (**3a**), 133.8 (**2a**), 131.3 (**3a**), 130.1 (**2a**), 129.4 (**3a**), 128.7 (**3a**), 126.3 (**2a**), 126.0 (**2a**), 125.7 (**2a**), 120.5 (**3a**), 102.5 (**2a**), 73.3 (**3a**), 41.0 (**2a**), 39.4 (**3a**), 32.6 (**2a**), 29.5 (**3a**); GC-MS: **2a**: *m/z* = 328 ($M^+$) (27), 272 (49), 201 (100), 186 (94), 159 (27), 145 (18), 129 (24), 115 (32); **3a**: *m/z* = 328 ($M^+$) (51), 243 (10), 201 (11), 186 (18), 159 (100), 158 (41), 129 (10), 115 (11); anal. calcd for $C_{13}H_3IO_2$ (328.15): C, 47.58; H, 3.99; I, 38.67; found C, 47.57; H, 4.00; I, 38.65.

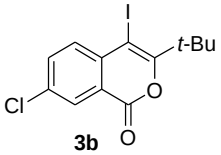


**2b**

*(*E)-6-Chloro-3-(1-iodo-2,2-dimethylpropylidene)-3H-isobenzofuran-1-one ***(2b)***. Yield: 124 mg, starting from 95 mg of **1b** (85%; Table 1, entry 7). White solid, mp = 66-68 °C. IR (KBr): *v* = 1772 (s), 1598 (w), 1460 (m), 1253 (m), 1223 (m), 1119 (m), 1013 (m), 891 (w), 840 (w), 680 (w) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.96 (d, *J* = 8.6, 1 H), 7.88 (dd, *J* = 2.1, 0.6, 1 H), 7.68 (dd, *J* = 8.6, 2.1, 1 H), 1.49 (s, 9 H, *t*-Bu); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 163.9, 142.9, 138.0, 136.3, 134.0, 127.3, 126.8, 125.3, 103.8, 40.8, 32.4; GC-MS: *m/z* = 364 [$(M+2)^+$] (19), 362 ($M^+$) (56), 347 (10), 306 (29), 235 (100), 220 (98), 193 (23), 149 (12), 128 (21), 110 (22); anal. calcd for $C_{13}H_{12}ClIO_2$ (362.59): C, 43.06; H, 3.34; Cl, 9.78; I, 35.00; found C, 43.09; H, 3.31; Cl, 9.79; I, 35.02.



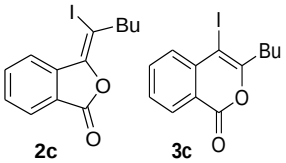
**2b**



**3b**

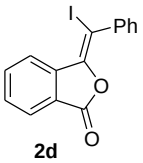
*Mixture of (E)-6-Chloro-3-(1-iodo-2,2-dimethylpropylidene)-3H-isobenzofuran-1-one (**2b**) + 3-tert-Butyl-7-chloro-4-iodo-1-isochromen-1-one (**3b**)*. Total yield: 120 mg, starting from 95 mg of **1b** (83%; **3b** / **2b** = 2.22, determined by GLC; Table 1, entry 6). White solid. IR (KBr): *v* = 1780 (s), 1721, 1462 (m), 1322 (w), 1101 (m), 1009 (m), 965 (m), 828 (m), 776 (w), 681 (w) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.96 (d, *J* = 8.6, 1 H, **2b**), 8.20 (d, *J* = 2.4, 1 H, **3b**), 7.92 (distorted d, *J* = 8.8, 1 H, **3b**), 7.87 (d, *J* = 2.1, 1 H, **2b**), 7.68 (dd, *J* = 8.8, 2.4, 1 H, **3b**), 7.61 (dd, *J* = 8.6, 2.1, 1 H, **2b**), 1.61 (s, 9 H, **3b**), 1.49 (s, 9 H, **2b**); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 163.9 (**2b**), 162.2 (**3b**), 160.4 (**3b**), 142.8 (**2b**), 138.0 (**2b**), 137.6 (**3b**), 136.3 (**2b**), 135.4 (**3b**), 134.8 (**3b**), 134.0 (**2b**), 132.9 (**3b**), 128.4 (**3b**), 127.3 (**2b**), 126.8 (**2b**), 124.9 (**2b**), 120.8 (**3b**),

103.8 (**2b**), 72.6 (**3b**), 40.8 (**2b**), 39.2 (**3b**), 32.4 (**2b**), 29.0 (**3b**); GC-MS: **2b**: *m/z* = 364 [(M+2)$^+$] (19), 362 (M$^+$) (57), 347 (10), 306 (28), 235 (100), 220 (99), 193 (23), 149 (12), 128 (21), 110 (22); **3b**: *m/z* = 364 [(M+2)$^+$] (35), 362 (M$^+$) (100), 347 (15), 319 (4), 277 (9), 249 (10), 235 (22), 220 (29), 193 (95), 157 (13), 122 (29); anal. calcd for $C_{13}H_{12}ClIO_2$ (362.59): C, 43.06; H, 3.34; Cl, 9.78; I, 35.00; found C, 43.05; H, 3.33; Cl, 9.80; I, 35.04.



**2c** **3c**

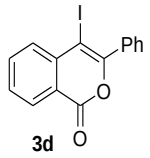
*Mixture of (E)-3-(1-Iodopentylidene)-3H-isobenzofuran-1-one (**2c**) + 3-Butyl-4-iodo-1-isochromen-1-one (**3c**).* Total yield: 97 mg, starting from 81 mg of **1c** (74%; **2c** / **3c** = 2.13, determined by GLC; Table 1, entry 9). Yellow oil. IR (film): *v* = 2957 (m), 2929 (m), 2871 (m), 1781 (s), 1738 (s), 1611 (m), 1472 (m), 1316 (m), 1053 (w), 1031 (m), 996 (m), 763 (m), 687 (m) cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.86 (dd, *J* = 8.1, 0.8, 1 H, **2c**), 8.25-8.18 (m, 1 H, **3c**), 7.96-7.89 (m, 1 H, **2c**), 7.81-7.70 (m, 1 H, **2c** + 2 H, **3c**), 7.58 (td, *J* = 8.1, 0.8, 1 H, **2c**), 7.58-7.46 (m, 1 H, **3c**), 3.10 (t, *J* = 7.4, 2 H, **2c**), 2.93 (t, *J* = 7.8, 2 H, **3c**), 1.80-1.69 (m, 2 H, **3c**), 1.69-1.55 (m, 2 H, **2c**), 1.47-1.33 [m, 2 H (**2c**) + 2 H (**3c**)], 1.01-0.89 [m, 3 H (**2c**) + 3 H (**3c**)]; $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 165.6 (**2c**), 161.9 (**3c**), 158.1 (**3c**), 144.1 (**2c**), 138.3 (**2c**), 138.0 (**2c**), 135.5 (**3c**), 134.1 (**3c**), 130.4 (**3c**), 130.2 (**2c**), 129.6 (**3c**), 128.5 (**3c**), 126.3 (**2c**), 125.7 (**2c**), 124.1 (**2c**), 119.9 (**3c**), 88.2 (**2c**), 76.1 (**3c**), 39.7 (**2c**), 37.1 (**3c**), 31.4 (**2c**), 29.3 (**3c**), 22.2 (**3c**), 21.7 (**2c**), 13.9 (**2c**), 13.8 (**3c**); GC-MS: **2c**: *m/z* =328 (M$^+$) (22), 285 (19), 272 (21), 257 (10), 201 (11), 183 (6), 159 (100), 147 (14), 130 (24), 115 (8), 102 (16), 75 (14); **3c**: *m/z* = 328 (M$^+$) (52), 285 (9), 272 (7), 257 (10), 201 (5), 183 (7), 159 (100), 147 (8), 131 (45), 115 (9), 102 (14); anal. calcd for $C_{13}H_3IO_2$ (328.15): C, 47.58; H, 3.99; I, 38.67; found C,47.60; H, 3.98; I, 38.65. The spectroscopic data for **3c** agreed with those reported.[30]



**2d**

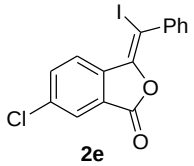
*(E)-3-(Iodophenylmethylene)-3H-isobenzofuran-1-one (**2d**).* Yield: 102 mg, starting from 89 mg of **1d** (73%; Table 1, entry 11). White solid, mp = 164-165 °C. IR (KBr): *v* = 1783 (s), 1640 (m), 1468 (w), 1253 (m), 1095 (m), 768 (m), 686 (m) cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.92 (d, *J* = 8.1, 1 H), 7.95 (d, *J* = 7.7, 1 H), 7.86-7.75 (m, 1 H), 7.68-7.51 (m, 3 H), 7.44-7.28 (m, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 165.1, 140.5, 138.8, 134.1, 131.6, 130.8, 130.2,

129.0, 128.2, 126.6, 125.9, 125.1, 79.9; GC-MS: *m/z* = 348 ($M^+$) (18), 221 (100), 193 (30), 165 (62), 139 (7), 110 (11); anal. calcd for $C_{15}H_9IO_2$ (348.14): C, 51.57; H, 2.61; I, 36.45; found C, 51.55; H, 2.64; I, 36.46.



