Università della Calabria

Doctorate Course:

"Methodologies for the Development of Molecules of Pharmacological Interest"

(MDMP, *cicle XXIII*)

New syntheses of heterocycles by metal-catalyzed processes

Supervisors

Prof. Giuseppe SALERNO

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Indice

Chapter 1

1.1 Introduction

Organic compounds containing five-membered aromatic eterocyclic rings are widely distributed in nature and often play an important role in various biochemical processes. As a result they are incorporated into new chemical entities by medicinal chemists (*Dalvie et al., 2002*). For example, the five-membered heterocycles, pyrrole and furan, are the basic constituents of many biological and chemical systems as well as functional materials, such as precursors of coenzymes and vitamins (such as Thiamine, Riboflavin, Nicotinic Acid, Adenine and Vitamin B12 and E); photosynthetic pigments (Chlorophyll) and oxygen-delivering molecules (Hemoglobin); Purine and pyrimidine bases, amino-acids (Histidine, Tryptophan, Proline) and Hormones (Serotonin, Histamine). Moreover among natural heterocyclic drugs the most important are purines (Caffeine), alkaloids (nicotine) and antibiotics (such as pennicilline). The development of efficient and selective synthetic methods for preparing both of furan derivatives of pyrrole derivatives is therefore of considerable interest in Organic Chemistry.

1.2 General importance of heterocycles

Heterocycles form, by far, the largest of the classical divisions of organic chemistry. Moreover, they are of immense importance not only biologically and industrially but also to the functioning of any developed human society as well. Their importance in a wide range of areas can hardly be overemphasized. Many molecules, active in the cellular metabolism present in their structure an heterocyclic moiety. Same example are here reported: precursors of coenzymes

and vitamins (such as Thiamine, Riboflavin, Nicotinic Acid, Adenine and Vitamin B12 and E); photosynthetic pigments (Chlorophyll) and oxygen-delivering molecules (Hemoglobin); Purine and pyrimidine bases, amino-acids (Histidine, Tryptophan, Proline) and Hormones (Serotonin, Histamine). Moreover among natural heterocyclic drugs the most important are purines (Caffeine), alkaloids (nicotine) and antibiotics (such as pennicilline). A large number of heterocyclic synthetic drugs that mimic natural products have been discovered and developed starting from the molecular structure of this biological products. These synthetic drugs belong to very different pharmacological classes: Hypnotics (barbiturates), anticonvulsive, antihistamines, antithyroid, fungicides. Other important practical applications of these compounds can also be cited; for instance, their use as additives and modifiers in a wide variety of industries including cosmetics, reprography, information storage, plastics, solvents, antioxidants, and vulcanization accelerators. Finally, as an applied science, heterocyclic chemistry is an inexhaustible resource of novel compounds. A vast number of combinations of carbon, hydrogen, and heteroatoms can be designed, providing compounds with the most different physical, chemical, and biological properties. Among the approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic, and approximately one-half are heteroaromatic. It is, therefore, easy to understand why both the development of new methods and the strategic utilization of known methods for the synthesis of complex heterocyclic compounds continue to drive the field of synthetic organic chemistry. Organic chemists have been engaged in extensive efforts to produce these heterocyclic compounds by developing new and efficient synthetic transformations. Among them, catalytic reactions are the most attractive methodologies for synthesizing heterocyclic compounds using both metallic or organic catalysts. Such protocols are hugely important as they may offer distinct advantages such as improved atom utilization or atom economy by avoidance of common derivation procedures; decreased by product formation and, hence, decreased waste resulting from purification procedures required to separate the desired product

from impurities; in many cases, reduced energy utilization both in the reaction and purification stages. Further improvements can be provided by the utilization of alternatives more eco-friendly solvents. The magnitude of these advantages is clear when considering the 12 Green Chemistry Principles and the international tendency to develop green and sustainable chemical processes, with lesser generation of toxic and nontoxic waste.

During my PhD course some innovative methodologies for the synthesis of different and important classes of heterocyclic compounds using metal or organic catalysts have been developed; three experimental projects will be presented and discussed. All of them involve the use of efficient catalytic systems for the synthesis of different heterocycles also in non conventional media such as carbon dioxide. These three projects (concerning the use of catalytic systems based on Pd or Cu), were carried out at the Department of Chemistry of the University of Calabria under supervision of Prof. G. Salerno and B. Gabriele.

