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Synthesis of High Value Added Molecules by Catalytic and Heterocyclization Approaches

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a Maria Carmen ed Eleonora
"essenza della mia esistenza"

Abstract

In the present PhD thesis is reported the development of new sustainable catalytic processes for the production of high value added molecules starting from simple and readily available building blocks, under safer and low-intensive energy conditions, by iodocyclization, carbonylation and cycloisomerization reactions in non-conventionl solvents such as Deep Eutectic Solvents (DES) and Ionic Liquids (ILs).

Catalytic processes, in which several different units can be assembled in one step in ordered sequence under the promoting action of a suitable catalyst, are destined to play a central role in current synthesis. Of particular importance is the development of novel catalytic processes for the reconversion of CO and CO_2 into organic molecules. CO is an inexpensive and readily available C-1 source, and its incorporation into an organic substrate (carbonylation) is now widely recognized as a very important tool in synthesis. Nowadays, carbonylations are at the basis of important industrial technologies for the conversion of easily available feedstocks into useful products of our daily life, and find increasing application in organic synthesis for the production of fine chemicals. CO2 is another very attractive C-1 feedstock for organic synthesis. It is ubiquitously available, low toxic, and abundant. Since the industrial revolution, CO_2 has been continuously released in huge amounts in the atmosphere from all combustion processes of organic carbon for the production of energy. Therefore, the efficient reconversion of CO_2 ("spent" carbon) into high value added products ("working"-carbon; chemicals, fuels, materials) is one of the current most important strategic goals in chemical research, which will allow to make a step forward toward a more sustainable economy.

Non-conventional solvents, such as polyethylene glycols, ionic liquids (ILs), Deep Eutectic Solvents, or supercritical CO_2 are less toxic and more eco-friendly than traditional organic solvents. Their use in the processes studied in this thesis allowed an easier separation and purification of the products and, in the case of catalytic reactions, the recycling of the catalyst as well.

The direct syntheses of ureas, oxamides, 2-oxazolidinones, and benzoxazolones by oxidative carbonylation of amines, β-amino alcohols, and 2-aminophenols allows

obtaining high value added molecules, with a large number of important applications in several fields, starting from very simple building blocks. In chapter two is reported the possibility to carry out these transformations using the PdI_2/KI catalytic system in an ionic liquid (IL), such as $BmimBF_4$, as the solvent. The catalyst-solvent system can be recycled several times with only a slight loss of activity, while the product can be easily recovered by crystallization.

In the some chapter the reactivity of 2-(2-alkynylphenoxy)anilines under PdI_2/KI-catalyzed oxidative carbonylation conditions has been studied. 8-endo-dig cyclization preferentially occurred when the triple bond was terminal, leading to the formation of carbonylated β-lactam derivatives. These novel medium-sized heterocyclic compounds showed anti-tumor activity against both estrogen receptor-positive (MCF-7) and triple negative (MDA-MB-231) breast cancer cell lines.

In chapter three is showed that the heterocyclodehydration and iodocyclization of readily available 1-mercapto-3-yn-2-ols has been performed in a deep eutectic solvent (DES), that is, ChCl/Gly, as a non-conventional green solvent. The DES/catalytic system could be easily recycled several times without appreciable loss of activity, after extraction of the thiophene product with hexane or Et_2O.

In chapter three the first example of a tandem thionation/S-cyclization process leading to benzo[c]thiophene-1(3H)-thione and 1H-isothiochromene-1-thione derivatives, starting from 2-alkynylbenzoic acids, is also reported. Depending on the nature of the substituent at the distal β carbon of the triple bond, either benzothiophenethiones or isothiochromenethiones were obtained selectively, in high to excellent yields.

In chapter four a novel methodology to easily access imidazolidin-2-ones from propargylamines, primary amine and CO_2 with guanidine bases as catalysts under solvent-free conditions is reported. Bicyclic guanidines, able to catalyze the formation of oxazolidinones from propargylamines and CO_2, are presented for the first time as effective organocatalysts for the chemical fixation of CO_2 into linear and cyclic ureas.

Chapter 1

General Introduction

1.1 Introduction

The achievements in chemical research, with particular regard to the development of efficient synthetic methodologies of novel molecules, have been contributing significantly to the improvement of the quality of life. On one hand, the chemical research has allowed the individuation of novel active principles for applications in the pharmaceutical, biomedical and agro-industrial fields; on the other hand, it has contributed in a fundamental way to the tremendous development of new materials that are used in many different fields of our daily life (from building to automotive or electronics, for example). For these reasons, research in Chemistry is still of essential importance, owing to the continuous need for the development of new technology aimed at producing novel materials for advanced applications as well as for the discovery and the synthesis of new active principles, that may result more active, more selective and less toxic with respect to those already known.

It is, however, clear that, in the future, the development of these methodologies will have to occur in a "sustainable" manner, that is, in such a way to minimize the process energetic requirements and the related environmental impact. Therefore, the development of synthetic methods that may be more and more efficient, selective and environmentally benign represents a central goal of modern scientific research. In order to achieve this aim, modern synthesis will have to take into account the following, fundamental criteria :

- Use of simple and readily available, non-toxic starting materials;
- Minimization of the number of synthetic steps which, starting from the substrates, lead to the final, high value added product (the ideal case being, of course, a one-step process),
- For each synthetic step, determination of synthetic methodologies that are highly chemo-, regio-, and stereoselective, for the formation of the desired intermediate/product;
- For each synthetic step, determination of synthetic methods that can be carried out under the mildest reaction conditions as possible;

- For each synthetic step, determination of synthetic methods that can be carried out in inexpensive, non-toxic, readily available, and possibly recyclable solvents;
- For each synthetic step, determination of synthetic methods characterized by the highest atom economy as possible, that is, leading to the incorporation, into the final product, of the maximum percentage of the atoms constituting the starting materials (the ideal being, of course, 100%)
- With atom economy lower than 100%, determination of synthetic methods leading to non-toxic and possibly recyclable by-products.

On the basis of these considerations, it is clear that the synthetic processes able to allow the direct production of high value added molecules through the selective assembly of simple units, with the lowest possible number of steps and under mild and eco-friendly conditions, are bound to assume an increasing importance in modern synthesis. In this view, catalytic processes in general, and metal-catalyzed in particular, are destined to play a central role in scientific research. In fact, with a catalytic process, it is possible to construct complex and multi-functionalized molecules in only one step, in a highly chemo-, regio-, and stereoselective manner, by employing simple and economical starting materials. Moreover, it is also often possible to modulate the efficiency and selectivity of the catalyst by simply suitably adjusting the reaction parameters, such as temperature, solvent, co-catalyst(s), ligand(s), and so on. Is therefore evident that catalysis is the synthetic technology that can better give an answer to the requirement for the realization of a “sustainable” chemical synthesis.

1.2 Use of carbon monoxide as a C-1 unit in novel catalytic processes for the direct synthesis of high value added molecules

Metal-catalyzed carbonylation reactions, which make use of the simplest and readily available carbon unit (CO) for the direct preparation of complex carbonyl compounds starting from simple building blocks, represent very important processes in view of the development of a "Sustainable Chemistry". Indeed, carbonylation represents the most powerful and convenient method for the direct and atom-economical synthesis of carbonyl compounds. Nowadays, many carbonylation reactions are at the basis of important industrial technologies for the conversion of feedstocks into widely used products of practical interest and find an increasing utilization in organic synthesis for the production of fine chemicals from CO.

1.2.1 Carbonylation reactions

The term carbonylation[1] can be described as the incorporation of CO molecule into an organic substrate either by the insertion of CO into an existing bond, such as 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"[2], step economy[3] and "green chemistry"[4]. 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[5]. This growing importance of carbonylation methods in organic synthesis is attested to by the increasing number of publications dealing with this topic, including reviews[1a].

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’’[6b], 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.

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)].[7] 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.[5]

Different kinds of carbonylation reactions can be defined; depending on the particular type of process under consideration four types of carbonylation processes are possible.

-Substitutive Carbonylation

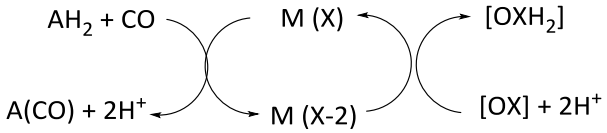
-Additive Carbonylation

-Reductive carbonylation

-Oxidative Carbonylation

1.2.2 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 1.1).



Scheme 1.1. 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.[7] 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.

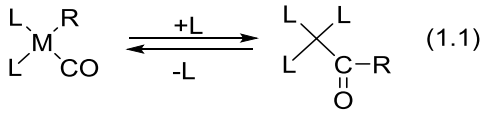
1.2.3 Transition metals in carbonylation reactions

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[8]. 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[9]) and in 1953. Reppe's first catalytic carbonylation process converted acetylene, CO, and water to acrylic acid (Hydroxycarbonylation) using $Ni(CO)_4$ as catalyst.[10] 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[11], Tl[12], Hg[13], Mn[14], Fe[15], Co[16], Ni[17], Cu[18], Ru[19], Rh[20], Pd[21], PdI_2[22], W[23], Pt[24], Ir[25] and Au[26]. 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. 1.1). 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.



(1.1)

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[27]. Under oxidative carbonylation conditions palladium can leads to the formation of mono and double carbonylated products[28]. Most commonly Pd(II) catalyst reacts with the organic substrates of electron-rich species, such as olefins, alkynes, and arenes[29]. 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[30] are $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, and $PdCl_2(RCN)_2$ and PdI_2[1,31]. Various carbonylation reactions catalyzed by palladium metal have been reported in literature.

PdI_2 Catalyst

The PdI_2 in conjunction with KI was introduced by Prof. Gabriele about 20 years ago[31], 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.[1] PdI_2 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 1.2, 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. 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 1.2, Eq. a, in the following scheme anionic iodide ligands are omitted for clarity). Reaction of HI with oxygen present in gas mixture occurs along with production of water as product (Scheme 1.2, Eq. c). Pd(0) reoxidation occurs through oxidative addition of I_2 (Scheme 1.2, Eq. d)

$$PdI_2 + 2\,KI \longrightarrow 2K^+ [\,PdI_4]^{2-} \quad (a)$$

$$AH_2 + CO + PdI_2 \longrightarrow A(CO) + Pd(0) + 2\,HI \quad (b)$$

$$2\,HI + (1/2)\,O_2 \longrightarrow I_2 + H_2O \quad (c)$$

$$Pd(0) + I_2 \longrightarrow PdI_2 \quad (d)$$

Scheme 1.2. 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.

1.2.4 PdI_2 Catalyzed Oxidative Carbonylation Reactions

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. 1.1) in single step.

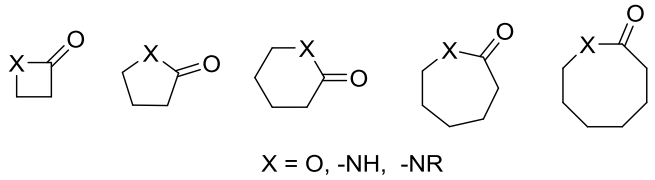
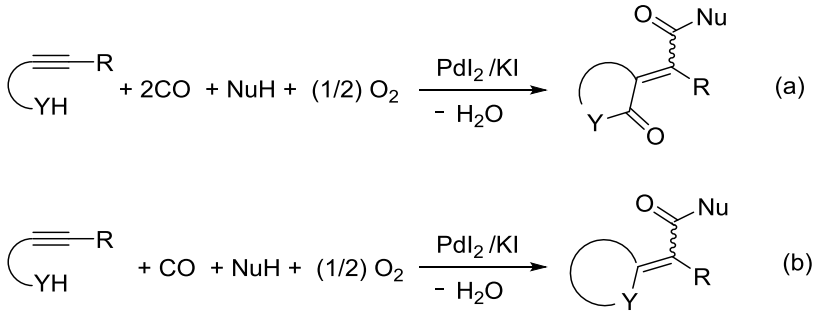


Figure 1.1 lactones and lactams of different size

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.

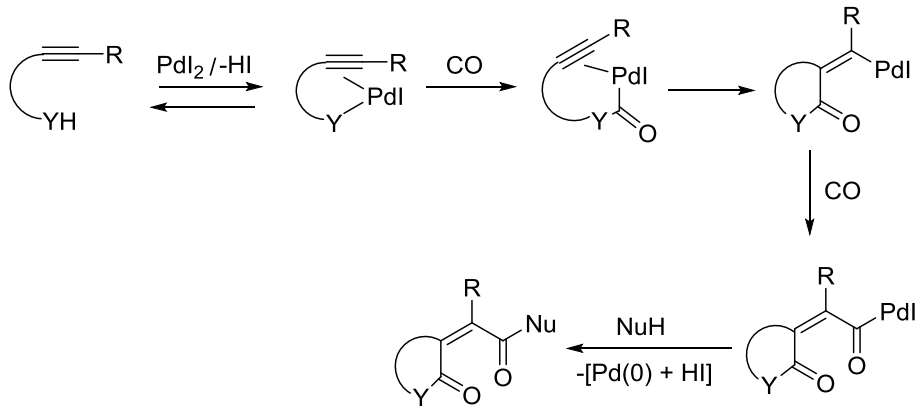
a) Oxidative Cyclization–Carbonylation (without incorporation of CO in the cycle) (Scheme 1.3 Eq. b).



Scheme 1.3

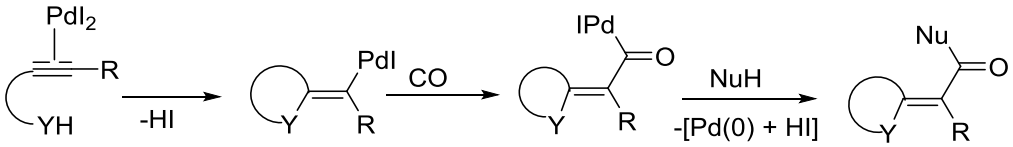
Cyclocarbonylative pathway (Scheme 1.4) proceeds via formation of an alkoxycarbonylpalladium (or carbamoylpalladium) intermediate[1e] through the reaction between the nucleophilic function of the substrate –YH (Y = O, NR), CO and PdI_2,

followed by intramolecular *syn* insertion of the triple bond, CO insertion and nucleophilic displacement by an external nucleophile (NuH).



Scheme 1.4

In oxidative heterocyclization-carbonylation, the *anti* intramolecular nucleophilic attack 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 1.5

1.3 Carbon Dioxide in carboxylation reactions

Carbon dioxide, produced by the combustion of fossil fuels, the fermentation of sugars and the respiration of all living organisms, is one of the major greenhouse gases responsible for the rise of the Earth's temperature and for the abnormal changes in the global climate. The increasing carbon dioxide levels in the atmosphere has led to the development of strategies and technologies to reduce carbon emission and to implement efficient carbon capture methodologies. Another innovative approach is based on the possibility to chemically convert CO_2 into high value added organic compounds. For this reason, CO_2 utilization as C-1 building block represents a promising field in view of sustainable development and environmental protection[32].

Carbon dioxide, therefore, can be considered as a very attractive starting material in organic synthesis, due to its abundance, availability and nontoxicity; however, activation and utilization of CO_2 is still problematic because of its chemical inertia. For this reason, during the past decade, several activation methodologies have been established. In particular, the use of active substrates, such as unsaturated compounds (alkenes, alkynes), three-membered ring compounds (aziridines and epoxides), and organometallic compounds is recognized as a powerful way for CO_2 activation, possibly in combination with organocatalysts and/or transition metal catalysts[33].

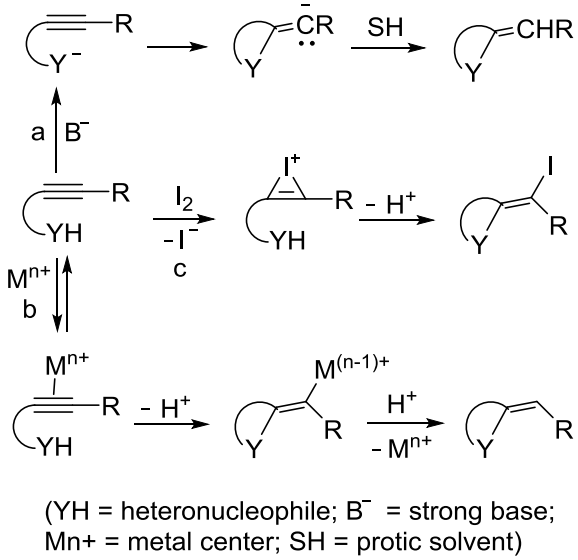
One of the more successful processes for CO_2 utilization in organic synthesis is the catalytic production of cyclic carbonates and polycarbonates from epoxides using metalloporphyrin, metal, dimetallic as well as metal-free catalysts. Other important processes are the catalytic reductive formylation and methylation of amines with CO_2 catalyzed by Ru; the oxidative couplings of CO_2 with various unsaturated hydrocarbons, such as olefins or alkynes, catalyzed by low-valent metal (Ni or Pd) complexes; and carboxylation reactions via CO_2 insertion into C-M bond catalyzed by transition metal catalyst (Rh, Pd, Ag, Ni, Cu). Highly reactive organolithium and Grignard reagents are typically utilized as strong nucleophiles to react with CO_2 directly to construct C-C bonds and furnish valuable carboxylic acids and their derivatives. The current industrial synthesis of salicylic acid derivatives is a classical example for this type of reaction[34].

1.4 Heterocyclization Reaction

Heterocyclization of acetylenic substrates bearing a suitably placed nucleophilic group is widely recognized as a methodology of primary importance for the direct preparation of a variety of heterocyclic systems in a regioselective fashion, starting from readily available acyclic precursors.[35]

This reaction can be promoted by strongly basic conditions, which favor the deprotonation of the nucleophilic group, followed by intramolecular nucleophilic attack to the triple bond (Scheme 1.6, pathway a; only the exo-dig mode is shown for simplicity).

To avoid possible substrate and/or product degradation, the heterocyclization is more conveniently carried out by electrophilic activation of the triple bond, usually ensuing from triple bond coordination to a suitable metal center (as in metal-catalyzed heterocyclizations, Scheme 1.6, pathway b) or from the interaction with an electrophilic species (such as iodine, as in the case of iodocyclization reactions that lead to iodinated heterocycles, Scheme 1, pathway c).



Scheme 1.6 Possible heterocyclization pathways of acetylenic substrates bearing a heteronucleophilic group (YH) leading to heterocycles (only the *exo-dig* mode is shown for simplicity).

1.4.1 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[35]. 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[36] and nitrogen-containing heterocyclic compounds[37] have maintained the interest of researchers through decades of historical development of organic synthesis. However, heterocycles with other heteroatoms such as oxygen[38], phosphorus[39] and selenium[40] also appears. Many natural drugs[41] 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.[42]

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[42] 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[43]. 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. 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 and function either as coenzymes or their precursors. Other vitamins such as ascorbic acid (vitamin C) and α-tocopherol (vitamin E) are oxygen heterocycles.

The essential amino acid proline, histidine and tryptophan[44], photosynthesizing pigment chlorophyll; the oxygen transporting pigment haemoglobin[44a], the hormones kinetin, heteroauxin, cytokinins[44b], neurotransmitter serotonin, histamine respectively are successful application of heterocyclic compounds.

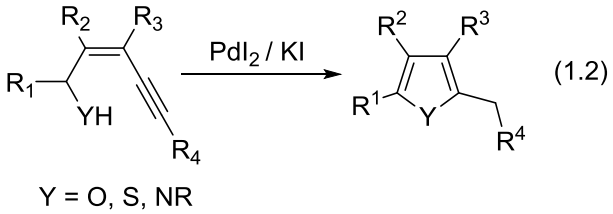
In conclusion, it can be questioned why it is specifically appropriate to emphasize the role of heterocycles, since analogies to the roles of other classes of organic compounds are easily found. In fact, dyes, luminophores, herbicides, pesticides and drugs do not necessarily have to be heterocyclic in 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.

1.4.2 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[45]. From the point of view of atom economy[2], the ideal approach

is clearly represented by a simple cycloisomerization process[46]. PdI_2 is an excellent catalyst for carrying out the cycloisomerization (Eq. 1.2) 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,[47] thiophenes,[48] and pyrroles[49], respectively has been reported by Gabriele research group.

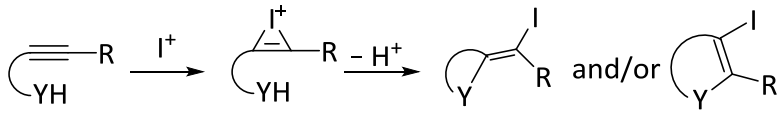


Cycloisomerization reactions leading to furans, thiophenes, and pyrrols have been performed under mild conditions in classical organic solvents, either dipolar aprotic (such as N,N-dimethylacetamide (DMA), dimethylsulfoxide (DMSO), or MeCN), apolar or slightly polar (such as toluene, THF, or CH_2Cl_2), 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[48b].

1.5 Iodocyclization reaction

The iodocyclization of acetylenic substrates bearing a suitably placed nucleophilic group for cyclization is a powerful synthetic tool for the direct and regioselective synthesis of iodinecontaining carbo- and heterocyclic derivatives starting from readily available substrates under mild reaction conditions.[50,51] The presence of the iodo substituent in the final product may be useful for further functionalization and diversification through metalcatalyzed cross-coupling reactions, which further increases the attractiveness of iodocyclization processes. This latter aspect makes the iodocyclization approach very attractive, and complementary with the well-known metal-catalyzed heterocyclization processes, which occur *via* activation of the triple bond by coordination to themetal center followed by intramolecular nucleophilic attack and protonolysis, with formation of the corresponding heterocyclic derivative. As shown in Scheme 1.7, 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.



(YH = nucleophilic group; I^+ = electrophilic iodine species)

Scheme 1.7 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).

Iodocyclizations are usually carried out under particularly mild conditions (room temperature, in several cases without the need for working under inert atmosphere), and show high functional group compatibility, the halogen, carbonyl, nitro and cyano groups being usually very well tolerated. Various aspects of these iodocyclization reactions have been recently reviewed, including the application of iodocyclization processes to the synthesis of natural products[50], heterocyclic derivatives[51], and carbocyclic derivatives[52], as well as the construction of heterocyclic libraries[52]. The present mini-review is intended to highlight some very recent and particularly interesting examples of the synthesis of heterocyclic derivatives by the iodoheterocyclization of functionalized alkynes.

1.6 Solvents for sustainable chemical processes

Solvents are major issue in the production of chemicals. Glaxo-Smith-kline researchers[53] 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[54], supercritical CO_2[55], fluorous biphasic[56] and ionic liquids[57] alone or in liquid–liquid biphasic combinations.

1.6.1 Ionic Liquids (IL)

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, and the number of reported articles in the literature has grown exponentially.

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[58] (RTILs). ILs are made of positively and negatively charged ions (Fig. 1.2), whereas water and organic solvents, such as toluene and dichloromethane, are made of molecules.

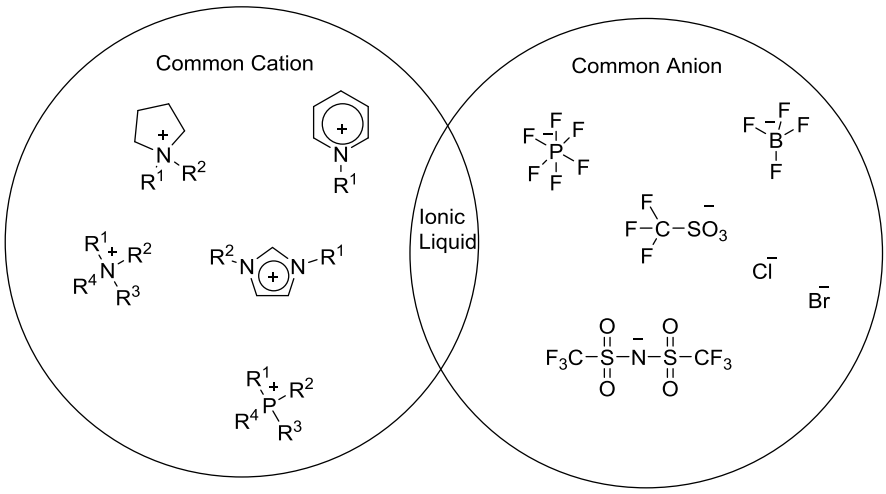


Figure 1.2 Schematic Presentation Of Ionic Liquid

The most commonly used cations in room-temperature ionic liquids are alkylammonium, alkylphosphonium, *N*,*N*'-dialkylimidazolium, and *N*-alkylpyridinium

cations (Fig. 1.2). The most commonly utilized alkyl chains are methyl, ethyl, butyl, hexyl, octyl, and decyl. The most commonly investigated IL anions are shown in Table 1.1.

Table 1.1 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:

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.

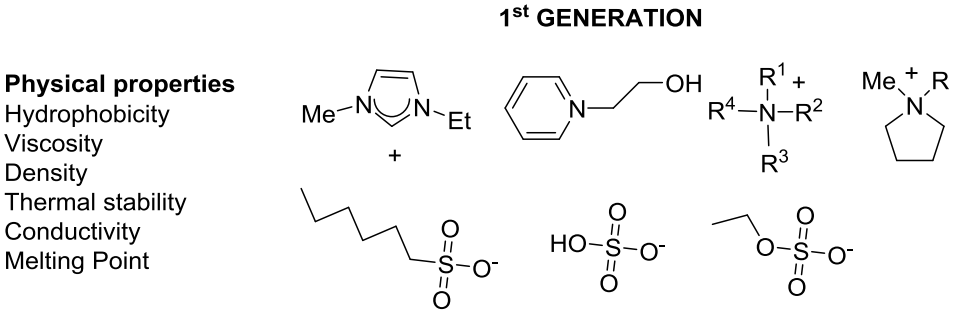


Figure 1.3

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

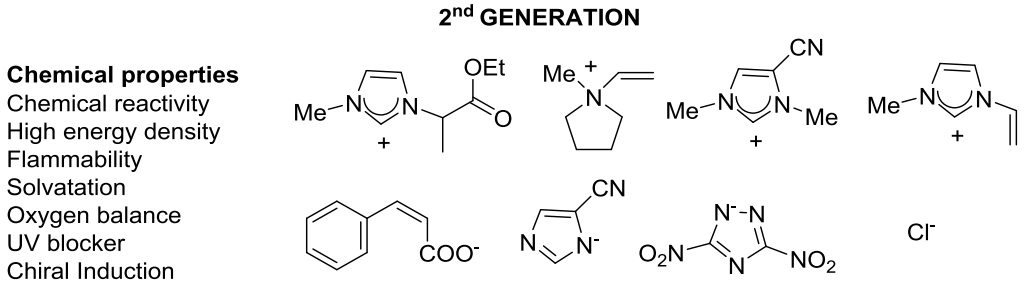


Figure 1.4

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

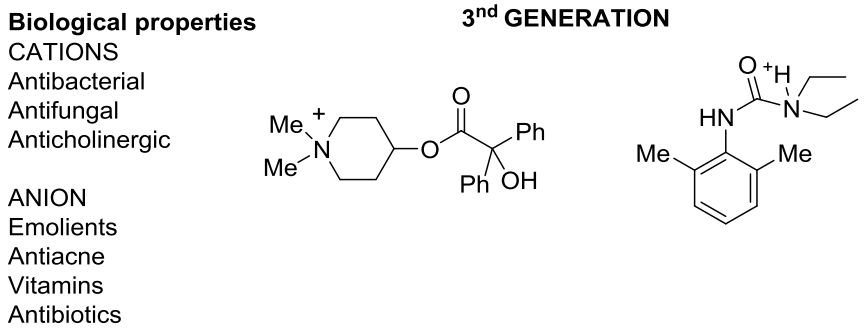


Figure 1.5

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. 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.

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.

As solvents, ILs posses following advantages over conventional organic solvents, which make them environmentally compatible.

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. 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.

1.6.2 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.[59] 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. 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.

1.6.3 Deep Eutectic Solvents (DES)

A new solvent foundation was laid in 2003 reported by Abbott and dubbed ‘‘Deep Eutectic Solvents’’ (DESs)[60]. Deep eutectic solvents are defined as[61] 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.[61]

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.[62]

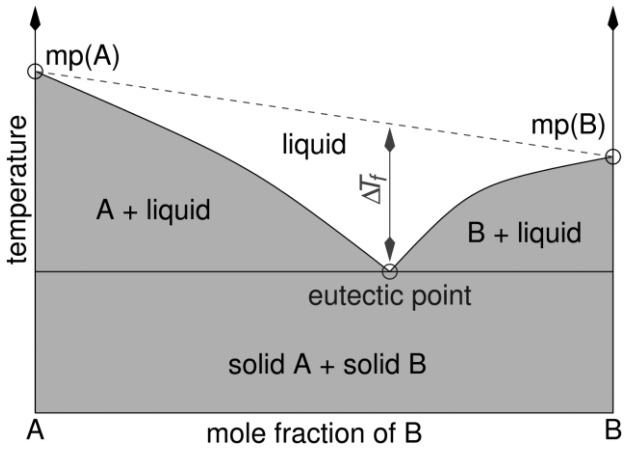


Figure-1.6 Schematic representation of a eutectic point on a two component phase diagram.

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.[63-65] A classic example is the mixture of choline chloride (m.p. = 302^{0}C, 2-hydroxyethyl

trimethylammonium chloride) and urea (m.p. = 133 °C) in a 1:2 molar ratio resulting in a room-temperature liquid (Tf =12 °C).[60] 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),[66] 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.[67] 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.[68]

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.[65-69] The first applications of choline-based eutectic solvents were in the electrodeposition and electropolishing of metals and in biodiesel production.[70] 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.[64,65] 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.[71–75]

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.[76] 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).[74]

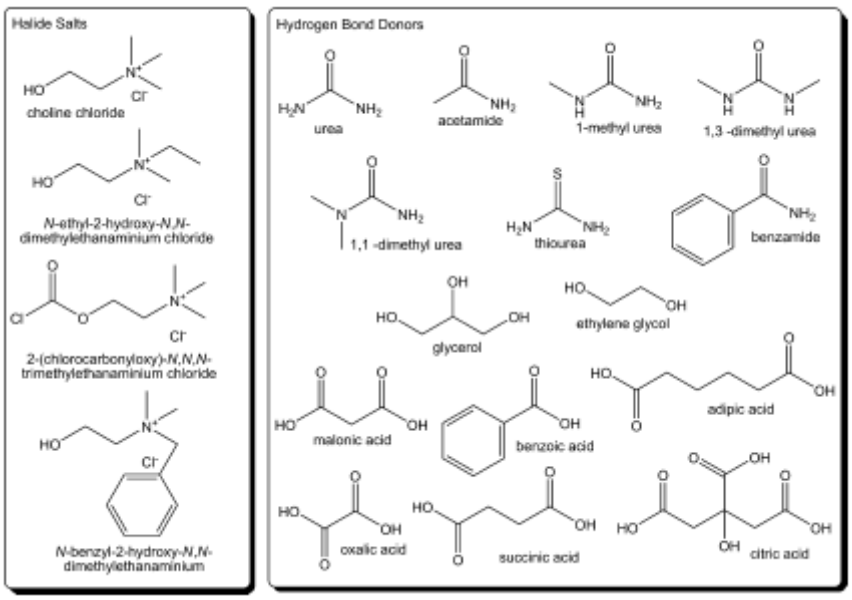


Figure -1.7 Structures of some halide salts and hydrogen bond donors used in the formation of deep eutatic solvents

Preparation of DES

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.[77] If the ChCl is combined with hydrogen bond donors (such urea), renewable carboxylic acids or renewable polyols, ChCl is capable of forming a DES

Charactricstics of DES

DESs are characterized by high conductivities, viscosities, and surface tensions, they also have lower vapor pressure in comparison to other solvents.[78] 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 °C and 302 °C respectively. The result was a eutectic mixture that melts at 12 °C[79]. 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 [80,81].

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.[82] And have been introduced as new alternative solvents to replace conventional ones for the use in synthetic processes[83] The refractive index is related to the electronic polarizability of the medium 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;

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. 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 [77,84] and many potential applications in different fields of chemistry and electrochemistry was found. Main applications of DESs were done in nanotechnology field.

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

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Chapter 2

Synthesis of Ureas, Oxamides, 2-Oxazolidinones, Benzoxazolones and (Z)-12-Oxa-5-azadibenzo[a,d]cycloocten-6-ones by PdI_2-Catalyzed Oxidative Carbonylation of Amines.

2.1 PdI_2-Catalyzed Oxidative Carbonylation of Amines in Ionic Liquids: A Recyclable Synthesis of Oxamides, Ureas, Oxazolidinones, and Benzoxazolones

2.1.1 General Importance of Ureas, Oxamides, 2-Oxazolidinones and Benzoxazolones

Ureas, oxamides, 2-oxazolidinones, and benzoxazolones are between the most important carbonyl derivatives.

Importance of Ureas

Ureas are a very important class of carbonyl compounds.

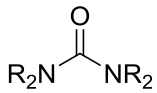


Figure 2.1 Ureas

Due to their strong, and tuneable hydrogen bonding abilities[1] and their relatively easy synthesis, which facilitates their use in both simple and complex systems.[2] Their occurrence in natural products made them valuable.[1g] They find extensive application as agrochemicals, dyes for cellulose fibres, antioxidants in gasoline, resin precursors, and synthetic intermediates[3] especially for the production of carbamates and isocyanates.[4] Their importance both in industrial and academic fields is well known such as in production of light coloured natural rubber,[5a] as plasticizer for production of cellulose film[5b] in thin film formation,[5c] as additives to petroleum compounds and polymers,[5d] recently their use to form deep eutectic solvent (DES) tremendously increased their value in the field of organo-synthesis and catalysis as green solvent.[5e] Moreover, many ureic derivatives have displayed a wide spectrum of biological activity.[6a-i] In particular, several substituted ureas have recently been shown to possess a marked inhibiting effect on HIV protease enzyme.[6b] CCK-B receptor antagonists,[6c-d] and endothelin antagonists.[6i] Recently, interesting application of ureas were reported by Peng Xiu, They performed molecular dynamics simulations of narrow single-walled carbon nanotubes (SWNTs) where they observed spontaneous and continuous filling of SWNT with a one-dimensional urea wire[7a] (Fig. 2.2). Furthermore, author found that the stronger dispersion interaction of urea with SWNT than water. These unique properties of molecular urea wires confined within both artificial and biological

nanochannels, and are expected to have practical applications such as the electronic devices for signal transduction and multiplication at the nanoscale.

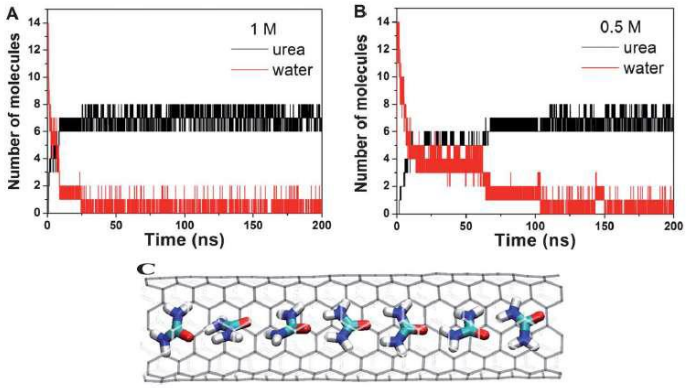


Figure 2.2 (A and B) Number of urea (shown in black; KBFF urea model is used) and water (shown in red) molecules within the 336-carbon (6,6) SWNT (with a length of 3.32 nm) as a function of simulation time, at 1 M (A) and 0.5 M (B) urea concentrations, respectively. (C) Representative snapshot to show a ''perfect'' urea wire at 1 M urea concentration.

Urea can significantly undermine the molecular hydrogen bond and hydrophobic interactions of chitin and chitosan[7b] and raise the critical micelle concentration. Alkali-urea solution can be used as a novel chitin/chitosan green solvent, which is expected to be used in some more demanding for stimulating fields such as food, biomedical, etc.

Very recently novel biological significance of ureas derivatives and urea linkage containing compounds was reported. R.P. Tripathi and co-worker reported novel c-Glycosidel derivatives containing urea linkage as potent antimalarial agents.[7c] In vitro antimalarial activities of compounds were tested against Plasmodium falciparum 3D7 (CQ sensitive) and K1 (CQ resistant) strains activity.

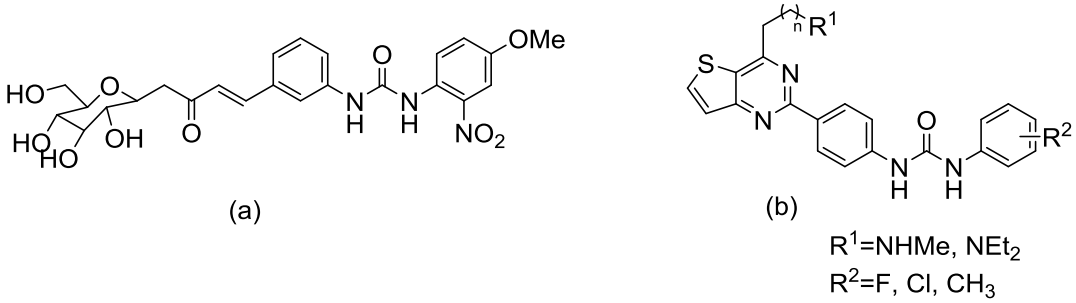


Figure. 2.3

Importance of Oxamides

Oxamides are well known for their coordination properties.[8]

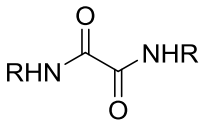


Figure 2.4 Oxamides

The Oxamide dianion acts as a bidentate ligand and, like the oxalate dianion, which is also capable of coordinating as a bridging ligand to give many kinds of mononuclear, dinuclear or polynuclear metal complexes[8c] The binuclear copper(II) complexes formed by the oxamide dianions are more stable than those formed by the oxalate dianion, owing to the high extent of magnetic interaction between two metal ions, especially in the N, N'-bis(coordinating group substituted)oxamides. It is hoped that the binuclear complexes formed by the N, N'-bis(coordinating group substituted) oxamides will lead to the development of a new field of coordination chemistry.

Their property to form coordination complexes with metals has wide applications in material and physical sciences. Oxamides coordinated with nitrito groups "oxamidato ligands" are able to mediate a strong antiferromagnetic interaction.[9a] Oxamides (*N,N*-bis(2-aminophenyl)oxamide) can coordinate selectively with copper ions, which helped physicist to enhance "Light Scattering" signals, which has wide application in analytical detection.[9b-c] Recently, Martin Shroder et al reported the application of substituted Oxamide derivatives in Metal Organic Frameworks[10] (MOF). MOFs (Fig. 2.5) are crystalline, porous materials with exceptionally high internal surface areas and tunable functional pore has great promising applications in gas storage and separation, notably in CO_2 gas storage.

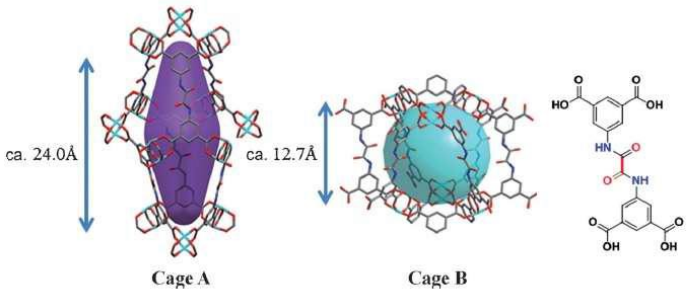


Figure 2.5 MOFs of substituted Oxamide derivatives

Also oxamides complexes with different transition metals[8c] showed antimicrobial activity which indicates the bright future of oxamide complexes in biological sciences too.

Terminal oxamide derivatives of mercapto-acetyltriglycine can help in renal excretions process.[11] Shi Hao Cui[11b] and Man Jiang[11c], reported the DNA-binding properties, and cyto-toxic activities of copper complexes with oxamides; K.O Yerleden evaluated different derivatives of oxamides as acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibitors[11d] against Alzheimer's disease (AD).

Importance of Oxazolidin-2-ones

Oxazolidin-2-ones are important compounds in both pharmaceutical[12a] and synthetic organic chemistry.

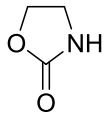


Figure 2.6 Oxazolidin-2-ones

They are widely used as chiral auxiliaries[13] Evan's Auxiliary in numerous asymmetric syntheses and are applied in the synthesis of a number of valuable natural products, antibiotics, and on the other hand they are synthetic new class of five-member heterocyclic ring exhibiting potential medicinal properties with preferential antibacterial activity against gram positive bacteria, which inhibits protein synthesis via binding to a distinct region of 23S-RNA near the peptidyl transferase center of the 50S-ribosomal subunit in prokaryotes.[12b] Due to the emergence of resistance to known antibiotics such as sulphonamides and β-lactam class to various organisms, for example, Staphylococcus, Streptococcus, Enterococci, and Pseudomonas there is a renewed interest in the discovery of new antibiotics. Since 1970's several antibiotics have been brought to market, but only four of these new chemical scaffolds found useful against drug resistance[12c] among them one is the Oxazolidinone. Oxazolidinone, a totally synthetic class of novel anti-bacterials, possess activity against drug-resistant Gram-positive pathogens, especially MRSA. Linezolid, the first approved drug from this class, has shown a great promise in saving lives of many patients by acting against drug-resistant Gram-positive organisms. After the successful launch of linezolid,

Oxazolidinone class of antibacterials got considerable interest from various research institutions, including pharmaceutical industries[12d] Turos and co-workers. recently reported the discovery of the compounds with Nthiolated 2-oxazolidinone[12f] rings (Fig. 2.7 a) as a new family of antibacterial agents, many of these N-thiolated derivatives showed potent antibacterial activity against methicillin-resistant Staphylococcus aureus[12g] (MRSA). G. Madhusudhan et al. reported new class of oxazoline based compounds (R)- and (S)-5-azidomethyl-2-oxazolidinones[12h] (Fig. 2.7 b) synthesized from (S)-epichlorohydrin, which showed potent anti bacterial activity.