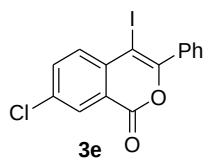
**3d**

*4-Iodo-3-phenylisochromen-1-one (**3d**).* Yield: 112 mg, starting from 89 mg of **1d** (73%; Table 1, entry 10). White solid, mp = 135-136 °C, lit.,[31] 136 °C. IR (KBr): *v* = 1739 (s), 1624 (m), 1473 (m), 1444 (w), 1306 (w), 1231 (m), 1072 (s), 1054 (m), 1027 (m), 1017 (m), 949 (m), 768 (s), 748 (m), 700 (s), 687 (s), 641 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 8.29 (dd, *J* = 7.8, 0.2, 1 H), 7.88 (distorted dd, *J* = 8.1, 0.2, 1 H), 7.81 (distorted td, *J* = 7.7, 1.4, 1 H), 7.73-7.66 (m, 2 H), 7.61-7.53 (m, 1 H), 7.51, 7.44 (m, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 161.5, 154.8, 138.1, 135.7, 135.2, 131.5, 130.2, 130.0, 129.7, 129.2, 128.1, 120.2, 76.5; GC-MS: *m/z* =348 [$M^+$] (100), 320 (41), 221 (10), 193 (44), 165 (46), 139 (6), 105 (49), 77 (37); anal. calcd for $C_{15}H_9IO_2$ (348.14): C, 51.57; H, 2.61; I, 36.45; found C, 51.56; H, 2.59; I, 36.48. The spectroscopic data agreed with those reported.[30]



**2e**

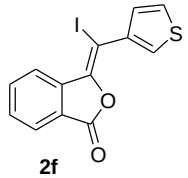
*(E)-6-Chloro-3-(iodophenylmethylene)-3H-isobenzofuran-1-one (**2e**).* Yield: 110 mg, starting from 103 mg of **1e** (72%; Table 1, entry 13). White solid, mp = 165-166 °C. IR (KBr): *v* = 1778 (s), 1462 (m), 1242 (m), 1176 (w), 1106 (w), 1008 (m), 904 (w), 862 (w), 783 (m), 692 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 8.88 (d, *J* = 8.5, 1 H), 7.92 (distorted d, *J* = 2.9, 1 H), 7.76 (dd, *J* = 8.5, 1.9, 1 H), 7.59-7.51 (m, 2 H), 7.44-7.28 (m, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 164.0. 143.7, 139.7, 137.1, 136.7, 134.4, 130.0, 129.2, 128.2, 127.7, 126.0, 125.6, 81.4; GC-MS: *m/z* =384 [$(M+2)^+$] (8), 382 ($M^+$) (27), 257 (33), 256 (18), 255 (100), 229 (10), 227 (29), 176 (8), 163 (31), 127 (14); anal. calcd for $C_{15}H_8ClO_2$ (382.58): C, 47.09; H, 2.11; Cl, 9.27; I, 33.17; found C, 47.11; H, 2.09; Cl, 9.25; I, 33.14.



**3e**

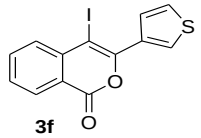
*7-Chloro-4-iodo-3-phenylisochromen-1-one (**3e**).* Yield: 135 mg, starting from 103 mg of **1e** (88%; Table 1, entry 12). White solid, mp = 197-199 °C. IR (KBr): *v* = 1734 (s), 1589 (m),

1467 (m), 1311 (w), 1217 (m), 1083 (m), 949 (m), 834 (w), 765 (w), 693 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 8.26 (d, $J$ = 1.5, 1 H), 7.84 (distorted d, $J$ = 8.6, 1 H), 7.76-7.63 (m, 3 H), 7.50-7.42 (m, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 160.4, 155.0, 136.8, 135.8, 135.3, 134.9, 133.3, 130.4, 129.9, 128.9, 128.1, 121.2, 75.1; GC-MS: *m/z* = 384 [$(M+2)^+$] (33), 382 [$M^+$] (100), 354 (45), 255 (10), 227 (34), 199 (36), 163 (26), 105 (52), 77 (42); anal. calcd for $C_{15}H_8ClIO_2$ (382.58): C, 47.09; H, 2.11; Cl, 9.27; I, 33.17; found C, 47.11; H, 2.08; Cl, 9.30; I, 33.16. The spectroscopic data agreed with those reported.[30]



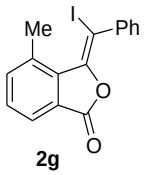
**2f**

*(E)-3-(Iodothiophen-3-yl-methylene)-3H-isobenzofuran-1-one (**2f**).* Yield: 106 mg, starting from 91 mg of **1f** (91%; Table 1, entry 15). White solid, mp = 73-75 °C. IR (KBr): $\nu$ = 1778 (s), 1469 (w), 1248 (m), 1096 (m), 1006 (s), 954 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 8.90 (d, $J$ = 8.2, 1 H), 7.94 (d, $J$ = 7.6, 1 H), 7.84-7.75 (m, 2 H), 7.66-7.55 (m, 2 H), 7.36 (dd, $J$ = 5.1, 3.1, 1 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 165.4, 143.6, 139.5, 138.8, 135.7, 134.2, 131.7, 130.6, 130.2, 129.2, 125.9, 125.0, 75.1; GC-MS: *m/z* = 354 ($M^+$) (29), 227 (100), 199 (55), 171 (35), 127 (14); anal. calcd for $C_{13}H_7ClO_2S$ (354.16): C, 44.09; H, 1.99; I, 35.83; S, 9.05; found C, 44.12; H, 1.97; I, 35.84; S, 9.08.



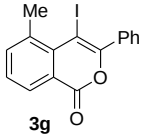
**3f**

*4-Iodo-3-thiophen-3-ylisochromen-1-one (**3f**).* Yield: 129 mg, starting from 91 mg of **1f** (91%; Table 1, entry 14). White solid, mp = 73-75 °C. IR (KBr): $\nu$ = 1728 (s), 1611 (m), 1469 (w), 1324 (w), 1236 (m), 1072 (m), 1021 (m), 968 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 8.26 (dd, $J$ = 8.0, 0.7, 1 H), 8.04-7.99 (m, 1 H), 7.86 (distorted d, $J$ = 8.2, 1 H), 7.82-7.74 (m, 1 H), 7.63 (dd, $J$ = 5.1, 1.2, 1 H), 7.54 (td, $J$ = 7.5, 1.1, 1 H), 7.39 (dd, $J$ = 5.1, 3.0, 1 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 161.3, 150.3, 138.3, 135.7, 135.2, 131.6, 129.7, 129.5, 129.1, 128.6, 125.1, 120.2, 75.6; GC-MS: *m/z* = 354 (100), 326 (66), 227 (13), 199 (79), 171 (52), 127 (17), 111 (41); anal. calcd for $C_{13}H_7ClO_2S$ (354.16): C, 44.09; H, 1.99; I, 35.83; S, 9.05; found C, 44.05; H, 1.96; I, 35.85; S, 9.07.



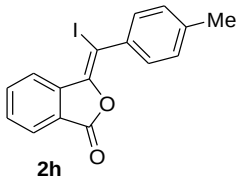

**2g**

*(E)-3-(Iodophenylmethylene)-4-methyl-3H-isobenzofuran-1-one (**2g**).* Yield: 109 mg, starting from 94.5 mg of **1g** (75%; Table 1, entry 17). White solid, mp = 65-66 °C. IR (KBr): $\nu$ = 1768 (s), 1484 (w), 1442 (w), 1266 (m), 1120 (m), 1068 (m), 990 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.80-7.74 (m, 1 H), 7.59-7.47 (m, 4 H), 7.41-7.33 (m, 2 H), 7.33-7.25 (m, 1 H), 3.00 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 165.4, 148.6, 142.0, 138.3, 137.4, 134.2, 130.9, 130.2, 128.8, 128.0, 127.4, 123.4, 81.1, 27.8; GC-MS: *m/z* = 362 ($M^+$) (11), 235 (100), 207 (19), 179 (24), 152 (6), 117 (8), 89 (29); anal. calcd for $C_{16}H_{11}IO_2$ (362.16): C, 53.06; H, 3.06; I, 35.04; found C, 53.08; H, 3.03; I, 35.02.

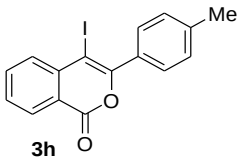



**3g**

*4-Iodo-5-methyl-3-phenylisochromen-1-one (**3g**).* Total yield: 80.5 mg, starting from 94.3 mg of **1g** (56%; Table 1, entry 16). White solid, mp = 95-97 °C. IR (KBr):1736 (s), 1587 (m), 1492 (w), 1383 (w), 1308 (w), 1221 (w), 1084 (m), 1029 (w), 957 (w9, 760 (m), 696 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 8.30 (d, J= 7.4, 1 H), 7.70-7.59 (m, 3 H), 7.49-7.42 (m, 4 H), 2.98 (s, 3 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ =162.0, 155.8, 139.4, 136.8, 136.1, 131.6, 130.1, 128.9, 128.5, 128.3, 128.2, 122.3, 77.2, 25.3; GC-MS: *m/z* = 362 ($M^+$) (86), 334 (14), 235 (14), 207 (24), 179 (22), 152 (7), 117 (6), 105 (100), 102 (9), 89 (8); anal. calcd for $C_{16}H_{11}IO_2$ (362.16): C, 53.06; H, 3.06; I, 35.04; found C, 53.05; H, 3.08; I, 35.01. The spectroscopic data for **3g** agreed with those reported.[30]



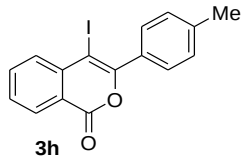

**2h**




**3h**

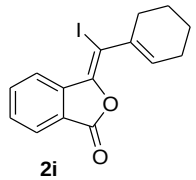
*Mixture of 3-(Iodo-p-tolylmethylene)-3H-isobenzofuran-1-one (**2h**) + 4-(Iodo-3-p-tolylisochromen-1-one (**3h**).* Total yield: 106 mg, starting from 94.5 mg of **1h** (73%; **2h** / **3h** = 2.32, determined by GLC; Table 1, entry 19). White solid. IR (KBr): $\nu$ = 1770 (s), 1732 (m), 1603 (m), 1469 (m), 1249 (m), 1006 (m), 894 (w), 810 (w), 763 (m), 686 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 8.91 (d, *J* = 8.1, 1 H, **2h**), 8.28 (d, *J* = 7.8, 1 H, **3h**), 7.94 (distorted d, *J* = 7.6, 1 H, **2h**), 7.90-7.74 [m, 1 H (**2h**) + 2 H (**3h**)], 7.67-7.51 [m, 1 H (**2h**) + 3 H (**3h**)], 7.46

(distorted d, *J* = 8.1, 2 H, **2h**), 7.26 (distorted d, *J* = 8.0, 2 H, **3h**), 7.18 (distorted d, *J* = 8.1, 2 H, **2h**), 2.43 (s, 3 H, **3h**), 2.38 (s, 3 H, **2h**); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 165.5 (**2h**), 161.6 (**3h**), 154.9 (**3h**), 144.1 (**2h**), 140.4 (**3h**), 139.1 (**2h**), 138.5 (**2h**), 138.3 (**3h**), 137.2 (**2h**), 135.6 (**3h**), 134.2 (**2h**), 132.3 (**3h**), 131.5 (**3h**), 130.6 (**3h**), 130.0 (**2h**), 129.9 (**3h**), 129.7 (**2h**), 129.1 (**3h**), 128.8 (**2h** + **3h**), 126.0 (**2h**), 125.8 (**2h**), 124.8 (**2h**), 120.2 (**3h**), 80.9 (**2h**), 76.1 (**3h**), 21.5 (**3h**), 21.3 (**2h**); GC-MS: (**2h**) *m/z* = 362 ($M^+$) (28), 235 (100), 207 (35), 179 (38), 152 (9), 117 (13); (**3h**) *m/z* = 362 ($M^+$) (100), 334 (64), 235 (25), 207 (62), 179 (62), 163 (7), 152 (13), 119 (32), 91 (48); anal. calcd for $C_{16}H_{11}IO_2$ (362.16): C, 53.06; H, 3.06; I, 35.04; found C, 53.03; H, 3.08; I, 35.01.