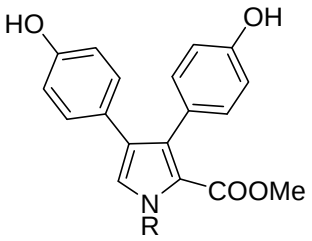
An introduction will be provided focusing on general aspects and on the most interesting and recent applications of catalysis.

1.3 Importance of Pyrrole and Furan derivatives

Pyrrole derivatives include several classes of natural and unnatural compounds that exhibit a variety of biological and biomedical properties. For example, the pyrrole derivative BM212 [1,5-diaryl-2-methyl-3-(4-methylpiperazin-1-yl)methyl-pyrrole] was shown to possess strong inhibitory activity against both *Mycobacterium tuberculosis* and some nontuberculosis mycobacteria. BM212 was inhibitory to drug-resistant mycobacteria and also exerted bactericidal activity against intracellular bacilli residing in the U937 human histiocytic lymphoma cellline[1]. Among the natural products structure pyrrole, those that are most important from the biochemical viewpoint are the porphyrins. The primary structure to this class of compounds consists of a structure in which the four tetrapyrrole rings pyrrole are linked by bridges-CH. Porphyrins are very stable molecules capable to coordinate with many metal ions giving rise to complexes

of organometallic extreme biological importance. These complexes have planar structures in which the metal ion is coordinated by four nitrogen atoms. Characteristic of porphyrin molecules is to be colorful, in fact they are the units fundamental to many natural pigments. The chlorophyll of the leaves, for example green. It is a complex of a porphyrin suitably replaced with Mg (II) and presents in its structure a long alkyl chain of 20 carbon atoms responsible for its solubility in fats. Even the human body contains in small quantities, some pigment porphyrin structure: the coproporfirina the deuteroporfirina and protoporphyrin. This combined with the bivalent iron form the prosthetic heme group that binds to the globular protein globin, gives origin to hemoglobin, the pigment that gives color to the breathing red blood cellsThe oxidized form hemin heme is representing the group prosthetic several human enzymes that play important physiological roles Among them, catalase, which decomposes hydrogen peroxide into water and oxygen. It together with other enzymes, acts as a scavenger of free radicals, which are makers of cellular aging. The heme is still this level of cytochrome P450 enzyme widely distributed throughout human the body and essential for the development of oxidative reactions and loa drug biotransformation. Between the porphyrin derivative-like focus should be paid to vitamin B12 or cianocobalammina. Vitamin B12 represents the most effective remedy against the pernicious anemia which in severe cases, maydetermine demyelination of white fibers of the spinal cord. Is also known that pyrrole derivatives with two aryl groups on adjacent positions include important classes of marine natural products (*fig.1*). Thus, lamellarins are 3,4-diarylpyrrole-2-carboxylic acid esters, which belong to a large group of DOPA-[1-amino-3-(30,40-dihydroxyphenyl)propionic acid]-derived pyrrole alkaloids first isolated from the prosobranch mollusc Lamellaria and later obtained from the ascidian Didemnum , the Australian sponge Dendrilla cactus, and an unidentified ascidian

collected from the Arabian sea.



R = 4-(MeO)$C_6H_4COCH_2$,
2-(HO),4-(MeO)$C_6H_3COCH_2$,
H, 4-(HO)C_6H_4

Fig.1

Virtually all of the lamellarins have been found to be cytotoxic to a wide range of cancer cell lines and the most potent of these compounds, i.e., lamellarins D , K and M , have been shown to exhibit cytotoxicity values in the midto-high nanomolar range . Interestingly, lamellarins are also single-digit micromolar inhibitors of P-glycoprotein (P-gp) responsible for the multidrug resistance (MDR) effect and even at noncytotoxic concentrations they reverse MDR by inhibiting P-gp-mediated drug efflux. Lamellarin D is also a potent inhibitor of human topoisomerase I and lamellarin H is a potent inhibitor of both Molluscum contagiosum virus topoisomerase and HIV-1 integrase. On the other hand, lamellarins O and P demonstrated antibiotic activity and lamellarin D caused inhibition of cell division. Other marine natural products possessing a 3,4-di(hetero)-aryl-substituted pyrrole ring as a common structural subunitinclude halitulin , which is a strongly cytotoxic pyrrole alkaloid isolated from the sponge *Haliclona tulearensis*, lukianols A and B , which have been found in an unidentified encrusting tunicate collected in the lagoon of the Palmyra atoll, polycitones A and B, which have been isolated from the Indo-Pacific ascidian *Polycitor* storniamides A , B , C and D, which are alkaloids isolated from marine sponges of the genus Clona, dictyodendrins A and B, which are the first