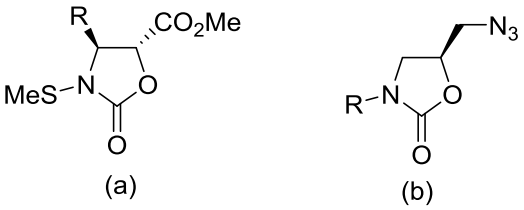


Figure 2.7 Oxazolidin-2-ones

Importance of Benzoxazolones

Benzoxazolones and its methoxy analogues widely found in natuaral products.[14a]

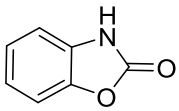


Figure 2.8 Benzoxazolones

Also benzoxazolinones are secondary metabolites and are found mainly in the plant family of the Poaceae, and, to a lesser extent, in the Acanthaceae, Ranunculaceae and Scrophulariaceae. They can act as “chemical weapons” both in defense against microorganisms and herbivores, and in attack, against susceptible plant competitors.[14b] Because of this property, their use in agriculture has been proposed as “bioherbicides” or “Biopesticides”.[14] Recently, synthetic analogues of benzoxazolones revealed novel application as enzyme inhibitors. Sánchez-Moreiras proposed a new series of benzoxazolone derivatives[14c] as potential cholinesterase inhibitors, while Qing-Shan Li reported novel 4-substituted benzoxazolone derivatives[14d] as human soluble epoxide hydrolase (sEH) inhibitors and anti-inflammatory agents. Also

structure-activity relationship (SAR) studies of novel benzoxazolone derivatives with various substituents at the amide part and C-5 position exhibited anxiolytic effect.[14e] While their property to bind Selectively to 18 kDa translocator protein (TSPO) ligands[14f] are expected to be therapeutic agents with a wide spectrum of action on psychiatric disorders.

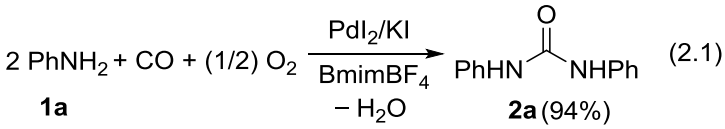
The classical approaches to these molecules are based on the use of toxic reactants, such as phosgene and its derivatives, or oxalyl chloride and its derivatives. Recently, the possibility to directly synthesize these important compounds by catalytic oxidative carbonylation of amines or β-amino alcohols has been extensively explored.[15] In fact, this approach may allow obtaining the target molecules in a multicomponent fashion starting from very simple and largely available building blocks (the organic substrate, CO, and an external oxidant). Moreover, when the oxidant corresponds to molecular oxygen, the process becomes particularly attractive from a sustainable perspective, since the coproduct formed is water and the atom economy is particularly high. Several methods have thus appeared in the literature for realizing these processes with oxygen as reoxidant.[16, 17] Unfortunately, most of the proposed methods have been proposed under potentially explosive conditions, with CO/O_2 mixtures in volume ratios very close to, or even within, the flammability range for this kind of mixture.[14c] Moreover, no oxidative carbonylation method reported so far has allowed the general synthesis of ureas, oxamides, 2-oxazolidinones, and benzoxazolones with recycling of the catalytic system and of the reaction medium, which would clearly increase the attractiveness of the process and its sustainability.[18]

By using a suitable ionic liquid (IL),[19] such as $BmimBF_4$, as the reaction medium, in the presence of the PdI_2/KI catalytic system, it is possible not only to convert primary aromatic amines to 1,3-aryl ureas, β-amino alcohols to 2-oxazolidinones, and 2-aminophenols to benzoxazolones (through an oxidative mono carbonylation process), but also secondary amines to tetrasubstituted oxamides (through an oxidative *double* carbonylation process). Moreover, primary aliphatic amines can be selectively converted into either 1,3-dialkyl ureas or *N*,*N*‘-dialkyloxalamides depending on

reaction conditions. In all cases, the process is carried out under conditions that allow an efficient recovery and recycling of the solvent-catalyst system.

2.1.2 Result and Discussion

Initial experiments were carried out with aniline **1a** as the substrate, using 1 mol % of PdI_2 in conjunction with 10 mol % of KI, at 100 °C under 20 atm of a 4:1 mixture of CO-air, in $BmimF_4$ as the solvent (0.5 mmol of **1a** per mL of solvent). After 24 h, substrate conversion was quantitative, and extraction with Et_2O followed by repeated crystallization from cold Et_2O allowed the isolation of pure 1,3-diphenylurea **2a** in almost quantitative yield (94%, Table 2.1, entry 1, run 1; eq. 2.1).



(2.1)

The ether used for extraction and purification could be easily recovered and reused for other experiments. We then verified the recyclability of the catalyst-ionic liquid system by adding fresh aniline to the recovered ionic liquid phase and repeating the carbonylation procedure under the same conditions reported above, but without adding fresh catalyst. After 24 h, **1a** conversion was still quantitative, and **2a** was recovered in 87% yield (Table 1, entry 1, run 2). The recycling process was repeated for additional 4 times, with formation of **2a** in yields ranging from 75 to 85% (Table 1, entry 1, runs 3-6). These results therefore confirmed the possibility to use an ionic liquid medium in the PdI_2/KI-catalyzed direct oxidative carbonylation of amines to ureas and to recycle the catalyst several times with only a slight loss of activity.

The method was then extended to other primary aromatic amines **1b-e**, and the results obtained are shown in Table 1, entries 2-5. As can be seen from Table 1, excellent results in terms of product yield and catalyst recycling were obtained with all the amines tested, bearing electron-donating (Table 1, entries 2-4) as well as electron-withdrawing (Table 1, entry 5) groups.

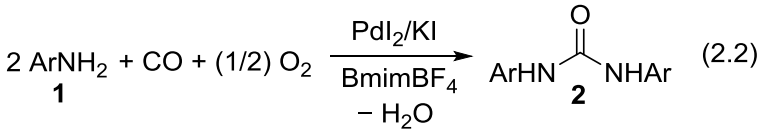
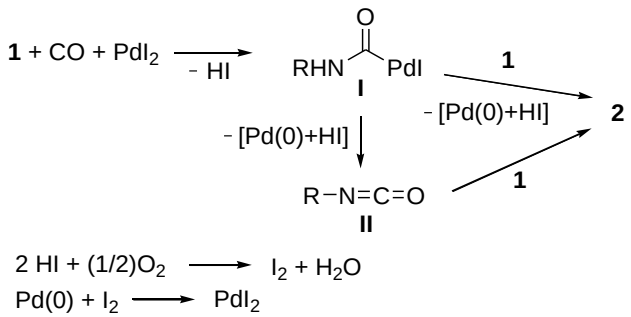


Table 2.1. Synthesis of 1,3-diaryl ureas **2a-e** by recyclable PdI_2/KI-catalyzed oxidative carbonylation of primary anilines **1a-e** in $BmimBF_4$[a]

Entry	Aryl amine **1**	Urea **2**	Yield of **2** [%][b]					
			Run 1	Run 2	Run 3	Run 4	Run 5	Run 6
1	$PhNH_2$ **1a**	PhHN, NHPh **2a**	94	87	85	80	77	75
2	Me, NH_2 **1b**	Me, Me **2b**	87	81	80	77	75	75
3	*i*-Pr, NH_2 **1c**	*i*-Pr, *i*-Pr **2c**	92	87	87	85	86	85
4	MeO, NH_2 **1d**	MeO, OMe **2d**	88	80	78	77	75	75
5	Cl, NH_2 **1e**	Cl, Cl **2e**	91	80	80	78	77	76

[a] All reactions were carried out at 100 °C for 24 h in $BmimBF_4$ (0.5 mmol of **1** at start per mL of $BmimBF_4$, 1 mmol scale based on **1**) using a **1**:KI:PdI_2 molar ratio of 100:10:1, under 20 atm (at 25 °C) of a 4:1 mixture of CO-air. Substrate conversion was quantitative. [b] Isolated yield from **1**. Run 1 corresponds to the 1st experiment, the next runs to recycles. See text for details.

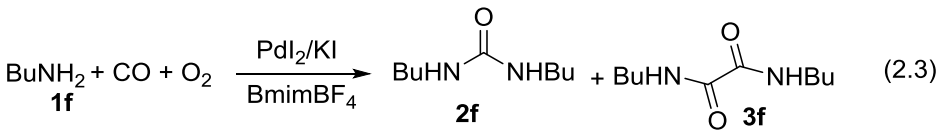
Mechanistically, the reaction may start with the formation of a carbamoylpalladium iodide intermediate **I**, from the reaction between PdI_2, the primary amine **1**, and CO (Scheme 1; anionic iodide ligands are omitted for clarity).



Scheme 2.1. Possible mechanistic pathways for the PdI_2-catalyzed oxidative monocarbonylation of primary amines **1a-h** to ureas **2a-h**. Both carbamoylpalladium complex **I** and isocyanate intermediate **II** may lead to the final product.

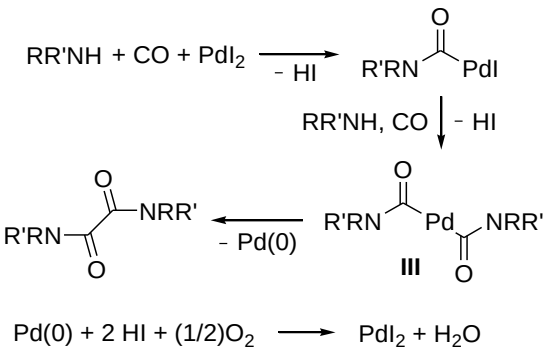
Either the direct nucleophilic displacement by the amine, or the formation of an isocyanate intermediate **II** (by formal β-elimination of HI from the I-Pd-(CO)NHR moiety) followed by addition of **1** to **II**, may then occur, leading to the formation of the final urea product **2** and Pd(0). The latter is eventually reoxidized back to PdI_2, according to the mechanism involving oxidation of HI (formally deriving from the carbonylation process) to I_2 followed by oxidative addition of I_2 to Pd(0).

When butylamine **1f** was subjected to the same carbonylation conditions as those reported in Table 2.1, a mixture of 1,3-dibutylurea **2f** and N,N'-dibutyloxalamide **3f** was obtained, as confirmed by GC-MS analysis (total yield: 84%; **3f/2f** molar ratio = 1.1, Table 2.2, entry 1; eq. 2.3).

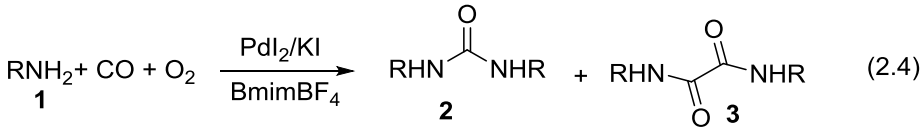


(2.3)

The formation of **3f**, ensuing from a double carbonylation process, is clearly due to the higher nucleophilicity of **1f** as compared to anilines **1a-e**, which allows for the formation of a bis-carbamoylpalladium complex $Pd(CONHR)_2$ **III** (from the reaction between PdI_2 and 2 mol of RNH_2 and CO, with formal elimination of 2 HI; Scheme 2.2, R = alkyl, R' = H). The latter, according to the literature,[16] is the key intermediate in the formation of the oxamide product, obtained by reductive elimination (Scheme 2.2).

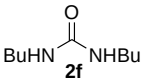
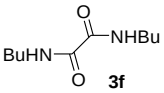
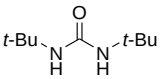
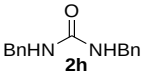
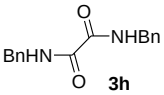


Scheme 2.2 Formation of oxamides by PdI_2-catalyzed oxidative double carbonylation of amines through the formation of *bis*-carbamoylpalladium complex **III**.



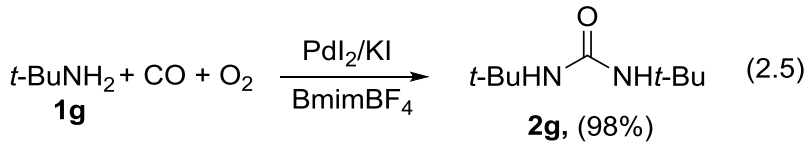
(2.4)

Table 2.2 PdI_2/KI-catalyzed oxidative carbonylation of primary amines **1f-h** in $BmimBF_4$ leading to 1,3-dialkylureas **2f-h** and/or *N,N'*-dialkyloxalamides **3f-g** [a]

Entry	Alkylamine **1**	Dialkylurea **2**	Yield of **2** [%][b]	Oxamide **3**	Yield of **3** [%][b]
1	$BuNH_2$ **1f**	 **2f**	40	 **3f**	44
2	*t*-$BuNH_2$ **1g**	 **2g**	98 (94-94-93-92-92)		
3	$BnNH_2$ **1h**	 **2h**	47	 **3h**	45
4[c]	**1f**	**2f**	83 (81-80-78-77-77)		
5[d]	**1h**	**2h**	90 (89-89-88-88-87)		
6[e]	**1f**			**3f**	82 (80-81-79-80-81)
7[e]	**1h**			**3h**	86 (85-85-84-83-84)

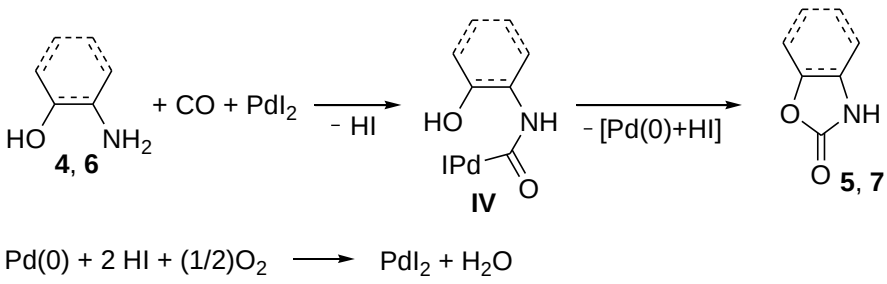
[a] Unless otherwise noted, all reactions were carried out at 100 °C for 24 h in $BmimBF_4$ (0.5 mmol of **1** at start per mL of $BmimBF_4$, 1 mmol scale based on **1**) using a **1**:KI:PdI_2 molar ratio of 100:10:1, under 20 atm (at 25 °C) of a 4:1 mixture of CO-air. Substrate conversion was quantitative. [b] Isolated yields from **1**. Figures in parentheses refer to recycles. [c] The reaction was carried out with a **1f**:KI:PdI_2 molar ratio of 200:10:1 and a substrate concentration of 1 mmol of **1f** per mL of $BmimBF_4$. [d] The reaction was carried out with a **1h**:KI:PdI_2 molar ratio of 500:10:1 and a substrate concentration of 1 mmol of **1h** per mL of $BmimBF_4$. [e] The reaction was carried out at 80 °C under 40 atm (at 25 °C) of a 4:1 mixture of CO-air.

Accordingly, a less nucleophilic, sterically hindered primary aliphatic amine, such as tert-butylamine **1g,** selectively led to the urea derivative in practically quantitative yield (Table 2.2, entry 2; eq. 2.5), while benzylamine **1h** behaved similarly to butylamine **1f** (Table 2, entry 3).



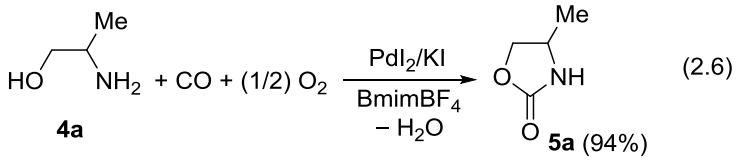
Very interestingly, both for $BuNH_2$ **1f** and $BnNH_2$ **1h**, it has been possible to work out suitable reaction conditions able to selectively promote the formation of either the urea or the oxamide derivative. In particular, when the carbonylation reaction of **1f** was carried out with a higher substrate concentration (1 mmol per mL of $BmimBF_4$) with a catalyst loading of 0.5%, urea **2f** was the only product formed in 83% yield (Table 2.2, entry 4). Under similar conditions, and with a catalyst loading as low as 0.2%, benzylamine **1h** was converted into dibenzylurea **2h** in 90% yield (Table 2.2, entry 5). On the other hand, oxamides **3f** and **3h** were selectively formed when the reactions were conducted at 80 °C under a total pressure of 40 atm (entries 6 and 7 of Table 2.2). As shown in Table 2, entries 2 and 4-7, the recyclability of the catalyst was successfully verified also in these experiments.

In the case of β-amino alcohols **4** as starting materials, an intramolecular nucleophilic attack may take place at level of the β-hydroxycarbamoylpalladium complex **IV**, with formation of particularly important products, 2-oxazolidinones (Scheme 2.3).

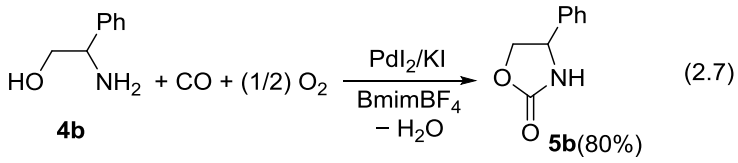


Scheme 2.3. Formation of 2-oxazolidinones **5** and benzoxazolones **7** by PdI_2-catalyzed oxidative monocarbonylation of β-amino alcohols **4** or 2-aminophenols **6**, respectively, by intramolecular trapping of the β-hydroxycarbamoylpalladium complex **IV**.

Accordingly, the reactivity of 2-aminopropan-1-ol **4a** and (R)-2-amino-2-phenylethanol **4b** was tested under our reaction conditions. Excellent yields in the corresponding 4-methyloxazolidin-2-one **5a** and (R)-4-phenyloxazolidin-2-one **5b** were obtained (Table 2.3, entries 1 and 2; eq. 2.6 and 2.7).



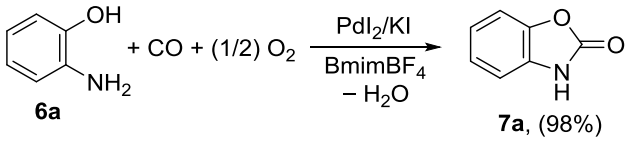
(2.6)



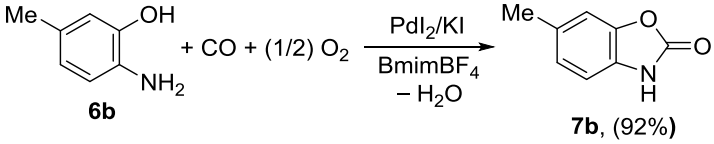
(2.7)

Again, 2-oxazolidinones were recovered by simple crystallization, while the ionic liquid-catalyst system could be successfully recycled several times.

Extension to 2-aminophenols **6a**, **b** to give the corresponding benzoxazolones **7a**, **b** was also successful (Table 2.3, entries 3-5; eq. 2.8 and 2.9), and the possibility to lower the catalyst loading to 0.2 mol% verified (Table 2.3, entry 4).

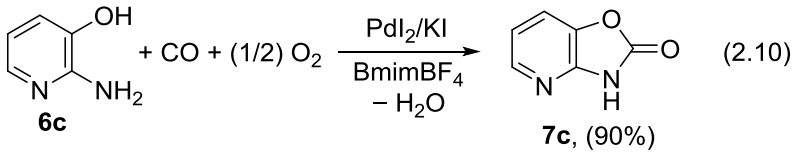


(2.8)



(2.9)

A pyridine ring was compatible with the reactions conditions, 2-aminopyridin-3-ol **6c** being converted into oxazolo[4,5-b]pyridin-2(3H)-one **7c** in 90% yield in the first experiment, and in 84-87% yield in the recycles (Table 2.3, entry 6).



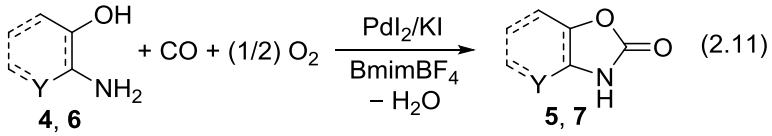
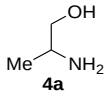
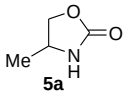
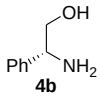
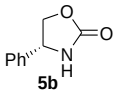
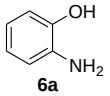
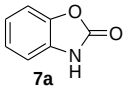
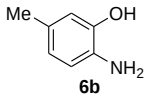
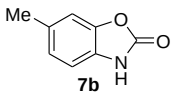
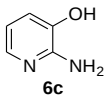
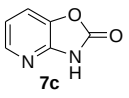


Table 2.3. Synthesis of 2-oxazolidinones **5** and benzoxazolones **7** by recyclable PdI_2/KI-catalyzed oxidative carbonylation of β-amino alcohols **4** and 2-aminophenols **6**, respectively, in $BmimBF_4$[a]

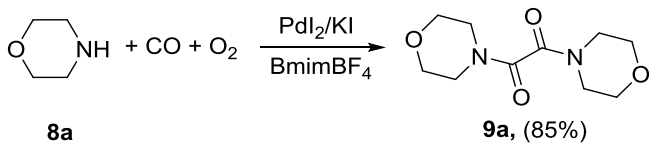
Entry	β-Aminoalcohol **4** or 2-aminophenol **6**	2-Oxazolidinone **5** or benzoxazolone **7**	Yield of **5** or **7** [%][b]					
			Run 1	Run 2	Run 3	Run 4	Run 5	Run 6
1	 **4a**	 **5a**	94	88	86	85	83	84
2	 **4b**	 **5b**	80	75	74	72	73	72
3	 **6a**	 **7a**	98	93	90	88	85	85
4[c]	**6a**	**7a**	95	94	90	88	88	89
5	 **6b**	 **7b**	92	90	88	86	85	86
6	 **6c**	 **7c**	90	87	85	83	84	84

[a] Unless otherwise noted, all reactions were carried out at 100 °C in $BmimBF_4$ (0.5 mmol of **5** at start per mL of $BmimBF_4$, 1 mmol scale based on **5**) using a **5**:KI:PdI_2 molar ratio of 100:10:1, under 20 atm (at 25 °C) of a 4:1 mixture of CO-air. Substrate conversion was quantitative. [b] Isolated yield from **5**. Run 1 corresponds to the 1st experiment, the next runs to recycles. [c] The reaction was carried out with a **5a**:KI:PdI_2 molar ratio of 500:10:1.

This class of compounds was smoothly converted into tetrasubstituted oxamides **9** under the conditions reported in the present work, through the intermediate

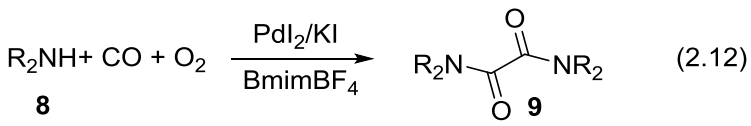
formation of the corresponding bis-carbamoylpalladium complex $Pd(CONRR')_2$ **III** (Scheme 2.2, R, R' = alkyl).

Thus, the reaction of morpholine **8a**, carried out in $BmimBF_4$ under the same conditions reported in Table 1, entry 1, run 1, led to the formation of 1,2-dimorpholinoethane-1,2-dione **9a** in 85% isolated yield, after extraction of the reaction mixture with Et_2O (Table 2.4, entry 1; eq. 2.12).[22]



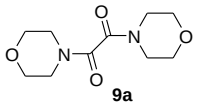
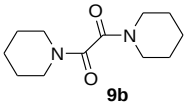
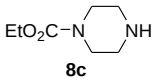
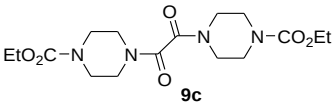
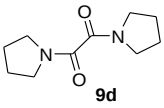
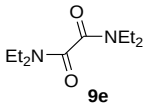
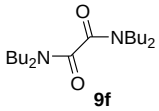
8a **9a**, (85%) (2.12)

Also in this case, the ethereal solvent used for crystallization could be recovered and reused, while the IL phase, still containing the active catalyst, could be recycled several times using a fresh amount of substrate **8a** in each run, without appreciable loss of activity (Table 2.4, entry 1, runs 2-6). The oxidative double carbonylation reaction leading to **9a** worked nicely even when the catalyst loading was lowered to 0.2% (Table 2.4, entry 2). Under the same conditions employed for morpholine **8a**, other cyclic and acyclic secondary amines **8b-f** were efficiently converted into the corresponding oxamides **9b-f** in high yields and excellent recyclability of the catalyst-IL system (Table 2.4, entries 2-7).



8 **9** (2.12)

Table 2.4. Synthesis of tetrasubstituted oxamides **9** by recyclable PdI_2/KI-catalyzed oxidative carbonylation of secondary amines **8** in $BmimBF_4$ [a]

Entry	Dialkyl amine **8**	Oxamide **9**	Yields of **9** [%] [b]					
			Run 1	Run 2	Run 3	Run 4	Run 5	Run 6
1	 **8a**	 **9a**	85	86	85	85	85	87
2 [c]	**8a**	**9a**	85	83	83	90	81	81
3	 **8b**	 **9b**	91	90	92	91	90	91
4	 **8c**	 **9c**	97	95	96	94	94	92
5	 **8d**	 **9d**	90	90	91	90	89	91
6	Et_2NH **8e**	 **9e**	92	90	87	85	85	86
7	Bu_2NH **8f**	 **9f**	89	86	84	83	83	82

[a] Unless otherwise noted, all reactions were carried out at 100 °C in $BmimBF_4$ (0.5 mmol of **8** at start per mL of $BmimBF_4$, 1 mmol scale based on **8**) using a **8**:KI:PdI_2 molar ratio of 100:10:1, under 20 atm (at 25 °C) of a 4:1 mixture of CO-air. Substrate conversion was quantitative. [b] Isolated yield from **8**. Run 1 corresponds to the 1st experiment, the next runs to recycles. [c] The reaction was carried out with a **8a**:KI:PdI_2 molar ratio of 500:10:1.

2.1.3 Conclusions

In conclusion, in this work I have obtained the first general recyclable Pd-catalyzed oxidative carbonylation of primary amines, β-amino alcohols, 2-aminophenols, and secondary amines to give 1,3-disubstituted ureas, 2-oxazolidinones, benzoxazolones, and oxamides, in high yields and selectivity. Carbonylations were carried out in an ionic liquid, such as $BmimBF_4$, as the reaction medium, under non-explosive conditions (100 °C and 20 atm of a 4:1 mixture of CO-air), using a particularly simple and robust

catalytic system, consisting of PdI_2 in conjunction with KI. While primary aromatic amines selectively led to 1,3-aryl ureas, tetrasubstituted oxamides were formed from secondary amines. On the other hand, primary aliphatic amines could be selectively converted into either 1,3-dialkyl ureas or *N*,*N*‘-dialkyloxalamides depending on reaction conditions. Oxazolidinones and benzoxazolones were obtained from β-amino alcohols and 2-aminophenols, respectively. All products were easily recovered by simple extraction with Et_2O from the reaction mixture followed by crystallization. The ethereal solvent was recovered and reused, while the IL phase, still containing the active catalyst dissolved in it, could be recycled several times without appreciable loss of activity.

2.2 A Palladium-Catalyzed Carbonylation Approach to 8-Membered Lactam Derivatives

2.2.1 Introduction

Medium sized ring-based scaffolds (7-11 membered, carbo- and heterocylic) are molecular framework of particular interest, owing to their biological activity[20] and occurrence in many important natural products.[21] Despite their significance, relatively few efficient synthetic methods for their preparation through cyclization of acyclic precursors are known so far,[22] compared to the quite abundant annulation protocols for the preparation of five- and six-membered rings. This is fundamentally due to a combination of unfavorable enthalpic (transannular interactions) and entropic (difficulty in closing a relatively large ring) factors, which tend to raise the cyclization activation energy.[23]

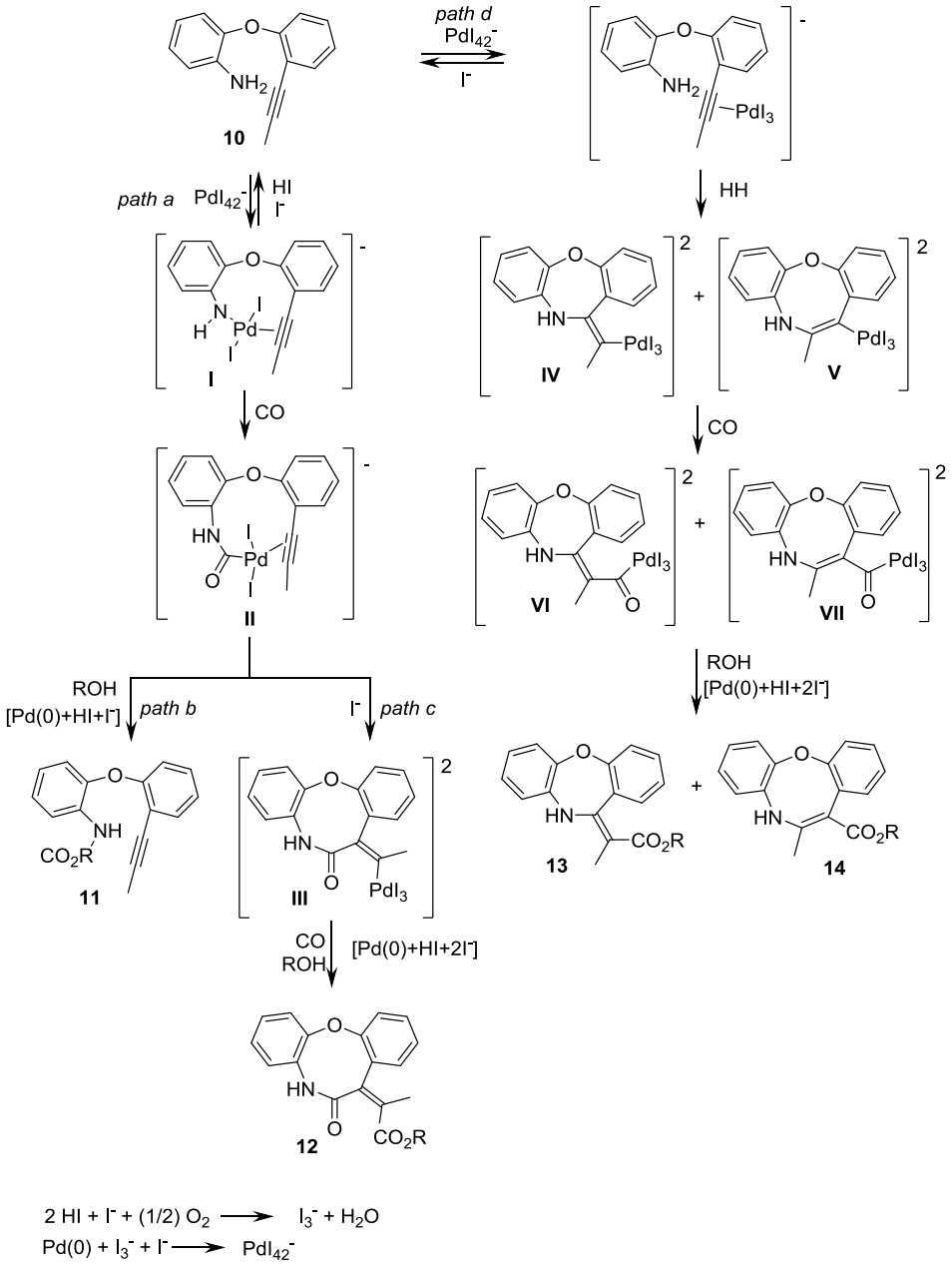
Catalytic cyclocarbonylation reactions are currently widely recognized as one of the most important and powerful synthetic tools for the direct preparation of cyclic carbonyl compounds starting from acyclic precursors.[24,25] Although numerous examples are known in the literature for the formation of five-, six-, and even 4-membered rings by cyclocarbonylation approaches, very few examples have been reported so far for the direct synthesis of medium-sized rings.[24b,25i]

Considering my experience in oxidative carbonylation chemistry,[25d,26] in particular using the PdI_2/KI catalytic system we proposed some years ago for alkyne carbonylation,[27] in this work I have studied the reactivity of 2-(2-alkynylphenoxy)anilines under PdI_2/KI-catalyzed oxidative carbonylation conditions, with the aim of obtaining novel carbonylated medium-sized rings of biological interes

2.2.2 Result and Discussion

In principle, different reaction pathways could be followed when 2-(2-alkynylphenoxy)anilines **10** are allowed to react in the presence of the PdI_2/KI catalytic system (leading in situ to K_2PdI_4) under oxidative carbonylation conditions (Scheme 2.4). A first possibility (path *a*) could correspond to *N*-palladation of **1**, with formation of complex **I**, stabilized by triple bond coordination, followed by CO insertion to give the carbamoylpalladium intermediate **II**. The latter species could then evolve either by

a direct attack by an external alcohol ROH, to afford acyclic carbamates **11** (path *b*), or through intramolecular *syn* 8-*exo*-*dig* triple bond insertion to yield vinylpalladium intermediate **III**. Alkoxycarbonylation of the latter would eventually lead to the 8-membered lactam derivative **12** (path *c*). In both cases, the obtained Pd(0) species would be reoxidized back to PdI_4^{2-} according to the mechanism we demonstrated several years ago,[27] involving oxidation of hydrogen iodide (also ensuing from the carbonylation process) to I_3^-, followed by oxidative addition of the latter to Pd(0) in the presence of iodide ligands.



Scheme 2.4. Possible divergent pathways in the PdI_2/KI-catalyzed oxidative carbonylation of 2-(2-alkynylphenoxy)anilines **10.**

However, another possible reaction pathway could start with the *anti* intramolecular attack of the nucleophilic amino group to the triple bond coordinated to the metal center (path *d*) (a reactivity that we have observed in several other carbonylative heterocyclization reactions),[24d] followed by alkoxycarbonylation of the ensuing vinylpalladium complexes **IV** and/or **V**, finally leading to carbonylated heterocycles **13** and/or **14**. Clearly, from a conceptual as well as synthetic point of view, the most interesting process would correspond to the carbonylative ς-lactamization route (path *a* followed by path *c*), leading to 8-membered lactams **12**, also considering the importance of the ς-lactam core, which is extensively found in natural and biologically relevant compounds.[28]

To predict which pathway, between those shown in Scheme 2.3, could be likely to be followed starting from substrates **10**, we have carried out theoretical calculations. Thus, a comparative analysis of the energies and geometries of the intermediates shown in Scheme 1 was carried out. First, the optimization of geometries of the *isoelectronic* reaction intermediates **III**, **VI** and **VII** (with $R^1 = CH_3$, chosen as simple model system for an internal triple bond) was carried out. All the frequencies of these intermediates were positive, indicating that they are minima in the respectively reaction pathways. The energy difference between the intermediate **III** and **VI** turned out to be +5,02 kcal/mol, while the difference between **III** and **VII** was -2.01 kcal/mol. These values indicate that path *a* (leading to **III**) and path *d* (leading to **VI** and/or **VII**) are virtually equally probable. With reference to path *d*, intermediates **IV** and **V** (precursors of **VI** and **VII**, respectively) were also found to be stable minima on the PES. However, going up towards the reactants, a discrimination between the two pathways *a* and *d* could in principle still be at work, and could be related to the different possible coordination modes of substrate **10** to the metal center.

To prove this assumption, three structures (**A-C**) were built, representing the starting geometries to be optimized (Fig. 2.9). In particular, structure **A** differs from **B,C** for the palladium orientation with respect to the triple bond: in structure **A**, the metal center is close to the amino group, whereas in **B,C** palladium is coordinated from the opposite position with respect to the $–NH_2$ group. In its turn, structure **B** differs from **C** for the –

NH_2 orientation with respect to the triple bond; in particular, in **B**, a NH···π (orbitals) hydrogen bonding is present.[29]

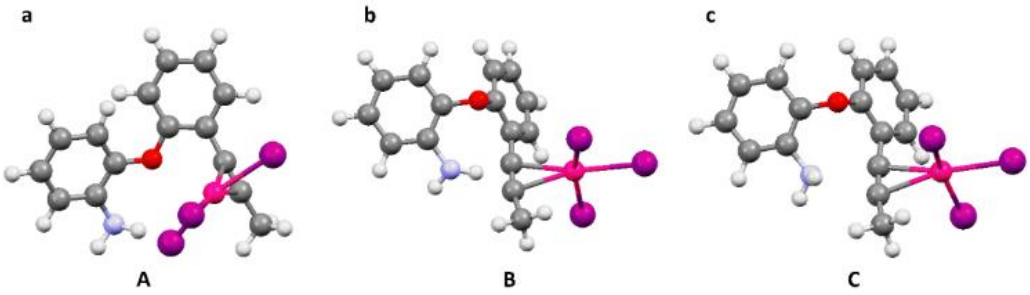


Figure 2.9. Possible coordination modes of substrate **10** (R^1 = Me) to the metal center: starting geometries **A** (a), **B** (b), and **C** (c) used for geometry optimization (pink: Pd; violet: I; red: O, grey: C; white: H).

All the optimized structures, obtained from these initial geometries, showed positive frequencies demonstrating that they are minima. The optimized geometries for structures **A** and **B**, indicated with **A'** and **B'** are shown in Fig. 2.9.

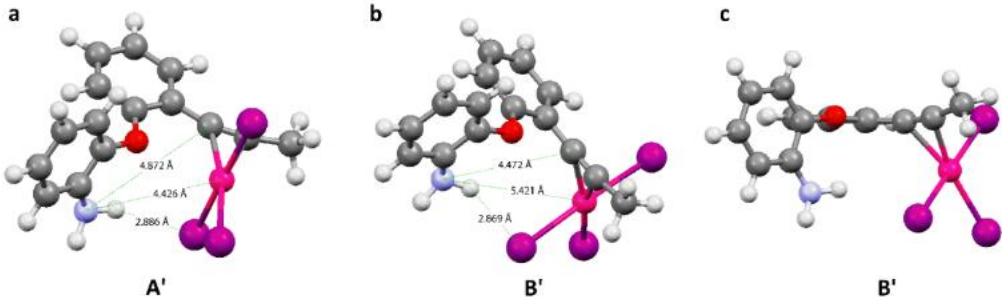


Figure 2.10. Optimized geometries for structures **A** and **B**, indicated with **A'** (a) and **B'** (b, c) respectively (pink: Pd; violet: I; red: O, grey: C; white: H).

These structures appear to be stabilized by an intramolecular hydrogen bond (NH···I, 2.10 Å) involving an iodine atom and a hydrogen atom on the amino group (Fig. 2.9 a,b). The energy difference between **B'** and **A'** was only -3,43 kcal/mol, suggesting that two minima are in equilibrium. Comparing **A'** (Fig. 2.10 a) with the non-optimized structure **A** (Fig. 2.9 a), it can be seen that the catalyst orientation does not change significantly from the initial (**A**) to the optimized (**A'**) structure. In **A'**, the N···Pd and N···C distances (where C is the carbon of triple bond closest to nitrogen) were 4.4 and 4.9 Å, respectively. This suggests that **A'** should preferentially evolve through the formation

of a N-Pd bond, leading to intermediate **I**, rather than of a N-C bond, which would lead to intermediate **IV**. On the other hand, comparing the optimized structure **B'** (Fig. 2.10 b) with the initial structure **B** (Fig. 2.9 b), it can be observed that the NH···π hydrogen bonding imposed in the initial geometry **B** is broken down after geometry optimization, in favor of a more stable NH···I noncovalent bond, with simultaneous rotation of the catalyst from its initial position. The displacement of the PdI_3···π moiety from its initial geometry is caused by a marked rotation of the Ph-O-Ph dihedral angle, as shown in Fig. 2.9 c. Key distances in **B'**, as those given for **A'**, are 5.4 Å (N···Pd bond) and 4.5 Å (N···C bond), respectively (Fig. 2.10 b). However, the formation of a N-C bond, leading to intermediate **IV**, would imply an unfavorable movement of the $–NH_2$ group toward the position shown in the non-optimized structure **B** (Fig. 2.9 b), with an inverse rotation of Ph-O-Ph dihedral angle. As regards the starting geometry **C**, shown in Fig. 2.10 c, a marked rotation of the dihedral angle Ph-O-Ph was always obtained after optimization; again, this rotation arranges the phenyl rings perpendicularly, with the $-NH_2$ farther away from the triple bond with respect to the starting geometry.

Therefore, this computational analysis suggests that pathway a, going through intermediate **I**, should be favored with respect to pathway d, going through intermediates **IV**/**V** (Scheme 2.4) and, as a result, products **11** and/or **12** (ensuing from pathway a) are predicted to be formed preferentially over products **13** and/or **14** (deriving from pathway d). It is important to emphasize that the geometry of intermediate **I** was also optimized, and its existence as a stable minimum on the PES was confirmed; the optimized structure is shown in Fig. 2.10.

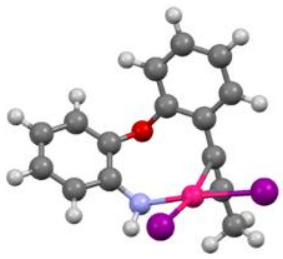
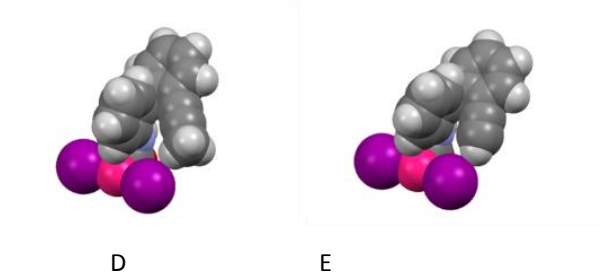


Figure 2.11. Optimized geometry for intermediate **I** ($R^1 = CH_3$).