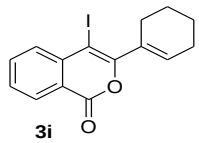
**3h**

*4-Iodo-3-p-tolylisochromen-1-one (**3h**).* Yield: 136 mg, starting from 94.5 mg of **1h** (94%; Table 1, entry 18). White solid, mp = 166-167 °C, lit.[31] 174 °C IR (KBr): *v* = 1731 (s), 1602 (m), 1509 (w), 1471 (w), 1326 (w), 1227 (w), 1075 (m), 817 (m), 753 (m), 685 (m) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.27 (d, *J* = 7.8, 1 H), 7.91 (distorted d, *J* = 7.8, 1 H), 7.79 (t, *J* = 7.6, 1 H), 7.59 (distorted d, *J* = 8.0, 2 H), 7.51 (distorted t, *J* = 7.1, 1 H), 7.25 (distorted d, *J* = 8.0, 2 H), 2.42 (s, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 161.3, 155.4, 140.5, 138.6, 135.5, 132.9, 131.5, 130.0, 129.8, 129.0, 128.8, 120.7, 75.7, 21.4; GC-MS: *m/z* = 362 ($M^+$) (100), 334 (67), 235 (15), 207 (62), 189 (6), 179 (62), 163 (7), 152 (12), 119 (32), 103 (10), 91 (44); anal. calcd for $C_{16}H_{11}IO_2$ (362.16): C, 53.06; H, 3.06; I, 35.04; found C, 53.05; H, 3.03; I, 35.05.



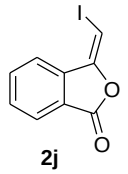
**2i**

*(E)-3-(Cyclohex-1-enyliodomethyene)-3H-isobenzofuran-1-one (**2i**).* Yield: 84.6 mg, starting from 90.5 mg of **1i** (60%; Table 1, entry 21). Yellow solid, mp = 148-149 °C. IR (KBr): *v* = 1775 (s), 1470 (w), 1340 (m), 1268 (w), 1196 (w), 997 (m), 768 (m), 714 (w), 687 (m) $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.90-7.80 (m, 2 H), 7.63 (td, *J* = 7.6, 1.1, 1 H), 7.53 (td, *J* = 7.6, 0.9, 1 H), 6.13-6.07 (m, 1 H), 2.43-2.25 (m, 2 H), 2.25-2.13 (m, 2 H), 1.91-1.80 (m, 2 H), 1.80-1.69 (m, 2 H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 165.9, 146.5, 136.82, 136.78, 134.5, 130.8, 129.9, 126.5, 125.7, 122.8, 86.8, 27.6, 25.8, 22.5, 21.7; GC-MS: *m/z* =352 ($M^+$) (45), 225 (100), 210 (11), 197 (7), 179 (10), 159 (67), 133 (29), 105 (19); anal. calcd for $C_{15}H_{13}IO_2$ (352.17): C, 51.16; H, 3.72; I, 36.04; found C, 51.18; H, 3.70; I, 36.01.



**3i**

*3-Cyclohex-1-enyl-4-iodoisochromen-1-one (**3i**).* Yield: 113 mg, starting from 90.5 mg of **1i** (80%; Table 1, entry 20). Yellow solid, mp = 82-83 °C, lit.,[32] 87-89 °C IR (KBr): $\nu$ = 1725 (s), 1603 (m), 1472 (w), 1202 (w), 1067 (m), 1038 (m), 685 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 8.23 (d, $J$ = 8.1, 1 H), 7.82-7.72 (m, 2 H), 7.55-7.46 (m, 1 H), 6.21-6.10 (m, 1 H), 2.41-2.16 (m, 4 H), 1.86-1.61 (m, 4 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ =161.6, 157.5, 138.6, 135.3, 135.1, 134.3, 131.4, 129.8, 128.7, 120.7, 74.6, 26.6, 25.2, 22.5, 21.7; GC-MS: *m/z* =352 ($M^+$) (100), 324 (39), 298 (16), 225 (17), 197 (42), 182 (12), 181 (11), 179 (37), 178 (15), 169 (17), 167 (9), 165 (12), 159 (9), 154 (11), 153 (16), 152 (15), 141 (29), 139 (11), 128 (13), 127 (8), 115 (19), 91 (15), 89 (21), 88 (31), 81 (16), 79 (18), 77 (14); anal. calcd for $C_{15}H_{13}IO_2$ (352.17): C, 51.16; H, 3.72; I, 36.04; found C, 51.15; H, 3.74; I, 36.07. The spectroscopic data agreed with those reported.[32]



**2j**

*(E)-3-Iodomethylene-3H-isobenzofuran-1-one (**2j**).* Yield: 90 mg, starting from 59 mg of **1j** (83%; Table 1, entry 22). Yellow solid, mp = 82-84 °C, lit.[32] 80-82 °C IR (KBr): $\nu$ = 1771 (s), 1469 (w), 1347 (w), 1268 (m), 1204 (m), 1146 (w), 1097 (w), 1078 (w), 1005 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 8.69 (distorted d, $J$ = 8.0, 1 H), 7.94 (distorted d, $J$ = 7.7, 1 H), 7.79 (td, $J$ = 7.4, 1.2, 1 H), 7.66 (distorted td, J = 7.4, 0.6, 1 H), 6.56 (s, 1 H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 165.5, 148.9, 137.7, 134.5, 131.2, 126.4, 125.8, 124.2, 57.7; GC-MS: *m/z* = 272 ($M^+$) (100), 231 (9), 203 (1), 168 (2), 140 (1), 117 (5), 104 (9), 69 (39); anal. calcd for $C_{16}H_{11}IO_2$ (272.04): C, 39.74; H, 1.85; I, 46.65; found C, 39.72; H, 1.83; I, 46.68. The spectroscopic data agreed with those reported.[32]

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# Chapter 5

## 5.1 Divergent Syntheses of (Z)-3-Alkylideneisobenzofuran-1(3H)-ones and 1H-Isochromen-1-ones by Copper-Catalyzed Cycloisomerization of 2-Alkynylbenzoic Acids in Ionic Liquids

Cycloisomerization of 2-alkynylbenzoic acids[1] is a convenient method for the direct and atom-economical synthesis of important heterocyclic derivatives, with important biological activities.[2,3]

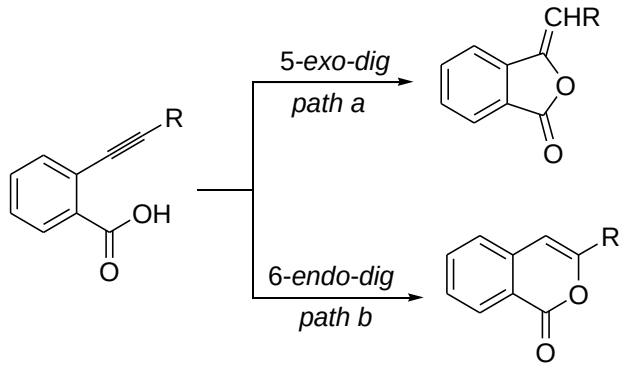
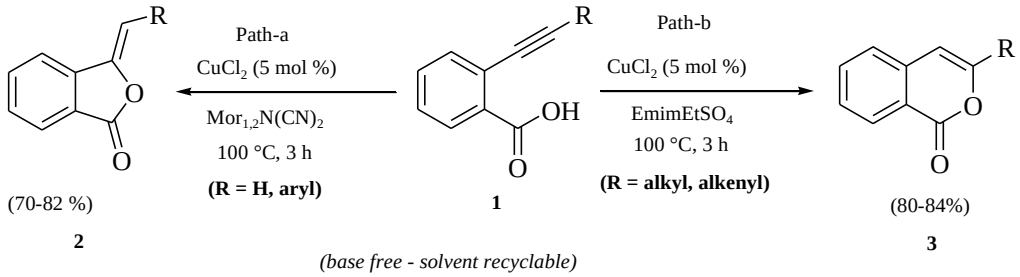



**Figure 1.** Cycloisomerization of 2-alkynylbenzoic acids leading to either 3-alkylideneisobenzofuran-1(3*H*)-ones (from 5-*exo-dig* mode, path *a*) or 1*H*-isochromen-1-ones (from 6-*endo-dig* mode, path *b*)

Considering the study reported[1]above we have studied the cycloisomerization in ionic liquids Depending on the substitution pattern of the substrate and reaction conditions, the process may lead to either 3-alkylideneisobenzofuran-1(3H)-ones (from 5-exo-dig cyclization) or 1H-isochromen-1-ones (from 6-endo-dig cyclization) (Scheme 5.1).




**Scheme 5.1** Cycloisomerization of 2-alkynylbenzoic acids leading to either 3-alkylideneisobenzofuran-1(3H)-ones (from 5-exo-dig mode, path a) or 1H-isochromen-1-ones (from 6-endo-dig mode, path b).