telomerase inhibitory marine natural products isolated from the Japanese marine sponge Dictyodendrilla verongiformis, and ningalins A and B, 3,4-diarylpyrrole derivatives bearing a 2-carboxylate group, which have been isolated from the ascidian of the genus Didemnum collected in Western Australia near Ningaloo Reef.[2]

In literature it is known that a considerable number of lamellarins and related pyrrole derived alkaloids have been found to be cytotoxic to a wide range of cancer cell lines. The most potent of these compounds (lamellarins D, K, and M) exhibited cytotoxicity values in the mid-to-high nanomolar range (38-110 nM). Lamellarins C and U demonstrated potent cytotoxicity against 10 human tumor cell lines (A549, HCT-116, LOX IMVI, MALME-3M, MCF-7, MOLT-4, OVCAR-3, PC-3, SF-295, UO-31) with IC50's ranging from 0.4 to 19.4 nM.4 Lamellarin D has potent cytotoxic activity against various tumor cells, especially to human prostate cancer cells (DU-145, LNCaP) and leukemia cells(K562). Lamellarin D is a potent inhibitor of DNA topoisomerase I90,91 and a potent pro-apoptotic agent with cytotoxic action that is fully maintained in MDR cells compared to the sensitive parental cell line. Lamellarin D maintained a marked cytotoxicity toward cell lines resistant to the reference topoisomerase I poison camptothecin. Bailly's group hypothesized that topoisomerase I is not the only cellular target for camptothecin, and lamellarin D acts on cancer cell mitochondria to induce apoptosis. Such a mechanism would reinforce the pharmacologic interest of the lamellarins and define lamellarin D as a lead in the search for treatments against chemoresistant cancer cells.Lamellarins I , K , and L exhibited comparable and significant cytotoxicity against P388 and A549 culturedcancer cell lines (IC50 _ 0.5 nM against each cell line). The tri-*O*-acetyl derivative of lamellarin K showed remarkable selectivity against the A549 human lung cancer cell line (IC50 _ 7.6 nM). In the NCI 60 cell-line panel, lamellarin N showed some selectivity toward the melanoma cell lines . Compounds llamellarin L triacetate , and lamellarin F have shown excellent activities against colorectal cancer cells (COLO-205). The lamellarin analogues were tested for activity against erythroleukemia, lung carcinoma, malignant

melanoma, colon adenocarcinoma, prostate carcinoma, breast adenocarcinoma, ovary adenocarcinoma, cervix epithelioid carcinoma, and pancreatic epitheloid carcinoma.[3]

Furans derivatives belong to aromatic heterocyclic group, consequently they are important structural fragment in many pharmaceutical and chemical compounds.[4] Furans compounds have been found to show nematocidal,[5] insecticidal,[6] antibacterial,[7] antifungal,[8] antiviral,[9] antioxidant activity[10] and they are, farther, potent biological mediators in the pathophysiology of inflammatory disorders, in particular asthma. Also, a recent study demonstrated that some furan derivatives could inhibit lipopolysaccharide (LPS)-stimulated production of nitric oxide (NO) and tumor necrosis factor (TNF)-α in the cultures of RAW 264 macrophages *in vitro*. In addition, these furan derivatives could not only inhibit cyclooxygenases (COXs) and 5-lipoxygenase activities but also inhibit COX-2 by-times more selectively than COX-1. Furthermore, they had more potent analgesic and anti-inflammatory effects than indomethacin, a conventional non-steroidal anti-inflammatory drug, in rats and mice without the ulcerogenic activity.[11] Is also known that furan derivates are finding new uses in organic and polymer synthesis applications including the pharmaceutical, flavors e fragrances, graphic arts and organic intermediates industries[12].