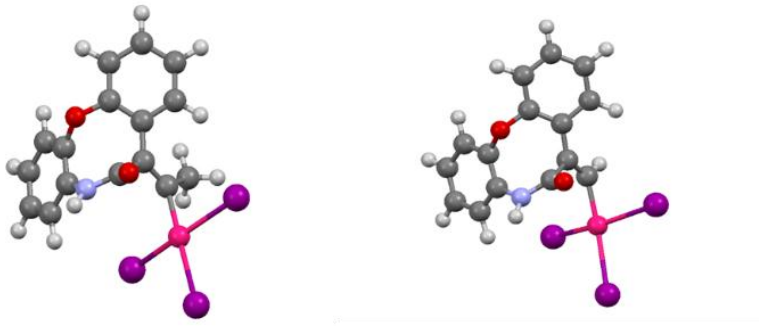
According to pathway *a* (Scheme 2.4), carbon monoxide insertion between the N-Pd bond of intermediate **I** would lead to carbamoylpalladium intermediate **II**, which, in its turn, could follow either pathway *b* (from external nucleophilic displacement by ROH, to give acyclic carbamates **11**) or pathway *c* (from intramolecular triple bond insertion into the C-Pd bond, to give intermediate **III**, followed by alkoxycarbonylation, eventually leading to ς-lactams **12**). The latter pathway was expected to be less favored in the case of an internal triple bond ($R^1 \neq H$), as usually observed in other PdI_4^{2-}-catalyzed heterocyclocarbonylation processes,[24] for steric reasons. Thus, in order to predict which product could be formed preferentially between **11** (ensuing from pathway *b*) or **12** (ensuing from pathway *c*), depending on the nature of the triple bond (internal or external), the geometries of intermediates **II** with both $R^1 = CH_3$ (**D**) and $R^1 = H$ (**E**) have been optimized (Fig. 2.11).



D E

Figure 2.12. Optimized geometries for intermediate **II** with R^1 = Me (**D**) and R^1 = H (**E**).

As can be seen from Fig. 2.12, in **D** (R^1 = Me) the C···C distance between the carbon of the carbonyl and the carbon of triple bond is 5.1 Å, and the H_2CH···I distance is 3.1 Å, while in **E** (R^1 = H), both the C···C distance and the H_2CH···I result appreciably shorter (4.6 Å and 2.9 Å, respectively). This finding indeed suggests that the cyclocarbonylation pathway (pathway *c*) may be favored with an external triple bond (R^1 = H), while, in the case of an internal triple bond (R^1 = Me), this route may be significantly more difficult, since the key distances are systematically longer owing to the steric hindrance exerted by the R^1 substituent. To further confirm this, the geometries of intermediates **III** with both $R^1 = CH_3$ (**F**) and $R^1 = H$ (**G**) have also been optimized (Fig. 2.13).



F G

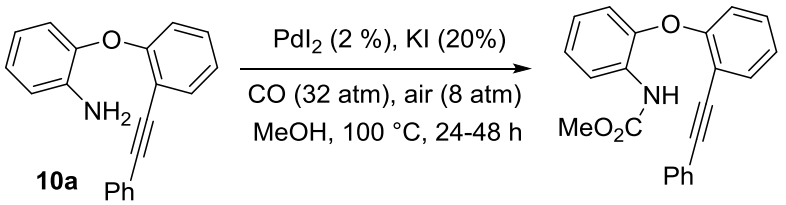
Figure 2.13. Optimized geometries for intermediate **III** with R^1 = Me (**F**) and R^1 = H (**G**).

For both structures **F** and **G**, the Hessian showed positive eigenvalues. Once again, they are minima on the PES, and, therefore, they are both possible. The energy difference between structures **F**, **G** and intermediates **D**, **E**, respectively, was then calculated, to support the hypothesis that the formation of **III** is favored when R^1 = H. From a thermodynamic point of view, the difference in energy between intermediates **III** and **II** yields information on the relative stability of these structures, in equilibrium between them. The energy gap between intermediates **G** and **E** (R^1 = H) turned out to be 8.24 kcal/mol larger than the corresponding energy difference between **F** and **D** (R^1 = CH_3). This means that the stability of intermediate **III** with respect to **II** is greater when R^1 = H, thus confirming that the formation of **III** is more favored when R^1 = H.

Thus, the results obtained by the theoretical calculations can be summarized as follows:

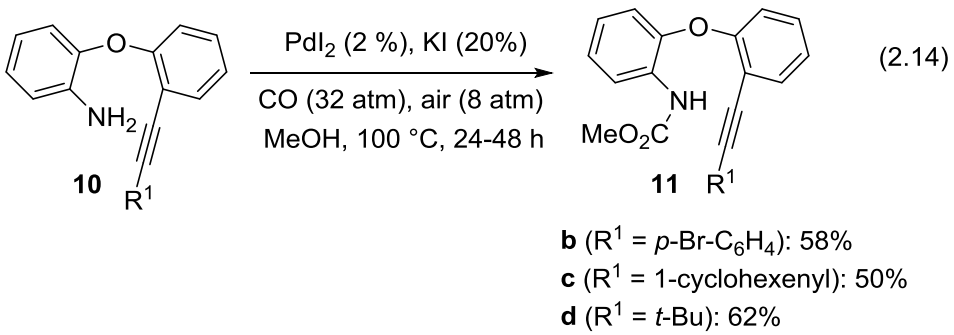
- Both path *a* and *d*, leading to intermediates **II** and **VI** and/or **VII**, respectively, can in principle be followed
- However, path *a* is expected to be more favored with respect to path *d*
- Path *c*, deriving from path *a* and leading to the desired ς-lactam derivative **3** through the formation of carbamoylpalladium complex **II**, is more likely to be followed when R^1 = H, otherwise pathway *b*, leading to acyclic carbamate **2**, is more favored. This may be ascribed to the steric effect exerted by the R^1 substituent on the triple bond, which hinders its insertion into the carbamoylpalladium bond when $R^1 \neq$ H.

To verify these hypotheses, we began to investigate the reactivity of a substrate bearing an internal triple bond, such as 2-[2-(2-phenylethynyl)phenoxy]aniline **10a** (R^1 = Ph). This substrate was allowed to react with CO, O_2 and MeOH (R = Me), also used as the solvent (substrate concentration = 0.05 mmol of **10** per mL of MeOH), at 100 °C and under 40 atm (at 25 °C) of a 4:1 mixture of CO-air, in the presence of catalytic amounts of PdI_2 (2 mol %) in conjunction with KI (KI:PdI_2 molar ratio = 10). After 24 h, carbamate **2a** was isolated in 74% yield (Eq. 2.13).



(2.13)

Similar results were obtained with other substrates, bearing a *p*-bromophenyl, an alkenyl or an alkyl substituent on the triple bond, the corresponding acyclic carbamates being formed in 50-62% yields after 24-48 h (Eq. 2.14).



(2.14)

The structure of **11b** (R^1 = *p*-Br-C_6H_4) was confirmed by X-ray diffractometric analysis (Fig. 2.13), while unidentified heavy products (chromatographically immobile materials) accounted for the remaining part of the converted substrates.

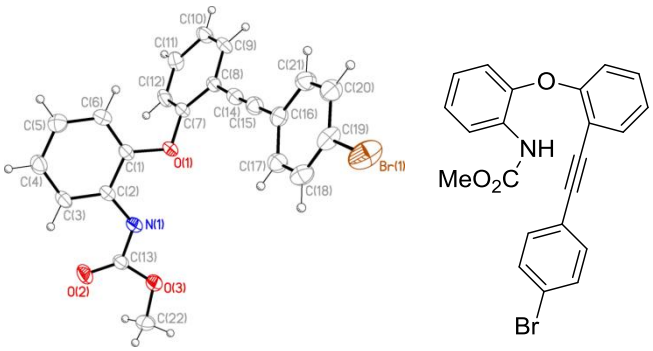


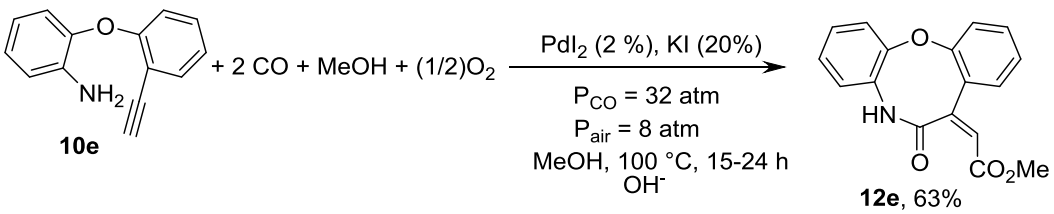
Figure 2.14. X-ray structure of **11b**

Thus, the results obtained with substrates bearing an internal triple bond showed that, in agreement to theoretical predictions, path *a* is preferentially followed with respect to path *d*, and then path *b* is favored over path *c*, eventually leading to acyclic carbamates **11**.

On the other hand, as seen above, theoretical calculations also predicted that intermediate **II** (from path *a*) could follow path *c* when the triple bond was *terminal* (R^1 = H).

Accordingly, the attention next has turned to the reactivity of substrates bearing a terminal triple bond. The first experiments were carried out with 2-(2-ethynylphenoxy)aniline **10e**, which was allowed to react under conditions similar to those employed before for substrate **10a-d**.

Gratifyingly, after 15 h, ς-lactam **12e** was obtained in 63% isolated yield (Table 2.5, entry 1; eq. 2.15), thus confirming the validity of hypotheses.



(2.15)

This result was noteworthy, considering the possible competitive pathways that could have been at work (Scheme 2.4), the importance of realizing a novel ς-lactamization

process by a direct carbonylative approach, and the potential applicative importance of the product obtained.

The reaction was repeated in EtOH, and a slightly higher yield of the corresponding ethyl ester **12e'** was obtained (71%, Table 2.6, entry 1).

The structure of **12e'** was confirmed by X-ray diffractometric analysis (Fig. 2.15), and the *Z* stereochemistry around the double bond was in perfect agreement with the mechanism shown in Scheme 2.3, path *c*.

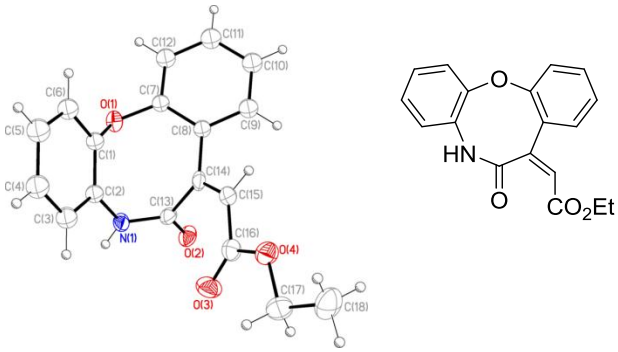
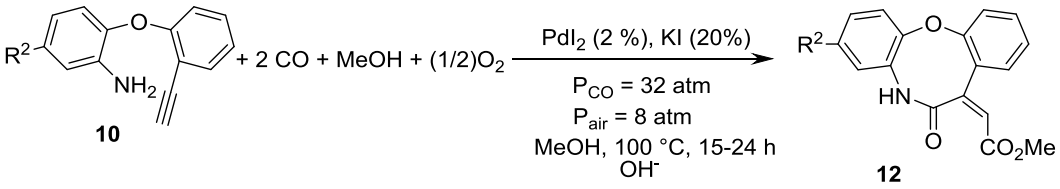


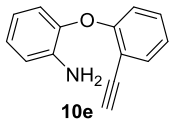
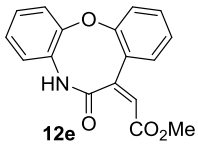
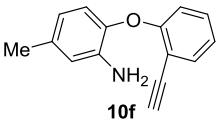
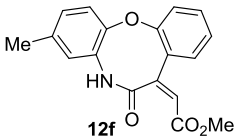
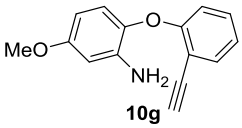
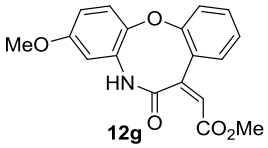
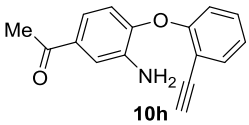
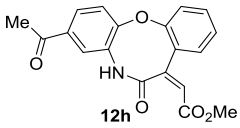
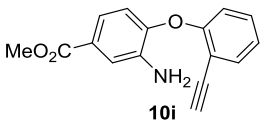
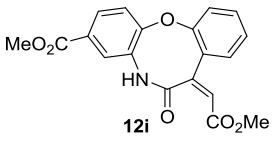
Figure 2.15. X-ray structure of **12e'**

The next experiments, carried out with differently substituted substrates, confirmed the formation of the corresponding 8-membered lactams **12f-i** and **12f'-k'** in satisfactory yields in all cases (53-75%, Table 2.5 and 2.6).

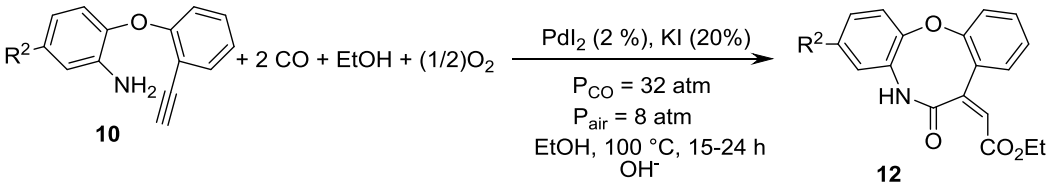


(2.16)

Table 2.5. Synthesis of alkyl (*Z*)-(6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[*a*,*d*]cycloocten-7-ylidene)acetates **12e-i** by PdI_2/KI-catalyzed oxidative cyclocarbonylation-alkoxycarbonylation of 2-(2-ethynylphenoxy)anilines **10e-k**[a]

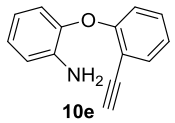
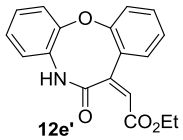
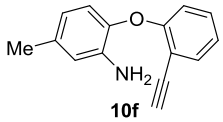
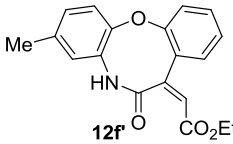
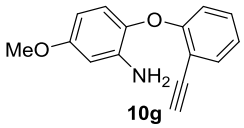
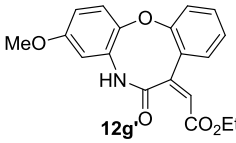
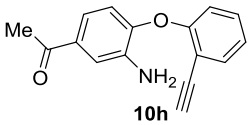
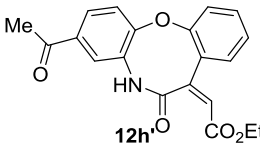
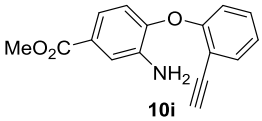
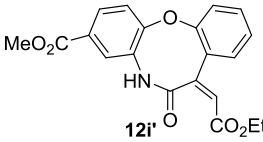
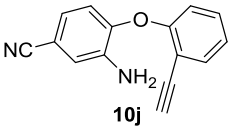
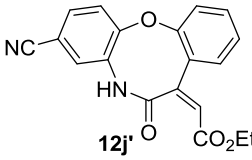
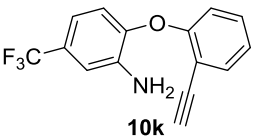
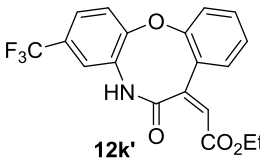
Entry	**10**	**12**	Yield of **12** [%][b]
1	 **10e**	 **12e**	63
2	 **10f**	 **12f**	72
3	 **10g**	 **12g**	62
4	 **10h**	 **12h**	73
5	 **10i**	 **12i**	72

[a] All reactions were carried out at 100 °C in MeOH as the solvent (0.05 mmol of **10** per mL of solvent) under 40 atm of a 4:1 mixture of CO-air (at 25 °C) in the presence of PdI_2 (2 mol %) in conjunction with KI (20 mol %), for 15 h. [b] Isolated yield based on starting **10**.



(2.17)

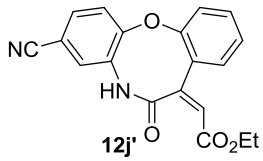
Table 2.6. Synthesis of alkyl (*Z*)-(6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[*a*,*d*]cycloocten-7-ylidene)acetates **12e'-k'** by PdI_2/KI-catalyzed oxidative cyclocarbonylation-alkoxycarbonylation of 2-(2-ethynylphenoxy)anilines **10e-k**[a]

Entry	10	12	Yield of **12** [%][b]
1	 **10e**	 **12e'**	71
2	 **10f**	 **12f'**	70
3	 **10g**	 **12g'**	75
4	 **10h**	 **12h'**	69
5	 **10i**	 **12i'**	63
6	 **10j**	 **12j'**	74
7	 **10k**	 **12k'**	56

[a] All reactions were carried out at 100 °C in EtOH as the solvent (0.05 mmol of **10** per mL of solvent) under 40 atm of a 4:1 mixture of CO-air (at 25 °C) in the presence of PdI_2 (2 mol %) in conjunction with KI (20 mol %), for 24 h. [b] Isolated yield based on starting **10**.

2.2.3 Biological activity

Considering the bioactivity shown in the literature by 8-membered lactam systems, we tested the newly synthesized ς-lactams for their biological activity, as antitumor agents against different breast cancer cell lines. To this aim, we evaluated the effects of increasing concentrations (1 μM, 10 μM, 25 μM, 50 μM, 75 μM, and 100 μM) of ς-lactams for 96 h on cell viability in estrogen receptor (ER)-positive MCF-7 and ER-negative, progesterone receptor (PR)-negative and human epidermal growth factor receptor 2 (HER2)-negative MDA-MB-231 human breast cancer cells by using MTT assays. While almost all tested compounds induced a decrease in breast cancer cells viability (data not shown), ς-lactam **12j'** resulted the most active in reducing anchorage-dependent growth of breast cancer cells (Fig. 2.16).



12j'

Figure 2.16

In particular, as shown in Fig. 2.17 A, treatment for 96 h with **12j'** induced a significant decrease in cell viability in MCF-7 (*upper panel*) and in MDA-MB-231 cells (*middle panel*).

The half-maximal inhibitory concentration (IC_{50}) values of ς-lactam **3j'** for the cell lines tested are shown in Table 2.

Table 2.7 IC_{50} of **12j'** for MDA-MB 231 and MCF-7 cells on anchorage-dependent growth

Cell Lines	IC_{50} (μM)	95% confidence interval
MDA-MB 231	27.34	20.37-36.69
MCF-7	21.29	11.96-37.89

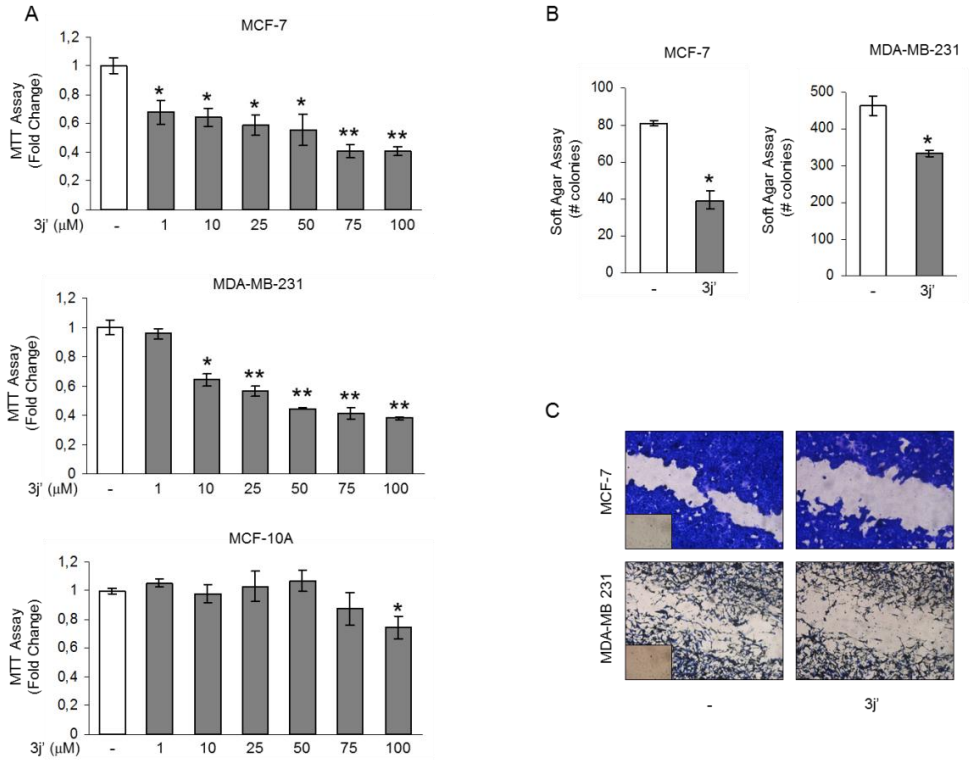


Figure 2.17. ç-lactam derivative 3j' inhibits breast cancer cell growth. A. MTT assays in MCF-7, MDA-MB-231 and MCF-10A cells treated with vehicle (-) or with increasing concentrations (1 μM, 10 μM, 25 μM, 50 μM, 75 μM and 100 μM) of **12j'** for 96 h. Cell proliferation is expressed as fold change versus control (vehicle-treated cells). The values represent the means ± SD of three different experiments, each performed with triplicate samples. B. Soft-agar growth assay in MCF-7 and MDA-MB-231 cells plated in 0.35% agarose and treated with ç-lactam **12j'** (50 μM). After 14 d of growth, colonies >50 μm diameter were counted. Data are the mean colony number ± SD of three plates and representative of two independent experiments. C. Cells were subjected to wound-healing scratch assays with images captured at 0 and 24 h after incubation with vehicle (-) or **12j'** (50 μM) using phase-contrast microscopy. Small squares, time 0. *P<0.05 and **P<0.001 compared with vehicle treated cells.

It is worth noting that treatment with ç-lactam **12j'** at doses of IC_{50} values calculated in our breast cancer models did not elicit any noticeable effects in MCF-10A non malignant breast epithelial cell viability (Figure 2.17 A, *lower panel*). The ability of **12j'** to inhibit cell growth was also evaluated using anchorage-independent growth assays (Soft Agar Assay), which better reflects *in vivo* three-dimensional tumor growth. MCF-7 and MDA-MB-231 cells were plated in soft agar and then treated with ç-lactam **12j'** (50 μM) for 14 d. At the end of the treatment colonies >50 π in diameter were counted. As shown in Figure 2.13 B, treatment with **12j'** significantly inhibited anchorage-independent growth of both MCF-7 and MDA-MB-231 cells. We then examined the

ability of **12j'** to inhibit cell movement in wound-healing scratch assays (Figure 2.17 C). MCF-7 and MDA-MB-231 cells during 24 h of observation moved in either direction to close the gap, while treatment with **12j'** strongly reduced breast cancer cell movement. Taken together, these data clearly indicate that the new ς-lactam derivative **12j'** is able to inhibit breast cancer cell proliferation and motility, without affecting normal breast epithelial cell viability.

2.2.4. Conclusions

In conclusion, I have found that readily available 2-(2-ethynylphenoxy)anilines **10**, bearing a terminal triple bond (R^1 = H), can be directly converted into a novel class of medium-sized heterocyclic derivatives **12**, through a new PdI_2/KI-catalyzed carbonylative ς-lactamization-alkoxycarbonylation process. In agreement with theoretical calculations, the process starts with *N*-palladation of **10**, followed by CO insertion, intramolecular triple bond insertion, and alkoxycarbonylation. The formation of □-lactams **12** from simple building blocks (**10**, CO, ROH, and O_2) in a multicomponent fashion, represents a significant achievement, also in view of the biological relevance of these compounds. In fact, biological tests showed that the newly synthesized □-lactam **12j'** exerts antiproliferative effects in different breast cancer cell lines, without affecting normal breast epithelial cell viability

2.3 Experimental Section

2.3.1 Experimental Procedure for preparation of Oxamides, Ureas, Oxazolidinones, and Benzoxazolones in IL

*Recyclable synthesis of 1,3-disubstituted ureas **2a–h***

The general procedure for the recyclable catalyzed oxidative carbonylation of primary amines **1a-h** is as follows: A 100 mL stainless steel autoclave was charged in air with PdI_2 (4.0 mg, 1.11×10^{-2} mmol), KI (18.4 mg, 1.11×10^{-1} mmol), and a solution of **1** [**1a**, 103 mg (1.11 mmol); **1b**, 120 mg (1.12 mmol); **1c**, 150 mg (1.11 mmol); **1d**, 137mg (1.11 mmol); **1e**, 142 mg (1.11 mmol); **1f**, 162 mg (2.22 mmol); **1g**, 81 mg (1.11 mmol); **1h**, 595 mg (5.55 mmol)] in $BmimBF_4$ (for **1a-g**: 2.2 mL; for **1h**: 5.5 mL). The autoclave was sealed and, with stirring of the mixture, pressurized with CO (16 atm) and air (4 atm). After stirring at 100 °C for 24 h, the autoclave was cooled, degassed, and opened. The crude reaction mixture was transferred to a round-bottom flask, and Et_2O (for **1a**, **1c-h**: 5 mL; for **1b**: 10 mL) was added. The mixture was stirred for 15 min, and the ethereal phase was decanted. Part of the urea product was thus extracted in Et_2O, while some part remained in the IL phase as a white solid in suspension. To recover the product suspended in the IL phase, CH_2Cl_2 (for **1a**, **1c-h**: 3 mL; for **1b**: 8 mL) was added to the IL phase, followed by stirring for 5 min. Excess of CH_2Cl_2 was evaporated, the distilled CH_2Cl_2 recovered in order to be reused again, and the IL residue re-extracted with Et_2O (for **1a**, **1c-h**: 5 mL; for **1b**: 10 mL). The extraction process was repeated for additional five times. The collected ethereal phases were evaporated to remove about the 80% of the solvent, and the distilled Et_2O recovered in order to be reused again. The residual ethereal solution was kept at 0 °C for 15 h. Crystals of the pure urea product separated, and were collected by decantation (1^{st} crop). The decanted solution was evaporated to remove about the 50% of the solvent, and the distilled Et_2O recovered in order to be reused again. The residual ethereal solution was kept at 0 °C for 15 h. Additional crystals of the pure urea product separated were collected by decantation (2^{nd} crop). The collected crystals (1^{st} crop + 2^{nd} crop) were eventually dried in vacuo. 1,3-Diphenylurea (**2a**): 111 mg yield (94% from **1a**); 1,3-di-p-tolylurea (**2b**):

116 mg yield (87% from **1b**); 1,3-bis-(4-isopropylphenyl)urea (**2c**): 151 mg yield (92% from **1c**); 1,3-bis-(4-methoxyphenyl)urea (**2d**): 133 mg yield (88% from **1d**); 1,3-bis-(4-chlorophenyl)urea (**2e**): 142 mg yield (91% from **1e**); 1,3-dibutylurea (**2f**): 159 mg yield (83% from **1f**); 1,3-di-tert-butylurea (**2g**): 94 mg yield (98% from **1g**); 1,3-dibenzylurea (**2h**): 600 mg yield (90% from **1h**).

Recycling Procedure:

The IL residue obtained as described above, still containing the catalytic system dissolved in it, was dried in vacuo for 15 h, in order to remove traces of Et_2O, CH_2Cl_2, and moisture. The dried IL residue was then used as such for the next recycle. Thus, it was transferred into the 100 mL stainless steel autoclave, the amine substrate was added, and then the same procedure described above was followed.

*Recyclable synthesis of disubstituted oxamides **3f** and **3h***

The general procedure for the recyclable catalyzed oxidative carbonylation of primary aliphatic amines **1f** and **1h** is as follows: A 100 mL stainless steel autoclave was charged in air with PdI_2 (4.0 mg, 1.11×10–2 mmol), KI (18.4 mg, 1.11×10–1 mmol), and a solution of **1** [(1.11 mmol); **1f**, 81 mg; **1h**, 119 mg] in $BmimBF_4$ (2.2 mL). The autoclave was sealed and, with stirring of the mixture, pressurized with CO (32 atm) and air (8 atm). After stirring at 80 °C for 24 h, the autoclave was cooled, degassed, and opened. The crude reaction mixture was transferred to a round-bottom flask, and Et_2O (5 mL) was added. The mixture was stirred for 15 min, the ethereal phase was decanted, and the IL residue was re-extracted with Et_2O (5 × 5 mL). the collected ethereal phases were evaporated to remove about the 80% of the solvent, and the distilled Et_2O recovered in order to be reused again. The residual ethereal solution was kept at 0 °C for 15 h. Crystals of the pure product separated, and were collected by decantation (1st crop). The decanted solution was evaporated to remove about the 50% of the solvent, and the distilled Et_2O recovered in order to be reused again. The residual ethereal solution was kept at 0 °C for 15 h. Additional crystals of the pure product separated, and were collected by decantation (2nd crop). The collected crystals (1^{st} crop + 2^{nd} crop) were eventually dried in vacuo. N,N'-Dibutyloxalamide (**3f**): 91 mg yield (82% from **1f**); N,N'-dibenzyloxalamide (**3h**): 128 mg yield (86% from **1h**).

Recycling Procedure:

The IL residue obtained as described above, still containing the catalytic system dissolved in it, was dried in vacuo for 15 h, in order to remove traces of Et_2O, CH_2Cl_2, and moisture. The dried IL residue was then used as such for the next recycle. Thus, it was transferred into the 100 mL stainless steel autoclave, the amine substrate was added, and then the same procedure described above was followed.

*Recyclable synthesis of 2-oxazolidinones **5a** and **5b** and benzoxazolones **7a-c***

The general procedure for the recyclable catalyzed oxidative carbonylation of β-amino alcohols **4a** and **4b** and 2-aminophenols **6a-c** is as follows. A 100 mL stainless steel autoclave was charged in air with PdI_2 (4.0 mg, 1.11×10^{-2} mmol), KI (18.4 mg, 1.11×10^{-1} mmol), and a solution of **4** [1.11 mmol; **4a**, 83 mg; **4b**, 152 mg] or **6** [1.11 mmol; **6a**, 121 mg; **6b**, 137 mg; **6c**, 122 mg] in $BmimBF_4$ (2.2 mL). The autoclave was sealed and, with stirring of the mixture, pressurized with CO (16 atm) and air (4 atm). After stirring at 100 °C for 24 h, the autoclave was cooled, degassed, and opened. The crude reaction mixture was transferred to a round-bottomed flask, and Et_2O (5 mL) was added. The mixture was stirred for 15 min, and the ethereal phase was decanted, and the IL residue was re-extracted with Et_2O (5 × 5 mL).

In the case of the reaction of **4a**, the collected ethereal phases were evaporated, and the residue purified by column chromatography on silica gel using 95:5 hexane/AcOEt to give pure 4-methyloxazolidin-2-one **5a** (105 mg yield; 94% from **4a**).

In the case of the reactions of **4b** and **6a-c**, the collected ethereal phases were evaporated to remove about the 80% of the solvent, and the distilled Et_2O recovered in order to be reused again. The residual ethereal solution was kept at 0 °C for 15 h. Crystals of the pure product separated, and were collected by decantation (1^{st} crop). The decanted solution was evaporated to remove about the 50% of the solvent, and the distilled Et_2O recovered in order to be reused again. The residual ethereal solution was kept at 0 °C for 15 h. Additional crystals of the pure product separated, and were collected by decantation (2^{nd} crop). The collected crystals (1^{st} crop + 2^{nd} crop) were eventually dried in vacuo. (*R*)-4-Phenyloxazolidin-2-one (**5b**): 144 mg yield (80% from **4b**); benzo[*d*]oxazol-2(3*H*)-one (**7a**): 147 mg yield (98% from **6a**); 6-

methylbenzo[*d*]oxazol-2(3*H*)-one (**7b**): 153 mg yield (92% from **6b**); oxazolo[4,5-*b*]pyridin-2(3*H*)-one (**7c**): 136 mg yield (90% from **6c**).

With 2-aminophenol **6a**, the oxidative carbonylation reaction was also carried out using only 0.2 mol % of catalyst. The general procedure described above was followed, starting from 606 mg of **6a** (5.55 mmol) in 11.1 mL of $BmimBF_4$. The reaction mixture was then extracted with 6 × 10 mL of Et_2O, and the product separated by crystallization as described above (yield: 710 mg, 95% from **6a**).

Recycling Procedure:

The IL residue obtained as described above, still containing the catalytic system dissolved in it, was dried in vacuo for 15 h, in order to remove traces of Et_2O and moisture. The dried IL residue was then used as such for the next recycle. Thus, it was transferred into the 100 mL stainless steel autoclave, the substrate was added, and then the same procedure described above was followed

*Recyclable synthesis of tetrasubstituted oxamides **9a-f***

The general procedure for the recyclable catalyzed oxidative carbonylation of secondary amines **8a-f** is as follows. A 100 mL stainless steel autoclave was charged in air with PdI_2 (4.0 mg, 1.11×10^{-2} mmol), KI (18.4 mg, 1.11×10^{-1} mmol), and a solution of **8** [1.11 mmol; **8a**, 97 mg; **8b**, 95 mg; **8c**, 176 mg; **8d**, 75 mg; **8e**, 81 mg, **8f**, 112 mg] in $BmimBF_4$ (2.2 mL). The autoclave was sealed and, with stirring of the mixture, pressurized with CO (16 atm) and air (4 atm). After stirring at 100 °C for 24 h, the autoclave was cooled, degassed, and opened. The crude reaction mixture was transferred to a round-bottom flask, and Et_2O (5 mL) was added. The mixture was stirred for 15 min, the ethereal phase was decanted, and the IL residue was re-extracted with Et_2O (5 × 5 mL).

In the case of the reactions of **8a-e**, the collected ethereal phases were evaporated to remove about the 80% of the solvent, and the distilled Et_2O recovered in order to be reused again. The residual ethereal solution was kept at 0 °C for 15 h. Crystals of the pure product separated, and were collected by decantation (1st crop). The decanted solution was evaporated to remove about the 50% of the solvent, and the distilled

Et_2O recovered in order to be reused again. The residual ethereal solution was kept at 0 °C for 15 h. Additional crystals of the pure product separated, and were collected by decantation (2^{nd} crop). The collected crystals (1^{st} crop + 2^{nd} crop) were eventually dried in vacuo. 1,2-Dimorpholinoethane-1,2-dione (**9a**): 108 mg yield (85% from **8a**); 1,2-di(piperidin-1-yl)ethane-1,2-dione (**9b**): 113 mg yield (91% from **8**); 1,2-di-(4-ethoxycarbonyl)piperazinoethane-1,2-dione (**9c**): 200 mg yield (97% from **8c**); 1,2-di(pyrrolidin-1-yl)ethane-1,2-dione (**9d**): 98 mg yield (90% from **8d**); tetraethyloxalamide (**9e**): 102 mg yield (92% from **8e**).

In the case of the reaction of **8f**, the collected ethereal phases were evaporated, and the residue purified by column chromatography on silica gel using 8:2 hexane/AcOEt to give pure tetraisopropyloxalamide **9f** (Yield: 154 mg; 89% from **8f**).
With morpholine **8a**, the oxidative carbonylation reaction was also carried out using only 0.2 mol % of catalyst (Table 4, entry 2). The general procedure described above was followed, starting from 484 mg of **8a** (5.55 mmol) in 11.1 mL of $BmimBF_4$. The reaction mixture was then extracted with 6 × 10 mL of Et_2O, and the product separated by crystallization as described above. (Yield: 540 mg; 85% from **8a**; Table 4, entry 2, run 1).

Recycling Procedure: The IL residue obtained as described above, still containing the catalytic system dissolved in it, was dried in vacuo for 15 h, in order to remove traces of Et_2O and moisture. The dried IL residue was then used as such for the next recycle. Thus, it was transferred into the 100 mL stainless steel autoclave, the substrate was added, and then the same procedure described above was followed.

2.3.2 Experimental Procedure for preparation of 8-Membered Lactam Derivatives

*General procedure for the preparation of 2-(2-alkynylphenoxy)anilines **10 a-d** and 2-(2-trimethylsilanylethynylphenoxy)anilines.*

2-(2-Alkynylphenoxy)anilines were prepared by coupling between the corresponding 2-(2-iodophenoxy)anilines[12] and the suitable terminal alkyne, followed (in the case of the reaction with trimethylsilylacetylene).

To solution of the 2-(2-iodophenoxy)aniline [1.6 mmol; 2-(2-iodophenoxy)aniline, 498 mg; 2-(2-iodophenoxy)-5-methylaniline, 520 mg; 2-(2-iodophenoxy)-5-methoxyaniline, 546 mg; 1-[3-amino-4-(2-iodophenoxy)phenyl]ethanone, 565 mg; methyl 3-amino-4-(2-iodophenoxy)benzoate, 591 mg; 2-(2-iodophenoxy)-5-cyanoaniline, 538 mg; 2-(2-iodophenoxy)-5-triluoromethylaniline, 607 mg] in anhydrous THF (5 mL) were added, under nitrogen and with stirring, anhydrous Et_3N (330 mg, 3.3 mmol), $PdCl_2(PPh_3)_2$ (12.8 mg, 3.2×10-2 mmol), CuI (30.4 mg, 0.16 mmol), and the 1-alkyne (2.4 mmol; phenylacetylene, 245 mg; p-bromophenylacetylene, 434 mg; 1-ethynylcyclohex-1-ene, 255 mg; tert-butylacetylene, 200 mg; trimethylsilylacetylene, 235 mg) in this order. The resulting mixture was allowed to stir at room temperature for 8 h (for p-bromophenylacetylene, tert-butylacetylene, and trimethylsilylacetylene) or at 40 °C for 15 h (for 1-ethynylcyclohex-1-ene). After cooling to room temperature, satd NH_4Cl was added (10 mL), and the mixture was extracted with AcOEt (3 × 15 mL). The collected organic layers were washed with brine (40 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by column chromatography using silica gel as the stationary phase and 7:3 hexane-AcOEt as the eluent, to give pure 2-(2-alkynylphenoxy)anilines **10a-d** and 2-(2-trimethylsilanylethynylphenoxy)anilines: 2-(2-Phenylethynylphenoxy)aniline (**10a**), yellow solid, 365 mg, 80%; 2-[2-(4-bromophenylethynyl)phenoxy]aniline (**10b**), yellow solid, 466 mg, 80%; 2-(2-cyclohex-1-eynylethynylphenoxy)aniline (**10c**), yellow oil, 375 mg, 81%; 2-[2-(3,3-dimethylbut-1-ynylphenoxy)aniline (**10d**), yellow solid, 344 mg, 81%; 2-(2-trimethylsilanylethynylphenoxy)aniline, grey solid, 342 mg, 76%; 5-methyl-2-(2-trimethylsilanylethynylphenoxy)aniline, yellow solid, 340 mg, 72%; 5-methoxy-2-(2-trimethylsilanylethynylphenoxy)aniline, brown oil, 419 mg, 84%; 1-[3-amino-4-(2-trimethylsilanylethynylphenoxy)phenyl]ethanone, brown solid, 440 mg, 85%; methyl 3-amino-4-(2-trimethylsilanylethynylphenoxy)benzoate, yellow solid, 478 mg, 88%; 3-amino-4-(2-trimethylsilanylethynylphenoxy)benzonitrile, white solid, 358 mg, 88%; 5-trifluoromethyl-2-(2-trimethylsilanylethynylphenoxy)aniline, yellow solid, 458 mg, 82%.

*Deprotection of 2-[2-(trimethylsilylethynyl)phenoxy]anilines to give 2-(2-ethynylphenoxy)anilines **10 e-k.***

To a solution of the 2-[2-(trimethylsilylethynyl)phenoxy]aniline, obtained as described above (1.5 mmol; 2-(2-trimethylsilanylethynylphenoxy)aniline, 422 mg; 5-methyl-2-(2-trimethylsilanylethynylphenoxy)aniline, 443 mg; 5-methoxy-2-(2-trimethylsilanylethynylphenoxy)aniline, 467 mg; 1-[3-amino-4-(2-trimethylsilanylethynylphenoxy)phenyl]ethanone, 485 mg; methyl 3-amino-4-(2-trimethylsilanylethynylphenoxy)benzoate, 509 mg; 3-amino-4-(2-trimethylsilanylethynylphenoxy)benzonitrile, 460 mg; 5-trifluoromethyl-2-(2-trimethylsilanylethynylphenoxy)aniline, 524 mg) in anhydrous methanol (5 mL) was added, with stirring and under nitrogen, K_2CO_3 (622 mg, 4.5 mmol). The resulting mixture was allowed to stir a room temperature for 3 h, and then it was filtered through Celite to remove K_2CO_3, followed by washing with MeOH (50 mL). The resulting filtrate was evaporated to dryness to give the crude product, which was solubilized in CH_2Cl_2 (40 mL) and washed with brine (50 mL) and water (50 mL). After drying over Na_2SO_4 and evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane-AcOEt from 95:5 to 7:3 as the eluent, to give pure 2-(2-ethynylphenoxy)anilines **10e-k**: 2-(2-ethynylphenoxy)aniline (**10e**), white solid, 245 mg, 78%; 5-methyl-2-(2-ethynylphenoxy)aniline (**10f**), yellow oil, 255 mg, 76%; 5-methoxy-2-(2-ethynylphenoxy)aniline (**10g**), yellow solid, 302 mg, 84%; 1-[3-amino-4-(2-ethynylphenoxy)phenyl]ethanone (**10h**), yellow solid, 305 mg, 81%; methyl 3-amino-4-(2-ethynylphenoxy)benzoate (**10i**), yellow solid, 337 mg, 84%; 3-amino-4-(2-ethynylphenoxy)benzonitrile (**10j**), white solid, 257 mg, 72%; 2-(2-ethynylphenoxy)-5-trifluoromethylaniline (**10k**), yellow oil, 362 mg, 87%

*General procedure for the oxidative carbonylation of 2-(2-alkynylphenoxy)anilines **10a-g** to give methyl 2-(2-alkynylphenoxy)phenylcarbamates **11a-d**.*

A 35 mL stainless steel autoclave was charged in the presence of air with PdI_2 (2.5 mg, 6.94×10^{-3} mmol), KI (11.5 mg, 6.93×10^{-2} mmol) and a solution of the 2-(2-alkynylphenoxy)aniline **10** [0.35 mmol: **10a** (100 mg), **10b** (127 mg), **10c** (101 mg), **10d** (93 mg)] in MeOH (7.0 mL). The autoclave was sealed and, while the mixture was stirred, the autoclave was pressurized with CO (32 atm) and air (up to 40 atm). After

being stirred at 100°C for the required time (24 h for **10a-c**; 48 h for **10d**), the autoclave was cooled, degassed and opened. The solvent was evaporated, and the products were purified by column chromatography on silica gel to give pure methyl 2-(2-alkynylphenoxy)phenylcarbamates **11a-d** (eluent: 7:3 hexane-AcOEt for **11a** and **11b**; 8:2 hexane-AcOEt for **11c** and **11d**): methyl 2-(2-phenylethynylphenoxy)phenylcarbamate (**11a**), yellow oil, 90 mg, 74%; methyl 2-[2-(4-bromophenylethynyl)phenoxy]phenyl]carbamate (**11b**), yellow solid, 86 mg, 58%; methyl [2-(2-cyclohex-1-eynylethynylphenoxy)phenyl]carbamate (**11c**), yellow oil, 61 mg, 50%; methyl 2-[2-(3,3-dimethylbut-1-ynylphenoxy)phenyl]carbamate (**11d**), yellow oil, 70 mg, 62%.