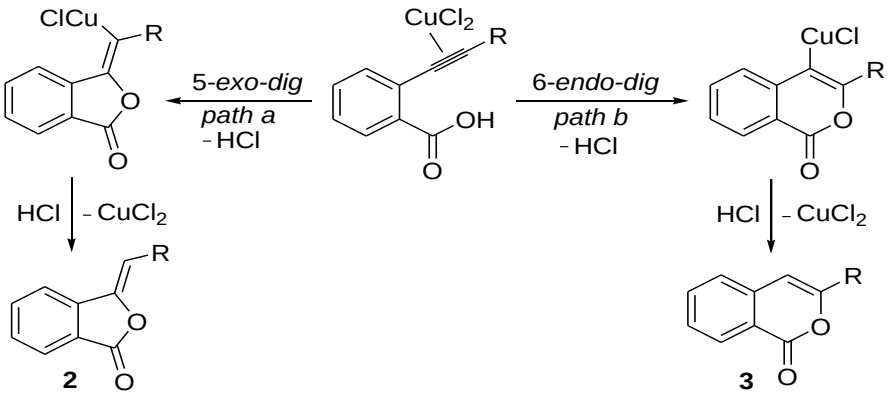
In this work (Scheme 5.1) we studied the cycloisomerization of readily available 2-alkynylbenzoic acids **1** in ionic liquids (ILs) as recyclable reaction under the catalytic action of $CuCl_2$ With substrates bearing an aryl group on the triple bond, a mixture of Z)-3-alkylideneisobenzofuran-1(3H)-ones (from 5-exo-dig cyclization) (**2**) and 1H-isochromen-1-ones (from 6-endo-dig cyclization) (**3)** was observed in 1-ethyl-3-methyl-1H-imidazol-3-ium ethyl sulfate ($EmimEtSO_4$), while the reaction turned out to be selective toward the formation of the isobenzofuranone only using N-ethyl-N-methylmorpholinium dicyanamide ($Mor_{1,2}N(CN)_2$),

as the solvent. The 5-membered product **2** was also obtained selectively when the substrate bearing a terminal triple bond was employed, either in $EmimEtSO_4$ or $Mor_{1,2}N(CN)_2$. On the other hand, 2-alkynylbenzoic acids bearing an alkyl or an alkenyl group on the triple bond selectively led, in $EmimEtSO_4$, to 1H-isochromen-1-ones, while the formation of a regioisomeric mixture was observed in $Mor_{1,2}N(CN)_2$. In any case, the IL solvent could be easily recycled after extraction of the product from the reaction mixture with diethyl ether., and the structures of two representative products, that are, (Z)-3-benzylideneisobenzofuran-1(3H)-one and (Z)-3-(4-methylphenylmethylidene) isobenzofuran-1(3H)-one, have been confirmed by X-ray diffraction analysis.

Although different catalysts have been proposed for promoting the cycloisomerization of 2-alkynyl benzoic acid reaction, including acid,[1e,1m] basic,[1e,1f,1g] and transition-metal catalysts,[1a-d,1h-l,1n,1o] to the best of our knowledge the use of copper-based catalytic systems has not been reported so far. Moreover, the process has been previously reported to occur in conventional volatile organic solvents,[1] while the use of non-conventional solvents, such as ionic liquids (ILs), has not been investigated. In this work we have filled this gap, by reporting on the cycloisomerization of 2-alkynylbenzoic acids under the catalytic action of $CuCl_2$ as very simple catalyst and using ILs as safer unconventional solvents.[4]

### 5.1.2. Reaction mechanism

**Scheme 5.2** shows the possible reaction mechanism using the catalyst $CuCl_2$

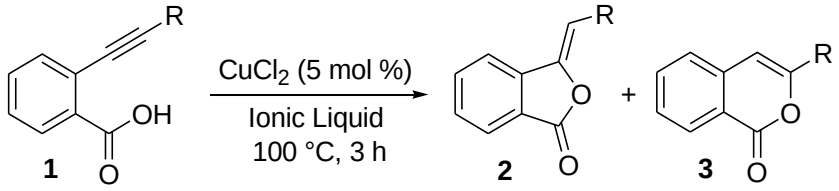



**Scheme 5.2.**

According to other $CuCl_2$-catalyzed cyclization processes of functionalized alkynes,[5] formation of products **2** and **3** can be interpreted as occurring through anti 5-exo-dig (path a) or 6-endo-dig (path b), respectively, nucleophilic attack of the carboxylate group to the triple bond coordinated to $CuCl_2$, followed by protonolysis As shown in Scheme 4.2 an anti attack is in perfect agreement with the (Z) stereochemistry observed in the 3-alkylideneisobenzofuran-1(3H)-ones **2**, as confirmed by the X-ray diffraction analysis of products **2a** and **2b**

### 5.1.3 Results and Discussion

Copper–Catalyzed Divergent Syntheses of (Z)-3-Alkylideneisobenzofuran-1(3H)-ones 2 and 1H-Isochromen-1-ones 3 by Cycloisomerization of 2-Alkynylbenzoic Acids 1 in Ionic Liquids, and Recycling Experiments



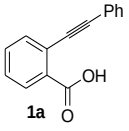
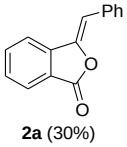
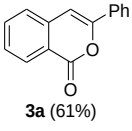

**(5.1)**

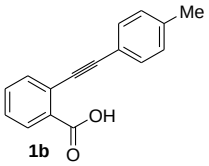
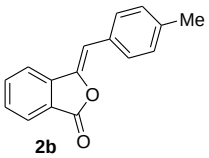
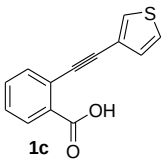
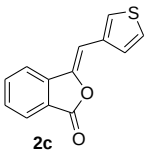
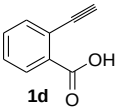
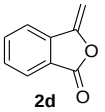
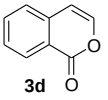
The first substrate tested is 2-alkynylbenzoic aids bearing an aryl group on the triple bond. 2-(2-Phenylethynyl)benzoic acid **1a** was initially allowed to react in 1-ethyl-3-methyl-1H-imidazol-3-ium ethyl sulfate (EmimEtSO) (substrate concentration = 0.2 mmol / mL of solvent) in the presence of 5 mol % of $CuCl_2$. After 3 h at 100 °C, a mixture of (Z)-3-benzylideneisobenzofuran-1(3H)-one **2a** (30%) and 3-phenyl-1H-isochromen-1-one **3a** (61%) was obtained, with a total yield of 91% (Table 5.1, entry 1). The process took place also in the absence of catalyst, even though with significantly less satisfactory results (total yield 48%, Table 4.1, entry 2). These results confirmed the possibility to perform the cycloisomerization of a 2-alkynylbenzoic acid in an ionic liquid as the solvent, using $CuCl_2$ as simple and inexpensive catalyst. To assess the influence of the solvent on the reaction outcome, several ILs were then tested. In 1-butyl-3-methylimidazolium trifluoromethanesulfonate (BmimOTf), 1-ethyl-3-methylimidazolium tosylate (EmimOTs), and 1,3-dimethylimidazolium dimethyl phosphate ($Mmim(MeO)_2PO_2$), again a mixture of **2a** and **3a** was obtained, **3a** being still formed preferentially (entries 3-5). On the other hand, in 3-butyl-1-methylimidazolium dicyanamide ($BmimN(CN)_2$), N-(cyanopropyl)-N-methyl pyrrolidinium triflimide ($(C_3CNmpyr)(NTf)_2$), and N-ethyl-N-methylmorpholinium dicyanamide ($Mor_{1,2}N(CN)_2$), the process turned out to be completely selective toward the formation of the 5-membered product **2a** (Table 4.1, entries 6-8), whose structure was confirmed by X-ray diffraction analysis. In particular, the highest yield (70%) was obtained in $Mor_{1,2}N(CN)_2$, as shown in Table 4.1 (entry 8). Under these latter conditions, we then tested the recyclability of the catalyst/solvent system, by extracting the product from the reaction mixture with diethyl ether and adding fresh substrate to the ionic liquid residue, still containing the catalyst dissolved in it. As shown in Table 1, entry 8, the $CuCl_2/Mor_{1,2}N(CN_2)$ could be successfully recycled up to 5 times, without appreciable loss of activity. It is worth noting that the same reaction, carried out in the absence of $CuCl_2$, led to **2a** in a significantly lower yield (35%, Table 4.1, entry 9)

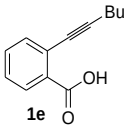
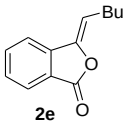
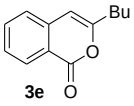
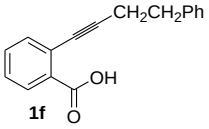
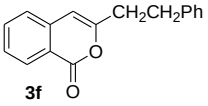
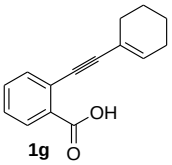
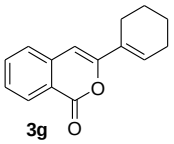
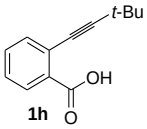
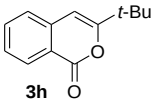
Under the same conditions as those reported in Table 4.1, entry 8, other 2-alkynylbenzoic acids, bearing a tolyl (**1b**) or a 3-thienyl (**1c**) substituent, behaved similarly, with selective formation of the corresponding (Z)-3-alkylideneisobenzofuran-1(3H)-ones **2b,c** in good yields and excellent recyclability of the solvent/catalyst system (Table 4.1, entries 10 and 11, respectively). The structure of (Z)-3-(4-methylphenylmethylidene)isobenzofuran-1(3H)-one **2b** was also confirmed by X-ray diffraction analysis (see the Supporting information for details). The isobenzofuranone derivative **2d** was also selectively obtained starting from 2-ethynylbenzoic acid **1d**, bearing a terminal triple bond, in $Mor_{1,2}N(CN)_2$ (Table 4.1, entry 12) as well as in $EmimEtSO_4$ (Table 4.1, entry 13).

Interestingly, the behavior of substrates substituted with an alkyl group on the triple bond was quite different from that observed with those bearing an aryl group. In fact, the reaction of 2-(hex-1-ynyl)benzoic acid **1e**, carried out in $Mor_{1,2}N(CN_2)$ under the same conditions as those of Table 4.1, entry 8, led to the formation of a mixture of the corresponding 5-membered and 6-membered cycloisomerization products (**2e** and **3e**, respectively) (Table 4.1, entry 14). However, the process turned out to be selective toward the formation of the isochromenone derivative **3e** when it was conducted in $EmimEtSO_4$, with a high product yield and an excellent catalyst/solvent recyclability (Table 4.1, entry 15). Under these conditions, other substrates bearing a phenethyl (**1f**, Table 4.1, entry 16), an alkenyl group such as 1-cyclohexenyl (**1g**, Table 4.1, entry 17), or even a sterically demanding alky group such as tert-butyl (**1h**, Table 4.1, entry 18) behaved similarly, leading to the corresponding isochromenones **3f-h** in a selective manner and in high yields.