1.4 The pyrrole and furan chemistry

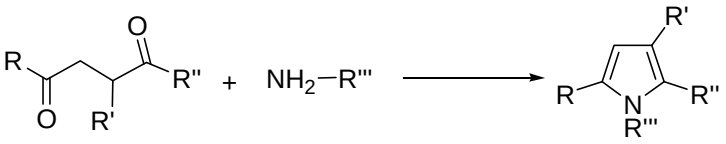
Pyrrole is a five membered nitrogen containing planar heterocyclic ring system exhibiting aromaticity and π-excessive character. The aromatic character of this heterocycle is due to the delocalization of the lone pair electrons from the hetero nitrogen atom to the π-system. Furan is a five membered heterocyclic, oxygen-containing, unsaturated ring compound. The heteroatom has at least one pair of non-bonding electrons that may combine with the four π-electrons of the double bonds to produce an annulene having an aromatic sextet of electrons. The heteroatom, O, becomes sp^2-hybridized and acquires a positive charge as its

electron pair is delocalized around the ring. An easily observed consequence of this delocalization is a change in dipole moment compared with the analogous saturated heterocycles, which all have strong dipoles with the heteroatom at the negative end. As expected, the aromatic heterocycles have much smaller dipole moments, or in the case of pyrrole a large dipole in the opposite direction. An important characteristic of aromaticity is enhanced thermodynamic stability, and this is usually demonstrated by relative heats of hydrogenation or heats of combustion measurements. Among other five membered ring systems such as furan and thiophene, pyrrole exhibits greater aromaticity than furan and less aromaticity than thiophene. This order of aromaticity is due to the extent of the involvement of the lone pair electrons on the heteroatom to the aromatic sextet and this involvement depends upon the electronegativity of the heteroatom. For instance, in thiophene the sulfur atom is less electronegative and thus the lone pair electrons are loosely held in its outer orbital leading to enhanced availability in the aromatic sextet as compared to the cases of pyrrole and furan. Furthermore, the high reactivity of pyrrole ring is due to its π-excessive character in which five sp^2 hybridized atoms sustain six π-electrons. Another characteristic of aromatic systems, of particular importance to chemists, is their pattern of reactivity with electrophilic reagents. Whereas simple cycloalkenes generally give addition reactions, aromatic compounds tend to react by substitution. Expectedly, pyrrole readily undergoes electrophilic aromatic substitution reactions. Pyrroles are more reactive towards electrophilic substitution than furan, thiophene and benzene. This particular reactivity has always attracted interest and we were made different methodologies for their synthesis

1.5 Synthesis of pyrroles

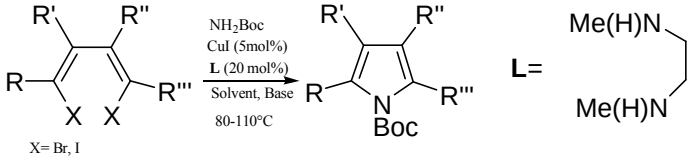
Among the traditional methods of synthesis of the pyrrole nucleus has included the synthesis of Knorr The Paal-Knorr pyrrole synthesis is the condensation of a

1,4-dicarbonyl compound with an excess of a primary amine or ammonia to give a pyrrole. The reaction can be conducted under neutral or weakly acidic conditions. Addition of a weak acid such as acetic acid accelerates the reaction, but the use of amine/ammonium hydrochloride salts or reactions at pH < 3 lead to furans as main products.(*Scheme 1*)



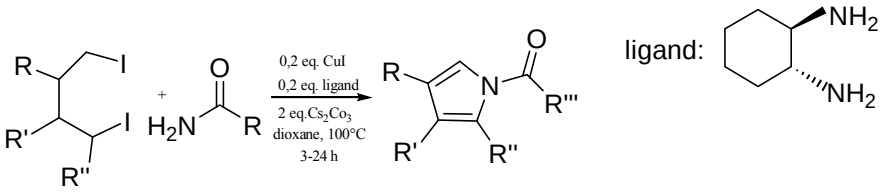
Scheme 1

Recently a highly efficient Cu-catalyzed tandem C−N bond-forming reaction of 1,4-dihalo-1,3-dienes has been developed. The transformation allows the synthesis of pyrroles and heteroarylpyrroles with a wide variety of functional groups and substitution patterns from readily available precursors.[13] *(Scheme 2)*