*General procedure for the oxidative carbonylation of 2-(2-ethynylphenoxy)aniline **10e-k** to give alkyl (Z)-(6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[a,d]cycloocten-7-ylidene)acetates **12e-i** and **12e'-k'**.*

A 35 mL stainless steel autoclave was charged in the presence of air with PdI_2 (2.5 mg, 6.94×10^{-3} mmol), KI (11.5 mg, 6.93×10^{-2} mmol) and a solution of the 2-(2-ethynylphenoxy)aniline **10** [0.35 mmol; **10e** (73 mg), **10f** (78 mg), **10g** (84 mg), **10h** (88 mg), **10i** (94 mg), **10j** (82 mg), **10k** (97 mg)] in ROH (R = Me or Et, 7 mL). The autoclave was sealed and, while the mixture was stirred, the autoclave was pressurized with CO (32 atm) and air (up to 40 atm). After being stirred at 100°C for the required time (15 h for the reaction of **10e-i** with MeOH; 24 h for the reactions of **10e-k** with EtOH), the autoclave was cooled, degassed and opened. The solvent was evaporated, and the product was purified by column chromatography on silica gel to give pure **12e-i** (R = Me) using as eluent 6:4 hexane-AcOEt or **12e'-3k'**(R = Et) using as eluent 65:35 hexane-AcOEt: methyl (*Z*)-(6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[*a*,*d*]cycloocten-7-ylidene)acetate (**12e**), yellow solid, 65 mg, 63%; ethyl (*Z*)-(6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[*a,d*]cycloocten-7-ylidene)acetate (**12e'**), white solid, 77 mg, 71%; methyl (*Z*)-(3-methyl-6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[*a,d*]cycloocten-7-ylidene)acetate (**12f**), yellow solid, 78 mg, 72%; ethyl (*Z*)-(3-methyl-6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[*a,d*]cycloocten-7-ylidene)acetate (**12f'**), yellow solid, 79 mg, 70%; methyl (*Z*)-(3-methoxy-6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[*a,d*]cycloocten-7-ylidene)acetate (**12g**), yellow solid, 71 mg, 62%; ethyl (*Z*)-(3-methoxy-6-oxo-5,6-

dihydro-12-oxa-5-azadibenzo[*a,d*]cycloocten-7-ylidene)acetate (**12g'**), grey solid, 89 mg, 75%; methyl (*Z*)-(3-acetyl-6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[*a*,*d*]cycloocten-7-ylidene)acetate (**12h**), white solid, 86 mg, 73%; ethyl (*Z*)-(3-acetyl-6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[*a*,*d*]cycloocten-7-ylidene)acetate (**12h'**), yellow oil, 85 mg, 69%; methyl (*Z*)-7-methoxycarbonylmethylene-6-oxo-6,7-dihydro-5*H*-12-oxa-5-azadibenzo[*a*,*d*]cyclooctene-3-carboxylate (**12i**), white solid, 89 mg, 72%; methyl (*Z*)-7-ethoxycarbonylmethylene-6-oxo-6,7-dihydro-5*H*-12-oxa-5-azadibenzo[*a*,*d*]cyclooctene-3-carboxylate (**12i'**), white solid, 81 mg, 63%; ethyl (*Z*)-(3-cyano-6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[*a*,*d*]cycloocten-7-ylidene)acetate (**12j'**), 87 mg, 74 %; ethyl (*Z*)-(3-trifluoromethyl-6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[*a*,*d*]cycloocten-7 ylidene)acetate (**12k'**), colorless solid, 70 mg, 53%.

Cell Cultures.

Human breast cancer epithelial cell line MCF-7 (estrogen receptor (ER)-positive) was cultured in DMEM containing 5% foetal bovine serum (FBS), 1% L-glutamine, 1% Eagle's nonessential amino acids, and 1 mg/ml penicillin-streptomycin at 37 °C with 5% CO_2 air. Triple-negative human breast cancer cell line MDA-MB-231 (ER-, PR-, HER2-negative) was cultured in DMEM:F12 containing 5% (FBS). Human normal breast epithelial cell line MCF-10A was grown in DMEM– F12 medium containing 5% horse serum. Before each experiment, cells were grown in phenol red free medium, containing 5% charcoal-stripped foetal bovine serum for 2 d and treated as described.

Cell Viability Assays.

Cell viability was determined with the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT, Sigma, Milan, Italy) assay. MCF-7, MDA-MB-231 and MCF-10A cells ($2x10^4$ cells/ml) were grown in 24-well plates and exposed to treatments as indicated for 96 h, in phenol red–free MEM containing 5% charcoal-stripped fetal bovine serum (FBS). The MTT assay was performed as the following: 100 µl MTT stock solution in PBS (2 mg/mL) was added into each well and incubated at 37°C for 2 h followed by media removal and solubilization in 500 µl DMSO. After shaking the plates for 15 min, the absorbance in each well, including the blanks at 570 nm in Beckman Coulter Spectrophotometer, was measured. The data are representative of three

independent experiments, each performed in triplicate. Data were analyzed for statistical significance using a two-tailed Student's t-test, performed by Graph Pad Prism 4 (GraphPad Software, Inc., San Diego, CA). Standard deviations (SD) are shown. A minimum of three experiments, contained 8 different doses of ς-lactam **3j'** in triplicate, was combined for IC_{50} calculations. The absorbance readings were used to determine the IC_{50} using GraphPad Prism 4. Briefly, values were log-transformed, then normalized, and nonlinear regression analysis was used to generate a sigmoidal dose-response curve to calculate IC_{50} values for each cell line.

Soft Agar Anchorage-Independent Growth Assays.

Cells (10^4/well) were plated in 4ml of 0.35% agarose with 5% charcoal stripped-FBS in phenol red-free media, with a 0.7% agarose base in six well plates. Two days after plating, media containing vehicle or ς-lactam **12j'** were added to the top layer, and replaced every 2 days. After 14 days, 300 µl of MTT was added to each well and allowed to incubate at 37°C for 4 hours. Plates were then placed at 4°C overnight and colonies >50 µm diameter from triplicate assays were counted. Data are the mean colony number of three plates and representative of two independent experiments, analyzed for statistical significance using a two-tailed Student's t-test, performed by Graph Pad Prism 4 (GraphPad Software, Inc., San Diego, CA).

Wound-Healing Scratch Assays.

Motility was assessed by wound-healing scratch assays. Briefly, cell monolayers were scraped and treated as indicated. Wound closure was monitored over 24 h; cells were fixed and stained with Coomassie brilliant blue. Pictures were taken at 10X magnification using phase-contrast microscopy and are representative of three independent experiments.

2.4-Characterization of Ureas (2), Oxamides (3), 2-Oxazolidinones (5, 7) Benzoxazolones (9) and (Z)-12-Oxa-5-azadibenzo[a,d]cycloocten-6-ones (12).

1,3-Diphenylurea (**2a**): colorless solid; mp 241-242°C. IR (KBr): *v* = 3327 (m, br), 3286 (m, br), 1649 (s), 1595 (m), 1556 (s), 1447 (w), 1314 (m), 1232 (m), 755 (m), 697 (m) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.66 (s, 2H, 2 H), 7.50-7.40 (m, 4 H), 7.36-7.22 (m, 4 H), 7.02-6.92 (m, 2 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 152.7, 139.8, 128.6, 121.9, 118.6. GC–MS: *m/z* = 212 (20) [M^+], 119 (6), 93 (100), 77 (10), 65 (12). Anal. calcd. For $C_{13}H_{12}N_2O$ (212.25): C 73.56, H 5.70, N 13.20; found: C 73.61, H 5.68, N 13.22.

1,3-Di-p-tolylurea (**2b**): whitish solid, mp 260-262 °C. IR (KBr): *v*= 3305 (m), 1640 (s), 1596 (m), 1567 (m), 1516 (w), 1309 (w), 1292 (w), 1239 (m), 815 (m), 780 (w) cm^{-1} . ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.46 (s, br, 2 H), 7.45-7.22 (m, 4 H,), 7.18-6.96 (m, 4 H), 2.24 (s, 6 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 152.9, 137.4, 130.8, 129.1, 118.7, 20.2. GC–MS: *m/z* = 240 (26) [M^+], 133 (7), 107 (100), 77 (14). MS (ESI+, direct infusion): *m/z* = 241 [$(M+H)^+$]; Anal. calcd. For $C_{15}H_{16}N_2O$ (240.30): C 75.97, H 6.71, N 11.66; found: C 75.03, H 6.69, N 11.67.

1,3-bis-(4-Isopropylphenyl)urea (**2c**): whitish solid, mp 200-202 °C. IR (KBr): *v*= 3313 (m, br), 2958 (m), 1649 (s), 1589 (m), 1553 (s), 1415 (w), 1308 (m), 1234 (m), 1054 (w), 831 (m) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.51 (s, 2 H), 7.40-7.30 (m, 4 H), 7.17-7.07 (m, 4 H), 2.82 (heptuplet, *J* = 6.9 Hz, 2 H), 1.18 (d, *J* = 6.9 Hz, 12 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 152.6, 141.7, 137.4, 126.4, 118.3, 32.7, 24.0. MS (ESI+, direct infusion): *m/z* = 297 [$(M+H)^+$]; Anal. calcd. For $C_{19}H_{24}N_2O$ (296.41): C 76.99, H 8.16, N 9.45; found: C 77.01, H 8.16, N 9.46.

1,3-bis-(4-Methoxyphenyl)urea (**2d**): whitish solid, mp 236-238 °C. IR (KBr): *v*= 3303 (m, br), 1634 (s), 1557 (m), 1508 (s), 1245 (s), 1169 (w), 1029 (m), 826 (s) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.38 (s, 2 H), 7.40-7.30 (m, 4 H), 6.90-6.80 (m, 4 H), 3.71 (s, 6 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 154.3, 152.9, 132.9, 119.9, 113.9, 55.1. MS (ESI+,

direct infusion): *m/z* = 273 [$(M+H)^+$]; Anal. calcd. For $C_{15}H_{16}N_2O_3$ (272.30): C 66.16, H 5.92; N 10.29; found: C 66.21, H 5.90, N 10.30.

1,3-bis-(4-Chlorophenyl)urea (**2e**): colorless solid, mp 308-309 °C. IR (KBr): *v* = 3296 (m, br), 1632 (s), 1560 (m), 1491 (m), 1396 (w), 1085 (w), 822 (m) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 8.91 (s, 2 H), 7.72-7.13 (m, 8 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 152.3, 138.5, 128.6, 125.4, 119.7. MS (ESI+, direct infusion): *m/z* = 281 [$(M+H)^+$]; Anal. calcd. For $C_{13}H_{10}Cl_2N_2O$ (281.14): C 55.54, H 3.59, Cl 25.22, N 9.96; found: C 55.58, H 3.58, Cl 25.19, N 9.98.

1,3-Dibutylurea (**2f**): colorless solid, mp 70-71 °C. IR (KBr): *v* = 3329 (m, br), 2958 (m), 2870 (m), 1620 (s), 1581 (w), 1460 (m), 1281 (w), 1232 (m) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 5.77 (t, br, *J* = 5.1 Hz, 2 H), 3.02-2.90 (m, 4 H), 1.40-1.17 (m, 8 H), 0.92-0.80 (m, 6 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 158.1, 38.9, 32.2, 19.5, 13.7. GC–MS: *m/z* = 172 (100) [M^+], 157 (16), 143 (15), 130 (33), 129 (28), 101 (35), 100 (26), 74 (47), 57 (47). Anal. calcd. For $C_9H_{20}N_2O$ (172.27): C 62.75, H 11.70; N 16.26; found: C 62.81, H 11.68, N 16.28.

1,3-Di-tert-butylurea (**2g**): colorless solid, mp 230-232 °C. IR (KBr): *v* = 3356 (m, br), 2964 (m), 2928 (w), 1637 (s), 1559 (m), 1361 (m), 1132 (w) cm^{-1} (w). ^1H NMR (300 MHz, DMSO-d_6): δ = 5.44 (s, br, 2 H), 1.19 (s, 18 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 157.0, 48.7, 29.3. GC–MS: *m/z* = 172 (2) [M^+], 157 (11), 139 (1), 84 (9), 83 (4), 61 (6), 58 (100), 57 (17). Anal. calcd. For $C_9H_{20}N_2O$ (172.27): C 62.75, H 11.79, N 16.26; found: C 62.79, H 11.80, N 16.28.

1,3-Dibenzylurea (**2h**): colorless solid, mp 165-166 °C. IR (KBr): *v* = 3357 (m, br), 1628 (s), 1492 (m), 1453 (w), 1254 (m), 752 (w), 696 (m) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 7.38-7.16 (m, 10 H, 2 Ph), 6.49 (t, br, *J* = 5.2, 2 H), 4.24 (d, br, *J* = 5.2, 4 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 158.0, 140.8, 128.1, 126.9, 126.5, 42.9. GC–MS: *m/z* = 240 (59) [M^+], 149 (22), 106 (100), 91 (51), 79 (19), 65 (12). Anal. calcd. For $C_{15}H_{16}N_2O$ (240.30): C 74.97, H 6.71, N 11.66; found: C 75.01, H 6.70, N 11.68.

N,N'-Dibutyloxalamide (**3f**): colorless solid, mp 141-146°C. IR (KBr): *v* = 3298 (m), 2955 (m), 2862 (w), 1651 (s), 1531 (m),1439 (w), 1218 (w), 1147 (w), 759 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (s, br, 2 H), 3.36-3.27 (m, 4 H), 1.61-1.49 (m, 4 H), 1.45-1.31 (m, 4 H), 0.98-0.89 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.3, 39.6, 31.5, 20.1, 13.5. GC–MS: *m/z* = 200 (11) [M^+], 172(10), 157(11), 145 (10), 143 (11), 129 (9), 102 (9), 101 (23), 100 (92), 86(3), 72(34). Anal. calcd. For $C_{10}H_{20}N_2O_2$ (200.28): C 59.97, H 10.07; N 13.99; found: C 59.95, H 10.08, N 14.02.

N,N'-Dibenzyloxalamide (**3h**): colorless solid, mp 210-216 °C. IR (KBr): *v* = 3279 (w), 1685 (m), 1658 (s), 1542 (w), 1471 (w), 1271 (m), 1074 (w), 968 (m) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.49-9.18 (m, 2 H), 7.40-7.12 (m, 10 H), 4.34-4.25 (m, 4 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.0, 138.6, 128.2, 127.2, 126.8, 42.3. GC–MS: *m/z* = 268 (8) [M^+], 178(5), 177 (48), 132 (3), 106 (23), 104 (4), 92 (14), 91 (100), 79 (3), 77 (4), 65 (10). Anal. calcd. For $C_{16}H_{16}N_2O_2$ (268.31): C 71.62, H 6.01; N 10.44; found: C 71.59, H 6.04, N 10.41.

4-Methyloxazolidin-2-one (**5a**): yellow oil. IR (film): *v* = 1741 (s), 1408 (w), 1240 (w), 1032 (m), 939 (w) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.84 (m, 1 H), 4.50 (t, *J* = 8.0, 1 H), 4.09-3.97 (m, 1 H), 3.95 (distorted dd, *J* = 8.0, 6.3 Hz, 1 H), 1.30 (d, *J* = 6.3 Hz, 3 H) . ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4, 71.7, 48.3, 20.8. GC–MS: *m/z* = 101 (21) [M^+], 86 (100), 70 (2), 58 (8). Anal. calcd. For $C_4H_7NO_2$ (101.10): C 47.52, H 6.98; N 13.85; found: C 47.60, H 6.97, N 13.83.

(R)-4-Phenyloxazolidin-2-one (**5b**): colorless solid, mp 128–130 °C. $[\alpha]^{295}_{D}$ ($CHCl_3$, *c* = 1.00×10^{-2} g mL^{-1}) = −60°; IR (KBr): *v* = 3247 (m), 1742 (s), 1700 (s), 1489 (w), 1402 (w), 1236 (m), 1098 (w), 1027 (w), 970 (w), 924 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45-7.30 (m, 5 H, Ph), 6.52 (s, br, 1 H), 5.03-4.90 (m, 1 H), 4.79-4.65 (m, 1 H), 4.24-4.10 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1, 139.6, 129.2, 128.7, 126.0, 72.5, 56.4. GC–MS: *m/z* = 163 (44) [M^+], 133 (100), 105 (76), 104 (93), 91 (35), 78 (26), 77 (27). Anal. calcd. For $C_9H_9NO_2$ (163.17): C 66.25, H 5.56; N 8.58; found: C 66.31, H 5.54, N 8.56.

Benzo[d]oxazol-2(3H)-one (**7a**): pale yellow solid, mp 129-131 °C. IR (KBr): *v* = 1774 (s), 1729 (s), 1480 (m), 1390 (m), 1305 (w), 1254 (m), 1136 (w), 950 (m), 746 (m), 712 (m), cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.65 (s, br, 1H), 7.36-7.26 (m, 1 H), 7.23-7.05 (m, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 154.5, 143.4, 130.4, 123.7, 121.8, 109.8, 109.5. GC–MS: *m/z* = 135 (100) [M^+], 106 (2), 91 (16), 79 (35), 52 (29). Anal. calcd. For $C_7H_5NO_2$ (135.12): C 62.22, H 3.73; N 10.37; found: C 62.26, H 3.72, N 10.38.

6-Methylbenzo[d]oxazol-2(3H)-one (**7b**): pale yellow solid, mp 141-143 °C. IR (film): *v* = 1790 (s), 1735 (s), 1400 (m), 1387 (m), 1269 (m), 931 (m), 709 (m) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.88 (s, br, 1 H), 7.05-6.92 (m, 3 H), 2.38 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.5, 144.0, 132.8, 127.1, 124.6, 110.7, 109.8, 21.4. GC–MS: *m/z* = 149 (100) [M^+], 104 (17), 93 (21), 78 (16), 66 (12), 51 (11). Anal. calcd. For $C_8H_7NO_2$ (149.15): C 64.42, H 4.73; N 9.39; found: C 64.51, H 4.71, N 9.41.

Oxazolo[4,5-b]pyridin-2(3H)-one (**7c**): yellow solid, mp 202-204 °C. IR (film): *v* = 1796 (s), 1770 (s), 1634 (m), 1480 (w), 1446 (m), 1266 (w), 1219 (m), 899 (m) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.05 (dd, *J* = 5.2, 1.2), 7.64 (dd, *J* = 8.0, 1.2, 1 H), 7.12 (dd, *J* = 8.0, 5.2 Hz, 1 H). *Note:* the NH signal was too broad to be detected. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 153.4, 146.3, 142.4, 137.4, 117.8, 115.9. GC–MS: *m/z* = 136 (100) [M^+], 109 (8), 93 (22), 80 (5), 65 (23), 53 (15). Anal. calcd. For $C_6H_4N_2O_2$ (136.11): C 52.95, H 2.96; N 20.58; found: C 53.01, H 2.95, N 20.60.

1,2-Dimorpholinoethane-1,2-dione (**9a**): colorless solid, mp 181-182 °C. IR (KBr): *v* = 1638 (s), 1434 (w), 1274 (w), 1183 (w), 1114 (w), 1065 (w), 760 (w) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.78-3.63 (m, 12 H), 3.49-3.42 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.1, 67.1, 66.7, 46.8, 41.9. GC–MS: *m/z* = 228 (5) [M^+], 200 (2), 185 (7), 114 (70), 86 (100), 70 (87), 56 (14). Anal. calcd. For $C_{10}H_{16}N_2O_4$ (228.25): C 52.62, H 7.07; N 12.27; found: C 52.69, H 7.06, N 12.29.

1,2-Di(piperidin-1-yl)ethane-1,2-dione (**9b**): whitish solid, mp 88-90°C. IR (KBr): *v* = 2937 (m), 2858 (w), 1642 (s), 1430 (m), 1251 (w), 1213 (w), 991 (w) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.62-3.54 (m, 4 H), 3.39-3.31 (m, 4 H), 1.74-1.55 (m, 12 H). ^{13}C NMR

(75 MHz, $CDCl_3$): δ = 163.9, 47.3, 42.0, 26.6, 25.5, 24.7. GC–MS: *m/z* = 224 (10) [M^+], 112 (78), 84 (100), 69 (63), 56 (19). Anal. calcd. For $C_{12}H_{20}N_2O_2$ (224.30): C 64.26, H 8.99; N 12.49; found: C 64.35, H 9.01, N 12.51.

1,2-Di-(4-ethoxycarbonyl)piperazinoethane-1,2-dione (**9c**): whitish solid, mp 135–137 °C. IR (KBr): *v* =1658 (s), 1645 (s), 1428 (m), 1254 (w), 1233 (m), 1052 (s), 768 (w) cm^{-1} . ^1H NMR (300 MHz, $CDCl_3$): δ = 4.17 (q, *J* = 7.1 Hz), 3.71-3.33 (m, 16 H), 1.28 (t, *J* = 7.1 Hz, 6 H) . ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.2, 155.5, 61.9, 46.2, 44.3, 43.6, 41.3, 14.6. GC–MS: *m/z* = 370 (70) [M^+], 342 (1), 325 (14), 256 (13), 227 (9), 212 (5), 185 (58), 157 (93), 141 (43), 130 (40), 128 (56), 113 (90), 111 (33), 70 (64), 56 (100). Anal. calcd. For $C_{16}H_{26}N_4O_6$ (370.40): C 51.88, H 7.08; N 15.13; found: C 51.95, H 7.07, N 15.15.

1,2-Di(pyrrolidin-1-yl)ethane-1,2-dione (**9d**): colorless solid, mp 79-80 °C. IR (KBr): *v* = 2971 (m), 2880 (m), 1635 (s), 1460 (w), 1400 (m), 1189 (w), 770 (w), 700 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.58-3.45 (m, 8 H), 2.01-1.86 (m, 8 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.4, 47.0, 45.2, 26.0, 24.2. GC–MS: *m/z* = 196 (2) [M^+], 168 (10), 99 (5), 98 (67), 71 (6), 70 (100), 56 (42), 55 (87). Anal. calcd. For $C_{10}H_{16}N_2O_2$ (196.25): C 61.20, H 8.22; N 14.27; found: C 61.29, H 8.21, N 14.29.

Tetraethyloxalamide (**9e**): withish solid, mp 27–28 °C. IR (KBr): *v* = 2976 (m), 2933 (w), 1637 (s), 1450 (w), 1423 (m), 1252 (m), 1113(w), 707 (w) cm^{-1} . ^1H NMR (300 MHz, $CDCl_3$): δ = 3.44 (q, *J* = 7.1 Hz, 4 H), 3.28 (q, *J* = 7.1 Hz, 4 H), 1.22 (t, *J* = 7.1 Hz, 6 H), 1.19 (t, *J* = 7.1 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 42.5, 38.6, 14.1, 12.6. GC–MS: *m/z* = 200 (4) [M^+], 171 (2), 129 (1), 100 (95), 72 (100). Anal. calcd. For $C_{10}H_{20}N_2O_2$ (200.28): C 59.97, H 10.07; N 13.99; found: C 60.06, H 10.05, N 14.01.

Tetrabutyloxalamide (**9f**): yellow oil. IR (film): *v*= 2959 (m), 2933 (m), 2873 (m), 1638 (s), 1466 (w), 1421 (m), 1208 (m), 1127 (w), 733 (w) cm^{-1} . ^1H NMR (300 MHz, $CDCl_3$): δ = 3.44-3.31 (m, 4 H), 3.23-3.11 (m, 4 H), 1.67-1.49 (m, 8 H), 1.43-1.20 (m, 8 H), 1.00-0.87 (m, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 47.9, 43.6, 30.6, 29.3, 20.2, 20.1, 13.8, 13.7. GC–MS: *m/z* = 312 (5) [M^+], 269 (4), 255 (6), 156 (66), 129 (14), 128 (100),

100 (35), 86 (5), 84 (5), 57 (100). Anal. calcd. For $C_{18}H_{36}N_2O_2$ (312.49): C 69.18, H 11.61; N 8.96; found: C 69.15, H 11.58, N 8.95.

2-(2-Phenylethynylphenoxy)aniline (**10a**): yellow solid, mp 119-120°C. IR (KBr): *v* = 3473 (m, br), 3384 (m, br), 3057 (m), 2215 (vw), 1619 (m), 1500 (s), 1447 (m), 1266 (m), 1221 (s), 1188 (w), 1099 (m), 889 (w), 753 (s), 691 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.63-7.39 (m, 3 H), 7.39-7.17 (m, 4 H), 7.12-6.64 (m, 6 H), 3.87 (s, br, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.8, 143.6, 138.5, 133.6, 131.7, 129.7, 128.3, 124.8, 123.4, 122.9, 119.7, 118.6, 117.2, 116.4, 114.7, 94.3, 85.2; GC-MS: *m/z* = 285 (100) [M^+], 268 (29), 256 (29), 244 (66), 230 (5), 215 (12), 183 (78), 176 (14), 165 (21), 150 (9), 127 (12), 80 (20); anal. calcd for $C_{20}H_{15}NO$ (285.34): C, 84.19; H, 5.30; N, 4.91; found C, 84.21; H, 5.29; N, 4.92.

2-[2-(4-Bromophenylethynyl)phenoxy]aniline (**10b**): yellow solid, mp 67-68°C. IR (KBr): *v* = 3466 (m, br), 3379 (m, br), 2218 (vw), 1619 (m), 1500 (s), 1478 (m), 1446 (w), 1264 (w), 1221 (s), 1187 (w), 1069 (w), 1010 (m), 823 (m), 747 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.58-7.51 (m, 1 H), 7.47-7.38 (m, 2 H), 7.34-7.26 (m, 2 H), 7.26-7.21 (m, 1 H), 7.10-7.02 (m, 1 H), 7.02-6.93 (m, 1 H), 6.91-6.82 (m, 3 H), 6.75-6.67 (m, 1 H), 3.76 (s, br, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.7, 143.5, 138.3, 133.5, 133.1, 131.5, 130.0, 124.8, 122.9, 122.5, 122.3, 119.6, 118.7, 117.2, 116.4, 114.3, 93.2, 86.3; GC-MS: *m/z* = 365 (51) [$(M+2)^+$], 363 (51) [M^+], 324 (36), 322 (36), 283 (65), 268 (18), 254 (27), 239 (10), 215 (9), 183 (100), 176 (18), 163 (15), 150 (12), 142 (30), 127 (22), 113 (8), 80 (20); anal. calcd for $C_{20}H_{14}BrNO$ (364.24): C, 65.95; H, 3.87; Br, 21.94; N, 3.85; found C, 65.99; H, 3.86; Br, 21.96; N, 3.86

2-(2-Cyclohex-1-enylethynylphenoxy)aniline (**10c**): yellow oil. IR (film): *v* = 3468 (m, br), 3381 (m, br), 2930 (m), 2204 (w), 1619 (m), 1501 (s), 1483 (s), 1446 (m), 1267 (w), 1218 (s), 748 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45 (dd, *J* = 7.6, 1.6, 1 H), 7.22-7.14 (m, 1 H), 7.05-6.92 (m, 2 H), 6.89-6.78 (m, 3 H), 6.75-6.66 (m, 1 H), 6.19-6.11 (m, 1 H), 3.86 (s, br, 2 H), 2.22-2.06 (m, 4 H), 1.70-1.52 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 143.6, 139.8, 138.5, 135.3, 133.4, 129.1, 124.7, 122.8, 119.8, 118.6, 117.0, 116.4, 96.2, 82.4, 29.1, 25.8, 22.4, 21.5; GC-MS: *m/z* = 289 (100) [M^+], 272 (14), 260

(47), 246 (95), 233 (27), 220 (27), 205 (16), 183 (78), 165 (19), 152 (16), 139 (8), 115 (14), 102 (7), 80 (20), 65 (12); anal. calcd for $C_{20}H_{19}NO$ (289.37): C, 83.01; H, 6.62; N, 4.84; found C, 83.04; H, 6.60; N, 4.83.

2-[2-(3,3-Dimethylbut-1-ynylphenoxy)aniline (**10d**): pale yellow solid, mp 75-76 °C. IR (KBr): *v* = 3384 (w, br), 3348 (m, br), 2969 (m), 2231 (vw), 1620 (s), 1485 (m), 1265 (m), 745 (vs) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (dd, *J* =7.8, 1.6, 1 H), 7.24-7.16 (m, 1 H), 7.07-6.99 (m, 1 H), 6.98-6.88 (m, 2 H), 6.83-6.74 (m, 2 H), 6.72-6.64 (m, 1 H), 3.90 (s, br, 2 H), 1.22 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2, 144.1, 138.0, 133.4, 128.8, 124.1, 123.0, 118.5, 118.2, 117.9, 116.1, 115.8, 103.8, 74.6, 30.8, 28.0; GC-MS: *m/z* =265 (100), 250 (98), 234 (37), 220 (62), 209 (48), 208 (69), 183 (55), 180 (27), 157 (14), 141 (13), 128 (15), 115 (22), 102 (8), 91 (11), 80 (17), 65 (15); anal. calcd for $C_{18}H_{19}NO$ (265.35): C, 81.47; H, 7.22; N, 5.28; found C, 81.51; H, 7.20; N, 5.29.

2-(2-Ethynylphenoxy)aniline (**10e**): colorless solid, mp 64-65^{o}C. IR (KBr): *v* = 3464 (w, br), 3377 (m, br), 3281 (m, br), 2107 (vw), 1620 (m), 1500 (s), 1482 (s), 1443 (m), 1270 (m), 1231 (s), 1192 (m), 886 (w), 748 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55-7.48 (m, 1 H, aromatic), 7.26-7.16 (m, 1 H, aromatic), 7.04-6.94 (m, 2 H, aromatic), 6.88 (distorted d, *J* = 8.1, 1 H, aromatic), 6.83-6.66 (m, 3 H, aromatic), 3.76 (s, br, 2 H, NH_2), 3.29 (s, 1 H, ≡CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ =158.6, 142.7, 138.6, 134.1, 130.2, 125.3, 122.5, 120.5, 118.7. 116.6, 116.0, 112.8, 81.9, 79.4; GC-MS: *m/z* =209 (100) [M^+], 183 (32), 180 (77), 168 (57), 152 (19), 139 (5), 108 (9), 89 (9), 80 (39), 65 (16); anal. calcd for $C_{14}H_{11}NO$ (209.24): C, 80.36; H, 5.30; N, 6.69; found C, 80.40; H, 5.29; N, 6.67.

5-Methyl-2-(2-ethynylphenoxy)aniline (**10f**): yellow oil. IR (film): *v*= 3466 (w, br), 3377 (w, br), 3280 (m, br), 2107 (vw), 1621 (m), 1510 (m), 1481 (s), 1444 (m), 1305 (w), 1232 (s), 1200 (m), 862 (w), 754 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ =7.51 (dd, *J* = 7.7, 1.8, 1 H), 7.24-7.17 (m, 1 H), 6.97 (td, *J* = 7.6, 1.1, 1 H), 6.80 (distorted d, *J* = 8.1, 1 H), 6.74 (dd, *J* = 8.4, 0.8, 1 H), 6.64-6.59 (m, 1 H), 6.55-6.50 (m, 1 H), 3.72 (s, br, 2 H), 3.18 (s, 1 H), 2.38 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 141.1, 138.6, 135.1, 134.3, 130.2, 122.4, 120.5, 119.4, 117.4, 116.2, 113.2, 81.7, 79.7, 20.9; GC-MS: *m/z* = 223 (100) [M^+],

208 (11), 194 (24), 183 (34), 182 (23), 168 (17), 152 (8), 122 (11), 94 (20), 77 (18); anal. calcd for $C_{15}H_{13}NO$ (223.27): C, 80.69; H, 5.87; N, 6.27; found C, 80.71; H, 5.86; N, 6.26.

5-Methoxy-2-(2-ethynylphenoxy)aniline (**10g**): yellow solid, mp = 36-38 °C. IR (KBr): *v*= 3468 (w, br), 3377 (w, br), 3278 (m, br), 2104 (vw), 1623 (m), 1509 (s), 1481 (m), 1443 (w), 1231 (s), 1208 (s), 1029 (w), 754 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ =7.49 (dd, *J* = 7.6, 1.7, 1 H), 7.23-7.15 (m, 1 H), 6.95 (td, *J* = 7.5, 1.1, 1 H), 6.85 (distorted d, *J* = 8.5, 1 H), 6.72 (dd, *J* = 8.5, 1.1, 1H), 6.35 (distorted d, *J* = 2.9, 1 H), 6.26 (dd, *J* = 8.8, 2.9, 1 H), 3.74 (s, 5 H), 3.31 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.7, 157.9, 140.0, 137.2, 134.3, 130.2, 122.2, 121.8, 115.7, 113.0, 104.0, 102.7, 81.8, 79.8, 55.7; GC-MS: *m/z* = 239 [M^+] (100), 224 (61), 196 (41), 183 (32), 167 (16), 152 (6), 138 (44), 110 (20), 95 (14); anal. calcd for $C_{15}H_{13}NO_2$ (239.27): C, 75.30; H, 5.48; N, 5.85; found C, 75.35; H, 5.47; N, 5.84.

1-[3-Amino-4-(2-ethynylphenoxy)phenyl]ethanone (**10h**): pale yellow solid, mp 92-93 ^{o}C. IR (KBr): *v*= 3466 (w, br), 3365 (m, br), 3281 (m, br), 2104 (vw), 1674 (m), 1619 (m), 1589 (m), 1507 (w), 1482 (m), 1442 (m), 1359 (w), 1302 (m), 1226 (s), 1195 (m), 755 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, *J*= 7.7, 1 H), 7.47-7.40 (m, 1 H), 7.36-7.23 (m, 2 H), 7.12 (t, *J*= 7.6, 1 H), 6.92 (d, *J* = 8.2, 1 H), 6.74 (d, *J*= 8.4, 1 H), 4.04 (s, br, 2 H), 3.22 (s, 1 H), 2.53 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.8, 157.5, 148.2, 138.3, 134.6, 134.2, 130.4, 124.0, 119.6, 118.9, 117.6, 115.9, 115.0, 82.3, 79.0, 26.2; GC-MS: *m/z* = 251 (100) [M^+], 236 (44), 208 (40), 195 (12), 181 (27), 180 (27), 168 (9), 152 (24), 118 (4), 77 (7); anal. calcd for $C_{16}H_{13}NO_2$ (251.28): C, 76.48; H, 5.21; N, 5.57; found C, 76.53; H, 5.20; N, 5.55.

Methyl 3-amino-4-(2-ethynylphenoxy)benzoate (**10i**): yellow solid, mp 63-64^{o}C. IR (KBr): *v*= 3435 (w, br), 3349 (w, br), 3281 (w, br), 3071 (w), 2106 (vw), 1725 (s), 1621 (m), 1592 (m), 1572 (m), 1509 (m), 1486 (m), 1445 (s), 1302 (s), 1260 (s), 1117 (m), 995 (w), 915 (w), 752 (m) cm^{-1}; H NMR (300 MHz, $CDCl_3$): δ = 7.55 (distorted dd, *J* = 7.6, 1.4, 1 H), 7.52-7.47 (m, 1 H), 7.41-7.34 (m, 1 H), 7.34-7.25 (m, 1 H), 7.10 (td, *J* = 7.6, 1.0, 1 H), 6.90, (dd, *J* = 8.3, 0.6, 1 H), 6.75 (d, *J* = 8.3, 1 H), 3.87 (s, 5 H), 3.24 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =166.9, 157.2, 147.5, 137.9, 134.4, 130.4, 126.1, 123.8, 120.3,

118.3, 117.7, 117.2, 114.3, 82.3, 78.8, 52.0; GC-MS: *m/z* = 267 (M^+, 100), 241 (9), 236 (28), 235 (19), 226 (13), 208 (36), 195 (21), 183 (21), 180 (24), 168 (13), 152 (17), 138 (4), 118 (6), 104 (7), 90 (11), 75 (8); anal. calcd for $C_{16}H_{13}NO_3$ (267.28): C, 71.90; H, 4.90; N, 5.24; found C, 71.94; H, 4.89; N, 5.23.

3-Amino-4-(2-ethynylphenoxy)benzonitrile (**10j**): pale yellow solid, mp 104-105 °C. IR (KBr): *v* = 3468 (w, br), 3360 (w, br), 3283 (w, br), 2225 (m), 1619 (m), 1507 (s), 1402 (m), 1305 (w), 1235 (s), 863 (m), 756 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.56 (dd, *J* = 7.7, 1.6, 1 H), 7.38-7.30 (m, 1 H), 7.15 (td, *J* = 7.6, 1.1, 1 H), 7.03 (distorted d, *J* = 1.8, 1 H), 6.98-6.89 (m, 2 H), 6.67 (distorted d, *J* = 8.4, 1 Hc, 4.20 (s, br, 2 H), 3.21 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.8, 147.9, 138.9, 134.7, 130.5, 124.6, 122.7, 119.4, 119.0, 118.7, 117.8, 115.3, 107.7, 82.7, 78.7; GC-MS: *m/z* = 234 (M^+, 100), 205 (52), 193 (27), 183 (26), 168 (6), 151 (10), 105 (17), 89 (12), 75 (16); anal. calcd for $C_{15}H_{10}N_2O$ (234.25): C, 76.91; H, 4.30; N, 11.96; found C, 76.96; H, 4.28; N, 11.95.

2-(2-Ethynylphenoxy)-5-trifluoromethylaniline (**10k**): yellow oil. IR (film): *v*= 3478 (w, br), 3389 (w, br), 3299 (w, br), 2109 (vw), 1625 (m), 1515 (w), 1484 (m), 1446 (m), 1339 (s), 1229 (s), 1196 (m), 1165 (m), 1119 (m), 862 (w), 755 (w) cm^{-1} ; H NMR (300 MHz, $CDCl_3$): δ = 7.55 (distorted dd, *J* = 7.5, 1.1, 1H), 7.34-7.24 (m, 1 H), 7.09 (td, *J* = 7.5, 1.1, 1 H), 7.05-6.98 (m, 1 H), 6.95-6.84 (m, 2 H), 6.80 (distorted d, *J* = 8.2, 1 H), 4.08 (s, br, 2 H), 3.25 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =157.2, 146.0, 138.4, 134.4, 130.5, 126.6 (q, *J* = 32.4), 124.2 (q, *J* = 271.9), 123.9, 118.4, 118.0, 115.4 (q, *J* = 4.2), 114.1, 112.8 (q, *J* = 3.7), 82.4, 78.9; ^{19}F NMR (471 MHz, $CDCl_3$): δ = –62.6 (s, 3 F, CF_3) ppm. GC-MS: *m/z* = 277 (100) [M^+], 248 (25), 236 (28), 208 (14), 180 (21), 148 (11), 128 (3), 101 (7), 75 (9); anal. calcd for $C_{15}H_{10}F_3NO$ (277.24): C, 64.98; H, 3.64; F, 20.56; N, 5.05; found C, 65.03; H, 3.63; F, 20.57; N, 5.03.

Methyl [2-(2-phenylethynylphenoxy)phenyl]carbamate (**11a**): yellow oil. IR (film): *v* = 3427 (m, br), 2220 (vw), 1739 (s), 1610 (m), 1529 (s), 1454 (s), 1326 (w), 1253 (s), 1065 (m), 753 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.26-8.16 (m, 1 H, NH), 7.59 (dd, *J* = 7.7, 1.4, 1 H), 7.39-7.22 (m, 7 H), 7.22-7.07 (m, 2 H), 7.07-6.91 (m, 2 H), 6.80 (distorted dd, *J* = 8.1, 1.3, 1 H), 3.73 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.5, 153.9, 145.6,

133.8, 131.6, 129.8, 129.4, 128.4, 128.3, 124.3, 123.9, 122.9, 119.5, 119.2, 117.0, 116.1, 94.9, 84.4, 52.3; GC-MS: *m/z* = 343 (66) [M^+], 311 (20), 310 (22), 283 (29), 282 (27), 268 (59), 254 (30), 244 (100), 241 (31), 226 (7), 209 (11), 176 (13), 165 (16), 150 (10), 127 (8), 91 (3), 77 (8); anal. calcd for $C_{22}H_{17}NO_3$ (343.38): C, 76.95; H, 4.99; N, 4.08; found C, 76.98; H, 4.98; N, 4.06.