**Table 5.1** Copper-Catalyzed Cycloisomerization Reactions of 2-Alkynylbenzoic acids **1** in Ionic Liquids.[a]

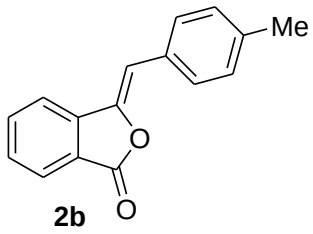
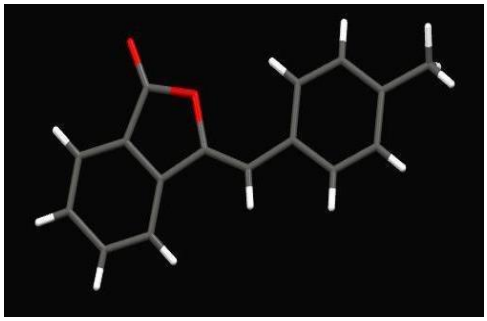
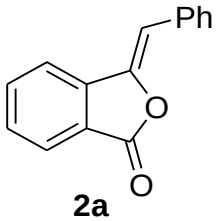
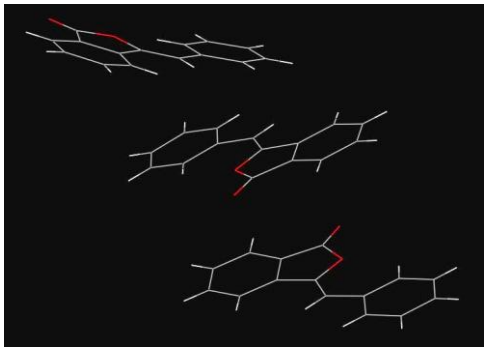
| Entry | **1** | Ionic Liquid | **2** | **3** | **2**/**3** molar ratio[b] | Total Yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 |  **1a** | $EmimEtSO_4$ |  **2a** (30%) |  **3a** (61%) | 0.49 | 91 |
| 2[d] | **1a** | $EmimEtSO_4$ | **2a** | **3a** | 1.67 | 48 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 3 | **1a** | BmimOTf | **2a** | **3a** | 0.11 | 49 |
| 4 | **1a** | EmimOTs | **2a** | **3a** | 0.08 | 65 |
| 5 | **1a** | $Mmim(MeO)_2PO_2$ | **2a** | **3a** | 0.46 | 60 |
| 6 | **1a** | $BmimN(CN)_2$ | **2a** | **3a** | **2a** only | 58 |
| 7 | **1a** | $(C_3CNmpyr)(NTf)_2$ | **2a** | **3a** | **2a** only | 64 |
| 8 | **1a** | $Mor_{1,2}N(CN)_2$ | **2a** | **3a** | **2a** only | 70[e] |
| 9[f] | **1a** | $Mor_{1,2}N(CN)_2$ | **2a** | **3a** | **2a** only | 34 |
| 10 |  **1b** | $Mor_{1,2}N(CN)_2$ |  **2b** | | **2b** only | 71[g] |
| 11 |  **1c** | $Mor_{1,2}N(CN)_2$ |  **2c** | | **2c** only | 70[h] |
| 12 |  **1d** | $Mor_{1,2}N(CN)_2$ |  **2d** |  **3d** | **2d** and traces of **3d** | 65[i] |

| | | | | | | |
|---|---|---|---|---|---|---|
| 13 | **1d** | $EmimEtSO_4$ | **2d** | | **2d** only | 86[j] |
| 14 |  **1e** | $Mor_{1,2}N(CN)_2$ |  **2e** |  **3e** | 1.34 | 54[k] |
| 15 | **1e** | $EmimEtSO_4$ | | **3e** | **3e** only | 84[l] |
| 16 |  **1f** | $EmimEtSO_4$ | |  **3f** | **3f** only | 80[m] |
| 17 |  **1g** | $EmimEtSO_4$ | |  **3g** | **3g** only | 84[n] |
| 18 |  **1h** | $EmimEtSO_4$ | |  **3h** | **3h** only | 82[o] |

[a] Unless otherwise noted, all reactions were carried out under nitrogen at 100 °C for 3 h with a substrate concentration of 0.2 mmol of **1** per mL of ionic liquid, in the presence of 5 mol % of $CuCl_2$. [b] Determined by GLC. [c] Isolated yield based on starting **1**. [d]

## Table 5.2 X-ray diffraction pattern of some selected compounds

| | | |
|---|---|---|
| 1 |  **2b** |  |
| 2 |  **2a** |  |

## 5.2. Experimental Section

### General Experimental Methods.

Solvent and chemicals were reagent grade and were used without further purification. All reactions were analyzed by TLC on silica gel 60 F254 and by GLC using capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase. Column chromatography was performed on silica gel 60 (70-230 mesh). Evaporation refers to the removal of solvent under reduced pressure. Melting points are uncorrected. $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded at 25 °C on a 300 or Spectrometer in $CDCl_3$ with $Me_4Si$ as internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. IR spectra were taken with an FT-IR spectrometer. Mass spectra were obtained using a GC-MS apparatus at 70 eV ionization voltage and by electrospray ionization mass spectrometry (ESI-MS). The LC-MS was operated in the positive ion mode. The experimental conditions were as follows: $N_2$ was employed as desolvation gas at 300°C and a flow rate of 8 L/min. The nebulizer was set to 45psig. The Sheat gas temperature was set at 400°C and a flow of 12 L/min. A potential of 3.5 kV was used on the capillary for positive ion mode. The fragmentor was set to 175 V. MS

spectra were recorded in the 150–1000 m/z range. Microanalyses were carried out in our analytical laboratory.

### 5.2.1Preparation of ILs.

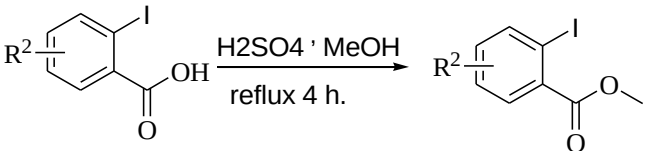
Ionic liquids 3-butyl-1-methylimidazolium tetrafluoroborate ($BmimBF_4$), 1-ethyl-3-methyl-1H-imidazol-3-ium ethyl sulfate ($EmimEtSO_4$), 3-butyl-1-methylimidazolium dicyanamide ($BmimN(CN)_2$), and *N*-ethyl-*N*-methylmorpholinium dicyanamide ($Mor_{1,2}N(CN)_2$) were prepared according to literature procedures. Structure and purity of all ILs were confirmed by $^1H$ and $^{13}C$ NMR spectroscopy.[7]

### 5.2.2 Preparation of Substrates.

2-Alkynylbenzoic acids **1** were prepared by Sonogashira coupling between the corresponding methyl 2-halobenzoates and terminal alkynes followed by hydrolysis,[15] as described below.

### 1st Step Preparation of Methyl 2-Halobenzoates.

Methyl 2-iodobenzoate was commercially available. Methyl 2-bromo-5-chlorobenzoate and methyl 3-methyl-2-iodobenzoate were prepared by Fischer esterification, according to the following procedure:



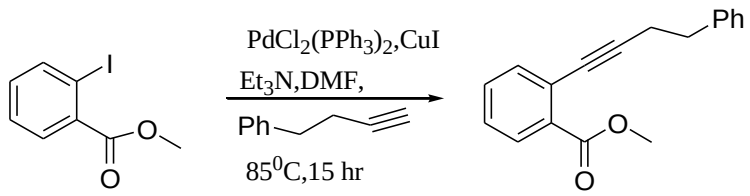

(5.2)

To a stirred solution of the 2-halobenzoic acid [10.0 mmol; 2-bromo-5-chlorobenzoic acid (commercially available), 2.35 g; 3-methyl-2-iodobenzoic acid,[16] 2.62 g) in MeOH (4.1 mL) was added, dropwise, concentrated $H_2SO_4$ (0.8 mL). The resulting mixture was allowed to reflux under stirring for 4 h. After cooling, water (10 mL) was added, and the mixture was extracted with $CH_2Cl_2$ (10 × 3 mL). The combined organic layers were washed with saturated $NaHCO_3$ to neutral pH and then dried over $Na_2SO_4$. After evaporation of the solvent, the crude methyl esters were sufficiently pure to be used as such for the next step without further purification.

**2nd Step Methyl 2-Alkynyl Benzoates**

**Sonogashira Coupling between Methyl 2-Halobenzoates and Terminal Alkynes**

2-Alkynylbenzoic acids **1a-e** and **1g-h** were prepared by Sonogashira coupling between the corresponding methyl 2-iodobenzoates and terminal alkynes followed by hydrolysis, as we already reported.in chapter 4 in the same thesis**.**



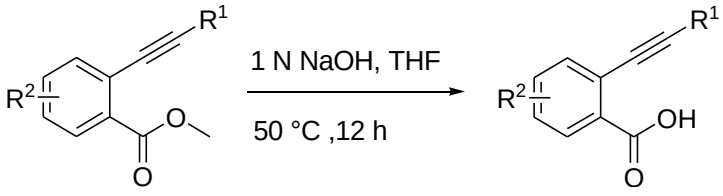

**(5.3)**

**Sonogashira Coupling Between Methyl 2-Iodobenzoates and But-3-ynylbenzene to Give Methyl 2-(4-Phenylbut-1-ynyl) benzoate**

General example of Substrates 2-(4-Phenyl-but-1-ynyl)-benzoic acid methyl ester is prepared in a similar way, according to the procedure given below.