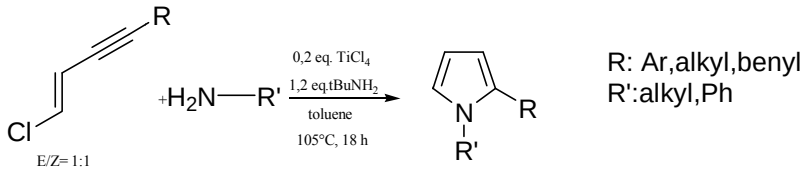
Scheme 2

Another efficient copper-catalyzed double alkenylation of amides with (1*Z*,3*Z*)-1,4-diiodo-1,3-dienes affords di- or trisubstituted *N*-acylpyrroles in good yields using CuI as the catalyst, Cs_2CO_3 as the base, and *rac-trans-N,N'*-dimethylcyclohexane-1,2-diamine as the ligand.[14] (*Scheme 3)*



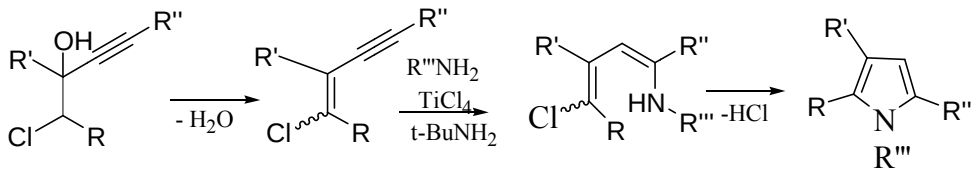
Scheme 3

Shown below are two examples of titanium-catalyzed reactions leading to the formation of pyrrole systems; Indeed it is known that titanium-catalyzed intermolecular hydroaminations enable efficient, user-friendly one-pot reactions for the preparations of 2-substituted and fully substituted pyrroles from (*E*/*Z*)-chloroenynes and easily accessible α-haloalkynols, respectively.[15] *(Scheme 4)*



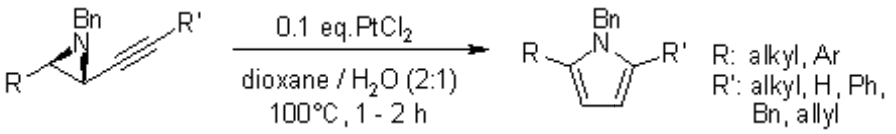
Scheme 4

Also titanium-catalyzed intermolecular hydroaminations of (*E*/*Z*)-chloroenynes enabled an efficient pyrrole synthesis, which set the stage for the development of a user-friendly one-pot reaction for the regioselective preparation of fully substituted pyrroles from easily accessible α-haloalkynols.[16] *(Scheme 5)*



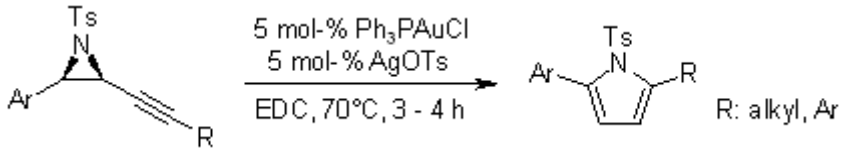
Scheme 5

Highly substituted furans were conveniently synthesized by the platinum-catalyzed reaction of propargylic oxiranes. Propargylic aziridines were also reacted with the platinum catalyst to produce the corresponding substituted pyrroles in good yields.[17] (*Scheme 6)*



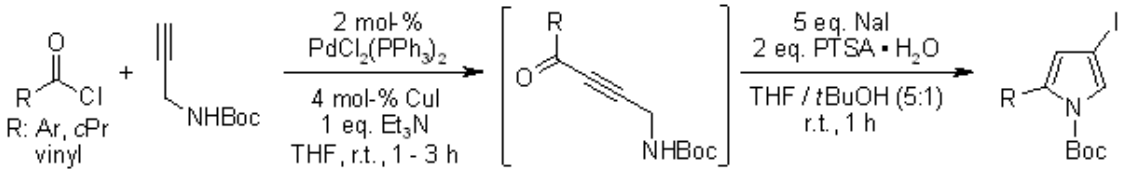
Scheme 6

Aryl-substituted *N*-tosyl alkynyl aziridines undergo a gold-catalyzed ring expansion to afford 2,5-substituted pyrrole products. Depending on the the counterion to the gold catalyst and the solvent, a ring-expansion and rearrangement leads to 2,4-substituted pyrroles.[18] (*Scheme 7)*