Methyl {2-[2-(4-bromophenylethynyl)phenoxy]phenyl}carbamate (**11b**): yellow solid, mp = 58-60 °C. IR (KBr): ν = 3459 (w, br), 2175 (vw), 1739 (s), 1608 (w), 1524 (s), 1474 (m), 1452 (m), 1323 (w), 1227 (s), 1208 (s), 1060 (m), 820 (m), 756 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, br, *J* = 7.6, 1 H), 7.57 (dd, *J*= 7.7, 1.4, 1 H), 7.48-7.38 (m, 3 H), 7.33 (td, *J* = 8.2, 1.7, 1 H), 7.22-7.15 (m, 3 H), 7.14-7.07 (m, 1 H), 7.01 (distorted d, *J* = 8.2, 1 H), 6.95 (td, *J* = 8.1, 1.5, 1 H), 6.78 (distorted dd, *J* = 8.2, 1.2, 1 H), 3.74 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4, 153.9, 145.5, 133.7, 133.0, 131.6, 130.1, 129.3, 124.3, 123.9, 123.0, 122.7, 121.8, 119.6, 119.2, 116.9, 115.6, 93.8, 85.5, 52.3; GC-MS: *m/z* = 423 (100) [$(M+2)^+$], 421 (98) [M^+], 391 (22), 389 (20), 348 (32), 346 (35), 324 (97), 322 (99), 310 (29), 254 (65), 241 (64), 209 (18), 176 (27), 150 (20), 126 (16), 113 (12); anal. calcd for $C_{22}H_{16}BrNO_3$ (422.27): C, 62.57; H, 3.82; Br, 18.92; N, 3.32; found C, 62.61; H, 3.83; Br, 18.94; N, 3.31.

Methyl [2-(2-cyclohex-1-eynylethynylphenoxy)phenyl]carbamate (**11c**): yellow oil. IR (film): *v* = 3433 (w, br), 3366 (w, br), 2929 (m), 2858 (w), 2208 (vw), 1740 (s), 1609 (w), 1529 (s), 1479 (m), 1445 (s), 1227 (s), 1065 (w), 751 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.22-8.11 (m, 1 H), 7.47 (distorted dd, *J* = 7.7, 1.7, 1 H), 7.30-7.22 (m, 2 H), 7.15-7.03 (m, 2 H), 7.00-6.88 (m, 2 H), 6.74 (distorted dd, *J* = 8.2, 1.2, 1 H), 6.09-6.01 (m, 1 H), 3.78 (s, 3 H), 2.16-1.96 (m, 4 H), 1.67-1.49 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =156.1, 153.9, 145.7, 135.7, 133.6, 129.3, 129.2, 124.2, 123.6, 122.8, 120.5, 119.6, 119.0, 117.3, 116.8, 96.9, 81.7, 52.3, 28.8, 25.8, 22.3, 21.5; GC-MS: *m/z* = 347 (100) [M^+], 319 (64), 315 (23), 304 (62), 286 (54), 278 (26), 272 (89), 260 (45), 245 (36), 231 (24), 218 (10), 208 (50), 194 (17), 183 (27), 165 (36), 152 (23), 139 (12), 115 (15); anal. calcd for $C_{22}H_{21}NO_3$ (347.41): C, 76.06; H, 6.09; N, 4.03; found C, 76.12; H, 6.08; N, 4.04.

Methyl {2-[2-(3,3-dimethylbut-1-ynylphenoxy)phenyl}carbamate (**11d**): yellow oil. IR (film): *v* = 3435 (m, br), 2969 (m), 2931 (m), 2867 (w), 2242 (w), 1739 (s), 1611 (m), 1539 (m), 1480 (w), 1456 (m), 1328 (w), 1219 (m), 1113 (w), 1065 (m), 954 (w), 755 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (d, br, *J* = 9.1, 1 H), 7.45 (distorted dd, *J* = 7.7, 1.4, 2 H), 7.31-7.23 (m, 1 H), 7.16-6.98 (m, 3 H), 6.91 (td, *J* = 8.1, 1.5, 1 H), 6.65 (distorted dd, *J* = 8.1, 1.2, 1 H), 3.79 (s, 3H), 1.12 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.8, 154.0, 146.1, 133.8, 128.9, 124.5, 123.2, 122.7, 120.3, 119.0, 115.9, 104.7, 89.1, 73.9, 52.3, 30.6, 28.0; GC-MS: *m/z* = 323 (97) [M^+], 308 (33), 291 (9), 276 (100), 266 (31), 248 (46), 234 (43), 233 (33), 219 (14), 209 (13), 178 (5), 165 (4), 152 (5), 141 (10), 128 (8), 115 (10); anal. calcd for $C_{20}H_{21}NO_3$ (323.39): C, 74.28; H, 6.55; N, 4.33; found C, 74.33; H, 6.53; N, 4.32.

*Methyl(Z)-(6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[a,d]cycloocten-7ylidene)acetate (**12e**):* yellow solid, mp = 223-225°C. IR (KBr): *v* = 3468 (w, br), 3378 (m, br), 2952 (w), 1723 (s), 1622 (m), 1503 (m), 1483 (m), 1435 (m), 1354 (w), 1306 (w), 1268 (m), 1216 (s), 755 (m) cm^{-1}; H NMR (300 MHz, $CDCl_3$): δ = 7.89 (s br, 1 H), 7.47-7.05 (m, 8 H), 5.79 (s, 1 H), 3.74 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 164.3, 157.0, 152.4, 149.9, 131.9, 131.7, 130.5, 129.2, 126.7, 126.4, 126.3, 125.1, 123.2, 121.3, 120.0, 51.6; GC-MS: *m/z* = 295 (59) [M^+], 278 (12), 263 (97), 236 (97), 235 (100), 207 (29), 190 (14), 180 (36), 165 (28), 152 (35), 139 (6), 104 (10), 89 (17), 75 (13); anal. calcd for $C_{17}H_{13}NO_4$ (295.29): C, 69.15; H, 4.44; N, 4.74; found C, 69.19; H, 4.43; N, 4.73.

Ethyl (Z)-(6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[a,d]cycloocten-7-ylidene)acetate (**12e'**): white solid, mp = 231-233 °C. IR (KBr): *v* = 3291 (w, br), 2926 (w), 1716 (s), 1674 (m), 1500 (w), 1470 (m), 1446 (m), 1384 (m), 1290 (w), 1260 (w), 1217 (m), 1190 (m), 1107 (w), 1032 (w), 755 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (s, br, 1 H), 7.47-7.09 (m, 8 H), 5.79 (s, 1 H), 4.20 (q, *J* = 7.1, 2 H), 1.29 (t, *J* =7.1, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.2, 163.8, 156.6, 151.9, 149.3, 131.9, 131.7, 130.4, 129.2, 126.7, 126.3, 126.0, 125.0, 123.1, 121.2, 120.3, 60.8, 14.1; GC-MS: *m/z* = 309 (37) [M^+], 281 (6), 264 (33), 263 (73), 236 (100), 235 (75), 219 (6), 207 (21), 190 (8), 180 (26), 165 (18), 152 (21), 89 (7); anal. calcd for $C_{18}H_{15}NO_4$ (309.32): C, 69.89; H, 4.89; N, 4.53; found C, 69.93; H, 4.88; N, 4.54.

Methyl (Z)-(3-methyl-6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[a,d]cycloocten ylidene)acetate (**12f**): pale yellow solid, mp = 205-207 °C. IR (KBr): *v* = 3307 (br), 1721 (s), 1673 (s), 1478 (w), 1448 (w), 1385 (m), 1211 (m), 1173 (m), 757 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (s, br, 1 H), 7.47-7.28 (m, 3 H), 7.21-6.93 (m, 4 H), 5.80 (s, 1 H), 3.75 (s, 3 H), 2.30 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0, 164.4, 157.1, 150.2, 150.0, 136.5, 131.8, 131.7, 130.5, 129.8, 127.1, 126.5, 125.0, 122.8, 121.3, 119.9, 51.6, 20.8; GC-MS: *m/z* =309 (94) [M^+], 277 (100), 250 (99), 249 (95), 235 (15), 221 (39), 207 (93), 193 (54), 179 (31), 165 (15), 147 (21), 135 (28), 89 (25), 73 (46); anal. calcd for $C_{18}H_{15}NO_4$ (309.32): C, 69.89; H, 4.89; N, 4.53; found C, 69.92; H, 4.90; N, 4.52.

Ethyl (Z)-(3-Methyl-6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[a,d]cycloocten-7-ylidene)acetate (**12f'**): yellow solid, mp = 220-222 °C. IR (KBr): *v* = 3396 (m, br), 1712 (s), 1674 (s), 1501 (w) 1477 (w), 1385 (m), 1305 (w), 1275 (w), 1209 (m), 1180 (m), 1037 (w), 758 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32 (s, br, 1 H), 7.47-7.29 (m, 3 H), 7.20-6.95 (m, 4 H), 5.80 (s, 1 H), 4.22 (q, *J* = 7.1, 2 H), 2.29 (s, 3 H), 1.30 (t, *J* = 7.1, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0, 163.9, 157.1, 150.2, 149.7, 136.4, 131.9, 131.6, 130.5, 129.7, 127.2, 126.5, 124.9, 122.8, 121.3, 120.4, 60.8, 20.8, 14.2; GC-MS: *m/z* = 323 (39) [M^+], 295 (5), 278 (33), 277 (66), 250 (100), 249 (79), 232 (7), 221 (17), 207 (14), 193 (18), 179 (15), 165 (11), 152 (9), 139 (3), 128 (4), 101 (6), 89 (9), 77 (8); anal. calcd for $C_{19}H_{17}NO_4$ (323.34): C, 70.58; H, 5.30; N, 4.33; found C, 70.61; H, 5.29; N, 4.31.

Methyl (Z)-(3-Methoxy-6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[a,d]cycloocten-7-ylidene)acetate (**12g**): yellow solid, mp = 243-245 °C. IR (KBr): v = 3429 (m, br), 2922 (w), 1709 (s), 1677 (s), 1607 (m), 1495 (w), 1476 (w), 1373 (w), 1258 (w), 1200 (s), 1161 (m), 1030 (m), 756 (m) cm^{-1}; 1H NMR (300 MHz, $CDCl_3$): δ = 7.47-7.28 (m, 4 H), 7.20-7.11 (m, 1 H), 7.05-6.98 (m, 1 H), 6.81-6.72 (m, 2 H), 5.81 (s, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.7, 164.4, 157.8, 157.3, 150.1, 146.4, 132.7, 131.7, 130.5, 127.0, 124.9, 123.7, 121.2, 119.8, 115.2, 111.1, 56.0, 51.6; GCMS: *m/z* = 325 (68) [M^+], 308 (4), 297 (11), 294 (41), 278 (20), 266 (100), 265 (71), 250 (41), 238 (20), 222 (31), 210 (10), 195 (16), 180 (6), 167 (23), 139 (13), 115 (4), 101 (9), 89 (7);

anal. calcd for $C_{18}H_{15}NO_5$ (325.32): C, 66.46; H, 4.65; N, 4.31; found C, 66.49; H, 4.64; N, 4.3.

Ethyl (Z)-(3-Methoxy-6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[a,d]cycloocten-7-ylidene)acetate (**12g'**): whitish solid, mp = 219-221°C. IR (KBr): *v* = 3294 (m, br), 2927 (w), 1712 (s), 1676 (s), 1609 (m), 1502 (m), 1477 (m), 1390 (m), 1270 (m), 1208 (s), 1180 (s), 1032 (m), 760 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.91 (s, br, 1 H), 7.46-7.28 (m, 3 H), 7.20-7.11 (m, 1 H), 7.0 (distorted d, *J* = 8.8, 1 H), 6.83-6.72 (m, 2 H), 5.80 (s, 1 H), 4.21 (q, *J* = 7.1, 2 H), 3.76 (s, 3 H), 1.29 (t, *J* = 7.1, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8, 164.0, 157.8, 157.3, 149.7, 146.3, 132.8, 131.5, 130.5, 127.1, 124.9, 123.6, 121.1, 120.3, 115.1, 111.1, 60.8, 56.0, 14.2; GC-MS: *m/z* = 339 (52) [M^+], 311 (8), 294 (31), 293 (41), 278 (17), 266 (100), 265 (68), 250 (37), 238 (22), 222 (23), 207 (13), 195 (15), 178 (7), 167 (23), 152 (8), 139 (11), 115 (4), 101 (9), 89 (7); anal. calcd for $C_{19}H_{17}NO_5$ (339.34): C, 67.25; H, 5.05; N, 4.13; found C, 67.30; H, 5.03; N, 4.12.

Methyl (Z)-(3-acetyl-6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[a,d]cycloocten-7-ylidene)acetate (**12h**): colorless solid, mp = 265-267 °C. IR (KBr): *v* = 3425 (w, br), 2952 (w), 1721 (s), 1673 (s), 1598 (w), 1448 (w), 1389 (w), 1283 (m), 1199 (s), 854 (w), 768 (w)cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 10.4 (s, br, 1 H), 7.93-7.83 (m, 1 H), 7.65 (s, br, 1 H), 7.61-7.21 (m, 5 H), 5.89 (s, 1 H), 3.65 (s, 3 H), 2.55 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 196.4, 167.6, 163.6, 155.3, 154.0, 149.3, 134.7, 133.2, 132.0, 130.3, 128.9, 126.4, 125.4, 124.5, 123.2, 121.1, 119.2, 51.5, 26.6; GC-MS: *m/z* = 337 (47) [M^+], 305 (48), 279 (100), 278 (65), 262 (41), 261 (31), 249 (12), 235 (22), 222 (15), 206 (21), 191 (7), 178 (14), 166 (10), 151 (18), 139 (15), 89 (10); anal. calcd for $C_{19}H_{15}NO_5$ (337.33): C, 67.65; H, 4.48; N, 4.15; found C, 67.69; H, 4.46; N, 4.15.

Ethyl (Z)-(3-acetyl-6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[a,d]cycloocten-7-ylidene)acetate (**12h'**): colorless solid, mp = 271-273. IR (KBr): *v* = 3342 (w, br), 2982 (w), 1723 (s), 1683 (m), 1596 (w), 1432 (w), 1263 (m), 1207 (s), 1027 (w), 759 (w) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 10.4 (s, br, 1 H), 7.89 (distorted dd, *J* = 8.5, 2.1, 1 H), 7.83 (d, *J* = 2.1, 1 H), 7.60-7.23 (m, 5 H), 5.85 (s, 1 H), 4.12 (q, *J* = 7.0, 2 H, CH_2CH_3), 2.55 (s, 3 H, MeCO), 1.21 (t, *J* = 7.0, 3 H, CH_2CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 196.3,

167.6, 163.2, 155.3, 154.0, 148.9, 134.7, 133.3, 131.9, 130.3, 129.0, 126.4, 125.4, 124.5, 123.2, 121.0, 119.6, 60.2, 26.6, 13.9; GC-MS: *m/z* = 351 (39) [M^+], 323 (3), 306 (7), 278 (45), 262 (25), 236 (100), 207 (11), 192 (6), 180 (8), 165 (30), 152 (11); anal. calcd for $C_{20}H_{17}NO_5$ (351.35): C, 68.37; H, 4.88; N, 3.99; found C, 68.40; H, 4.88; N, 4.00.

Methyl (Z)-7-methoxycarbonylmethylene-6-oxo-6,7-dihydro-5H-12-oxa-5-azadibenzo[a,d]cyclooctene-3-carboxylate (**12i**): colorless solid, mp = 244-246 °C. IR (KBr): *v* = 3512 (m, br), 1721 (s), 1675 (m), 1398 (m), 1280 (w), 1201 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.02-7.82 (m, 4 H), 7.52-7.30 (m, 2 H), 7.25-7.15 (m, 2 H), 5.83 (s, 1 H), 3.91 (s, 3 H), 3.77 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0, 165.6, 164.1, 156.0, 155.1, 149.0, 132.1, 132.0, 130.5, 130.4, 128.4, 127.3, 126.6, 125.5, 123.3, 121.3, 120.4, 52.4, 52.0; GC-MS: *m/z* = 353 (80) [M^+], 322 (40), 321 (74), 294 (100), 293 (58), 262 (41), 235 (20), 206 (26), 178 (19), 151 (11), 131 (11), 89 (11); anal. calcd for $C_{19}H_{15}NO_6$ (353.33): C, 64.59; H, 4.28; N, 3.96; found C, 64.63; H, 4.27; N, 3.97.

Methyl (Z)-7-ethoxycarbonylmethylene-6-oxo-6,7-dihydro-5H-12-oxa-5-azadibenzo[a,d]cyclooctene-3-carboxylate (**12i'**): white solid, mp = 220-222 °C. IR (KBr): *v* = 3461 (m, br), 1720 (s), 1682 (m), 1400 (m), 1283 (m), 1178 (m), 1100 (w), 759 (w) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 10.43 (s, br, 1 H), 7.85 (dist dd, *J* = 8.5, 2.2, 1 H), 7.70 (d, *J* = 2.2, 1 H), 7.61-7.23 (m, 5 H), 5.86 (s, 1 H), 4.12 (q, *J* = 7.1, 2 H), 3.84 (s, 3 H), 1.21 (t, *J* =7.1, 3 H); ^{13}C NMR (75 MHz, DMSO): δ = 167.6, 164.9, 163.2, 155.2, 154.0, 148.9, 133.3, 131.9, 130.3, 129.3, 127.5, 126.3, 125.9, 125.5, 123.5, 121.0, 119.7, 60.3, 52.3, 13.8; GC-MS: *m/z* = 367 (55) [M^+], 339 (7), 322 (35), 321 (61), 294 (100), 293 (49), 262 (28), 235 (15), 108 (17), 178 (15), 152 (8), 131 (4), 89 (7); anal. calcd for $C_{20}H_{17}NO_6$ (367.35): C, 65.39; H, 4.66; N, 3.81; found C, 65.42; H, 4.64; N, 3.83.

Ethyl (Z)-(3-Cyano-6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[a,d]cycloocten-7-ylidene)acetate (**12j'**): colorless solid, mp = 249-251 °C. IR (KBr): *v*= 3396 (m, br), 2233 (vw), 1712 (s), 1670 (m), 1634 (w), 1477 (w), 1385 (m), 1198 (m), 1026 (m), 767 (w) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 10.45 (s, br, 1 H), 7.78 (distorted dd, *J* = 8.4, 2.1, 1

H), 7.63-7.40 (m, 5 H), 7.33-7.25 (m, 1 H), 5.89 (s, 1 H), 4.15 (q, *J* = 7.1, 2 H), 1.23 (t, *J* = 7.1, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 167.5, 163.2, 155.2, 154.1, 148.3, 134.6, 132.5, 131.9, 130.1, 129.1, 126.6, 125.6, 124.6, 121.1, 120.4, 117.4, 109.2, 60.4, 13.9; GC-MS: *m/z* = 334 (16) [M^+], 288 (68), 261 (100), 260 (63), 247 (10), 232 (22), 216 (11), 205 (29), 190 (22), 177 (19), 164 (5), 151 (20), 116 (6), 101 (18), 89 (24), 75 (27); anal. calcd for $C_{19}H_{14}N_2O_4$ (334.33): C, 68.26; H, 4.22; N, 8.38; found C, 68.31; H, 4.21; N, 8.39.

Ethyl (Z)-(3-Trifluoromethyl-6-oxo-5,6-dihydro-12-oxa-5-azadibenzo[a,d]cycloocten-7-ylidene)acetate (**12k'**): colorless solid, mp = 218-220°C. IR (KBr): *v* = 3103 (m, br), 1718 (s), 1673 (m), 1504 (m), 1478 (m), 1449 (m), 1391 (m), 1339 (s), 1198 (m), 1167 (m), 1126 (m), 882 (w), 856 (w), 767 (w) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.48 (s, br, 1 H), 7.71-7.63 (m, 1 H), 7.61-7.39 (m, 5 H), 7.33-7.24 (m, 1 H), 5.89 (s, 1 H), 4.13 (q, *J* = 7.1, 2 H), 1.20 (t, *J* = 7.1, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 167.6, 163.2, 155.1, 153.2, 148.7, 134.0, 132.0, 130.3, 126.8 (q, *J* = 32.6), 126.3, 125.6, 125.5 (q, *J* = 1.5), 124.3, 123.4 (q, *J* = 272.2), 121.1, 120.0, 60.3, 13.8; ^{19}F NMR (471 MHz, $CDCl_3$): δ = –60.6 (s, 3 F, CF_3) ppm. GC-MS: *m/z* = 377 (M^+, 45), 349 (5), 332 (28), 331 (58), 305 (17), 304 (100), 276 (20), 275 (22), 248 (19), 234 (5), 208 (8), 207 (12), 178 (13), 152 (9), 128 (5), 101 (11), 89 (12), 75 (18); anal. calcd for $C_{19}H_{14}F_3NO_4$ (377.31): C, 60.48; H, 3.74; F, 15.11; N, 3.71; found C, 68.45; H, 3.72; F, 15.13; N, 3.73

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Chapter 3

New Synthesis of Thiophene, 2-Iodothiophene, Benzothiophenethione and Isothiochromenethione Derivatives

3.1 General Importance of *S*-Heterocycles

Substituted thiophenes and benzothiopene are among the most important aromatic heterocyclic derivatives[1]. Many molecules incorporating the thiophene nucleus have, in fact, shown important pharmacological activities. Moreover, thiophene and benzothiophene derivatives find large application in material science and in coordination chemistry, and as intermediate in organic synthesis. The classical approaches to substituted thiophenes and benzothiophenes are mainly based on condensation-like reactions or on subsequent functionalization of the thiophene ring. However, during the last years, innovative approaches to the regioselective synthesis of substituted thiophenes starting from acyclic precursors have been developed, mainly based on metal-catalyzed heterocyclization or iodocyclization of suitably functionalized substrates.

Catalytic processes, in which several different units can be assembled in one step in ordered sequence under the promoting action of a suitable catalyst, are destined to play a central role in current synthesis [2]. Catalysis-based chemical syntheses account for ca. 60% of current chemical products and 90% of current chemical processes, and advancement in catalysis is expected to become of essential importance for the advancement of sustainable chemical syntheses.

Heterocyclization of acetylenic substrates bearing a suitably placed nucleophilic group is widely recognized as a methodology of primary importance for the direct preparation of a variety of heterocyclic systems in a regioselective fashion, starting from readily available acyclic precursors.[3]

Compared to the considerable number of examples reported in the literature for the synthesis of O- or N-heterocycles, there are still relatively few examples of heterocyclizations of S-containing alkyne substrates leading to sulfur heterocycles . This is probably connected with the relatively low stability of the thiol group as compared to the hydroxyl or the amino group and, in the case of metal-catalyzed heterocyclization, to the “poisoning” effect exerted by the sulfur atom on the metal catalyst, owing to its strong coordinating and adsorptive properties.[4]

Nevertheless, during the last years, several important S-cyclization reactions, starting from substrates bearing a free as well as a masked thiol group, have been developed,[3a,5] including several contributions from our research group.[5b,l,j, 6]

In this part of PhD work, I have studied Pd-catalyzed heterocyclodehydration7 and iodocyclization[8,9] of 1-mercapto-3-yn-2-ols **1** (readily available by alkynylation of α-mercapto ketones) to give thiophene derivatives[10] in DESs and a tandem thionation/S-cyclization process leading to benzo[c]thiophene-1(3H)-thione **7** and 1*H*-isothiochromene-1-thione **8** derivatives, starting from 2-alkynylbenzoic acids **6**.

3.2 Heterocyclodehydration and Iodocyclization of 1-mercapto-3-yn-2-ols in a deep eutectic solvent (DES) for the synthesis of thiophene and 2-iodothiophene derivatives

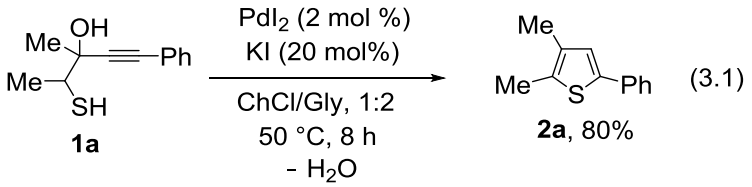
3.1.2 Introduction

Deep eutectic solvents (DESs) are an emerging new class of unconventional solvents, characterized by low toxicity and high eco-friendliness.[11] 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.[12-14] 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 DES swhich are generally less chemically inert with respect to classical organic solvents and ionic liquids,[15] so the success in using DESs in a particular chemical transformation cannot be taken for granted.

Pd-catalyzed heterocyclodehydration[7] and iodocyclization[8,9] of 1-mercapto-3-yn-2-ols **1** (readily available by alkynylation of α-mercapto ketones) to give thiophene derivatives[10] in DESs as safer and greener unconventional solvents, thereby expanding the field of metal-catalyzed reactions and introducing the use of DES in iodocyclizations are reported in this chapter.

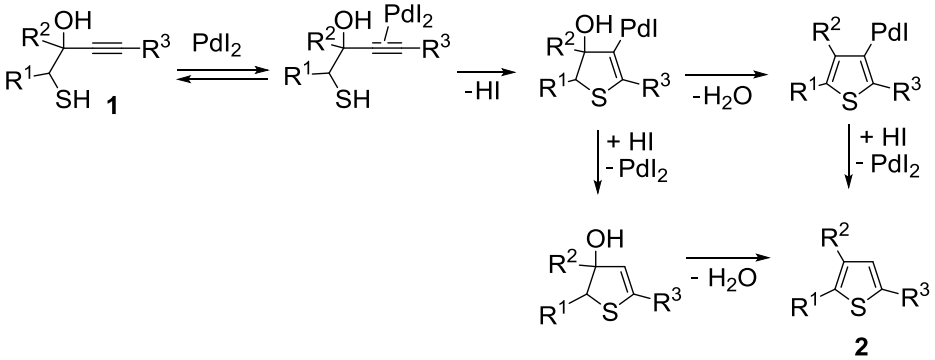
3.1.3 Result and Discussion

The first heterocyclization experiments were 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 (ChCl = choline chloride) at 50 °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 (Gly = glycerol). 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 °C (Table 3.1, entry 1, run 1; eq. 3.1).



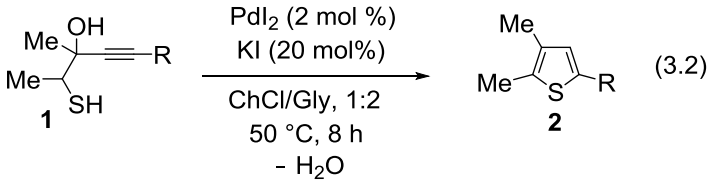
This result testifies that DESs are not interchangeable with each other and that their nature can have a profound and unpredictable influence on the outcome of a particular reaction.

The process leading to **2a** may be interpetred as occurring through 5-*endo*-*dig* intramolecular attack of the mercapto group to the triple bond coordinated to the metal center, followed by protonolysis and dehydrative aromatization or vice versa (Scheme 3.1)



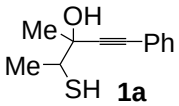
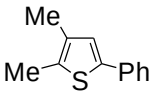
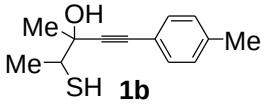
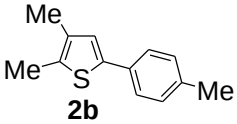
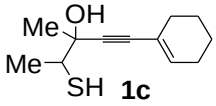
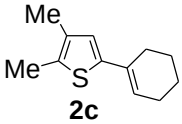
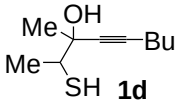
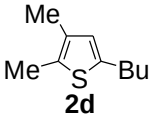
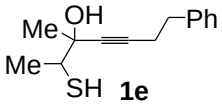
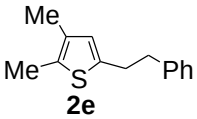
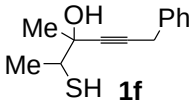
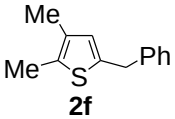
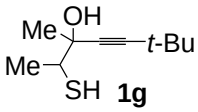
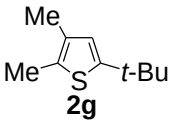
Scheme 3.1. Formation of substituted thiophenes **2** from 1-mercapto-3-yn-2-ols by PdI_2-catalyzed heterocyclodehydration

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, has verifyed. After 8 h, **2a** was formed again with the same yield as that of the first experiment (Table 3.1, entry 1, run 2). The recycling procedure was repeated for additional four runs, with **2a** being consistently obtained in 78-80% yields (Table 3.1, entry 1, runs 3-6).



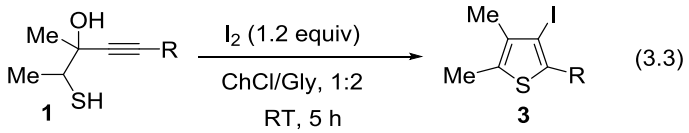
(3.2)

Table 3.1. Synthesis of substituted thiophenes **2** by PdI_2/KI-catalyzed heterocyclization of 1-mercapto-3-alkyn-2-ols **1** in ChCl/Gly (1:2) as the solvent and recycling experiments[a]

Entry	1	2	Yield of **2**[b,c] (%)					
			Run 1	Run 2	Run 3	Run 4	Run 5	Run 6
1	 **1a**	 **2a**	80	80	79	80	79	78
2	 **1b**	 **2b**	80	79	79	78	78	79
3	 **1c**	 **2c**	69	68	68	67	69	67
4	 **1d**	 **2d**	78	77	76	76	75	77
5	 **1e**	 **2e**	83	82	82	83	82	82
6	 **1f**	 **2f**	73	73	72	73	73	72
7	 **1g**	 **2g**	65	63	64	64	63	64

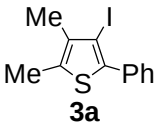
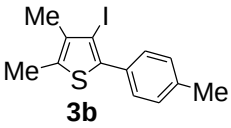
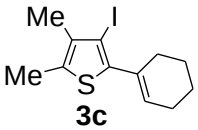
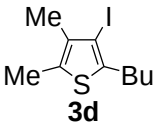
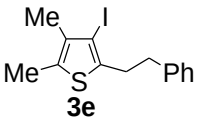
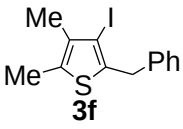
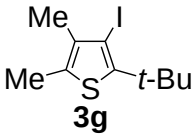
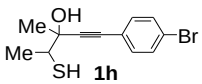
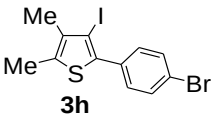
[a] All reactions were carried out at 50 °C for 8 h in 1:2 ChCl/Gly mixture (ChCl = choline chloride; Gly = glycerol) as the solvent (0.20 mmol of starting **1** per mL of DES) in the presence of PdI_2 (2 mol %) in conjunction with KI (20 mol %). Conversion of **1** was quantitative in all cases.[b]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

The generality of the process was then assessed, by varying the nature of the substituent on the triple bond.



(3.3)

Table 3.2. Base-free synthesis of 3-iodothiophenes **3** by iodocylization of 1-mercapto-3-alkyn-2-ols **1** in ChCl/Gly (1:2) as the solvent and recycling experiments[a]

	1	2	Yield of 3[b,c] (%)					
			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	75
6	**1f**	 **3f**	76	73	74	74	76	75
7	**1g**	 **3g**	65	63	64	63	62	63
8	 **1h**	 **3h**	62	62	60	61	60	61

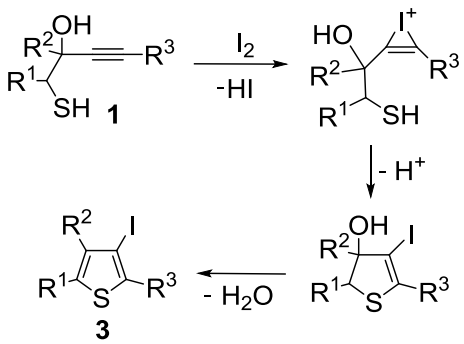
[a] All reactions were carried out with I_2 (1.2 equiv) at 25 °C for 5 h in a 1:2 Chl/Gly (ChCl = choline chloride; Gly = glycerol) mixture as the solvent (0.20 mmol of starting **1** per mL of DES). Conversion of **1** was quantitative in all cases.
[b] Isolated yield based on starting **1**.
[c] Run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

As can be seen from the results reported in Table 3.1 (entries 2-7), 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 4-7) on the triple bond (including a sterically demanding *tert*-butyl group, entry 7). In all cases, the recyclability of the DES/catalyst system could be successfully achieved.

Considering the good results obtained in the Pd-catalyzed heterocyclization of 1-mercapto-3-yn-2-ols **1**, I 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 3.2, Eq. 3.3).

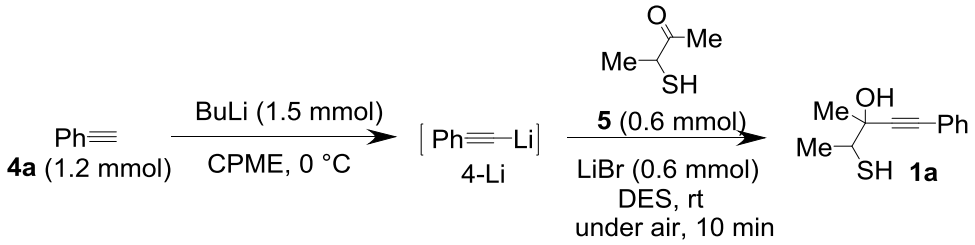
The iodocyclization process may occur through the formation of an iodonium cation intermediate followed by cyclization and dehydration (Scheme 3.2). As far as I know, this reaction represents the first example in the literature of an iodocyclization reaction carried out in a DES as the reaction medium.



Scheme 3.2. Formation of substituted 3-iodothiophenes **3** from 1-mercapto-3-yn-2-ols by iodocyclization.

In order to increase the green merit of the overall transformation from commercially available β-mercapto ketones to the final thiophenes, and in consideration of the fact that nucleophilic additions to carbonyl compounds promoted by Grignard and organolithium reagents have been proved to be effective in DESs,[13b,14d-f] we have also investigated the possibility of carrying out the alkynylation reactions for the preparation of 1-mercapto-3-yn-2-ols **1** in such unconventional solvents.

Thus, we first subjected a cyclopentyl methyl ether (CPME) solution of phenylacetylene **4a** (1.2 mmol) to lithiation with *n*-BuLi (1.5 mmol). The resulting solution of the putative lithiated intermediate **4a-Li** was then added to a solution of 3-mercaptobutan-2-one **5** (0.6 mmol) in a 1:2 ChCl–Gly eutectic mixture (1 g) in the presence of 0.6 mmol of LiBr at room temperature and under air. Pleasingly, the corresponding alkynylation product **1a** was recovered with a yield of 50% after 10 min reaction time (Table 3.e, entry 1, Scheme 3.3).



Scheme 3.3

When performed in other different eutectic mixtures, the reaction proved to be less effective, and afforded lower yields of **1a** (up to 28%, Table 3.3, entries 2–4).

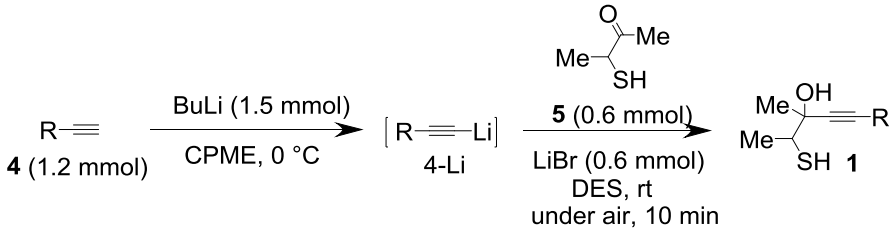


Table 3.3. Addition reaction of various lithium acetylides **4**-Li to 3-mercaptobutan-2-one **5** in DES mixtures [a]

Entry	4	DES	1	Yield of **1** (%)
1	Ph— **4a**	ChCl/Gly (1:2)	**1a**	50 [b]
2	**4a**	ChCl/urea (1:2)	**1a**	8 [c]
3	**4a**	ChCl/D-sorbitol (1:1)	**1a**	28 [c]
4	**4a**	ChCl/D-fructose (1:1)	**1a**	23 [c]
5	Me— **4b**	ChCl/Gly (1:2)	**1b**	61 [b]
6	Bu— **4d**	ChCl/Gly (1:2)	**1d**	41 [b]

[a] 1 g of DES per 1.2 mmol of **4**.
[b] Isolated yield based on **5**.
[c] Determined by ^{1}H NMR analysis of the crude reaction mixture

The nucleophilic addition of other lithium acetylides, bearing a *p*-tolyl (**4b**) or a butyl (**4d**) group, run in the above ChCl/Gly (1:2) eutectic mixture, furnished the expected 1-mercapto-3-yn-2-ols **1b** and **1d** in 61% and 41% yield, respectively (Table 3.3, entries 5 and 6). Although these yields are overall lower than those obtained in THF at low temperature,[7a] these results testify that alkynylation reactions of β-mercaptoketones can also be alternatively run in DESs as unconventional solvents, at RT under air, and competitively with protonolysis.

3.1.4 Conclusions

In conclusion, the *S*-heterocyclization and iodocyclization of 1-mercapto-3-yn-2-ols in chloride/glycerol both run in the deep eutectic solvent ChCl/Gly (1:2) as a nonconventional, safe, inexpensive and "green" reaction medium, is reported. Substituted thiophenes **2** and 3-iodothiophenes **3** were efficiently obtained starting from readily available 1-mercapto-3-alkyne-2-ols **1**, which, in turn, could also be synthesized by carrying out the alkynylation of commercially available β-mercaptoketone **5** in the above DES. The heterocyclodehydration of **1** to thiophenes **2** was carried out using a simple catalytic system, consisting of PdI_2 in conjunction with 10 equiv of KI, which could be conveniently recycled together with the DES several times without loss of activity. The DES solvent could also be easily recycled in the iodocyclization process leading to 3-iodothiophenes **3**.

3.2 Thionation-heterocyclization process leading to benzo[c]thiophene-1(3H)-thione and 1H-isothiochromene-1-thione derivatives

Here is reported a new thionation-heterocyclization process leading to benzo[*c*]thiophene-1(3*H*)-thione and 1*H*-isothiochromene-1-thione derivatives (**7** and **8**, respectively)[16-18] in one step starting from readily available 2-alkynylbenzoic acids **6**[19,20] (Scheme 2).

The tandem process is carried out under microwave (MW) irradiation,[21] in the presence of 1 equiv of the Lawesson's reagent (fig. 3.1).[22]

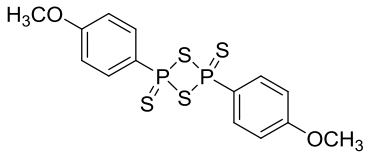
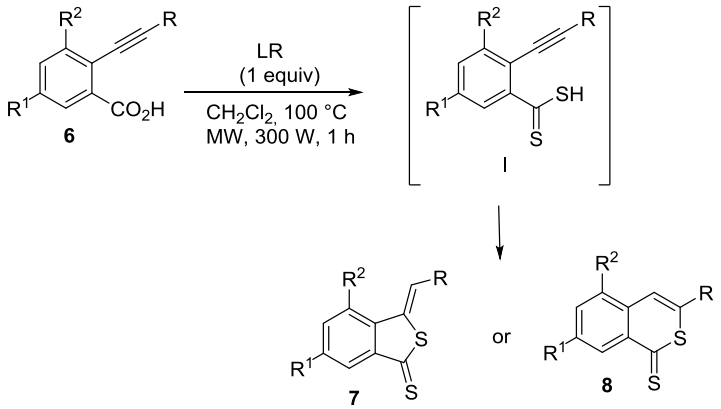


Fig.3.1 Lawesson's Reagent (LR)

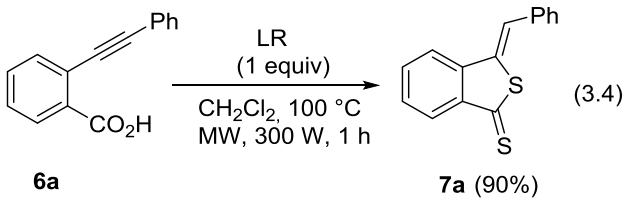
2-alkynylbenzodithioic acids **I**,[23] obtained in situ by thionation of **6**, undergo *S*-cyclization to give **7** or **8** without the need for activation from an external electrophilic promoter (Scheme 3.4).



Scheme 3.4. MW-assisted tandem thionation-heterocyclization of 2-alkynylbenzoic acids **6**, carried out in the presence of 1 equiv of the Lawesson's reagent, that leads to (*Z*)-3-alkylidenebenzo[*c*]thiophene-1(3*H*)-thiones **7** and 1*H*-isothiochromene-1-thiones **8** through the formation of 2-alkynylbenzodithioic acids **I** as intermediates.

The initial substrate we tested was 2-(2-phenylethynyl)benzoic acid **6a** ($R^1 = R^2 =$ H, R = Ph), which was allowed to react with 1 equiv of the Lawesson's reagent in

CH_2Cl_2 at 100°C under MW irradiation. After 1 h, (*Z*)-3-benzylidenebenzo[c]thiophene-1(3*H*)-thione **7a** was obtained in 90% isolated yield, with complete regio- and stereoselectively (Eq. 3.4).



(3.4)

It is worth noting that the same reaction, carried out under conventional heating (refluxing CH_2Cl_2, 1,2-dichloroethane, toluene or MeCN for 6-24 h) led to the formation of **2a** in only small amounts (0-5%), with partial decomposition of the substrate. A peculiar aspect of our MW-assisted synthetic approach is that the *S*-cyclization of the intermediate 2-alkynylbenzodithioic acids **I** occurs without the need for the presence of an external electrophilic promoter.

The structure of products **7** was elucidated by ^{1}H NMR and ^{13}C NMR spectroscopies and MS spectrometry. In particular, the *Z* stereochemistry around the exocyclic double bond was assigned on the basis of selective 1D NOESY experiments, carried out on compound **7a** (Fig. 3.2A). When H_4 was irradiated (7.53 ppm), the selective 1D NOESY spectrum clearly showed cross-peaks between H_4 and H_8 (7.94 ppm), H_4 and H_{orto} (7.62 ppm) in the phenyl substituent, as the result of the spatial proximity of these protons, which is only possible if they are in the *Z*-configuration.