A solution of methyl 2-iodobenzoate (4.0 mmol; 1.05 g), $PdCl_2(PPh_3)_2$ (99.2 mg, 0.14 mmol), CuI (61.0 mg, 0.32 mmol) and $Et_3N$ (1.9 mL) in anhydrous DMF (10 mL) was allowed to stir under nitrogen for 1 h. The but-3-ynylbenzene, 625 mg (4.8 mmol), was then added under nitrogen, and the resulting mixture was heated at 85 °C (oil bath) for 15 h. After cooling, $CH_2Cl_2$ (100 mL) was added, and the mixture washed with water (3 × 100 mL). After drying over $Na_2SO_4$, the solvent was evaporated, and the residue purified by column chromatography on silica gel using hexane-AcOEt from 99:1 to 95:5 as eluent

**3rd Step Hydrolysis of Methyl 2-Alkynylbenzoates to Give 2-Alkynylbenzoic Acids 1.**

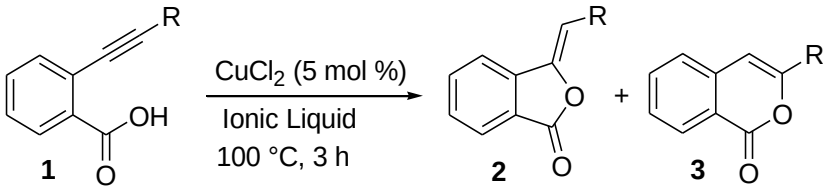



**(5.5)**

The method of Kundu[20] was adapted. A stirred solution of the methyl 2-alkynylbenzoate [2.5 mmol; methyl 2-(3,3-dimethylbut-1-ynyl)benzoate, 541 mg; methyl 5-chloro-2-(3,3-dimethylbut-1-ynyl)benzoate, 627 mg; methyl 2-(hex-1-ynyl)benzoate, 541 mg; methyl 2-(2-phenylethynyl)benzoate, 591 mg; methyl 5-chloro-2-(2-phenylethynyl)benzoate, 677 mg; methyl 2-[2-(thiophen-3-yl)ethynyl]benzoate, 606 mg; methyl 3-methyl-2-(2-phenylethynyl)benzoate, 626 mg; methyl 2-(2-*p*-tolylethynyl)benzoate, 626 mg; methyl 2-[(1-

cyclohexenyl)ethynyl]benzoate, 601 mg; methyl 2-[2-(trimethylsilyl)ethynyl]benzoate, 581 mg and 1 N NaOH (14.0 mL) in THF (3.0 mL) was heated at 50 °C for 12 h. After cooling to room temperature, the mixture was washed with $Et_2O$ (3 × 15 mL), further cooled with the aid of an ice bath, and neutralized with 1 N HCl. The resulting mixture was extracted at room temperature with $CH_2Cl_2$ (3 × 50 mL), and the collected organic layers dried over $Na_2SO_4$. Filtration and evaporation of the solvent afforded the crude 2-alkynylbenzoic acid derivatives (in the case of methyl 2-[2-(trimethylsilyl)ethynyl]benzoate, triple bond deprotection also occurred together with ester hydrolysis to give 2-ethynylbenzoic acid). 2-(Hex-1-ynyl)benzoic acid **1c** was a low melting yellowish solid, and was sufficiently pure to be used as such in the iodocyclization reactions. All other 2-alkynylbenzoic acids **1a,b** and **1d-i** and 2-ethynylbenzoic acid **1j** were further purified by crystallization with $Et_2O$/hexane.

### 5.2.3 General Procedure for the Recyclable Copper-Catalyzed Cycloisomerization of of 2-Alkynylbenzoic Acids in Ionic Liquids (Table 2).




**(5.1)**

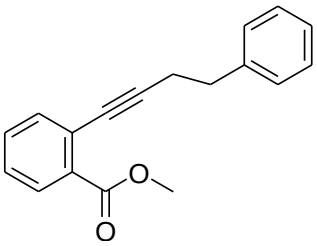
To a solution of **1** (0.4 mmol) (**1a**, 90.0 mg; **1b**, 95.0 mg; **1c**, 91.5 mg; **1d**, 59.0 mg; **1e**, 81.5 mg; **1f**, 100.5 mg; **1g**, 91.5 mg; **1h**, 81.0 mg) in $EmimEtSO_4$ or $MorfN(CN)_2$ (2 mL) were added $CuCl_2$ (2.7 mg, $2.0 \times 10^{-2}$ mmol) under nitrogen in a Schlenk flask. The mixture was allowed to stir at 100 °C for 3 h. After cooling, the product was extracted with diethyl ether (6 × 5 mL), and the residue (still containing the catalyst dissolved in the IL) was used as such for the next recycle (see table 4.2). The collected ethereal phases were concentrated. After evaporation of the solvent, the products **2a-d** and **3e-3h** were purified by column chromatography on silica gel using 98 : 2 hexane–AcOEt as the eluent. Mixtures 2a+3a and 2e+3e were collected by column chromatography on silica gel using 9 : 1 hexane–AcOEt as the eluent.

**Recycling Procedure.** To the residue obtained as described above, still containing the catalyst dissolved in the ionic liquid, was added a solution of fresh **1** (0.4 mmol) in $Et_2O$ (3 mL). $Et_2O$ was removed under vacuum, and then the same procedure described above was followed.

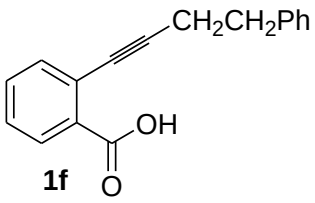
## 5.3 Conclusion

We have shown that it is possible to efficiently carry out the cycloisomerization of readily available 2-alkynylbenzoic acids using an ionic liquid as the reaction medium in the presence of $CuCl_2$ as a simple and inexpensive catalyst. Although in principle two different cyclization pathways can be followed, leading to either (Z)-3-alkylideneisobenzofuran-1(3H)-ones (from 5-exo-dig mode) or 1H-isochromen-1-ones (from 6-endo-dig mode), we have found that substrates bearing an aryl group on the triple bond or a terminal triple bond can be selectively converted into the isobenzofuranone derivatives, using N-ethyl-N-methylmorpholinium dicyanamide ($Mor_{1,2}N(CN)_2$) as the solvent. On the other hand, and in a complementary manner, substrates substituted with an alkyl or an alkenyl group on the triple bond selectively led to isochromenones when the reaction was carried out in 1-ethyl-3-methyl-1H-imidazol-3-ium ethyl sulfate ($EmimEtSO_4$). In all cases, products were obtained in good to high yields and with excellent recyclability of the catalyst/ionic liquid system.

**5.4 Characterisation Data**




Methyl 2-(4-Phenylbut-1-ynyl)benzoate. Yield: 856 mg, starting from 1.05 g of methyl 2-iodobenzoate (81 %). Yellow oil. IR (film): ν = 2924 (m), 2856 (w), 2228 (w), 1733 (s), 1596 (w), 1485 (w), 1432 (w), 1294 (w), 1277 (w), 1252 (m), 1128 (w), 1083 (m), 963 (w), 757 (m), 698 (m) $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$): δ = 7.88 (td, J = 7.8, 1.5, 1 H), 7.50-7.44 (m, 1 H, on aromatic ring), 7.39 (td, J = 7.4, 1.4, 1 H, on aromatic ring), 7.35-7.16 (m, 6 H, on aromatic ring), 3.86 (s, 3 H, OMe), 2.96 (t, J = 7.5, 2 H, $CH_2CH_2Ph$), 2.76 (t, J = 7.5, 2 H, $CH_2CH_2Ph$); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ =166.8, 140.7, 134.2, 131.2, 131.5, 130.1, 128.5, 128.4, 127.3, 126.3, 124.3, 95.0, 79.9, 52.0, 35.0, 22.0; GC-MS: m/z = 264 (22) [$M^+$], 263 (56), 249 (35), 248 (8), 232 (55), 231 (69), 215 (15), 205 (9), 203 (17), 202 (13), 173 (8), 143 (35), 115 (18), 114 (9), 102 (12), 101 (7), 92 (8), 91 (100), 88 (6), 65 (17) ; anal. calcd for $C_{18}H_{16}O_2$ (264.32): C, 81.79; H, 6.10; found C, 81.80; H, 6.10.

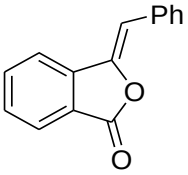



**1f**

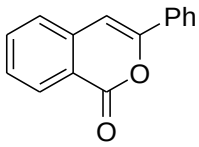
2-(4-Phenylbut-1-ynyl)benzoic acid (**1f**). Yield: 513 mg, starting from 661 mg of methyl 2-(4-phenylbut-1-ynyl)benzoate (82%). White solid, mp = 54-56°C, IR (KBr): ν = 3414 (w, br), 2920 (w), 2220 (w), 2644 (w), 1703 (s), 1595 (w), 1565 (w), 1484 (m), 1410 (m), 1302 (m), 1265 (m), 1163 (w), 1086 (w), 933 (w, br), 805 (w), 757 (s), 703 (m) $cm^{-1}$; $^{1}H$ NMR (300 MHz, $CDCl_3$): δ =9.05 (d, J = 8.0, 1 H, on aromatic ring), 7.96 (d, J=7.5, 1 H, on aromatic ring), 7.83 (td, J = 7.7, 1 H, on aromatic ring), 7.71 (d, J = 7.5, 1 H, on aromatic ring), 6.16 (s, 1 H, C=CH), 3.84 (s, 3H, OMe); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ =171.8, 140.6, 134.4, 132.4, 131.0, 130.5, 128.5, 128.3, 127.4, 126.2, 124.8, 96.2, 79.8, 34.8, 22.0; LC-MS: m/z =273.09 [$(M+Na)^+$]; anal. calcd for $C_{17}H_{14}O_2$ (250.29): C, 81.58; H, 5.64; found C, 81.56; H, 5.62.

**The data of other starting material were same as reported in chapter 4 (page 21-29) in the same thesis**

Mixture of (Z)-3-Benzylidene-3H-isobenzofuran-1-one (**2a**) + 3-Phenylisochromen-1-one (**3a**).