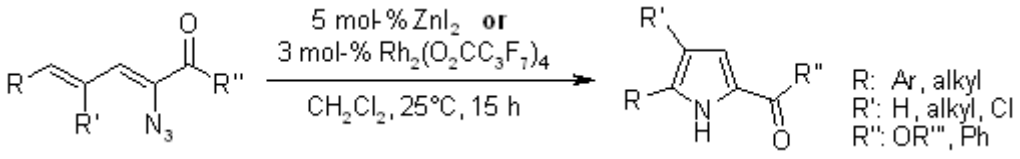
Scheme 7

(Hetero)aryl-, alkenyl-, and selected alkyl-substituted acid chlorides can be efficiently coupled with *N*-Boc-protected propargylamine to produce ynones which are converted to 2-substituted *N*-Boc-4-iodopyrroles in a one-pot reaction. Upon addition of a further alkyne, another Sonogashira coupling can be carried out in a one-pot fashion.[19] *(Scheme 8)*



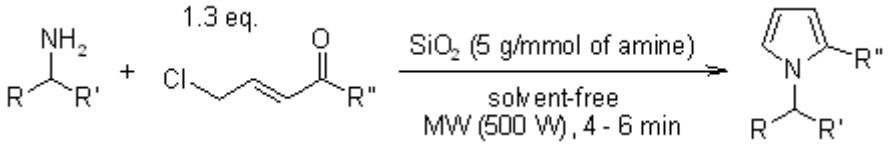
Scheme 8

A range of 2,5-disubstituted and 2,4,5-trisubstituted pyrroles can be synthesized from dienyl azides at room temperature using ZnI_2 or $Rh_2(O_2CC_3F_7)_4$ as catalysts.[20](*Scheme 9)*



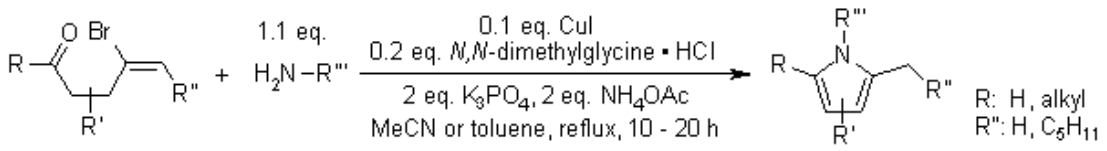
Scheme 9

An efficient, solvent-free, microwave-assisted coupling of chloroenones and amines on the surface of silica gel gave 1,2-disubstituted homochiral pyrroles in good yields[21] (*Scheme 10)*



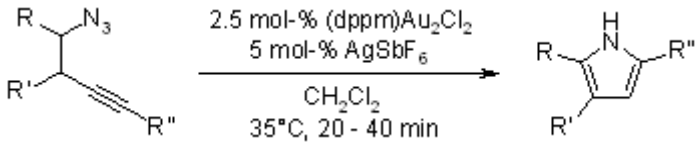
Scheme 10

The CuI/*N,N*-dimethylglycine-catalyzed reaction of amines with γ-bromo-substituted γ,δ-unsaturated ketones in the presence of K_3PO_4 and NH_4Oac gave the corresponding polysubstituted pyrroles in very good yields.[22] (*Scheme 11)*



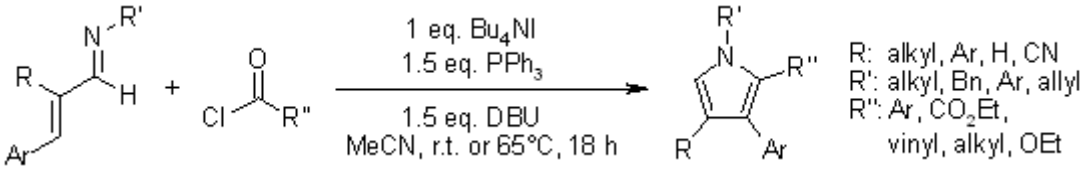
Scheme 11

A mild, gold(I)-catalyzed acetylenic Schmidt reaction of homopropargyl azides gave regiospecific substituted pyrroles. [23] (*Scheme 12)*