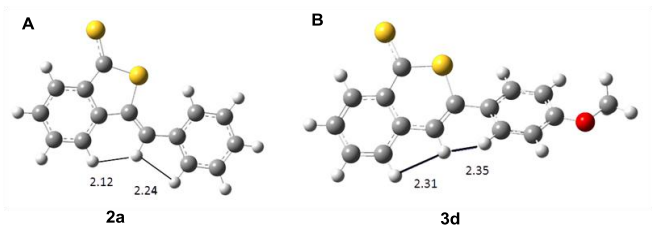


Figure 3.2. Molecular structure of compounds **7a** and **8d** optimized by Gaussian at 6-31g**b3lyp level.

The *Z* stereochemistry was further confirmed by X-ray crystallographic analysis (Fig. 3.3)

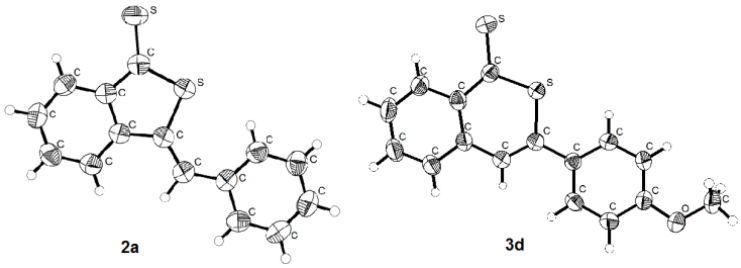
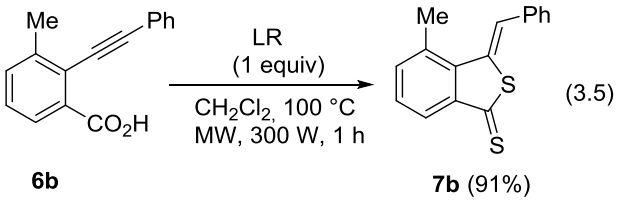
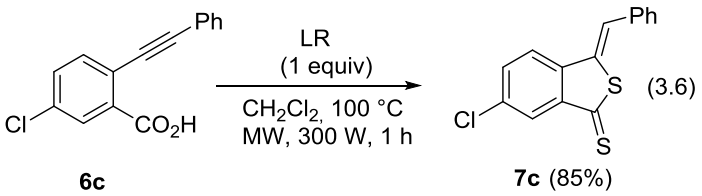


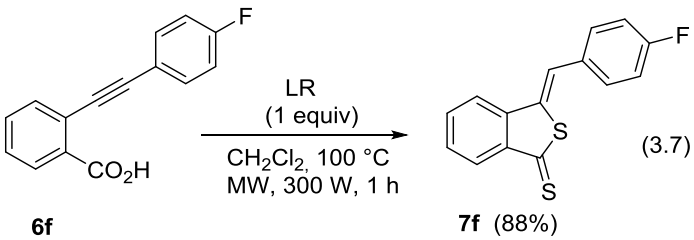
Figure 3.3. X-ray crystal structures of products **7a** and **8d**, showing 50% probability ellipsoids for non-H atoms and spheres of arbitrary size for H atoms.

This protocol could be also be successfully applied to substrates substituted in *ortho* or in *para* with respect to the carboxyl group, as in the case of **6b** (R^2 = Me) and **6c** (R^1 = Cl), which led to the corresponding benzo[*c*]thiophene-1(3*H*)-thiones **7b** and **7c** in 91% and 85% yields, respectively (eq. 3.5 and 3.6).

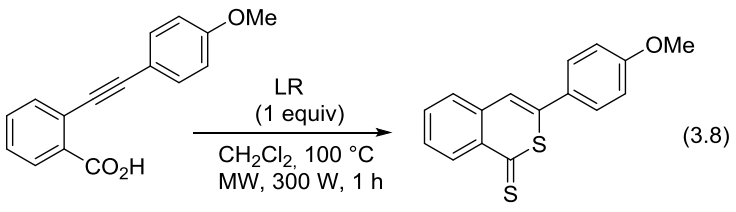




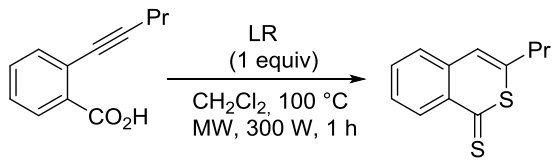
Moreover, a substrate bearing a *p*-fluorophenyl substituent on the triple bond, such as **6f**, led to the corresponding benzo[*c*]thiophene-1(3*H*)-thione derivative **7f** in high yield (88%, eq. 3.7).



Interestingly, 2-alkynylbenzoic acids carrying on the triple bond an alkyl substituent (such as propyl, as in **6g**) or a phenyl group substituted in the *para* position with a strong π-donating group (such as methoxyl, as in **6d**) selectively underwent, after *in situ* thionation, a 6-*endo*-*dig* rather than a 5-*exo*-*dig* cyclization, to give the corresponding 1*H*-isothiochromene-1-thiones **8g** and **8d**, respectively, in excellent yields (eq. 3.8 and 3.9).



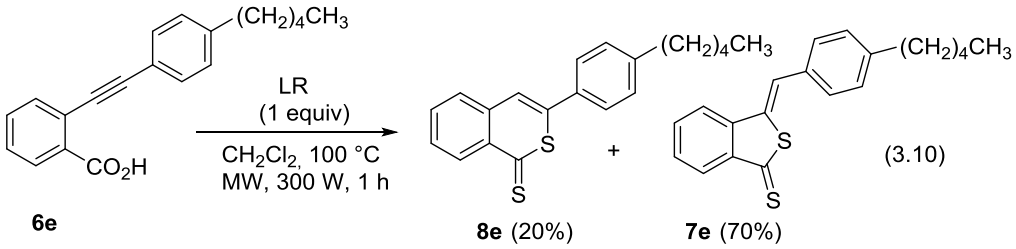
6d **8d** (90%) (3.8)



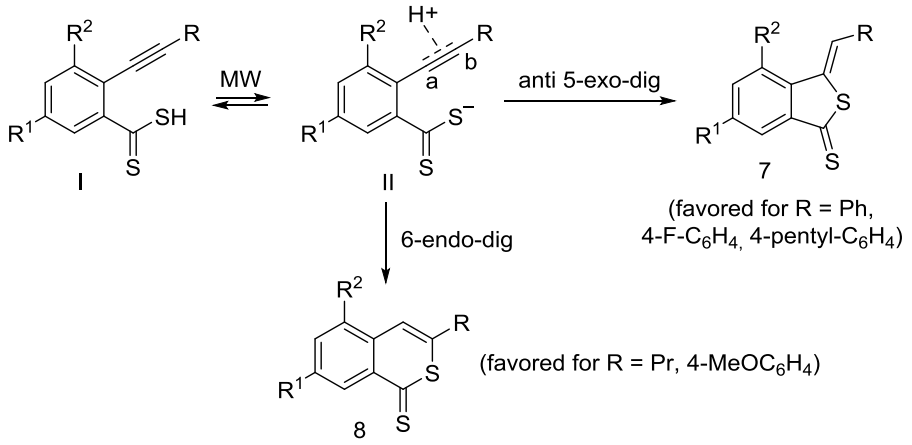
6g **8g** (86%) (3.9)

The structure of products **8d** was confirmed by MS spectrometry, ^{1}H NMR and ^{13}C NMR spectroscopies (in particular, no NOESY effect was observed by irradiation of proton H_4 in compound **8d**, see Fig. 3.2 B), and confirmed by X-ray crystallographic analysis (Fig. 3.3)

Quite consistently, a substrate bearing on the triple bond a phenyl group substituted in *para* position with a weakly electron-donating substituent (such as the *n*-pentyl, as in **6e**) afforded (*Z*)-3-(4-pentylbenzylidene)benzo[*c*]thiophene-1(3*H*)-thione **7e** as the major product (70% yield) together with 3-(4-pentylphenyl)-1*H*-isothiochromene-1-thione **8e** in 20% yield. (eq. 3.10) The observed change in regioselectivity moving from an electron-withdrawing substituent to an electron-donating substituent on the triple bond is in agreement with the results previusoly obtained in other heterocyclizations of functionalized alkynes.[24]



Mechanistically, the cyclization process may start with MW-induced dissociation of the dithiocarboxyl group[25] of **I** with simultaneous proton coordination by the triple bond, with formation of intermediate **II**, as shown in Scheme 3.5.



Scheme 3.5. Proposed mechanism for the heterocyclization of 2-alkynylbenzodithioic acids **I**: the initial MW-induced dissociation of the dithiocarboxyl group, with simultaneous proton coordination by the triple bond, is followed by *anti* 5-*exo-dig* or by 6-*endo-dig* intramolecular nuclophilic attack of the dithiocarboxylate group to the electrophilically-activated triple bond.

This intermediate, according to the electronic nature of the triple bond, can lead to compound **7** or **8**. In particular, the presence of an electron withdrawing group at the β carbon of the triple bond promotes the protonation on this carbon followed by the *anti* 5-*exo-dig* intramolecular nuclephilic attack of the dithiocarboxylate group, leading to the formation of compound **7**. An *anti* intramolecular attack is in perfect agreement with the observed *Z* stereochemistry of the final product **7**. Alternatively, the presence of an electron releasing group on the β carbon of the triple bond promotes the 6-*endo-dig* cyclization, with protonation on the more negative carbon of the triple bond (β carbon), thus leading to the formation of 1*H*-isothiochromene-1-thione derivatives **8.**

3.2.1 Conclusions

In summary, the first example of tandem thionation/heterocyclization of 2-alkynylbenzoic acids **6** is reported. The process occurs using 1 equiv of the Lawesson's reagent as the thionation agent under MW irradiation (100 °C at 300 W) in CH_2Cl_2 for 1 h, and leads to (*Z*)-benzothiophenethiones **7** or isothiochromenethiones **8**, depending on the nature of the substituent at the distal β position of the carbon-carbon triple bond. In particular, compounds **7** were regio- and stereoselectively obtained starting from substrates bearing an aryl group (Ph, 4-F-C_6H_4, or 4-pentyl-C_6H_4) as substituent on the carbon-carbon triple bond, through thionation followed by a 5-*exo*-*dig* cyclization, while substrates carrying an alkyl group (such as Pr) or an electron-rich aryl substituent (such as *p*-$MeOC_6H_4$) at the same position selectively underwent a 6-*endo*-*dig* cyclization to yield **8**. The study of the bioactivity of the newly synthesized *S*-heterocycles is currently underway and will be reported in due course.

3.3 Experimental Section

3.3.1 Experimental Procedure for preparation of thiophene and 2-iodothiophene derivatives

*Preparation of 1-Mercapto-3-alkyn-2-ols **1a–h**.*

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) (phenylacetylene, 4.55 g; p-methylphenylacetylene, 5.17 g; p-bromophenylacetylene, 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. 4-Mercapto-3-methyl-1-phenylpent-1-yn-3-ol (**1a**) was a yellow oil (3.16 g, 90%); 4-Mercapto-3-methyl-1-p-tolylpent-1-yn-3-ol (**1b**) was a yellow oil (2.99 g, 80%); 1-Cyclohex-1-enyl-4-mercapto-3-methyl-pent-1-yn-3-ol (**1c**) was a yellow oil, (3.11 g, 87%); 2-Mercapto-3-methylnon-4-yn-3-ol (**1d**) was a yellow oil, (2.69 g, 85%); 2-Mercapto-3-methyl-7-phenylhept-4-yn-3-ol (**1e**) was a yellow oil, (1.59 g, 40); 2-Mercapto-3-methyl-6-phenyl-hex-4-yn-3-ol (**1f**) was a yellow oil, (1.91 g, 51%); 2-Mercapto-3,6,6-trimethyl-hept-4-yn-3-ol (**1g**)., (2.91 g, 92%).

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.

Substrates **1a**, **1b**, and **1d** were also prepared by alkynylation of commercially available 3-mercaptobutan-2-one **5** in the ChCl/Gly (1:2) eutectic mixture as described below. All other materials were commercially available and were used without further purification

Preparation of DES

Eutectic mixtures of solvents [ChCl−Gly (1:2 mol/mol); ChCl/d-fructose (1:1 mol /mol); ChCl–urea (1:2 mol/mol); ChCl/d-sorbitol (1:1 mol/mol] were prepared by heating with stirring up to 90 °C for 10–30 min the corresponding individual components until a clear solution was obtained.

Preparation of 1-mercapto-3-alkyne-2-ols 1a, 1b, and 1d in DES.

A solution of the desired lithium acetylide was initially prepared by adding, at 0 °C and under nitrogen, 0.6 mL of a 2.5 M solution of n-BuLi in hexanes (1.5 mmol) to a stirred solution of the 1-alkyne **4** [1.2 mmol; phenylacetylene (**4a**) 124 mg; p-tolylacetylene (**4b**), 140 mg; 1-hexyne (**4d**), 100 mg] dissolved in cyclopentyl methyl ether (1 mL). To a stirred solution of commercially available 3-mercapto-2-butanone **5** (63 mg, 0.60 mmol) and LiBr (52 mg, 0.6 mmol) in ChCl–Gly (1:2) (1.0 g) was added, at RT and under air, a solution of the above alkynyllithium reagent (1.2 mmol). After stirring for 10 min, the reaction was quenched by adding a saturated aqueous solution of NH_4Cl and 1 N HCl (2 mL). The mixture was then extracted with Et_2O (3 × 10 mL), and the collected organic phases were washed with brine and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by column chromatography on silica gel (95:5 hexane/AcOEt as the eluent), to give the pure product as a ca. 1:1 mixture of diastereoisomers: 4-mercapto-3-methyl-1-phenylpent-1-yn-3-ol **1a** was a yellow oil (62 mg, 50%); 4 mercapto-3-methyl-1-p-tolylpent-1-yn-3-ol **1b** was a yellow oil (82 mg, 61%); 2-mercapto-3-methylnon-4-yn-3-ol **1d** was a yellow oil (46 mg, 41%).

General procedure for the synthesis of substituted thiophenes 2 by PdI_2/KI-catalyzed heterocyclization of 1-mercapto-3-alkyn-2-ols 1 in ChCl/Gly (1:2) as the solvent

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, 8.3×10^{-3} mmol) and KI (13.8 mg, 8.3×10^{-2} mmol) in this order under nitrogen in a Schlenk flask. The mixture was allowed to stir at 50 °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 °C (yield: 63 mg, 80%); 2,3-dimethyl-5-*p*-tolylthiophene **2b** was a yellow solid, mp 47-49 °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 °C (75 mg, 83%); 5-benzyl-2,3-dimethylthiophene 2f was a yellow solid, mp 38-39 °C (62 mg, 73%); 5-tert-butyl-2,3-dimethylthiophene **2g** was a yellow oil (46 mg, 65%).

Recycling procedure.

To the DES residue obtained as described above was added a solution of **1** (0.42 mmol) in Et_2O (3 mL). The Et_2O was removed under vacuum and then the same procedure described above was followed.

*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.*

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 (152 mg, 0.60 mmol) under nitrogen. The mixture was allowed to stir at 25 °C for 5 h and then extracted with Et_2O (6 × 5 mL). After evaporation of the solvent, the products **3a–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

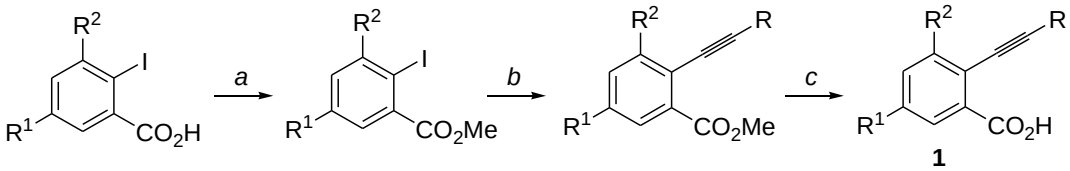
(96 mg, 65%); 2-(4-bromophenyl)-3-iodo-4,5-dimethylthiophene **3h** was a colorless solid, mp 104-105 °C (122 mg, 62%).

Recycling procedure.

To the DES residue obtained as described above was added a solution of 1 (0.50 mmol) and I_2 (0.55 mmol) in Et_2O (3 mL). The Et_2O was removed under vacuum and then the same procedure described above was followed.

3.3.2 Experimental Procedure for preparation of benzo[*c*]thiophene-1(3*H*)-thione and 1H-isothiochromene-1-thione derivatives

Starting materials **6** were prepared by Sonogashira coupling between methyl 2-iodobenzoates (prepared by esterification of commercially available 2-iodobenzoic acids) followed by hydrolysis, according to Scheme:



(a) Preparation of methyl 2-halobenzoates.

Methyl 2-iodobenzoate was commercially available. Other were prepared by Fischer esterification, according to the following procedure: To a stirred solution of the 2-halobenzoic acid [10.0 mmol]] 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.

(b) Sonogashira coupling between methyl 2-halobenzoates and terminal alkynes to give methyl 2-alkynyl benzoates.

A solution of the methyl 2- halobenzoate derivative (4.0 mmol), $PdCl_2(PPh_3)_2$ (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 (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.

*(c) Hydrolysis of methyl 2-alkynylbenzoates to give 2-alkynylbenzoic Acids **6***.

A stirred solution of the methyl 2-alkynylbenzoate [2.5 mmol] 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 further purified by crystallization with Et_2O/hexane. 2-(2-Phenylethynyl)benzoic acid (**6a**), yellow solid, 0.52g, 93%; 3-methyl-2-(2-phenylethynyl)benzoic acid (**6b**), white solid, 0.59g, 90%; 5-chloro-2-(2-phenylethynyl)benzoic acid (**6c**), white solid, 0.59 g, 92%; 2-[(4-methoxyphenyl)ethynyl]benzoic acid (**6d**), pale yellow needles, 0.57g, 90%; 2-[(4-pentylphenyl)ethynyl]benzoic acid (**6e**), white solid, 0.62g, 85%; 2-[(4-fluorophenyl)ethynyl]benzoic acid (**6f**), white solid, 0.42 g, 82%; 2-(1-pentynyl)benzoic acid (**6g**), pale yellow needles, 0.40g, 86%;

*General procedure for the tandem thionation-heterocyclization of 2-alkynylbenzoic acids **6** to benzo[c]thiophene-1(3H)-thiones **7** and 1H-isothiochromene-1-thiones **8***

A sealed tube (10 mL) was charged with a solution of **6** (0.45 mmol) and the Lawesson's reagent (0.182 g, 0.45 mmol) in CH_2Cl_2 (3 mL). The mixture was irradiated under microwave conditions at 300 W and 100 °C for 1 h. After cooling, the reaction mixture was concentrated under reduced pressure and the product purified by MPLC (medium pressure liquid chromatography) using 9:1 cyclohexane/CH_2Cl_2 as eluent. (Z)-

3-Benzylidenebenzo[*c*]thiophene-1(3*H*)-thione (**7a**), red crystals, 103 mg, 90%; (*Z*)-3-Benzylidene-4-methylbenzo[*c*]thiophen-1(3*H*)-thione (**7b**), red crystals, 103 mg, 91%; (*Z*)-3-Benzylidene-6-chlorobenzo[*c*]thiophene-1(3*H*)-thione (**7c**), red crystals, 96 mg, 85%;*(Z)*-3-(4-Methoxybenzylidene)benzo[*c*]thiophene-1(3*H*)-thione (**7d**), amorphous red solid, 6 mg, 5%; *(Z)*-3-(4-Pentylbenzylidene)benzo[*c*]thiophene-1(3*H*)-thione (**7e**), red oil, 78 mg, 70%; *(Z)*-3-(4-Fluorobenzylidene)benzo[*c*]thiophene-1(3*H*)-thione (**7f**), orange solid, 100 mg, 88%; 3-(4-Methoxyphenyl)-1*H*-isothiochromene-1-thione (**8d**), amorphous coral solid**,** 101 mg, 90%; 3-(4-Pentylphenyl)-1H-isothiochromene-1-thione (**3e**), red oil, 22 mg, 20%; 3-Propyl-1*H*-isothiochromene-1-thione (**8g**), red brown oil**,** 100 mg, 86%.

3.4-Characterization of thiophenes (2), 2-iodothiophenes (3), benzo[c]thiophene-1(3H)-thiones (7) and 1*H*-isothiochromene-1-thiones (8).

4-Mercapto-3-methyl-1-phenylpent-1-yn-3-ol (**1a**): mixture of Diastereoisomers A+B, A:B ratio = 2.0, determined by 1H NMR. Yellow oil. IR (film): ν = 3448 (s, br), 2567 (vw), 2230 (vw), 756 (s), 692 (s) cm^{-1}; 1H NMR (300 MHz, $CDCl_3$): δ = 7.47−7.40 [A (m, 2 H) + B (m, 2 H)], 7.37−7.28 [A (m, 3 H) + B (m, 3 H)], 3.37 [B (s, br, 1 H)], 3.29 [A (quintuplet, J = 6.7, 1 H)], 3.01−2.92 [B (m, 1 H)], 2.82 [A (s, br, 1 H)], 1.96 [A (d, J = 6.7, 1 H)], 1.77 [B (d, J = 10.9, 1 H)], 1.65 [B (s, 3 H)], 1.63 [A (s, 3 H)], 1.56 [B (d, J = 6.9, 3 H)], 1.43 [A (dd, J = 6.7, 0.8, 3 H)]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.74, 131.69, 128.5, 128.3, 122.32, 122.28, 91.4, 89.4, 85.0, 84.4, 72.0, 71.3, 48.5, 46.3, 26.8, 25.5, 22.0, 18.5; GC-MS: diastereomer A: m/z = 206 (0.5) [M^+], 145 (100), 43 (72); diastereoisomer B: m/z = 206 (0.6) [M+], 145 (100), 43(81); anal. calcd for $C_{12}H_{14}OS$ (206.30): C, 69.86; H, 6.84; S, 15.64; found C, 69.71; H, 6.85; S, 15.67.

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. Yellow oil. IR (film): ν = 3434 (m, br), 2566 (vw), 2229 (w), 816 (s) cm−1; ^{1}HNMR(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.

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. 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, 4H) + 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.

2-Mercapto-3-methylnon-4-yn-3-ol (**1d**): mixture of diastereomers A+B, A:B ratio = 1.4, determined by ^{1}H NMR. 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.

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. Yellow oil. IR (film): ν = 3439 (m, br), 2559 (vw), 2237 (w), 698 (m) cm^{-1}; ^{1}H 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.

2-Mercapto-3-methyl-6-phenyl-hex-4-yn-3-ol (**1f**): mixture of diastereomers A+B, A:B ratio = 2.0, determined by ^{1}H NMR. Yellow oil. IR (film): ν = 3432 (s, br), 2567 (vw), 2243 (w), 697 (m) cm^{-1}; ^{1}H 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.

2-Mercapto-3,6,6-trimethyl-hept-4-yn-3-ol (**1g**). Mixture of diastereomers A+B, A:B ratio = 1.1, determined by ^{1}H NMR. Yellow oil. IR (film): ν = 3436 (m, br), 2570 (vw), 2220 (w), 915 (m), cm^{-1}; ^{1}HNMR (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 =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

2,3-Dimethyl-5-phenylthiophene (**2a**): yellow amorphous solid, mp = 46−47 °C, 46−47 °C. IR (KBr) ν 2915 (m), 2855 (w), 1598 (w), 1502 (m), 1444 (m), 1172 (w), 755 (s), 699 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.47 (m, 2 H), 7.35−7.26 (m, 2 H), 7.24−7.16 (m, 1 H), 6.99 (s, 1 H), 2.33 (s, 3 H), 2.12 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 134.7, 134.0, 131.4, 128.7, 126.8, 126.0, 125.3, 13.6, 13.1; GC−MS m/z 188 (100) [M^+], 187 (54), 173 (69), 153 (9), 128 (15), 115 (10), 102 (7), 77 (18). Anal. Calcd for $C_{12}H_{12}S$ (188.29): C, 76.55; H, 6.42; S, 17.03. Found: C, 76.60; H, 6.41; S, 16.99.

2,3-Dimethyl-5-p-tolylthiophene (**2b**): yellow amorphous solid, mp = 46−47 °C. IR (KBr) ν 2918 (m), 1516 (m), 1447 (w), 811 (s), 757 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.37 (m, 2 H), 7.16−7.08 (m, 2 H), 6.94 (s, 1 H), 2.33 (s, 3 H), 2.32 (s, 3 H), 2.12 (s, 3 H); 13C 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 m/z 202 (100) [M^+], 201 (54), 171 (5), 153 (5), 141 (4), 128 (6), 115 (6), 101 (5). Anal. Calcd for $C_{13}H_{14}S$ (202.32): C, 77.18; H, 6.97; S, 15.8. Found: C, 77.26; H, 6.95; S, 15.79

5-Cyclohex-1-enyl-2,3-dimethylthiophene (**2c**): yellow oil. IR (film): *ν* = 2957 (m), 2924 (m), 2863 (m), 1562 (w), 1456 (s), 1375 (m), 1167 (w), 1111 (w), 1007 (w), 742 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.60 (s, 1 H), 6.02 (s, 1 H), 2.41-2.28 (m, 1 H), 2.28 (s, 3 H), 2.18-2.08 (m, 1 H), 2.06 (s, 3 H), 1.81-1.54 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.0, 132.9, 131.2, 130.1, 124.2, 122.6, 27.2, 25.6, 22.8, 22.3, 13.6, 13.1; GC-MS: m/z = 192 (100) [M^+], 191 (19), 178 (10), 177 (71), 164 (34), 163 (20), 149 (42), 135 (10), 125 (9), 115 (7), 91 (7), 77 (7); anal. calcd for $C_{12}H_{16}S$ (192.32): C, 74.94; H, 8.39; S, 16.67; found C, 74.91; H, 8.38; S, 16.69.

5-Butyl-2,3-dimethylthiophene (**2d**): yellow oil. IR (film) ν 2961 (s), 2839 (w), 1464 (s), 1147 (w), 828 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44, (s, 1 H, H-4), 2.69 (t, J = 7.7, 2 H), 2.27 (s, 3H), 2.06 (s, 3 H), 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 m/z 168 (26) [M+], 125 (100), 111 (4), 91 (13), 77 (4). Anal. Calcd for $C_{10}H_{16}S$ (168.30): C, 71.36; H, 9.58; S, 19.05. Found: C, 71.40; H, 9.56; S, 19.04.

2,3-Dimethyl-5-phenethylthiophene (**2e**): yellow solid, mp 28-30 °C. IR (KBr): *v* = 2939 (m), 2916 (m), 2855 (m), 1492 (m), 1450 (m), 1151 (w), 1069 (w), 848 (m), 824 (m), 749 (s), 702 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31-7.23 (m, 2 H), 7.22-7.13 (m, 3 H), 6.45 (s, 1 H), 3.05-2.85 (m, 4 H), 2.27 (s, 3 H), 2.05 (s, 3 H); ^{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.

5-Benzyl-2,3-dimethylthiophene (**2f**): yellow solid, mp 38-39 °C. IR (KBr): *v* = 2914 (w), 2854 (w), 1498 (m), 1462 (m), 1442 (w), 1203 (w), 1072 (w), 1029 (w), 831 (m), 754 (s), 687 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40-7.30 (m, 5), 6.45 (s, 1 H, =CH), 4.01 (s, 2 H), 2.25 (s, 3 H), 2.04 (s, 3 H); ^{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

5-tert-Butyl-2,3-dimethylthiophene (**2g**): yellow oil. IR (film): *v* = 2923 (s), 2851 (m), 1642 (m), 1464 (m), 1215 (w), 760 (s) cm^{-1}; ^{1}H 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.

3-Iodo-4,5-dimethyl-2-phenylthiophene (**3a**): yellow oil. IR (film): ν = 1598 (m), 1501 (m), 1441 (m), 1167 (m), 1012 (m), 749 (s), 695 (s) cm^{-1}; $^{1}HNMR$ (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.

3-Iodo-4,5-dimethyl-2-p-tolylthiophene (**3b**): 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

2-Cyclohex-1-enyl-3-iodo-4,5-dimethylthiophene (**3c**): yellow solid, mp = 25−26 °C. IR (KBr): ν = 1435 (s), 758 (s) cm^{-1}; $^{1}HNMR$(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.

2-Butyl-3-iodo-4,5-dimethylthiophene (**3d**): 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); $^{13}CNMR$(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.

3-Iodo-4,5-dimethyl-2-phenethylthiophene (**3e**): 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, 5H), 3.07−2.82 (m, 4 H), 2.36 (s, 3 H), 2.13 (s, 3 H); ^{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.

2-Benzyl-3-iodo-4,5-dimethylthiophene (**3f**): 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.

2-tert-Butyl-3-iodo-4,5-dimethylthiophene (**3g**): yellow solid, mp= 114−115 °C. IR (KBr): ν = 1463 (m), 1363 (m), 1214 (m), 1168 (m), 760 (s) cm^{-1}; ^1H 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.

2-(4-Bromophenyl)-3-iodo-4,5-dimethylthiophene (**3h**): white solid, mp = 104−105 °C. IR (KBr): ν = 1500 (m), 1384 (m), 1072 (s), 1009 (s), 826 (s), 782 (s) cm^{-1}; ^1H 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

2-(2-Phenylethynyl)benzoic acid (**6a**): yellow solid, mp = 126-127 °C. IR (KBr): ν = 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, $CDCl_3$): δ = 11.26 (s, br, 1 H), 8.13 (dd, J = 7.9, S10 1.2, 1 H), 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, $CDCl_3$): δ = 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.

3-Methyl-2-(2-phenylethynyl)benzoic acid (**6b**): white solid, mp = 72-73 °C. IR (KBr): ν =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, $CDCl_3$): δ = 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, $CDCl_3$): δ =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.

5-Chloro-2-(2-phenylethynyl)benzoic acid (**6c**): white solid, mp = 138-139 °C. IR (KBr): *v*= 3083 (m, br), 2218 (w), 1697 (s), 1494 (w), 1475 (w), 1302 (m), 1252 (m), 1107 (m), 835 (w),787 (w), 751 (m), 685 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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.

2-[(4-methoxyphenyl)ethynyl]benzoic acid (**6d**): withe solid, mp: 102 – 104 °C; IR (KBr): ν= 3446 cm^{-1}, 2964, 2844, 2218, 1704, 1685, 1606, 1595, 1566, 1511, 1457, 1444, 1302, 1270, 1249, 1177, 1024, 940, 836, 757; ^1H NMR (DMSO-d6, 300 MHz): δ = 3.80 (s, 3 H), 7.00 (d, J = 8.8, 2 H), 7.42-7.50 (m, 3 H), 7.58 (td, 3H, J = 7.4, 1.4 1 H), 7.63 (dd, J=7.6,1.4, 1 H), 7.88 (d, J= 7.6, 1 H), 13.08 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.2, 87.2, 93.8, 114.3, 114.5, 122.5, 128.0, 129.9, 131.5, 132.8, 132.9, 133.2 , 159.6, 167.1; MS m/z = 253 (17), 252 (100) [M]+, 237 (23), 224 (11), 209 (18), 152 (10), 135 (7); HRMS $C_{16}H_{12}O_3$: calcd. 252.0786, found 252.0764.

2-(1-Pentynyl)benzoic Acid (**6g**):pale yellow needles: IR 2962, 2234, 1692, 757 cm^{-1}; ^1H *δ*=11.4 (1 H, br), 8.06 (1 H, dd, J =7.9, 1.1 Hz), 7.55 (1 H, dd, J =7.7, 1.2 Hz), 7.48 (1 H, td, J = 7.4, 1.5 Hz), 7.35 (1 H, td, J= 7.4, 1.5 Hz), 2.47 (2 H, t, J =7.0 Hz), 1.68 (2 H, sextet, J =7.4 Hz), 1.09 (3 H, t, J=7.4 Hz); ^{13}C δ=171.53, 134.31, 132.34, 131.06, 130.64, 127.27, 124.91, 97.24, 79.00, 21.95, 21.77, 13.50; MS m/z 188 (M^+), 160, 159, 131, 118; HRMS calcd for $C_{12}H_{12}O_2$: 188.0837, found 188.0829.

(Z)-3-Benzylidenebenzo[c]thiophene-1(3H)-thione (**7a**): red crystals; mp 121-123 °C; R_f 0.51 cyclohexane/CH_2Cl_2 (8:2). ^1H NMR (500 MHz, $CDCl_3$) δ = 8.11 (d, *J* = 7.9, 1H), 7.94 (d, *J* = 8.0, 1H), 7.71 (t, *J* = 7.7, 1H), 7.62 (d, *J*=7.7, 2H), 7.53 (s, 1H), 7.50 (d, *J* = 7.8, 1H), 7.46 (t, *J* = 7.6, 2H), 7.38 (t, *J* = 7.4, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 219.54, 143.47,

141.87, 137.06, 135.49, 132.81, 130.05, 129.37, 129.28, 129.12, 128.85, 124.16, 123.09, 120.61. HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{15}H_{11}S_2$: 255.0302; found 255.0299.

(Z)-3-Benzylidene-4-methylbenzo[c]thiophen-1(3H)-thione (**7b**): red crystals; mp 107-109 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.06 (d, *J* = 7.9, 1H), 7.69 (s, 1H), 7.58 (d, *J* = 7.7, 2H), 7.52 (d, *J* = 7.3, 1H), 7.45 (t, *J* = 7.6, 2H), 7.41 – 7.33 (m, 2H), 2.84 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 220.00, 143.38, 140.00, 139.89, 136.57, 136.50, 134.45, 129.91, 129.09, 128.96, 128.56, 128.12, 122.81, 23.19. HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{16}H_{13}S_2$: 269.0459; found: 269.0456.

(Z)-3-Benzylidene-6-chlorobenzo[c]thiophene-1(3H)-thione (**7c**): red crystals; mp 186-188 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.05 (d, *J* = 1.6, 1H), 7.87 (d, *J* = 8.5, 2H), 7.65 (dd, *J* = 8.5, 1.6, 2H), 7.60 (d, *J* = 7.8, 3H), 7.49 (s, 2H), 7.48 – 7.44 (m, 3H), 7.39 (t, *J* = 7.2, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 217.36, 142.72, 141.63, 136.17, 136.04, 135.25, 132.66, 130.05, 129.37, 123.77, 123.71, 121.71. HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{15}H_{10}ClS_2$: 288.9912; found: 288.9903.

(Z)-3-(4-Methoxybenzylidene)benzo[c]thiophene-1(3H)-thione (**7d**): amorphous red solid; mp 135-137 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.11 (d, *J*=7.9, 1H), 7.92 (d, *J*=8.0, 1H), 7.69 (ddd, *J*=8.1, 7.2, 1.2, 1H), 7.58 (d, *J*=8.8, 2H), 7.51 – 7.46 (m, 2H), 6.99 (d, *J*=8.8, 2H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 219.08, 160.50, 143.83, 1.41.77, 134.54, 132.69, 131.83, 128.89, 128.22, 124.19, 123.16, 120.42, 114.85, 55.56. HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{16}H_{13}OS_2$: 285.0408; found: 285.0404

(Z)-3-(4-Pentylbenzylidene)benzo[c]thiophene-1(3H)-thione (**7e**): red oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.11 (ddd, *J* = 7.9, 1.0, 0.6, 1H), 7.93 (d, *J* = 8.1, 1H), 7.69 (ddd, *J* = 8.1, 7.2, 1.2, 1H), 7.54 (d, *J* = 8.1, 2H), 7.51 (s, 1H), 7.50 – 7.47 (m, 1H), 7.27 (d, *J* = 8.3, 2H), 2.72 – 2.58 (m, 3H), 1.70 – 1.60 (m, 3H), 1.38 – 1.32 (m, 4H), 0.91 (t, *J*=7.0, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 219.41, 144.68, 143.66, 141.83, 135.93, 132.90, 132.73, 130.15, 129.43, 129.12, 124.14, 123.35, 120.54, 35.98, 31.64, 31.01, 22.68, 14.17. HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{20}H_{21}S_2$: 325.1085; found: 325.1081

(Z)-3-(4-Fluorobenzylidene)benzo[c]thiophene-1(3H)-thione (**7f**): orange solid; mp 147-149 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.10 (d, *J* = 7.9, 1H), 7.91 (d, *J* = 8.1, 2H), 7.70 (t, *J* = 7.8, 1H), 7.59 (dd, *J* = 8.5, 5.4, 2H), 7.54 – 7.49 (m, 1H), 7.47 (s, 1H), 7.15 (t, *J* = 8.6, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 219.15, 163.94, 162.96 (d, *J* = 258.7), 143.38, 141.83, 136.78 (d, *J* = 2.5), 135.32, 132.86, 131.83 (d, *J* = 8.5), 129.41, 124.17 (d, *J* = 6.2), 121.73 (d, *J* = 8.2), 120.53, 116.55 (d, *J* = 21.2). HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{15}H_{10}FS_2$: 273.0208; found: 273.0205.

3-(4-Methoxyphenyl)-1H-isothiochromene-1-thione (**8d**): amorphous coral solid; mp 128-130 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.90 – 8.85 (m, 1H), 7.76 – 7.71 (m, 1H), 7.63 – 7.60 (m, 1H), 7.58 (d, *J* = 8.5, 2H), 7.56 – 7.53 (m, 1H), 7.52 (s, 1H), 7.00 (d, *J* = 8.9, 2H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 212.03, 161.16, 144.72, 135.36, 134.33, 133.93, 131.13, 129.37, 128.03, 121.85, 114.83, 55.58. HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{16}H_{13}OS_2$: 285.0408; found: 285.0401.

3-(4-Pentylphenyl)-1H-isothiochromene-1-thione (**8e**): red oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.90 – 8.86 (m, 1H), 7.74 (ddd, *J* = 8.2, 7.1, 1.3, 1H), 7.65 – 7.61 (m, 1H), 7.60 – 7.55 (m, 4H), 7.54 (s, 1H), 7.29 (d, *J* = 8.3, 2H), 2.68 – 2.63 (m, 2H), 1.70 – 1.61 (m, 2H), 1.39 – 1.31 (m, 4H), 0.91 (t, *J* = 7.0, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 212.10, 145.36, 145.00, 135.48, 134.31, 133.76, 132.96, 131.22, 129.51, 128.03, 126.56, 122.44, 35.84, 31.61, 31.10, 22.67, 14.16. HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{20}H_{21}S_2$: 325.1085; found: 325.1079.

3-Propyl-1H-isothiochromene-1-thione (**8g**): red brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.85 (d, *J* = 8.3, 1H), 7.71 (t, *J* = 7.4, 1H), 7.57 – 7.44 (m, 2H), 7.19 (s, 1H), 2.59 (t, *J* = 7.5, 2H), 1.77 – 1.69 (m, 2H), 1.00 (t, *J* = 7.3, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 212.53, 147.11, 135.51, 134.21, 133.53, 130.46, 129.09, 127.96, 123.23, 37.59, 23.23, 13.57. HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}S_2$: 221.0459; found: 221.0456

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Chapter 4

Imidazolidin-2-ones from Carbon Dioxide and Amines by Guanidine Catalysis under Solvent-Free Conditions

4.1 General Importance of Imidazolidin-2-ones

Imidazolidin-2-one is an ubiquitous structural motif found in a plethora of heterocyclic compounds that display a wide range of biological activities (Figure 4.1). [1]

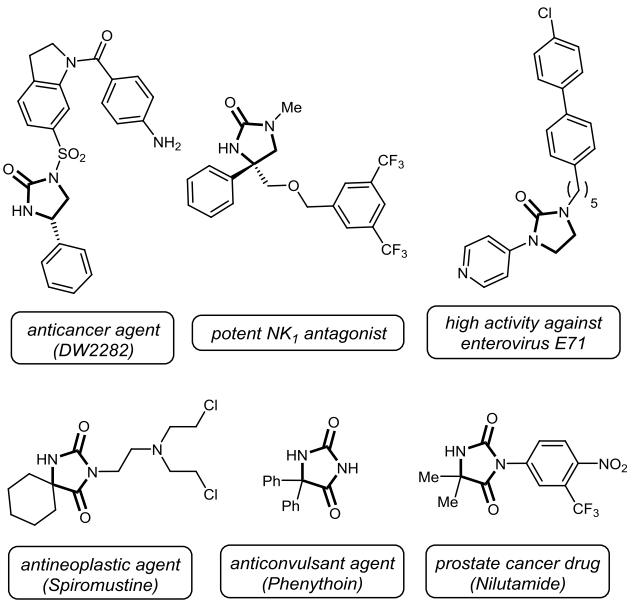
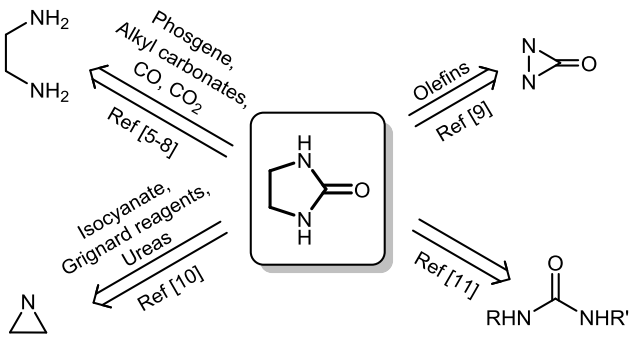


Figure 4.1. Selected bioactive imidazolidin-2-ones (up) and hydantoins (down).