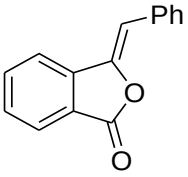



**2a**




**3a**

Total yield: 81.0 mg, starting from 90.0 mg of **1a** (91%; **2a** / **3a** = 0.49, determined by GLC; Table 1, entry 1). IR (KBr): ν = 3024 (m), 2924 (m), 2849 (m), 2328 (w), 2246 (w), 2049 (w), 1950 (w), 1774 (s), 1739 (m), 1662 (m), 1663 (w), 1609 (m), 1572 (w), 1493 (m), 1463 (s), 1352 (m), 1301 (w), 1272 (m), 1215 (m), 1180 (m), 1158 (w), 1091 (s), 1029 (w), 978 (s), 918 (w), 764 (s), 689 (s), 638 (w), 521 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 8.32-8.23 (m, 1 H, on aromatic ring, **3a**), 7.90 (d, J = 7.8, 1 H, on aromatic ring, **2a**), 7.81 [d, J = 7.8, 2 H, on aromatic ring, 1 H (**2a**)+1 H (**3a**)], 7.76-7.64 [m, 4H, on aromatic ring, 3 H (**2a**) + 1 H (**3a**)], 7.41-7.46 (m, 1 H, on aromatic ring, **3a**), 7.44-7.42 (m, 1H, on aromatic ring, **3a**) 7.42-7.47 (m, 2 H, on aromatic ring, **2a**), 7.33-7.22 [m, 2 H, on aromatic ring, 1 H (**2a**), 1H (**3a**)], 6.91 (s, br, 1 H, C=CH, **3a**) 6.39 (s, 1 H, C=CH, **2a**); GC-MS: **2a**: m/z = 222 ($M^+$) (100), 194 (15), 193 (7), 166 (12), 165 (61), 164 (6), 111 (5), 104 (6), 89 (9), 82 (7), 76 (14); **3a**: m/z =222 ($M^+$) (100), 194 (67), 193 (9), 166 (12), 165 (64), 164 (7), 139 (5), 105 (15), 89 (20), 82 (12), 77 (22); anal. calcd for $C_{15}H_{10}O_2$ (222.24): C, 81.07; H, 4.54; found C, 81.04; H, 4.56.

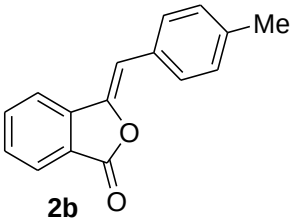



**2a**

(Z)-3-Benzylidene-3H-isobenzofuran-1-one (2a).Yield: 62.5 mg, starting from 90.0 mg of **1a** (70%; Table 1, entry 8). White solid, mp = 80-83 °C. IR (KBr): ν = 3024 (m), 2924 (m), 2849 (m), 1950 (w), 1774 (s), 1662 (m), 1609 (m), 1493 (m), 1463 (s), 1352 (m), 1272 (m), 1215 (m), 1158 (w), 1091 (s), 1029 (w), 978 (s), 918 (w), 764 ( s), 689 (s), 638 (w) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, J = 7.7, 1 H, on aromatic ring), 7.83 (d, J = 7.3, 1 H, on aromatic ring), 7.78-7.66 (m, 2 H, on aromatic ring), 7.56-7.48 (m, 1 H, on aromatic ring), 7.44-7.35 (m, 1 H, on aromatic ring), 7.34-7.26 (m, 1 H, on aromatic ring), 6.40 (s, 1 H, C=CH); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 167.0, 144.6, 140.6, 134.5, 133.1, 130.1, 129.8, 128.4, 125.6, 125.5,

119.8, 107.1; GC-MS: m/z = 222 ($M^+$) (100), 194 (16), 193 (7), 166 (13), 165 (61), 164 (7), 163 (5), 111 (5), 104 (7), 90 (8), 89 (11), 82 (7), 76 (13); anal. calcd for $C_{15}H_{10}O_2$ (222.24): C, 81.07; H, 4.54; found C, 81.09; H, 4.51.

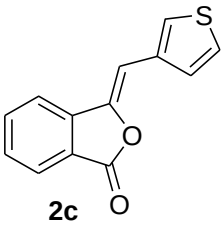
**(Z)-3-(4-Methyl-benzylidene)-3H-isobenzofuran-1-one (2b).**




**2b**

Yield: 67.0 mg, starting from 95.0 mg of **1b** (71%; Table 1, entry 10). White solid, mp = 109-111 °C. IR (KBr): ν = 3023 (m), 2916 (m), 1780 (s), 1605 (m), 1510 (m),1475 (m), 1352 (m), 1329 (w), 1201 (w), 1174 (w), 1077 (m), 972 (s); 857 (m), 815 (m), 760 (s), 688 (m), 522 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.81 (d, J= 7.9, 1H, on aromatic ring), 7.70-7.55 (m, 4H, on aromatic ring), 7.45 (t, J = 7.3, 1H, on aromatic ring), 7.20 (d, J = 7.3, 3H, on aromatic ring), 6.26 (s, 1H, C=CH), 2.27 (s, 3H, Me); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 167.2, 143.9, 140.7, 138.6, 134.4, 130.3, 130.1, 129.5, 125.5, 123.3, 119.7, 107.2, 21.4; GC-MS: m/z = 236 ($M^+$) (100), 207 (7), 193 (13), 179 (10), 178 (13), 165 (32), 103 (7), 77 (7), 76 (12); anal. calcd for $C_{16}H_{12}O_2$ (236.27): C, 81.34; H, 5.12; found C, 81.33; H, 5.14.

**4) (Z)-3-Thiophen-3-ylmethylene-3H-isobenzofuran-1-one (2c).**

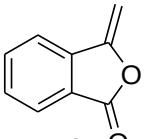



**2c**

Yield: 64.0 mg, starting from 91.5 mg of **1c** (70%; Table 1, entry 11). White solid, mp = 54.1-55.1 °C. IR (KBr): ν = 1775 (s), 1664 (w), 1609 (w), 1474 (m), 1346 (w), 1154 (w), 1078 (m), 982 (m), 860 (w), 777 (m), 761 (m), 689 (m), 640 (w), 610 (w) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.93-7.85 (m, 1 H, on aromatic ring), 7.75-7.66 (m, 3 H, on aromatic ring), 7.60-7.54 (m, 1 H, on aromatic ring), 7.53-7.46 (m, 1 H, on aromatic ring), 7.56-7.30 (m, 1 H, on aromatic ring), 6.49 (s, 1 H, C=CH); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ =166.9, 143.6, 140.2,

134.4, 134.2, 129.5, 128.8, 126.7, 125.9, 125.52, 123.49, 119.6, 101.5; GC-MS: m/z = 228 ($M^+$) (100), 227 (6), 200 (9), 199 (7), 183 (5), 173 (6), 172 (25), 171 (58), 114 (5), 96 (7), 85 (6), 76 (12); anal. calcd for $C_{13}H_8O_2S$ (228.27): C, 68.40; H, 3.53; S, 14.05; found C, 68.42; H, 3.503; S, 14.06.

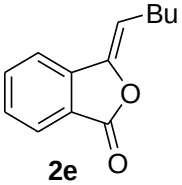
**5) (Z)-3-Methylene-3H-isobenzofuran-1-one (2d).**



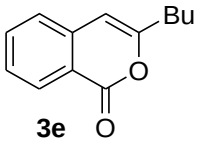
**2d**

Yield: 50.5 mg, starting from 59.0 mg of **1d** (86%; Table 1, entry 13). White solid, mp = 50-51 °C. IR (KBr): ν = 3451 (m), 2917 (m), 1779 (s), 1599 (w), 1469 (m), 1378 (w), 1288 (m), 1106 (w), 1011 (w), 900 (w), 759 (m), 691 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CD_3CN$): δ = 7.91-7.85 (m, 2H, on aromatic ring), 7.83-7.76 (m, 1H, on aromatic ring), 7.68-7.61 (m, 1H, on aromatic ring), 5.39 (d, J = 3.1, 1H, C=CHH), 5.23 (d, J = 3.1, 1H, C=CHH); $^{13}C$ NMR (75 MHz, $CD_3CN$): δ = 167.8, 153.0, 139.9, 135.9, 131.8, 125.8, 122.1, 118.4, 92.0; GC-MS: m/z = 146 ($M^+$) (100), 118 (21), 105 (11), 104 (58), 90 (43), 89 (19), 76 (66), 75 (11), 63 (11), 50 (28); anal. calcd for $C_9H_6O_2$ (146.14): C, 73.97; H, 4.14; found C, 73.95; H, 4.15.

**6) Mixture of Z-3-Pentylidene-3H-isobenzofuran-1-one (2e) + 3-Butylisochromen-1-one (3e)**



**2e**

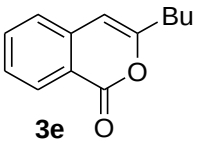


**3e**

.Total yield: 43.8 mg, starting from 81.5 mg of **1e** (54%; **2e** / **3e** = 1.34, determined by GLC; Table 1, entry 14). IR (KBr): ν = 2957 (m), 2931 (m), 2873 (w), 1781 (w), 1728 (s), 1657 (m), 1607 (w), 1484 (m), 1329 (w), 1161 (m), 1105 (w), 1023 (m), 965 (w), 828 (m), 758 (m), 692 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 9.01 (d, J = 8.2, 1 H, **2a**), 8.21 (d, J = 7.6, 1 H, **3a**), 8.02-7.87 [m, 1 H (**2a**) + 1 H (**3a**)], 7.82-7.68 [m, 1 H (**2a**) + 1 H (**3a**)], 7.63-7.46 [m, 1 H (**2a**) + 1 H (**3a**)], 1.62 (s, 9 H, **3a**), 1.50 (s, 9 H, **2a**); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 165.0 (**2a**), 162.4 (**3a**), 161.1 (**3a**), 143.8 (**2a**), 140.2 (**2a**), 139.5 (**3a**), 135.2 (**3a**), 133.8 (**2a**), 131.3 (**3a**), 130.1 (**2a**), 129.4 (**3a**), 128.7 (**3a**), 126.3 (**2a**), 126.0 (**2a**), 125.7 (**2a**), 120.5 (**3a**), 102.5 (**2a**), 73.3 (**3a**), 41.0 (**2a**), 39.4 (**3a**), 32.6 (**2a**), 29.5 (**3a**); GC-MS: **2e**: m/z =202 ($M^+$) (29), 184 (6), 160 (16), 159 (100), 146 (89), 131 (46), 105 (13), 104 (33), 77 (21), 76 (15); **3e** : m/z = 202 ($M^+$)

(27), 160 (26), 131 (15), 119 (10), 118 (100), 103 (6), 90 (6), 89 (19), 77 (5); anal. calcd for $C_{13}H_{14}O_2$ (202.25): C, 77.20; H, 6.98; found C, 77.22; H, 7.00.