Substituted imidazolidin-2-ones are also chiral auxiliaries in asymmetric synthesis[2] and valuable intermediates for organic chemists,[3] allowing, for instance, a facile access to hydantoins.[4] The most common approach to imidazolidin-2-ones consists in the carbonylation of diamines with phosgene,[5] carbon monoxide,[6] dialkyl carbonate,[7] or carbon dioxide[8]. Alternative methodologies involve metal-catalyzed diamination of olefins[9], aziridine ring expansion[10] or cyclization of preformed urea derivatives[11] (Scheme 1). Among these, processes exploiting the inexpensive, abundant, non-flammable and nontoxic CO_2 as carbonylating agent represent an attractive route to cyclic ureas from the environmental point of view.[8] In this context, Munoz et al. reported the formation of cyclic ureas under mild conditions with a stoichiometric amount of DPPA as phosphorylating agent[8b]. However, the co-production of salts and a stoichiometric amount of phosphine oxide induced to develop efficient catalysts for the reaction between diamines and CO_2, that, without any suitable additive, requires quite harsh conditions (>150 °C, >6 MPa).[8c,d]



Scheme 4.1. Conventional strategies to imidazolidin-2-one derivatives

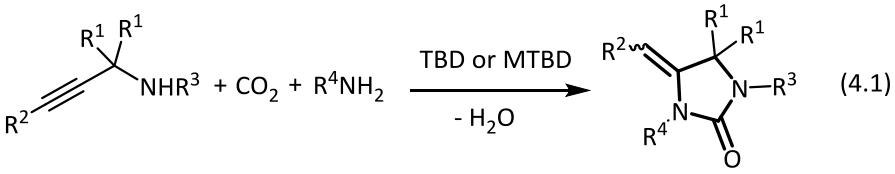
Polyethylene-glycol supported potassium hydroxide (KOH/PEG1000)[8e] is an efficient heterogeneous catalyst at 8 MPa CO_2 pressure and 150 °C, while CeO_2 was found to be active at 160 °C and lower pressure (0.5 MPa) but 20 mol% of catalyst was needed.[8f] Ph_3SbO/P_4S_{10}[8g] catalyzed the synthesis of imidazolidinones at lower temperatures (80-150 °C) and 4.9 MPa, however only dialkylamines were employed. Aromatic *ortho*-diamines led to the synthesis of benzimidazolones in the presence of $TBA_2[WO_4]$ as catalyst [8h] at 140 °C and with atmospheric pressure of CO_2, or by means of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU)-based ionic liquid at 120 °C and 9 MPa CO_2 pressure under solvent free conditions.[8j] Generally, harsh conditions or a very narrow reaction scope are the main drawbacks of these methodologies.

In the last decades, guanidines (Fig. 4.2) are regarded as an important class of organic superbases able to catalyze various types of base-mediated organic reactions.[12] In particular, bicyclic guanidines (Fig. 4.2), featuring a rigid framework and unique electronic and chemical properties, have shown to be active catalysts in CO_2 chemical fixation.[12]

These organosuperbases have displayed high efficiency in the formation of oxazolidinones from secondary propargylamines and CO_2.[13] Moreover, in the course of research on new methodologies for CO_2 activation,[14] I has recently demonstrated that bicyclic guanidines, such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), act as organocatalysts for the synthesis of

cyclic carbonates and, in the presence of primary amines, carbamates by carboxylation of propargyl alcohols with carbon dioxide as reagent and solvent.[14a]

In the last part of PhD work is reported a new one-pot synthesis of 5-methyleneimidazolidin-2-ones based on the use of bicyclic guanidines as catalysts, starting from propargylamines, primary amines and CO_2 under solvent-free and mild conditions (Eq. 4.1). To the best of my knowledge, this one-pot transformation has not been previously reported, and represent a further advancement in the direction of carbon dioxide conversion into high value added organic compounds.[15]

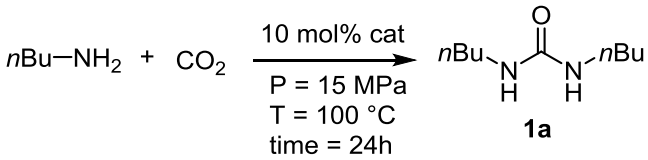


(4.1)

4.2 Reaction of Alkylamines with CO_2 in the Presence of Organic Superbases

The first investigations were focused to test the activity of several organic superbases in the formation of simmetric ureas from alkylamines and CO_2.

In the model reaction, *n*-butylamine reacted with CO_2 in the presence of 10 mol% of catalyst (Fig. 4.2) under solvent-free conditions (Eq. 4.2) .



(4.2)

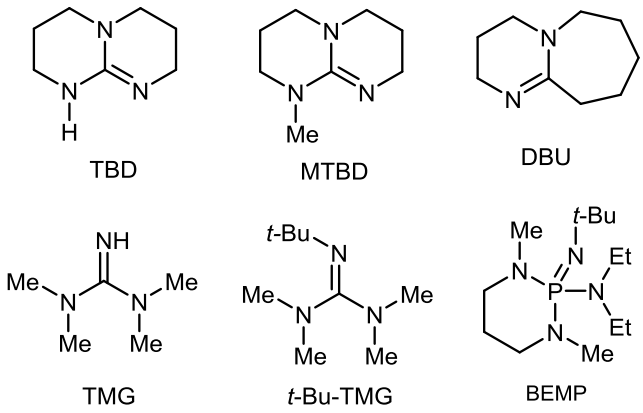


Figure 4.2. Organocatalyst-Guanidines and bicyclic guanidine

The mixture was kept at 100 °C under stirring for 24h and the results are reported in Table 4.1.

Table 4.1. Organocatalyzed-synthesis of **1a** from *n*-butylamine and CO_2.[a]

Entry	cat	pK_a[b]	Solvent	Yield [%][c]
1	TBD	26.03	-	63
2	MTBD	25.49	-	53
3	DBU	24.34	-	24
4	TMG	23.30	-	8
5	*t*-Bu-TMG	n.d.[d]	-	19
6	BEMP	27.58	-	37
7	TBD		MeCN (1 mL)	64
8	TBD		MeCN (2 mL)	67
9	TBD		MeCN (4 mL)	69

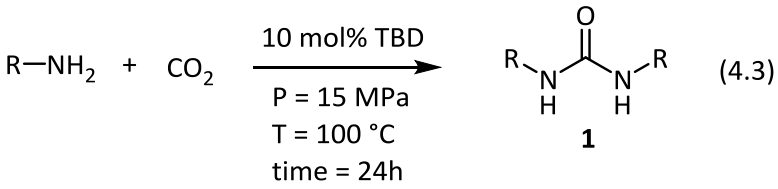
[a] Reaction conditions: stainless-steel autoclave (125 mL capacity) was charged with *n*-butylamine (5 mmol), CO_2 (15 MPa at 100 °C), cat (10 mol%), 24h. [b] pKa is referred to its conjugate acid in MeCN.[12] [c] Yield of **1a** was determined via ^{1}H NMR analysis. [d] Not determined, but a value between 23.5 and 24.5 could be assigned.[13] [e] A small amount of *N*-butylacetamide (<5%), obtained by hydrolysis of MeCN and subsequent transamidation, was detected by GC-MS analysis

Among the tested superbases, TBD and MTBD gave the best yields with selectivity above 98% (Table 4.1, entries 1 and 2). Under these conditions the other catalysts were less effective, suggesting that only strong bases having pK_a (MeCN) in the range 25-27 afford satisfactory yields. The basicity,[12e] however, is not the only factor influencing the reaction described here. It becomes evident with the use of a phosphazene base, such as BEMP ($pK_a^{(MeCN)}$>27), which did not bring forward any improvement in comparison with bicyclic guanidines. The course of the reaction turns out to be influenced not only by basicity but also by other structural effects likely due to steric hindrance and hydrogen bridges.

In this case, the catalytic performance of TBD at 100 °C is modest (63% yield) but remarkable, since almost all existing catalytic systems give, without dehydrating agents, comparable results at higher reaction temperatures (>140 °C).[8,16] Noteworthy, the addition of organic aprotic polar solvents was similarly negative. Only MeCN in small amount, produced slightly better results (Table 4.1, entries 7-9). This is probably

ascribable to its reaction with water,[16a] whose removal from the equilibrium promotes the urea formation.

We then explored the generality of this protocol testing other primary amines (Table 4.2). Apparently, under the employed reaction conditions, only linear alkylamines, such as n-hexylamine and n-octylamine, gave satisfactory results (Table 4.2, entries 1-3). A more hindered saturated amine, such as cyclohexyl amine, led to poor yield of the corresponding urea (Table 4.2, entry 4). Unsaturated or less nucleophilic amines did not react at all (Table 4.2, entries 5-7).



(4.3)

Table 4.2. Scope and limitations for the TBD-catalyzed synthesis of symmetric ureas **1** from RNH_2 and CO_2.[a]

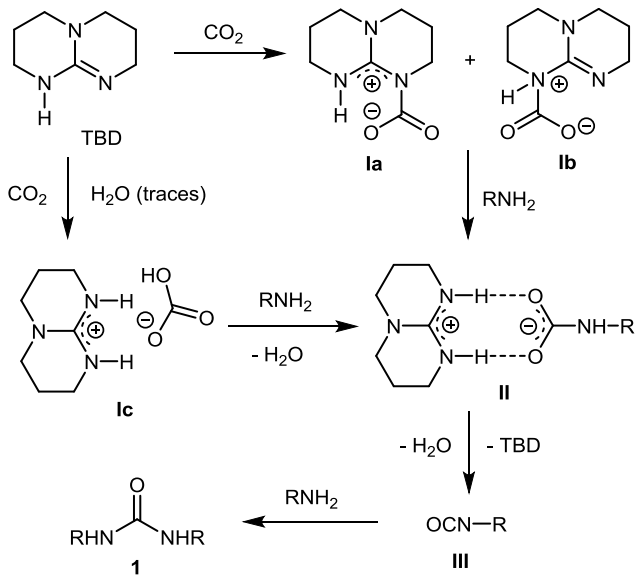
Entry	R	Yield [%][b]
1	*n*-Butyl	**1a**, 63
2	*n*-Hexyl	**1b**, 65
3	*n*-Octyl	**1c**, 57
4	Cyclohexyl	**1d**, 12
5	Allyl	-
6	Benzyl	-
7	Phenyl	-

[a] Reaction conditions: stainless-steel autoclave (125 mL capacity) was charged with RNH_2 (5 mmol), liquid CO_2 (15 MPa at 100 °C), TBD (0.5 mmol), 24h. [b] Determined via ^1H NMR analysis.

Referring to known data and the above described results we can propose a plausible mechanism involving bicyclic guanidines as catalysts (Schemes 4.2).

Three species (**Ia**-**c**) resulting from TBD-CO_2 system have been postulated on the basis of NMR experiments and TGA-FTIR analyses (Scheme 4.2).[17] In particular **Ia** has been synthesized and characterized by working under strictly anhydrous conditions.[12f] Traces of water can favor bicarbonate-guanidinium salt **Ic** over the zwitterionic adducts **Ia** and **Ib**. In all cases, reversibility of intermediates **Ia**-**c**[17] allows the primary amine to attack the electrophilic carbon of CO_2 generating carbamate **II**. Stable hydrogen

bridges, shown in the solid state by X-ray analysis for acetate or trifluoroacetate/TBDH salts,[18] can be reasonably assumed even for the carbamate-guanidinium ionic pairs **II**. Furthermore, a similar intermediate have been quantitatively isolated from propargylamine, TBD and CO_2 at room temperature by He and co-workers.[12d] Then, elimination of water from **II** leads to the formation of isocyanate **III**, which readily react with another amine providing urea **1**. Isocyanate **III** was not detected in our experiments, however, according to literature[8c,h,j] its formation *in situ* seems to be reasonable and the rate determining step at the same time.



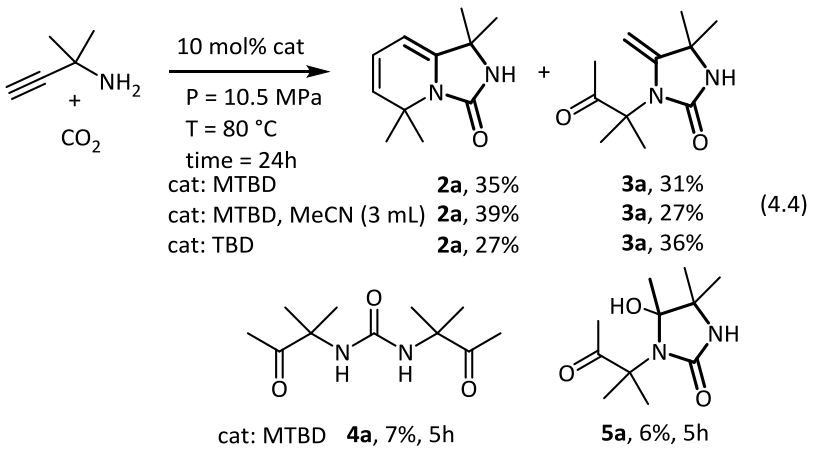
Scheme 4.2. Proposed mechanism for bicyclic guanidine-catalyzed urea formation.

4.3 Reaction of Primary Propargyl Amines with CO2 in the Presence of Bicyclic Guanidines

An unexpected behaviour was displayed by primary propargyl amines (Scheme 4). 2-Methyl-3-butyn-2-amine, 1-ethynylcyclohexan-1-amine and 2-propynamine readily reacted with CO_2 under lower reaction temperatures compared to aliphatic amines. Unlike secondary propargyl amines that under similar conditions afforded smoothly oxazolidinones,[13] primary propargyl amines led mainly to urea derivatives.

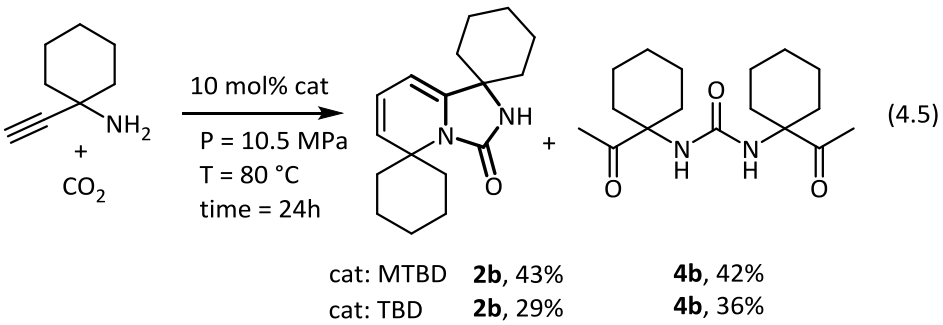
In particular starting from 2-methyl-3-butyn-2-amine and MTBD as catalyst, compounds **2a** and **3a** were isolated in almost equimolar amount (35 and 31%

respectively, Eq. 4.4). Both products arise from two molecules of propargyl amine and one of CO_2. At lower reaction time intermediate **4a** and **5a** were also detected in significant amount (7 and 6% respectively after 5h). The dimeric adduct 2,3,3,5,6,6-hexamethyl-3,6-dihydropyrazine resulted as a by-product (<5%) from the condensation of two molecules of hydrated 1,1-dimethylpropargylamines.[19] As expected, the addition of MeCN (3 mL) to the reaction with 2-methyl-3-butyn-2-amine increased to some extent the yield of **2a** (39%) and reduced those of **3a** (27%).



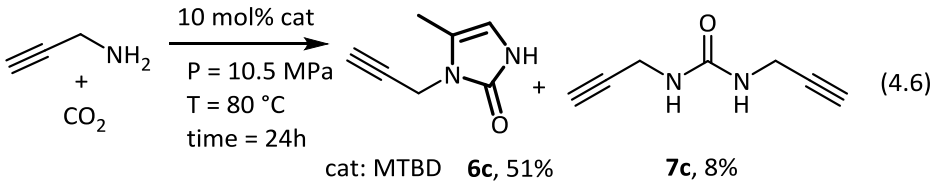
(4.4)

Compound **2b**, analogous of **2a**, was obtained in 43% yield together with symmetric urea **4b** bearing two carbonyl groups (42%) starting from the more hindered 1-ethynylcyclohexan-1-amine (Eq. 4.5).



(4.5)

Imidazolidinone **6c** (51%) and dipropargyl urea **7c** (8% yield) were obtained under the same conditions from 2-propynamine (Eq. 4.6).



Notably, the addition of water to triple bonds occurs easily under our reaction protocol without metals.[20] We verified experimentally that hydration of both the triple bonds of dipropargyl urea leading to **4a** and **4b** was promoted by TBD and MTBD only in the presence of CO_2 likely through the action of guanidinium bicarbonate species.[21] On the contrary, urea **7c** and imidazolidinone **6c**, probably due to theirs steric configuration were not involved in water addition. An analogous behavior was noticed in the reactions of propargyl alcohols with CO_2 under similar conditions in the presence of TBD and MTBD.[14a]

All compounds have been fully characterized and structures of **2b**, **4b** and intermediate **5a** were also confirmed by X-ray crystallography (Fig. 4.3).

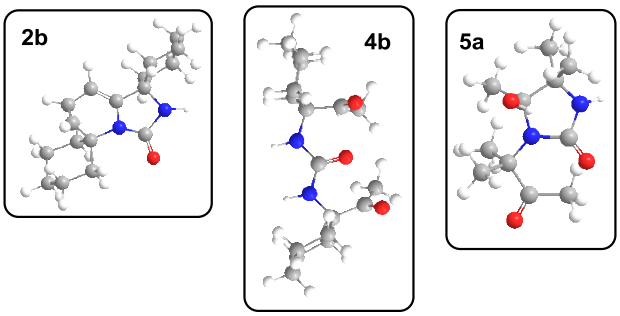
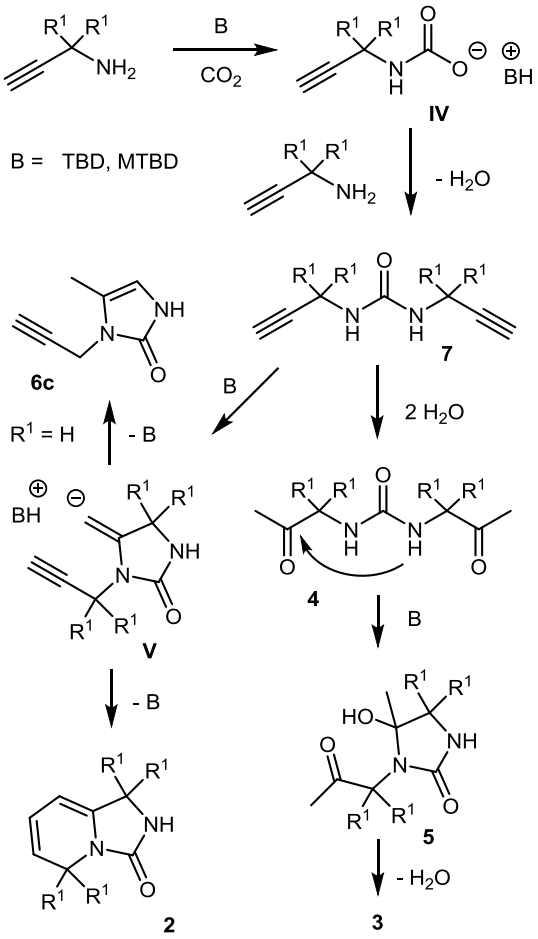


Figure 4.3. X-Ray structures for compounds **2b**, **4b** and **5a**.

Proposed reaction pathways for their formation are presented in Scheme 4.3.

According to Scheme 4.2, the catalytic cycle should start with the fast formation of intermediate **IV** (analogous to **II** in Scheme 4.2), which can evolve, likely *via* isocyanate, towards urea **7** by H_2O elimination. Then, acetylenic urea **7** can lead to compound **2** by a sequential double cyclization process. Firstly an NH group attacks the triple bond on the internal carbon with formation of the intermediate **V**. The latter undergoes a further annulation step by nucleophilic attack of the carbanion to the near triple bond without any mediation of metals, providing compound **2**. The other isolated

intermediate **4** can be generated from acetylenic urea **7** by addition of H_2O. The fast intramolecular nucleophilic attack of NH to the carbonyl group of **4** affords intermediate **5** which, after elimination of H_2O, leads to product **3**. Finally, when R^1 is H, compound **6c** can be obtained from **V** by neutralization and isomerization steps.



Scheme 4.3. Proposed reaction pathways for the formation of compounds **2**, **3** and **4**.

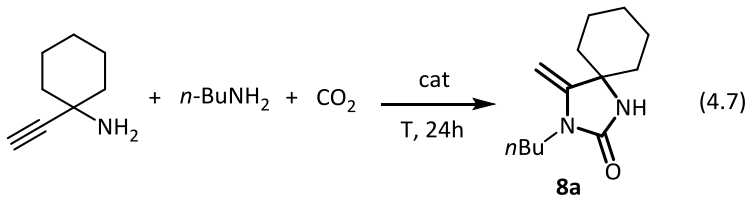
Clearly, the limited selectivity and generality of these reactions prevent any meaningful synthetic application at present stage, however, based on these singular structures, some considerations can be done.

Concerning the urea formation, the reported findings show a higher activity of primary propargylamines in comparison with saturated alkylamines, which are often totally unreactive at 100 °C. Moreover, taking into account the proposed pathways, an alkylamine in the reaction mixture, would compete with the second molecule of propargylamine for the formation of a non-symmetric urea (Scheme 4.4). The

subsequent annulation step would provide an imidazolidinone scaffold incorporating two different amines. This new transformation should benefit from improved reaction scope and selectivity as well, thanks to the considerable different reactivity between acetylenic and not acetylenic amines.

4.4 The Propargyl Amines/Primary Amines/CO_2 system under TBD/MTBD Catalysis: A New Route to Imidazolidinones

To verify our hypothesis we initially caused to react 1-ethynylcyclohexan-1-amine with *n*-butylamine and CO_2 in the presence of 10 mol% of TBD at 80 °C without any organic solvent (Table 4.3, entry 1, Eq. 4.7). We were pleased to find that, under these conditions, the desired imidazolidinone **8a** was obtained with an encouraging 22% yield (calculated by ^{1}H NMR analysis on the reaction crude) together with compounds **2b** and **4b** which were formed in 12 and 11% yield, respectively.



(4.7)

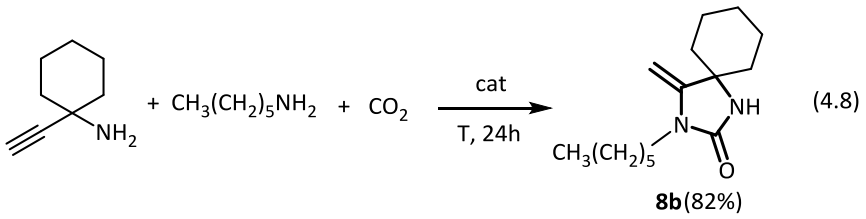
Table 4.3. Organocatalyzed-synthesis of 8a from 1-ethynylcyclohexan-1-amine, *n*-butylamine and CO_2.[a]

Entry	cat	*n*-$BuNH_2$ (equiv)	P CO_2 (MPa)	T (°C)	Conv[b] (%)	Yield[c] (%) **8a**
1	TBD	1	5	80	61	22
2	TBD	1	7	100	82	31
3	TBD	2	7	100	90	42
4	**TBD**	**4**	**7**	**100**	**99**	**88**
5	TBD[d]	4	7	100	72	56
6	-	4	7	100	50	23
7	MTBD	4	7	100	74	43
8	DBU	4	7	100	69	49
9	TBD	4	3	100	83	65
10	TBD	4	10	100	85	70

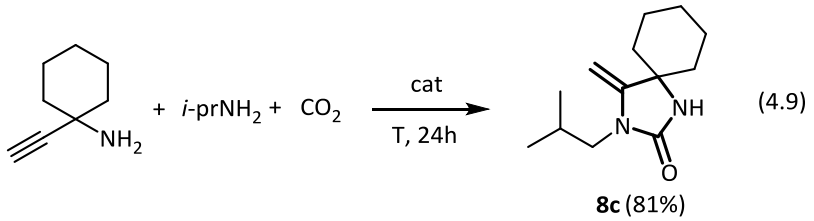
[a] Reaction conditions: 1-ethynylcyclohexan-1-amine (2 mmol), *n*-butylamine, CO_2, cat (10 mol%), 45 ml autoclave, 24h. [b] Conversion of 1-ethynylcyclohexan-1-amine was determined by GC analysis. [c] Yield of **8a** was determined via ^{1}H NMR analysis (internal standard method). [d] 5 mol%.

A higher temperature (100 °C) was beneficial for conversion but marginal for yield (Table 4.3, entry 2). Selectivity toward **8a** improved when a twofold amount of *n*-butylamine was employed (Table 4.3, entry 3). A further excess of alkylamine (4 equiv) led to 88% yield of imidazolidinone (Table 4.3, entry 4). Interestingly, under these reaction conditions formation of urea **1a** was limited (only a 2% of the starting *n*-butylamine gave the corresponding symmetric urea **1a**). The reaction still proceeded with 5% of TBD (56%, Table 4.3, entry 5), and even in the absence of organocatalyst a 23% yield of the desired cyclic urea was obtained (Table 4.3, entry 6). MTBD, which gave comparable results for the synthesis of ureas **1**, was here less effective (43%, Table 4.3, entry 7) while DBU, often used as CO_2 activator,[8j,13,22] afforded **8a** with 49% yield at 69% conversion of propargylamine **1a** (Table 4.3, entry 8). The pressure of CO_2 seems to be crucial for the formation of imidazolidinone **8a**, being 7 MPa the best compromise (Table 4.3, entry 4, 9-10).

With the optimized conditions in hand (Table 4.3, entry 4), the scope of this three-component cyclization was demonstrated with a series of primary amines using TBD as the best catalyst (Table 4.4). High yields of isoxazolidin-2ones **8a**-**c** were obtained by the reaction of 1-ethynylcyclohexan-1-amine with CO_2 and simple alkylamines, such as *n*-butyl, *n*-hexyl or *i*-butyl amines.



8b (82%) (4.8)

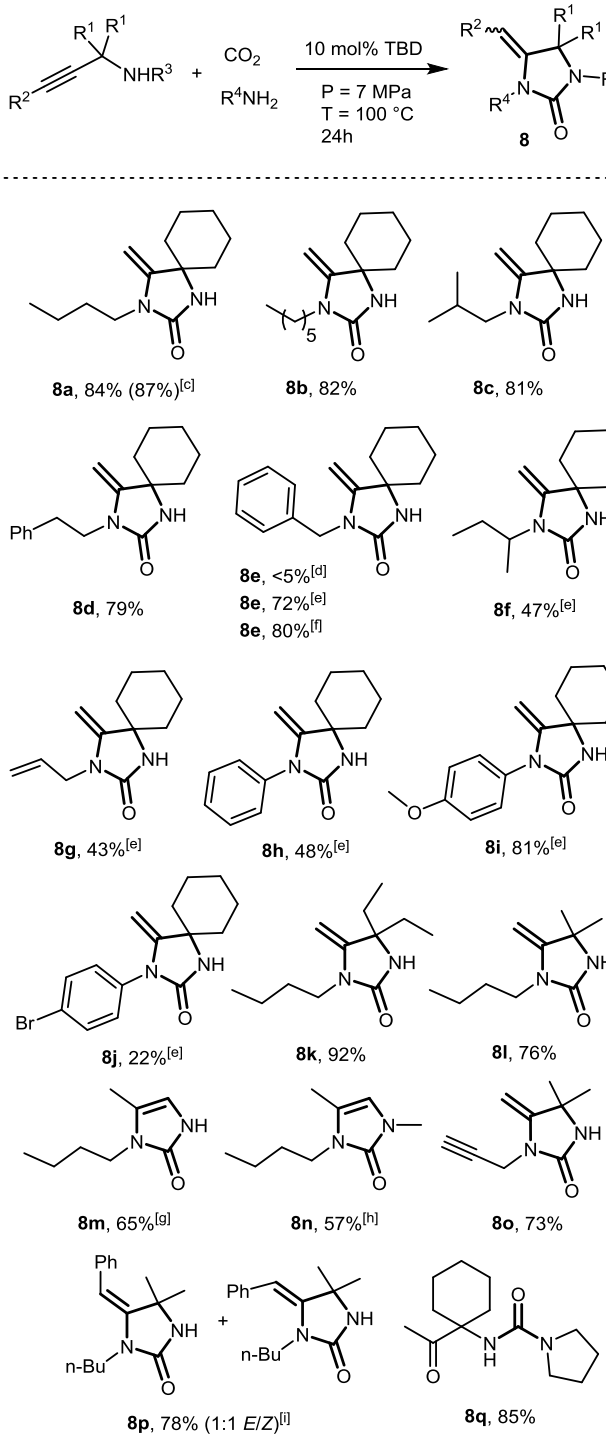


8c (81%) (4.9)

Remarkably, the yield of **8a** was not affected when the reaction was performed on gram-scale (87%). The presence of a phenyl ring on C-2 of the alkylamine did not

significantly influence the reaction outcome, being cyclic urea **8d** isolated with 79% yield.

Table 4.4 Scope of the TBD-catalyzed synthesis of imidazolidinones **8** from propargyl amines, primary amines and CO_2.[a,b]



[a] Reaction conditions: propargylamine (2 mmol), R^4NH_2 (8 mmol), CO_2 (7 MPa), TBD (10 mol%), 45 ml autoclave, 100 °C, 24h. [b] Isolated yield. [c] Gram-scale reaction (see SI for details) [d] Conversion of propargylamine was less than 10%. [e] 120 °C. [f] MTBD (10 mol%) at 120 °C. [g] 80 °C. [h] A 30% yield of 3-methyl-5-methyleneoxazolidin-2-one was also obtained. [i] determined by ^{1}H NMR.

Surprisingly, when a phenyl was placed on C-1, as in benzylamine, the yield of the corresponding product **8e** was less than 5%. A good yield of the desired product was obtained at 120 °C (72%) and an even better result was achieved using MTBD in place of TBD (80%). This singular behavior could be ascribed to the higher stability of the carbamate intermediate arising from benzylamine.

A more hindered primary amine, such as *s*-butylamine, gave only 47% yield of the corresponding cyclic urea **8f**. Also in this case, a temperature of 120 °C was required. An unsaturated amine, such as allylamine, led to the corresponding cyclic urea **8g** in moderate 43% yield at 120 °C. Notably, aniline, despite its quite low nucleophilicity, afforded imidazolidinone **8h** in satisfactory yield. The electronic properties strongly affected the reaction output since 4-OMe-aniline, having an electronically rich aromatic ring, gave **8i** with an excellent 81% yield while a worse performance was reached using 4-Br-aniline (**8j**, 22%).

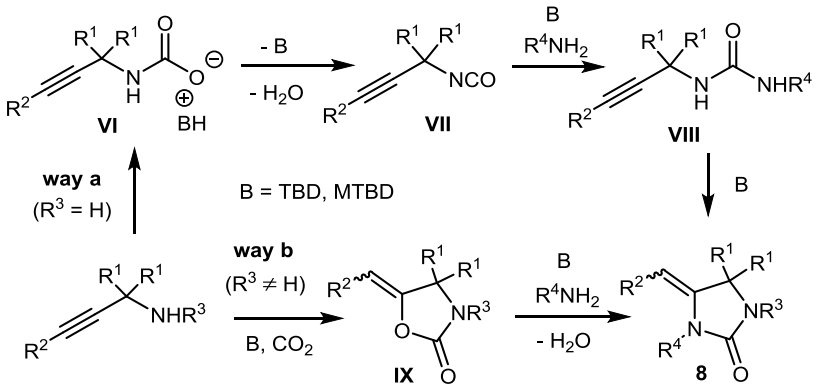
The scope of different primary propargylamines with *n*-$BuNH_2$ was then explored (Table 4.4). Under our reaction protocol, 3-ethylpent-1-yn-3-amine readily reacted with CO_2 and *n*-$BuNH_2$ providing the urea derivative **8k** in excellent yield (92%), while the less hindered 2-methylbut-3-yn-2-amine furnished the corresponding imidazolidinone in slightly lower yield (**8l**, 76%). Simple unsubstituted propargylamine generated compound **8m**, displaying the most stable endocyclic double bond, in 65% yield at 80 °C. The reaction also worked well with 2-methyl-4-phenylbut-3-yn-2-amine, bearing an internal triple bond, which, under the usual conditions, was successfully converted into imidazolidinone **8p** as a *ca.* 1:1 mixture of *E/Z* diastereoisomers (78% total yield). We also tested the reactivity of secondary propargylamines.

It is well-known that secondary propargylamines show a strong tendency to give the corresponding oxazolidin-2-ones by reaction with CO_2.[12d,23] Using this protocol, a 57% yield of cyclic urea **8n** was obtained starting from *N*-methylprop-2-yn-1-amine and *n*-$BuNH_2$.

Unfortunately, other secondary propargylamines afforded only oxazolidinone derivatives, confining the applicability of this protocol mostly to primary ones. The combination of two different propargylamines, that are 2-methylbut-3-yn-2-amine and

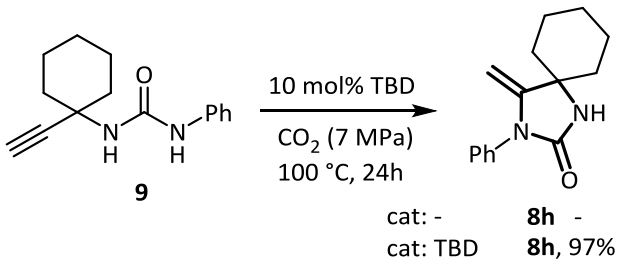
prop-2-yn-1-amine led to the selective formation of **8o** in 73% yield. Finally, by reacting an acetylenic amine with a secondary amine, such as pyrrolidine, the linear ketourea **8q** was obtained in high yield (85%). In general, all reactions showed good to excellent selectivity with respect to the primary amine (R^4NH_2), which can be successfully recovered at the end of the reaction and recycled.

The possible formation pathways for compound **8** are presented in Scheme 4.5.



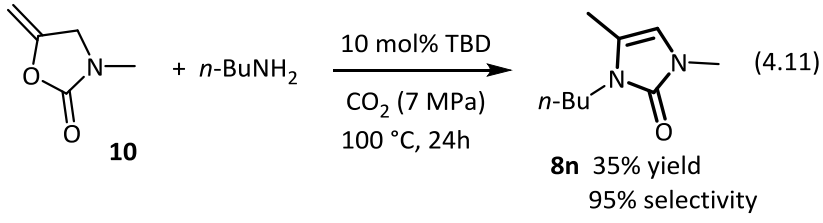
Scheme 4.4. Proposed reaction pathways to compounds **8**.

The more reactive propargylamine forms with CO_2 and the bicyclic guanidine a carbamate intermediate **VI** which undergoes *in situ* dehydration to isocyanate **VII**.[8c,h,j] Then, the excess of primary amine (R^4NH_2) drives the selectivity towards acyclic urea **VIII** and a fast cyclization step affords product **8** (Scheme 4.4, way *a*). For the above mentioned reasons, formation of carbamate **VI** and isocyanate **VII** appears reasonable and the active role of the base can be highly plausible in both the urea **VIII** formation[12g] and the following cyclization step[11]. In addition, the non-symmetric urea **9**, analogous to **VIII**, was synthesized independently, and, under our reaction conditions, it afforded imidazolidinone **8h** in almost quantitative yield (Eq. 4.10).



(4.10)

The alternative way *b*, involving the initial formation of oxazolidinone **IX** (from the reaction of propargylamine and CO_2), followed by amination, seems less plausible for primary propargylamines (Scheme 4.5, way *b*). In fact, we have never detect oxazolidinones starting from primary propargyl amines, while linear urea species were frequently found under our reaction conditions. Moreover, Shi and coworkers reported the formation of oxazolidinones from primary α-substituted propargylamines and CO_2 at room temperature and under palladium catalysis,[16f] but they essentially failed when they tried to convert cyclic carbamates into the corresponding ureas by reaction with a primary amine. On the other hand, secondary propargylamines cannot provide urea derivatives according to way *a* (isocyanate) and way *b* in this case is definitely more probable, also in view of their propensity to give oxazolidinones by reaction with CO_2 under various reaction conditions.[12d,23] In our case, *N*-methylprop-2-yn-1-amine was the only tested secondary propargylamine able to provide an imidazolidinone. Together with **8n**, 3-methyl-5-methyleneoxazolidin-2-one **10** was isolated in 30% yield, supporting our rationale. Moreover, compound **10**, in the presence of *n*-$BuNH_2$ and under the optimized reaction conditions, was partially transformed into imidazolidinone **8n** (35% yield) with high selectivity (Eq 4.11). All these experimental data suggest that primary and secondary propargylamines may follow different pathways: way *a* seems to be more plausible for primary propargylamines, while way *b*, when is feasible, can be the preferred route for secondary ones.



(4.11)

4.5 Conclusions

In summary, the synthesis of linear and cyclic ureas from carbon dioxide and various amine derivatives under bicyclic guanidine catalysis has been investigate. In particular, we have disclosed a new and general bicyclic guanidine-catalyzed synthesis of 5-methyleneimidazolidin-2-ones by reaction of propargylamines, primary amines and CO_2. The main features of this methodology include (i) a metal-free, ligand-free, VOCs-free and isocyanate-free protocol for the synthesis of imidazolidinone core, (ii) an easily scalable and highly atom economical process, (iii) the formation of imidazolidinone ring under mild reaction temperatures (80-120 °C), (iv) proposed reaction pathways based on experimental tests and isolated intermediates, and (v) a further advancement in the direction of carbon dioxide utilization for the synthesis of high-value chemicals.

4.6 Experimental Section

4.6.1 Experimental Procedure for preparation of Imidazolidinones

*Typical Experimental Procedure for the Catalytic Synthesis of Symmetric Urea **1***

An oven dried 125-mL stainless-steel autoclave was charged with the amine (5.0 mmol), the catalyst and the solvent (when requested). The autoclave was sealed, purged at room temperature three times with CO_2 with stirring (10 bar), and eventually charged with liquid CO_2 (14-44g) at room temperature (by weighing it before and after the pressurization). After stirring of the mixture at 80-120 °C for 24 h, the autoclave was cooled, degassed and opened. The reaction crude was recovered using CH_2Cl_2 or EtOAc and the resulting organic solution was analyzed by GC, GC-MS and 1H NMR using methylbenzoate as internal standard. Recrystallization of the residue from diethyl ether/petroleum ether (1:1) gave pure symmetric ureas **1**. 1,3-Dibutylurea (**1a**), white solid, 0.499 g, 58%; 1,3-Dihexylurea (**1b**): colorless crystals,; 1,3-Dioctylurea (**1c**): white solid,; 1,3-Dicyclohexylurea (**1d**): white solid,;

*Typical Experimental Procedure for the Catalytic Synthesis of Compounds **2, 3, 4, 5** and **7***

An oven dried 125-mL stainless-steel autoclave was charged with the propargyl amine (5.0 mmol), the catalyst (10 mol%, 0.5 mmol TBD or MTBD) and the solvent (when requested). The autoclave was sealed, purged at room temperature three times with CO_2 with stirring (10 bar), and eventually charged with liquid CO_2 (44g) at room temperature (by weighing it before and after the pressurization). After stirring of the mixture at 80 °C for 24 h, the autoclave was cooled, degassed and opened. The reaction crude was recovered using CH_2Cl_2 or EtOAc and the resulting organic solution was analyzed by GC, GC-MS and 1H NMR using methylbenzoate as internal standard. The crude material was purified *via* column chromatography using hexane/ethyl acetate (1/1) as eluent. 1,1,5,5-tetramethyl-1,5-dihydroimidazo[1,5-*a*]pyridin-3(2*H*)-one (**2a**) pale yellow solid, 0.34 g, 35%; 4,4-dimethyl-1-(2-methyl-3-oxobutan-2-yl)-5-methyleneimidazolidin-2-one (**3a**), white solid, 0.32 g, 31%; 1,3-Bis(2-methyl-3-oxobutan-2-yl)urea (**4a**), white solid, 80 mg, 7%; 5-Hydroxy-4,4,5-trimethyl-1-(2-methyl-3-oxobutan-2-yl)imidazolidin-2-one (**5a**), withe solid, 68 mg, 6%; Dispiro[cyclohexane-1,1'-imidazo[1,5-a]pyridine-5',1''-cyclohexan]-3'(2'H)-one (**2b**),

white solid, 0.58g, 43%; 1,3-Bis(1-acetylcyclohexyl)urea (**4b**), white solid, 646 mg, 42%; 5-Methyl-1-(prop-2-yn-1-yl)-1,3-dihydro-2H-imidazol-2-one (**6c**), yellow solid, 347 mg, 51%; 1,3-Di(prop-2-yn-1-yl)urea (**7c**), with solid, 54 mg, 8%.

*Typical Experimental Procedure for the Catalytic Synthesis of 5-Methyleneimodazolidin-2-ones **8***

An oven dried 45-mL stainless-steel autoclave was charged with the propargyl amine (2.0 mmol), the desired primary amine and the catalyst (10 mol %, 0.2 mmol TBD or MTBD). The autoclave was sealed, purged at room temperature three times with CO_2 with stirring (10 bar), and eventually charged with liquid CO_2 (8g) at room temperature (by weighing it before and after the pressurization). After stirring of the mixture at 80-120 °C for 24 h, the autoclave was cooled, degassed and opened. The reaction crude was recovered using CH_2Cl_2 or EtOAc and after removal of the solvent, the residue was purified *via* column chromatography using hexane/ethyl acetate as eluent. 5-Methyleneimodazolidin-2-ones (**8a**), pale yellow solid, 373 mg, 84% yield; 3-Hexyl-4-methylene-1,3-diazaspiro[4.5]decan-2-one (**8b**), brown solid,; 3-isoButyl-4-methylene-1,3-diazaspiro[4.5]decan-2-one (**8c**), pale yellow solid,; 4-Methylene-3-phenethyl-1,3-diazaspiro[4.5]decan-2-one (**8d**), pale yellow solid,; 3-Benzyl-4-methylene-1,3-diazaspiro[4.5]decan-2-one (**8e**), yellow solid*,; 3-(sec-Butyl)-4-methylene-1,3-diazaspiro[4.5]decan-2-one* (**8f**), white solid,; 3-Allyl-4-methylene-1,3-diazaspiro[4.5]decan-2-one (**8g**), brown solid,; 4-Methylene-3-phenyl-1,3-diazaspiro[4.5]decan-2-one (**8h**), white solid,; 3-(4-Methoxyphenyl)-4-methylene-1,3-diazaspiro[4.5]decan-2-one (**8i**), white solid,; 3-(4-Bromophenyl)-4-methylene-1,3-diazaspiro[4.5]decan-2-one (**8j**), white solid,; 1-Butyl-4,4-diethyl-5-methyleneimidazolidin-2-one (**8k**), pale yellow solid,; 1-Butyl-4,4-dimethyl-5-methyleneimidazolidin-2-one (**8l**), yellow oil; 1-Butyl-5-methyl-1,3-dihydro-2*H*-imidazol-2-one (**8m**), oil product*,; 3-Butyl-1,4-dimethyl-1,3-dihydro-2H-imidazol-2-one* (**8n**): pale yellow oil, *; 4,4-Dimethyl-5-methylene-1-(prop-2-yn-1-yl)imidazolidin-2-one* (**8o**), white solid,; 5-Benzylidene-1-butyl-4,4-dimethylimidazolidin-2-one (**8p**), colorless oil,; N-(1-Acetylcyclohexyl)pyrrolidine-1-carboxamide (**8q**), white solid.

*Experimental procedure for the TBD/MTBD-catalyzed formation of compounds **2a** and **3a** from propargylurea **7a***

An oven dried 45-mL stainless-steel autoclave was charged with the propargyl urea **7a** (384 mg, 2.0 mmol), and TBD or MTBD (0.2 mmol, 10 mol%). The autoclave was sealed, purged at room temperature three times with CO2 with stirring (10 bar), and eventually charged with liquid CO2 (8g) at room temperature (by weighing it before and after the pressurization). After stirring of the mixture at 80 °C for 24 h, the autoclave was cooled, degassed and opened. The reaction crude was recovered using CH2Cl2 and the resulting organic solution was analyzed by GC, GC-MS and 1H NMR using methylbenzoate as internal standard. In the presence of TBD products **2a** and **3a** were obtained with 43% and 32% yield, respectively (NMR analysis). With MTBD products **2a** and **3a** were obtained with 46% and 29% yield, respectively (NMR analysis). No conversion was observed without TBD.

*Production of 1-(1-Ethynylcyclohexyl)-3-phenylurea **9***

A dry 3-necked flask containing a magnetic stir bar was charged with 1-ethynylcyclohexan-1-amine (0.61 g, 5 mmol), phenyl isocyanate (0.59 g, 5 mmol) and THF (20 mL). The resulting mixture was stirred at room temperature for 1 h. The solvent was removed. The product precipitated out after addition of a mixture 9:1 hexane/ethyl acetate. The solid was collected to give compound **9** in 89% yield (1.077 g) as a white solid (mp 157-158 °C).

*Production of 3-Methyl-5-methyleneoxazolidin-2-one **10***

Compound **10** was obtained, together with **8n**, from the reaction of *N*-methylprop-2-yn-1-amine (138 mg, 2 mmol), *n*-butylamine (584 mg, 8 mmol) and CO2 (8g) at 100 °C using TBD (28 mg, 0.2 mmol) as catalyst (Table 4). The crude product was purified by column chromatography using hexane/ethyl acetate (8/2) as eluent to give 67 mg (30% yield) as a yellow oil.

*Experimental procedure for the TBD/MTBD-catalyzed formation of compounds **2a** and **3a** from propargylurea **7a***

An oven dried 45-mL stainless-steel autoclave was charged with the propargyl urea **7a** (384 mg, 2.0 mmol), and TBD or MTBD (0.2 mmol, 10 mol%). The autoclave was sealed, purged at room temperature three times with CO2 with stirring (10 bar), and eventually charged with liquid CO2 (8g) at room temperature (by weighing it before and after the pressurization). After stirring of the mixture at 80 °C for 24 h, the autoclave was cooled, degassed and opened. The reaction crude was recovered using CH2Cl2 and the resulting organic solution was analyzed by GC, GC-MS and 1H NMR using methylbenzoate as internal standard. In the presence of TBD products **2a** and **3a** were obtained with 43% and 32% yield, respectively (NMR analysis). With MTBD products **2a** and **3a** were obtained with 46% and 29% yield, respectively (NMR analysis). No conversion was observed without TBD.

*Experimental procedure for the TBD-catalyzed selective cyclization of propargyl urea **9** to imidazolidin-2-one **8h***

The propargyl urea **9** (242 mg, 1.0 mmol) was transferred to a 45-mL stainless steel autoclave together with TBD (14 mg, 10 mol%). The autoclave was sealed, purged at room temperature several times with CO2 with stirring (10 bar), and eventually charged with 8 g of liquid CO2 at room temperature. The reaction mixture was stirred at 100 °C for 24 h, then the autoclave was cooled, degassed and opened. The crude product was recovered (EtOAc, 20 mL) and then purified by column chromatography using hexane/ethyl acetate (1/1) as eluent to give **8h** in almost quantitative yield (235 mg, 97%).

*Experimental procedure for the TBD-catalyzed transformation of 3-methyl-5-methyleneoxazolidin-2-one **10** to imidazolidin-2-one **8n***

Oxazolidinone **10** (50 mg, 0.44 mmol) and *n*-butylamine (146 mg, 2.0 mmol) were transferred to a 45-mL stainless steel autoclave together with TBD (6 mg, 10 mol%). The autoclave was sealed, purged at room temperature several times with CO2 with stirring (10 bar), and eventually charged with 8 g of liquid CO2 at room temperature. The reaction mixture was stirred at 100 °C for 24 h, then the autoclave was cooled,

degassed and opened. The reaction crude was recovered (EtOAc, 20 mL) and compound **8n** was quantified (35% yield) by 1H NMR analysis with the internal standard method. Yield of unreacted compound **10** amounted to *ca.* 60%

4.6.2-Characterization of Imidazolidinones

1,3-Dibutylurea (**1a**): white solid. mp= 71–72 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.78 (t, br, J = 5.1 Hz, 2 H), 3.18–3.09 (m, 4 H), 1.51–1.26 (m, 8 H), 0.91 (t, J = 7.3 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.5, 40.0, 32.6, 20.2, 13.9; IR (KBr): ν (cm^{-1}) 3330, 1620. MS (EI, 70 eV,): m/z : 172 (M^+, 100), 157 (17), 143 (17), 130 (39), 129 (33), 101 (45), 100 (33), 87 (31), 74 (69), 73 (27), 72 (33), 58 (16), 57 (67), 56 (33), 55 (17). C 62.75%; H 11.68%; N 16.26%; Experimental C 62.52%; H 11.70%; N 16.08%

1,3-Dihexylurea (**1b**): colorless crystals, mp 73.5-74 °C ; IR (KBr) 3330, 1588, 1509 cm^{-1} ; ^{1} H NMR δ=0.88 (t, J = 6.6 Hz, 6H), 1.28-1.34 (m, 12H), 1.43–1.50 (m, 4H), 3.10–3.18 (m, 4H), 4.50 (br. s, 2H); EI-MS m/z 228 (M^+ , 100), 199 (45.5), 185 (56.7), 171 (15.4), 158 (39.9), 145 (9.9), 128 (25.6), 115 (17.9), 102 (29.9), 87 (12.1), 74 (17.2).

1,3-Dioctylurea (**1c**): white solid, mp 89−90 °C; ^{1} H NMR ($CDCl_3$) δ=5.00−5.01 (bb, 2H), 3.03− 3.09 (m, 4H), 1.42−1.37 (m, 4H), 1.30−1.10 (m, 20H), 0.80 (t, J = 6.0 Hz, 6H); ^{1}3C NMR ($CDCl_3$) δ 158.9, 40.2, 31.8, 30.4, 29.4, 29.3, 27.0, 22.6, 14.0; HRMS (EI) m/z (M^+) calcd for $C_{17}H_{36}N_2O$ 284.2827, found 284.2812.

1,3-Dicyclohexylurea (**1d**): white solid, m.p. 233–234 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 4.09 (d, J = 7.1 Hz, 2 H), 3.61–3.33 (m, 2 H), 2.00–1.03 (m, 20H) ppm. ^{13}C NMR (101 MHz, CDCl3): δ = 156.87, 49.10, 33.95,25.68, 24.95 ppm. IR: *v*= 3326, 1629, 1580, 1535, 1436, 1311, 1271,1244, 1186 cm–1. MS (EI): m/z = 224 $[M]^+$, 143.

1,1,5,5-tetramethyl-1,5-dihydroimidazo[1,5-a]pyridin-3(2H)-one (**2a**): pale yellow solid: mp 198-199 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.75 (br s, 1H), 5.67 (dd, *J* = 9.7, 5.8 Hz, 1H), 4.89 (d, *J* = 9.7 Hz, 1H), 4.67 (d, *J* = 5.8 Hz, 1H), 1.57 (s, 6H), 1.30 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.4, 147.6, 125.9, 118.3, 89.0, 56.3, 55.0, 28.9, 28.0; IR (ATR): *v* = 3244, 2943, 2842, 1719, 1660, 1575, 1542, 1461, 1354, 1329 cm^{-1}; MS (EI): *m/z* = 192

(M^+, 20), 177 (40), 162 (10), 134 (100), 118 (10), 106 (10), 92 (10); anal. calcd. for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57; O, 8.32; found: C 68.93, H 8.32, N 14.51.

4,4-dimethyl-1-(2-methyl-3-oxobutan-2-yl)-5-methyleneimidazolidin-2-one (**3a**): white solid: mp 128-129 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 7.53 (s, 1H), 4.09 (d, *J* = 2.7 Hz, 1H), 4.03 (d, *J* = 2.7 Hz, 1H), 2.03 (s, 3H), 1.41 (s, 6H), 1.26 (s, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 206.2, 156.5, 152.5, 80.5, 63.9, 55.7, 29.0, 23.6, 21.6; IR (ATR): *v* = 3345, 3252, 2981, 2901, 2837, 1726, 1647, 1577, 1424, 1360, 1282 cm^{-1}; MS (EI): *m/z* = 210 (M^+, 5), 167 (100), 153 (5), 124 (80), 111 (30), 96 (15), 82 (15); anal. calcd. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32; O, 15.22; found: C 62.64, H 8.70, N 13.29.

1,3-Bis(2-methyl-3-oxobutan-2-yl)urea (**4a**): withe solid. ^{1}H NMR (300 MHz, $CDCl^3$): δ = 5.62 (br s, 2H), 2.19 (s, 6H), 1.38 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.5, 156.3, 60.5, 24.3, 23.7; MS (EI): m/z = 228 (M^+, 3), 202 (60), 187 (100), 158 (15), 144 (30), 118 (25), 104 (20), 91 (15).

5-Hydroxy-4,4,5-trimethyl-1-(2-methyl-3-oxobutan-2-yl)imidazolidin-2-one (**5a**): white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.92 (br s, 1H), 4.05 (br s, 1H), 2.25 (s, 3H), 1.69 (s, 3H), 1.55 (s, 3H), 1.53 (s, 3H), 1.28 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (75 MHz $CDCl_3$): δ = 204.0, 160.6, 92.6, 65.6, 60.9, 26.03, 25.95, 24.8, 23.1, 22.5, 21.3; MS (EI): *m/z* = 185 [$(M-43)^+$, 20], 167 (10), 124 (5), 102 (5), 84 (10), 58 (100).

Dispiro[cyclohexane-1,1'-imidazo[1,5-a]pyridine-5',1''-cyclohexan]-3'(2'H)-one (**2b**): white solid (mp 264-265 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.77 (dd, *J* = 10.0, 5.7 Hz, 1H), 5.56 (d, *J* = 10.0 Hz, 1H), 5.39 (br s, 1H), 4.71 (d, *J* = 5.7 Hz, 1H), 1.79-1.32 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.4, 148.3, 120.8, 119.1, 90.1, 48.1, 48.0, 37.6, 34.4, 24.9, 24.7, 22.3, 22.1, 21.2; IR (ATR): ν = 3214, 2933, 2861, 1714, 1668, 1595, 1550, 1451, 1355, 1320 cm^{-1}; MS (EI): *m/z* = 272 (M^+, 30), 247 (10), 229 (100), 216 (15), 200 (15), 186 (80), 173 (25), 160 (10), 144 (15), 130 (10), 119 (10), 107 (10), 91 (10). Anal. calcd. for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28; O, 5.87; found: C 75.1, H 8.8, N 10.2.

1,3-Bis(1-acetylcyclohexyl)urea (**4b**): white solid, mp 261-262 °C. ^{1}H NMR (300 MHz, DMSO-*d*6): δ = 6.59 (s, 2H), 2.00 (s, 6H), 1.76-1.24 (m, 20H); ^{13}C NMR (75 MHz, DMSO-*d*6): δ = 209.9, 156.0, 61.6, 30.6, 24.7, 23.4, 20.6; IR (ATR): ν = 3334, 3143, 1641, 1580, 1566, 1468, 1310 cm^{-1}; MS (EI): *m/z* = 290 [(M-H_2O)$^{+}$, 5], 272 (10), 247 (100), 229 (20), 217 (15), 204 (20), 186 (15), 167 (20), 145 (10), 124 (15), 111 (10), 98 (15), 81 (20). Anal. calcd. for $C_{17}H_{28}N_2O_3$: C, 66.20; H, 9.15; N, 9.08; O, 15.56; found: C 66.3, H 9.0, N 9.1.

5-Methyl-1-(prop-2-yn-1-yl)-1,3-dihydro-2H-imidazol-2-one (**6c**): with solid, mp 122-124 °C; IR ($CHCl_3$) ν 1682 cm^{-1} (CdO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (3H, s), 2.24 (1H, dd, J =2.6 2.2), 4.42 (2H, d, J=2.6), 6.02 (1H, s), 9.90 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ=10.22, 29.87, 71.87, 78.26, 104.43, 119.44, 154.33 (CdO); MS (EI) m/z=136 (100) (M^{+}), 97 (63.98), 42 (28.98). Anal. Calcd for $C_7H_8N_2O$: C, 61.76, H, 5.88, N, 20.59. Found: C, 61.66, H, 6.14, N, 20.67

1,3-Di(prop-2-yn-1-yl)urea (**7c**)*:* white crystals, m.p.192-194°C. IR (KBr): 3315, 1594, 1426, 1355, 1288, 1251 cm^{-1}; m/z= 327.2 ([M+H]$^{+}$, 100); ^{1}HNMR(DMSO-d6) 6.31 (2H, t, J=6.0, 2NH), 3.78 (4H, dd, J=6.0, 2.5), 3.04 (2H, t, J=2.5, 2CCH); ^{13}CNMR(100MHz, DMSO-d6) 156.9, 82.3, 72.6, 28.8; m/z(ES+) 137.1 ([M+H]$^{+}$, 100%); HRMS(ES+): Calcd for [M+H]$^{+}$, $C_7H_9ON_2$: 137.0709; found: 137.0707.

5-Methyleneimodazolidin-2-ones (**8a**): pale yellow solid, m.p.: 112.8-113.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.27 (br s, 1H), 3.95 (br s, 1H), 3.87 (br s, 1H), 3.38 (t, *J* = 7.2 Hz, 2H), 1.78-1.16 (m, 14H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 153.7, 77.5, 59.1, 39.5, 38.5, 28.5, 24.9, 22.2, 19.9, 13.7; IR (ATR): *v* = 3359, 2963, 2941, 2916, 2870, 1702, 1630, 1527, 1392, 1353; MS (EI): *m/z* = 222 (M^{+}, 80), 207 (20), 193 (15), 180 (70), 167 (100), 151 (20), 137 (30), 123 (30), 111 (50), 94 (10). Anal. Calcd. for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 69.9; H, 9.9; N, 12.5

3-Hexyl-4-methylene-1,3-diazaspiro[4.5]decan-2-one (**8b**): brown solid, m.p. 93.5-95.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.54 (br s, 1H), 3.93 (d, *J* = 2.2 Hz, 1H), 3.86 (d, *J*

= 2.2 Hz, 1H), 3.36 (t, *J* = 7.2 Hz, 2H), 1.76–1.16 (m, 18H), 0.84 (t, *J* = 6.7 Hz, 3H); 13C NMR (100 MHz, $CDCl_3$): δ = 158.2, 153.8, 77.4, 59.1, 39.7, 38.5, 31.4, 26.34, 26.31, 24.9, 22.5, 22.2, 13.9; IR (ATR): *v* = 3190, 2932, 2845, 1717, 1653, 1562, 1455, 1423. 1377, 1339, 1303, 1243, 1067, 778, 662, 637 cm^{-1}; MS (EI): *m/z* = 250 (M^+, 100), 233 (26), 207 (20), 195 (62), 180 (99), 167 (40), 137 (24), 111 (41). Anal. Calcd. for $C_{15}H_{26}N_2O$: C, 71.95; H, 10.47; N, 11.19. Found: C, 72.1; H, 10.5; N, 11.1.

3-isoButyl-4-methylene-1,3-diazaspiro[4.5]decan-2-one (**8c**): pale yellow solid, m.p. 142.4-143.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (s, 1H), 3.88 (s, 1H), 3.83 (s, 1H), 3.15 (d, *J* = 7.5 Hz, 2H), 2.02 (m, 1H), 1.73-1.35 (m, 9H), 1.27-1.10 (m, 1H), 0.83 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6, 154.1, 77.3, 59.1, 46.8, 38.6, 25.6, 24.9, 21.9, 19.9; IR (ATR): *v* = 3213, 2931, 1712, 1654, 1592, 1456, 1423, 1325, 1244, 1062, 862, 796, 663, 635 cm^{-1}; MS (EI): *m/z* = 222 (M^+, 35), 180 (10), 167 (100), 136 (30), 124 (14), 111 (25). Anal. Calcd. for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 70.0; H, 10.1; N, 12.7.

4-Methylene-3-phenethyl-1,3-diazaspiro[4.5]decan-2-one (**8d**): pale yellow solid, m.p. 172.8-173.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34-7.21 (m, 5H), 6.60 (br s, 1H), 4.04 (d, *J* = 2.3 Hz, 1H), 3.95 (d, *J* = 2.4 Hz, 1H), 3.71-3.62 (m, 2H), 2.94-2.85 (m, 2H), 1.82-1.63 (m, 5H), 1.58- 1.39 (m, 4H), 1.37-1.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8, 153.4, 138.7, 128.8, 128.3, 126.3, 77.7, 59.2, 41.1, 38.4, 32.7, 24.9, 22.1; IR (ATR): *v* = 3191, 2932, 2845, 1717, 1653, 1562, 1455, 1423. 1377, 1339, 1303, 1243, 1067, 778, 662, 637 cm^{-1}; MS (EI): *m/z* = 270 (M^+, 100), 215 (15), 179 (23), 136 (47), 111 (15), 105 (28), 104 (85). Anal. Calcd. for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.7; H, 8.2; N, 10.2.

3-Benzyl-4-methylene-1,3-diazaspiro[4.5]decan-2-one (**8e**): yellow solid, m.p. 132.0-133.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.38-7.21 (m, 5H), 6.46 (br s, 1H), 4.62 (s, 2H), 3.91 (s, 2H), 1.80- 1.69 (m, 5H), 1.58-1.37 (m, 4H), 1.35-1.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3, 153.1, 136.7, 128.5, 127.4, 126.9, 79.5, 59.4, 43.6, 38.5, 24.9, 22.3; IR (ATR): *v* = 3189, 2930, 2841, 1715, 1653, 1564, 1453, 1423. 1338, 1300, 1241,

778, 664 cm^{-1}; MS (EI): *m/z* = 256 (M^+, 90), 201 (37), 165 (13), 123 (13), 91 (100). Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 75.2; H, 7.9; N, 11.1.

3-(sec-Butyl)-4-methylene-1,3-diazaspiro[4.5]decan-2-one (**8f**): white solid, m.p. 168.8-170.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78 (br s, 1H), 4.05 (br s, 1H), 3.97-3.81 (two overlapping signals: m and br s centred at 3.85 ppm, 2H), 2.02-1.88 (m, 1H), 1.75-1.35 (m, 10H), 1.29 (d, *J* = 6.9 Hz, 3H), 1.25-1.13 (m, 1H), 0.81 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5, 153.1, 78.5, 58.7, 49.3, 38.7, 38.6, 25.6, 25.0, 22.1, 17.0, 11.1; IR (ATR): *v* = 3226, 2921, 1714, 1651, 1596, 1455, 1421, 1323, 1241, 1062, 864, 799, 663 cm^{-1}; MS (EI): *m/z* = 222 (M^+, 58), 167 (100), 166 (14), 124 (26), 111 (57). Anal. Calcd. for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 70.0; H, 10.1; N, 12.7.

3-Allyl-4-methylene-1,3-diazaspiro[4.5]decan-2-one (**8g**): brown solid, m.p. 125.7-126.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (br s, 1H), 5.76-5.62 (m, 1H), 5.12 (d, *J* = 6.5 Hz, 1H), 5.08 (br s, 1H), 4.00, 3.99 (two partly overlapped broad singlets, 2H), 3.92 (br s, 1H), 3.87 (br s, 1H), 1.75- 1.60 (m, 5H), 1.53-1.38 (m, 4H), 1.30-1.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 153.4, 131.8, 116.1, 78.4, 59.3, 42.0, 38.5, 24.9, 22.0; IR (ATR): *v* = 3211, 2930, 2841, 1716, 1658, 1567, 1459, 1424. 1378, 1332, 1240, 1063, 774, 659, 633 cm^{-1}; MS (EI): *m/z* = 206 (M^+, 89), 177 (24), 163 (48), 151 (100), 137 (17), 123 (18). Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found: C, 69.6; H, 8.9; N, 13.4.

4-Methylene-3-phenyl-1,3-diazaspiro[4.5]decan-2-one (**8h**): white solid, m.p. 224.0-225.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47-7.40 (m, 2H), 7.34-7.28 (m, 3H), 6.12 (br s, 1H), 4.07 (br s, 1H), 3.96 (br s, 1H), 1.87 (d, *J* = 12.7 Hz, 2H), 1.82-1.68 (m, 3H), 1.58 (td, *J* = 13.1, 3.2 Hz, 3H), 1.50- 1.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 157.1, 154.4, 135.0, 129.2, 127.6, 127.4, 80.1, 59.4, 38.5, 24.8, 22.2; IR (ATR): *v* = 3234, 2925, 2852, 1717, 1652, 1455, 1423, 1336, 1305, 1244, 777, 661 cm^{-1}; MS (EI): *m/z* = 242 (M^+, 100), 199 (22), 187 (95), 118 (10), 77 (23). Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.5; H, 7.3; N, 11.5.

3-(4-Methoxyphenyl)-4-methylene-1,3-diazaspiro[4.5]decan-2-one (**8i**): white solid, m.p. 214.2-215.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.25-7.21 (m, 2H), 7.00-6.96 (m, 2H), 5.76 (br s, 1H), 4.00 (d, *J* = 1.5 Hz, 1H), 3.96 (d, *J* = 1.5 Hz, 1H), 3.84 (s, 3H), 1.93-1.73 (m, 5H), 1.70-1.54 (m, 2H), 1.50-1.23 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 157.3, 155.0, 129.0, 127.6, 114.7, 79.9, 59.3, 55.5, 38.5, 24.9, 22.4; IR (ATR): *v* = 3217, 2925, 2927, 1710, 1663, 1512, 1414, 1309, 1242, 781, 663 cm^{-1}; MS (EI): *m/z* = 272 (M^+, 100), 257 (5), 243 (15), 230 (16), 217 (100). Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29; O, 11.75. Found: C, 70.7; H, 7.3; N, 10.3.

3-(4-Bromophenyl)-4-methylene-1,3-diazaspiro[4.5]decan-2-one (**8j**): white solid, m.p. 181.0-182.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.29-7.25 (m, 2H), 7.04-6.99 (m, 2H), 6.04 (br s, 1H), 4.04 (d, *J* = 1.5 Hz, 1H), 4.00 (d, *J* = 1.5 Hz, 1H), 2.00-1.75 (m, 5H), 1.73-1.60 (m, 2H), 1.58-1.25 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 157.4, 155.1, 127.7, 124.5, 114.8, 80.0, 59.4, 38.6, 25.0, 22.5; IR (ATR): *v* = 3223, 2920, 1719, 1648, 1414, 1300, 1259 cm^{-1}; MS (EI): *m/z* = 322 (M^+, 100), 320 (100), 293 (18), 291 (19), 280 (23), 278 (22), 267 (91), 265 (92), 197 (27), 185 (27). Anal. Calcd. for $C_{15}H_{17}BrN_2O$: C, 56.09; H, 5.33; Br, 24.88; N, 8.72; O, 4.98. Found: C, 55.9; H, 5.2; N, 8.6.

1-Butyl-4,4-diethyl-5-methyleneimidazolidin-2-one (**8k**): pale yellow solid, m.p. 47.0-48.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.94 (br s, 1H), 4.02-3.99 (m, 1H), 3.76 (d, *J* = 2.3 Hz, 1H), 3.35 (t, *J* = 7.3 Hz, 2H), 1.64-1.40 (m, 6H), 1.34-1.23 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H), 0.77 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 159.0, 149.9, 77.5, 63.2, 39.5, 33.7, 28.5, 20.0, 13.7, 7.4; IR (ATR): *v* = 3266, 2962, 2929, 2869, 1719, 1654, 1566, 1457, 1409. 1360, 1287, 1170, 1243, 1125, 1059, 929, 833, 781 cm^{-1}; MS (EI): *m/z* = 210 (M^+, 15), 183 (18), 182 (43), 181 (100), 168 (18), 155 (13), 140 (17), 139 (36), 125 (23), 111 (22). Anal. Calcd. for $C_{12}H_{22}N_2O$: C, 68.53; H, 10.54; N, 13.32. Found: C, 68.8; H, 10.7; N, 13.2.

1-Butyl-4,4-dimethyl-5-methyleneimidazolidin-2-one (**8l**): yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 6.37 (br s, 1H), 3.87 (d, *J* = 2.3 Hz, 1H), 3.82 (d, *J* = 2.3 Hz, 1H), 3.29 (t, 7.3 Hz, 2H), 1.53-1.37 (m, 2H), 1.27-1.13 (two overlapping signals: m and s centred at 1.25

ppm, 8H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1, 153.5, 77.2, 56.1, 39.4, 29.4, 28.4, 19.8, 13.5; IR (ATR): *v* = 3272, 2961, 2932, 2873, 1722, 1664, 1567, 1421 cm-1; MS (EI): *m/z* = 182 (M^+, 50), 167 (70), 140 (100), 127 (80), 111 (60), 97 (50), 84 (50). Anal. Calcd. for $C_{10}H_{18}N_2O$: C, 65.90; H, 9.95; N, 15.37. Found: C, 70.1; H, 9.8; N, 15.5.

1-Butyl-5-methyl-1,3-dihydro-2H-imidazol-2-one (**8m**): oil product; IR ν =1672 cm^{-1} (CdO); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 0.94 (3H, t, J =7.3), 1.40-1.26 (2H, m), 1.56-1.64 (2H, m), 2.06 (3H, s), 3.58 (2H, t, J =7.3), 5.99 (1H, s), 9.98 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.37, 13.79, 20.05, 31.87, 40.64, 103.92, 119.52, 154.91; MS (EI) m/z 154 (51.45) (M^+), 98 (64.60), 73 (100), 44 (89.0)); HRMS (EI) m/z 154.1117, $C_8H_{13}N_2O$ requires M, 154.1106

3-Butyl-1,4-dimethyl-1,3-dihydro-2H-imidazol-2-one (**8n**): pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.89 (br s, 1H), 3.60 (t, *J* = 7.3 Hz, 2H), 3.21 (s, 3H), 2.04 (s, 3H), 1.65-1.53 (m, 2H), 1.38-1.24 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2, 118.1, 107.1, 40.7, 31.6, 29.7, 19.7, 13.5, 10.0; IR (ATR) *v* = 3447, 2958, 1669, 1472, 1408, 1030 cm^{-1}; MS (EI): *m/z* = 168 (M^+, 52), 151 (34), 139 (9), 126 (38), 112 (100), 83 (26), 42 (83). Anal. Calcd. for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.1; H, 9.4; N, 16.5.

4,4-Dimethyl-5-methylene-1-(prop-2-yn-1-yl)imidazolidin-2-one (**8o**): white solid, m.p. 100.8-102.4 °C. ^{1}H NMR (300 MHz, DMSO-*d*6): δ = 7.54 (br s, 1H), 4.11 (d, *J* = 2.5 Hz, 2H), 4.06 (d, *J* = 2.1 Hz, 1H), 4.03 (d, *J* = 2.1 Hz, 1H), 3.12 (t, *J* = 2.5 Hz, 1H), 1.26 (s, 6H); ^{13}C NMR (75 MHz, DMSO-*d*6): δ = 155.4, 152.1, 78.4, 78.0, 73.3, 55.5, 29.1, 28.7; IR (ATR): *v* = 3238, 2974, 2360, 2129, 1717, 1676, 1558, 1438 cm^{-1}; MS (EI): *m/z* = 164 (M^+, 30), 149 (35), 120 (90), 112 (20), 106 (50), 94 (15), 80 (100). Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06; O, 9.74. Found: C, 66.1; H, 7.3; N, 17.2.

5-Benzylidene-1-butyl-4,4-dimethylimidazolidin-2-one (**8p**): colorless oil as a 1:1 mixture of *E/Z* isomers indicated as A and B. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33-7.15

(m, 5H(A) and 5H(B)), 6.09, 5.80 (two br s, 1H(A) and 1H(B)), 5.70, 5.48 (two s, 1H(A) and 1H(B)), 3.53-3.48, 3.33-3.26 (two m, 2H(A) and 2H(B)), 1.68-1.55 (m, 2H), 1.45 (s, 6H), 1.41-1.22 (two partly overlapping signals: m and singlet centred at 1.28 ppm, 8H), 1.10-1.00 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.87- 0.75 (m, 2H), 0.60 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 157.9, 146.3, 145.8, 136.0, 130.3, 129.6, 127.8, 127.5, 126.3, 126.1, 98.7, 96.7, 57.2, 56.9, 40.9, 39.4, 30.1, 28.97, 28.89, 28.4, 20.0, 19.2, 13.8, 13.4; IR (ATR) *v* = 3234, 2939, 2833, 1711, 1657, 1564, 1331, 772 cm^{-1}; MS (EI): *m/z* = 258 (M^+, 75), 243 (100), 215 (30), 203 (16), 201 (32), 187 (53), 91 (29). Anal. Calcd. for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.6; H, 8.7; N, 10.7.

N-(1-Acetylcyclohexyl)pyrrolidine-1-carboxamide (**8q**): white solid, m.p. 188.9-190.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.54 (br s, 1H), 3.32 (t, J = 6.7 Hz, 4H), 2.13 (s, 3H), 1.95-1.81 (m, 6H), 1.73-1.55 (m, 5H), 1.42-1.11 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.5, 155.4, 62.6, 45.5, 31.5, 25.5, 25.2, 24.2, 21.6; IR (ATR) *v* = 3218, 3111, 2933, 2869, 1720, 1662, 1568, 1452, 1421, 1067, 784 cm^{-1}; MS (EI): m/z = 238 (M^+, 1), 195 (50), 152 (5), 124 (5), 115 (5), 98 (100), 81 (15). Anal. Calcd. for $C_{13}H_{22}N_2O_2$: C, 65.52; H, 9.30; N, 11.75; O, 13.43. Found: C, 65.2; H, 9.4; N, 11.6.

1-(1-Ethynylcyclohexyl)-3-phenylurea (**9**): white solid, mp 157-158 °C. ^{1}H NMR (DMSO-*d*6): δ = 8.21 (s, 1H), 7.38-7.35 (m, 2H), 7.24-7.19 (m, 2H), 6.92-6.87 (m, 1H), 6.30 (s, 1H), 3.16 (s, 1H), 2.02-1.98 (m, 2H), 1.79- 1.72 (m, 2H), 1.61-1.47 (m, 5H), 1.32-1.21 (m, 1H); ^{13}C NMR (DMSO-*d*6): δ = 153.9, 140.5, 128.9, 121.3, 117.7, 87.3, 73.0, 50.3, 37.1, 25.1, 22.1; IR (ZnSe): *v* = 3347, 3309, 3293, 2931, 2856, 1678, 1652, 1598, 1551, 1497, 1440, 1309, 1237, 1037, 869, 752, 692 cm^{-1}; MS (EI): *m/z* = 242 (M^+, 37), 227 (2), 214 (23), 187 (18), 118 (37), 91 (28), 77 (42), 65 (17), 51 (17), 41 (23).

3-Methyl-5-methyleneoxazolidin-2-one (**10**): Colourless oil, IR (film), ν = 2929, 1791, 1680, 1488, 1383, 1245, 954, 876, 756 cm^{-1}; 1H NMR (400 MHz; CDCl3), δ =2.85 (3H, s, Me), 4.11 (2H, t, J=2.5), 4.22 (1H, dt, J=2.8, 2.7), 4.64 (1H, dt, J=2.8, 2.7); GC/MS (m/z)= 113 (M^+, 100%), 98 (2), 85 (10), 69 (5), 57 (20), 42 (20). $C_5H_7NO_2$; C, 53.1; H, 6.2; N, 12.4;found: C, 53.1; H, 6.2; N, 12.3.

4.7 References

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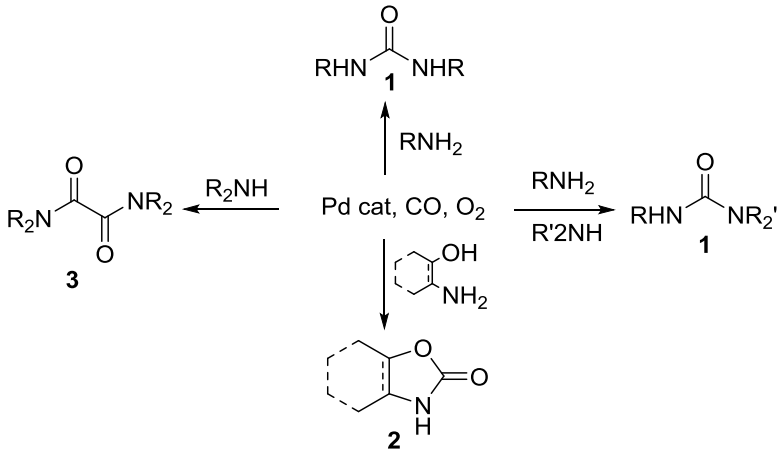
Chapter 5

Conclusions

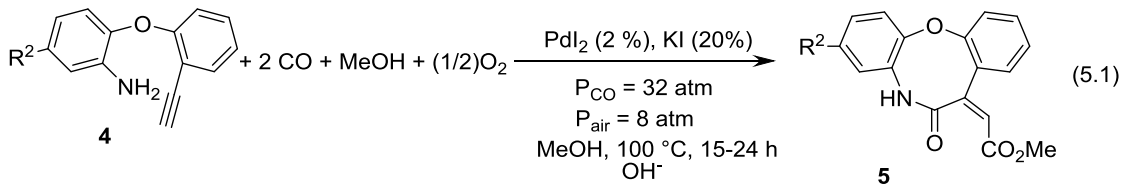
In the first chapter is reported the first general recyclable Pd-catalyzed oxidative carbonylation of primary amines, β-amino alcohols, 2-aminophenols, and secondary amines to give 1,3-disubstituted ureas **1**, 2-oxazolidinones **2**, benzoxazolones **2**, and oxamides **3**, in high yields and selectivity (Scheme 5.1).



Scheme 5.1

Carbonylations were carried out in an ionic liquid, such as $BmimBF_4$, as the reaction medium, under non-explosive conditions (100 °C and 20 atm of a 4:1 mixture of CO-air), using a particularly simple and robust catalytic system, consisting of PdI_2 in conjunction with KI. While primary aromatic amines selectively led to 1,3-aryl ureas, tetrasubstituted oxamides were formed from secondary amines. On the other hand, primary aliphatic amines could be selectively converted into either 1,3-dialkyl ureas or *N*,*N*'-dialkyloxalamides depending on reaction conditions. Oxazolidinones and benzoxazolones were obtained from β-amino alcohols and 2-aminophenols, respectively. All products were easily recovered by simple extraction with Et_2O from the reaction mixture followed by crystallization. The ethereal solvent was recovered and reused, while the IL phase, still containing the active catalyst dissolved in it, could be recycled several times without appreciable loss of activity.

In chapter one is also reported that readily available 2-(2-ethynylphenoxy)anilines **4**, bearing a terminal triple bond (R^1 = H), can be directly converted into a novel class of medium-sized heterocyclic derivatives **5**, through a new PdI_2/KI-catalyzed carbonylative ς-lactamization-alkoxycarbonylation process (Eq. 5.1).

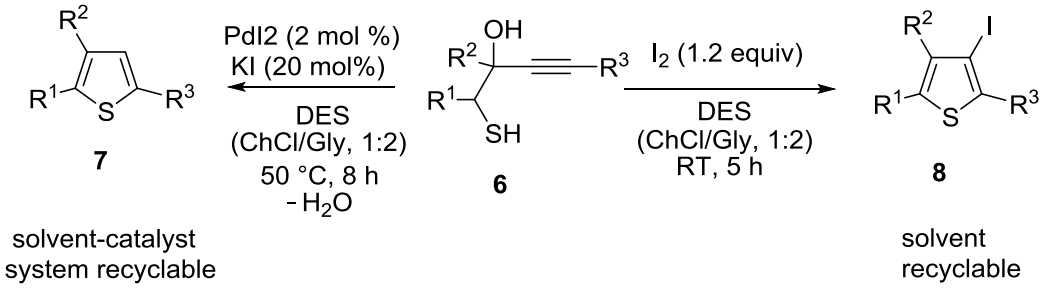


(5.1)

In agreement with theoretical calculations, the process starts with *N*-palladation of **4**, followed by CO insertion, intramolecular triple bond insertion, and alkoxycarbonylation. The formation of ς-lactams **5** from simple building blocks (**4**, CO, ROH, and O_2) in a multicomponent fashion, represents a significant achievement, also in view of the biological relevance of these compounds. In fact, biological tests showed that the newly synthesized ς-lactam **5** exerts antiproliferative effects in different breast cancer cell lines, without affecting normal breast epithelial cell viability

The *S*-heterocyclization and iodocyclization of 1-mercapto-3-yn-2-ols in chloride/glycerol both run in the deep eutectic solvent ChCl/Gly (1:2) as a nonconventional, safe, inexpensive and "green" reaction medium, is reported in the chapter two.

Substituted thiophenes **7** and 3-iodothiophenes **8** were efficiently obtained starting from readily available 1-mercapto-3-alkyne-2-ols **6**, which, in turn, could also be synthesized by carrying out the alkynylation of commercially available β-mercaptoketone in the above DES (Scheme 5.2).

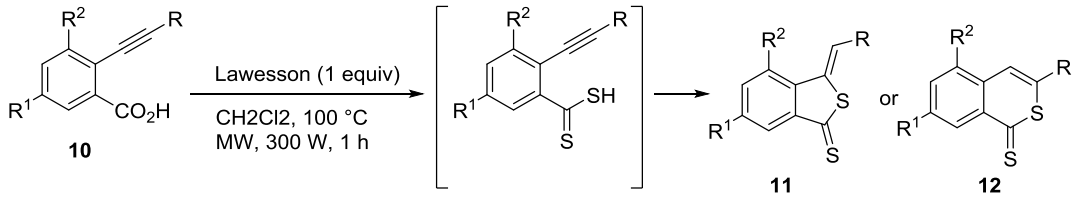


Scheme 5.2

The heterocyclodehydration of **6** to thiophenes **7** was carried out using a simple catalytic system, consisting of PdI_2 in conjunction with 10 equiv of KI, which could be

conveniently recycled together with the DES several times without loss of activity. The DES solvent could also be easily recycled in the iodocyclization process leading to 3-iodothiophenes **8**.

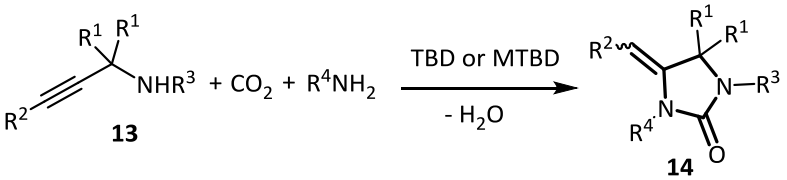
In the chapter two is reported also the first example of tandem thionation/heterocyclization of 2-alkynylbenzoic acids **9** is reported (Scheme 5.3).



Scheme 5.3

The process occurs using 1 equiv of the Lawesson's reagent as the thionation agent under MW irradiation (100 °C at 300 W) in CH_2Cl_2 for 1 h, and leads to (*Z*)-benzothiophenethiones **10** or isothiochromenethiones **11**, depending on the nature of the substituent at the distal β position of the carbon-carbon triple bond. In particular, compounds **11** were regio- and stereoselectively obtained starting from substrates bearing an aryl group (Ph, 4-F-C_6H_4, or 4-pentyl-C_6H_4) as substituent on the carbon-carbon triple bond, through thionation followed by a 5-*exo-dig* cyclization, while substrates carrying an alkyl group (such as Pr) or an electron-rich aryl substituent (such as *p*-$MeOC_6H_4$) at the same position selectively underwent a 6-*endo-dig* cyclization to yield **12**. The study of the bioactivity of the newly synthesized *S*-heterocycles is currently underway and will be reported in due course.

The synthesis of linear and cyclic ureas from carbon dioxide and various amine derivatives under bicyclic guanidine catalysis has been investigate in the last chapter. In particular, we have disclosed a new and general bicyclic guanidine-catalyzed synthesis of 5-methyleneimidazolidin-2-ones **14** by reaction of propargylamines **13**, primary amines and CO_2 (Eq. 5.2).



(5.2)

The main features of this methodology include (i) a metal-free, ligand-free, VOCs-free and isocyanate-free protocol for the synthesis of imidazolidinone core, (ii) an easily scalable and highly atom economical process, (iii) the formation of imidazolidinone ring under mild reaction temperatures (80-120 °C), (iv) proposed reaction pathways based on experimental tests and isolated intermediates, and (v) a further advancement in the direction of carbon dioxide utilization for the synthesis of high-value chemicals.

L'Unica Maniera di Ottenere l'Impossibile
è Pensare che sia Possibile