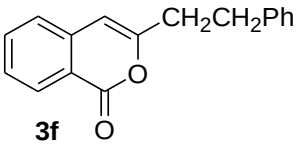
**7) 3-Butylisochromen-1-one (3e). Yield: 68.0 mg, starting from 81.5 mg of 1e**




**3e**

(84%; Table 1, entry 15). White solid, mp = 30.3-31.8 °C. IR (KBr): ν = 2953 (w), 2931 (w), 2869 (w), 1718 (s), 1656 (m), 1603 (w), 1481 (w), 1380 (w), 1287 (w), 1138 (w), 1046 (w), 965 (w), 831 (w) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ =8.05 (dd, J = 8.0, 0.6, 1 H, on aromatic ring), 7.71-7.62 (m, 1 H, on aromatic ring), 7.49-7.40 (m, 1 H, on aromatic ring), 7.35 (d, J = 7.8, 1 H, on aromatic ring), 6.26 (s, 1 H, C=CH), 2.53 (t, J = 7.5, 2 H, $CH_2CH_2CH_2CH_3$), 1.76-1.62 (m, 2 H, $CH_2CH_2CH_3$), 1.47-1.34 (m, 2 H, $CH_2CH_3$), 1.00-0.90 (m, 3 H, $CH_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ =163.1, 158.3, 137.6, 134.7, 129.5, 127.5, 125.0, 120.1, 102.9, 33.2, 29.0, 22.1, 13.8; GC-MS: m/z=202 ($M^+$) (27), 160 (26), 131 (15), 119 (10), 118 (100), 103 (6), 90 (6), 89 (19), 77 (5); anal. calcd for $C_{13}H_{14}O_2$ (202.25): C, 77.20; H, 6.98; found C, 77.22; H, 7.00.

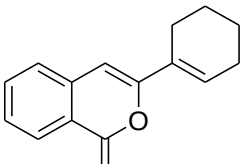
**8) 3-Phenethylisochromen-1-one (3f).**




**3f**

Yield: 80.4 mg, starting from 100.5 mg of **1f** (80%; Table 1, entry 16). White solid, mp = 32-34 °C. IR (KBr): ν = 3023 (w), 2922 (w), 1728 (s), 1654 (m), 1481 (w), 1161 (w), 1051 (w), 973 (w), 743 (w), 687 (w) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 8.25 (d, J = 8.0, 1H, on aromatic ring), 7.69-7.61 (m, 1 H, on aromatic ring), 7.48-7.40 (m, 1 H, on aromatic ring), 7.34-7.18 (m, 6 H, on aromatic ring), 6.20 (s, 1 H, C=CH), 3.03 (t, J = 7.8, 2H, $CH_2CH_2Ph$), 2.82 (t, J = 7.8, 2H, $CH_2CH_2Ph$); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 163.0, 156.9, 140.3, 137.4, 134.7, 129.5, 128.5, 128.4, 127.7, 126.3, 125.1, 120.1, 103.5, 35.5, 33.2; GC-MS: m/z = 250 ($M^+$) (27), 159 (3), 131 (7), 103 (5), 92 (8), 91 (100), 89 (7), 77 (5), 65 (5); anal. calcd for $C_{16}H_{12}O_2$ (250.29): C, 81.58; H, 5.64; found C, 81.56; H, 5.62.

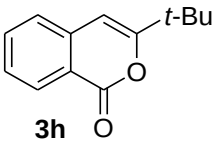
**9) 3-Cyclohex-1-enylisochromen-1-one (3g)**



**3g**

Yield: 76.3 mg, starting from 91.5 mg of **1g** (84%; Table 1, entry 17). White solid, mp = 80-82 °C. IR (KBr): ν = 3091 (w), 2922 (m), 2060 (w), 1715 (s), 1640 (m), 1621 (m), 1562 (w), 1482 (w), 1336 (w), 1221 (w), 1076 (m), 1021 (w), 925 (w), 836 (w), 751 (w), 687 (w), 530 (w) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 8.25-8.18 (m, 1H, on aromatic ring), 7.67-7.58 (m, 1H, on aromatic ring), 7.44-7.33 (m, 2 H, on aromatic ring), 6.78 (1 H, C=C$HCH_2$), 6.33 (s, 1 H, C=CH), 2.33-2.14 (m, 4 H, on cyclohexenyl ring), 1.83-1.53 (m, 4 H, on cyclohexenyl ring); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ =162.0, 155.0, 138.1, 134.5, 134.0, 130.1, 129.7, 127.5, 125.8, 121.1, 100.1, 25.8, 24.4, 22.6, 22.1; GC-MS: m/z = 226 ($M^+$) (100), 211 (13), 198 (23), 197 (23), 183 (16), 172 (13), 170 (12), 169 (9), 165 (9), 145 (14), 142 (9), 141 (16), 128 (9), 118 (12), 115 (10), 90 (10), 89 (47), 79 (7); anal. calcd for $C_{15}H_{14}O_2$ (226.27): C, 79.62; H, 6.24; found C, 79.60; H, 6.22.

**10) 3-tert-Butylisochromen-1-one (3h).**



**3h**

3-tert-Butylisochromen-1-one (**3h**). Yield: 66.7 mg, starting from 81.0 mg of **1h** (82%; Table 1, entry 18). White solid, mp = 129-130 °C. IR (KBr): ν = 2968 (m), 1735 (s), 1648 (m), 1483 (w), 1340(w), 1202 (w), 1086 (m), 1016 (w), 953 (w), 757 (m), 691 (m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.9 (d, J = 8.25, 1 H, on aromatic ring), 7.67 (td, J = 1.2, 7.9, 1 H, on aromatic ring), 7.44 (td, J = 1.2, 7.9, 1 H, on aromatic ring), 7.38 (d, J = 7.9, 1 H, on aromatic ring), 6.30 (s, 1 H, C=CH), 1.33 (s, 9H, $C(CH_3)_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 165.1, 163.0, 137.7, 134.6, 129.4, 127.6, 125.5, 120.1, 99.7, 35.6, 28.0; GC-MS: m/z = 202 ($M^+$) (63), 188 (13), 187 (100), 169 (18), 160 (60), 159 (13), 145 (47), 131 (32), 117 (13), 114 (12), 91 (11), 89 (60), 63 (12); anal. calcd for $C_{13}H_{14}O_2$ (202.25): C, 77.20; H, 6.98; found C, 77.19; H, 6.96.

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**List of publications**

1. "Synthesis of thiophenes in a deep eutectic solvent: heterocyclodehydration and iodocyclization of 1-mercapto-3-yn-2-ols in a choline chloride/glycerol medium"
Mancuso,R.; Maner,a.; Cicco,L.;Perna,F.M.; Capriati,V.; Gabriele,B.
*Tetrahedron* 72 ,**2016,** 4239-4244.

2. "Auto-Tandem Catalysis in Ionic Liquids: Synthesis of 2-Oxazolidinones by alladium-Catalyzed Oxidative Carbonylation of Propargylic Amines in EmimEtSO4.
Mancuso,R.; Maner,a.;, Ziccarelli,I.; Pomelli,C.; Chiappe,C.; Della.N.; Veltri,L.; Bartolo Gabriele.
*Molecules* **2016**, 21, 897

3. "Divergent Syntheses of iodinated isobenzofuranones and isochromenones by Iodolactonization of 2-Alkynylbenzoic Acids in ionic liquids"
Mancuso,R..; Pomelli,C.; Malafronte,F.; Maner,A.; Marino,N.; Chiappe,C..; Gabriele,B.
*Organic and Biomolecular Chemistry,* Accepted, **2017,** 15, 4831-4841.

4. Divergent Syntheses of (Z)-3-Alkylideneisobenzofuran-1(3H)-ones and 1H-Isochromen-1-ones by Cycloisomerization of 2-Alkynylbenzoic Acids in Ionic Liquids.
**Manuscript in preparation.**

**Conferences and Poster Presentations**

1. Raffaella Mancuso, Asif Maner, Vito Capriati, Bartolo Gabriele."Synthesis of Thiophene Derivatives in DES"$10^{th}$ International School of Organometallic Chemistry, 5-9 september **2015**, Camerino. Abstract Book: P57

2. Raffaella Mancuso, Asif Maner, Vito Capriati, Bartolo Gabriele,"A Recyclable Method for the Synthesis of Thiophenes in DES"; XXXVI Convegno Nazionale della Divisione di Chimica Organica della Società Chimica Italiana; 13-17 settembre **2015**, Bologna. Abstract Book: PC104, pg. 233.

3. Raffaella Mancuso, Asif Maner, Luciana Cicco, Vito Capriati, Bartolo Gabriele, "Synthesis of Thiophene Derivatives in DES" Convegno Congiunto delle Sezioni Calabria e Sicilia 2015; 3-4 dicembre **2015**, Catanzaro. Abstract Book: P51.

4. Raffaella Mancuso, Asif Maner, Ida Ziccarelli, Bartolo Gabriele"Auto-tandem catalysis in ionic liquids: Palladium-Iodide catalyzed recyclable synthesis of 2-Oxazolidinones"12$^{th}$ Congress of the Interdivisional Group of Organometallic Chemistry (CoGiCo 2016).5-8 giugno **2016**, Genova. Abstract Book: pg 71, P20.

5. Raffaella Mancuso, Asif Maner, Ida Ziccarelli, Nicola Della Cà, Bartolo Gabriele."Synthesis of 2-Oxazolidinines by Carbonylative Auto-Tandem Catalysis in Ionic Liquids" XXXVII Convegno Nazionale della Divisione di Chimica Organica della Società Chimica Italiana; 18-22 settembre **2016**, Mestre (Ve). Abstract Book: pg 148, PC35

6. Raffaella Mancuso, Asif Maner, Ida Ziccarelli, Bartolo Gabriele."Palladium-Iodide Catalyzed Recyclable Synthesis of 2-Oxazolidinones"WorpShop delle Sezioni Sicilia e Calabria 20179-10 Febbraio **2017**, Messina. P18

7. Raffaella Mancuso, Asif Maner, Bartolo Gabriele "Base-free Iodocyclization of 2-Alkynylbenzoic acid in Ionic Liquids" WorpShop delle Sezioni Sicilia e Calabria 20179-10 Febbraio **2017**, Messina. P-18,P-19