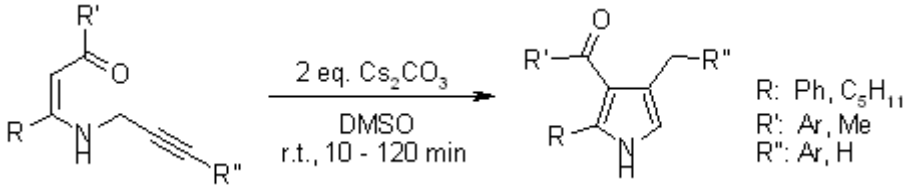
Scheme 12

A one-step reaction to assemble pyrroles from α,β-unsaturated imines and acid chlorides is mediated by triphenylphosphine, which eliminates phosphine oxide to allow cyclization. This reaction has been employed to access broad range of pyrroles via modulation of the two building blocks and applied as well to the synthesis of lukianol.[24] (*Scheme 13)*



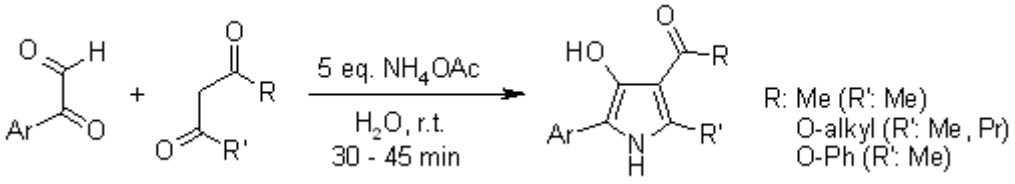
Scheme 13

N-Propargylic β-enaminones are common intermediates for the synthesis of polysubstituted pyrroles and pyridines. In the presence of Cs_2CO_3 *N*-propargylic β-enaminones are cyclized to pyrroles in good to high yields, whereas CuBr leads to pyridines.[25] (*Scheme 14)*



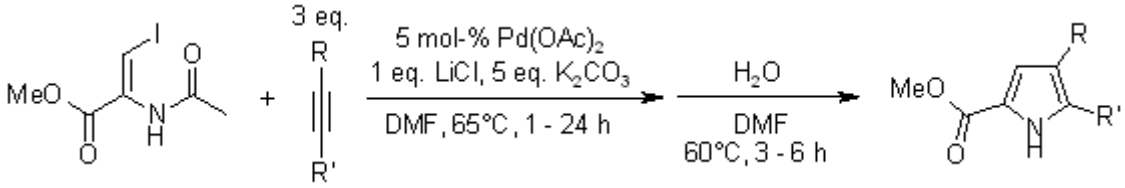
Scheme 14

Various 2-alkyl-5-aryl-(1*H*)-pyrrole-4-ol derivatives were synthesized via a multicomponent reaction of β-dicarbonyl compounds with arylglyoxals in the presence of ammonium acetate in water at room temperature.[26] (*Scheme 15)*



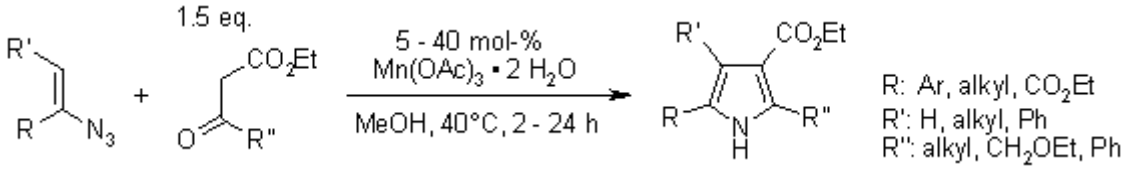
Scheme 15

An efficient and regioselective palladium-catalyzed cyclization of internal alkynes and 2-amino-3-iodoacrylates gave good yields of highly functionalized pyrroles.[27] (*Scheme 16)*



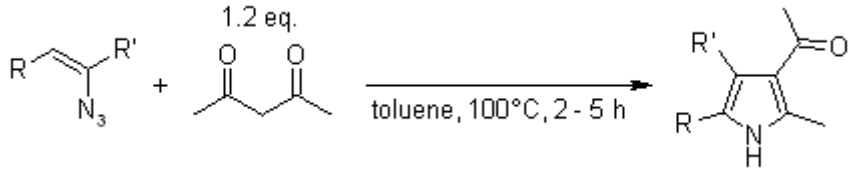
Scheme 16

A Mn(III)-catalyzed reaction of vinyl azides with 1,3-dicarbonyl compounds gave a broad range of polysubstituted N-H pyrroles in good yields.[28] (*Scheme 17)*



Scheme 17

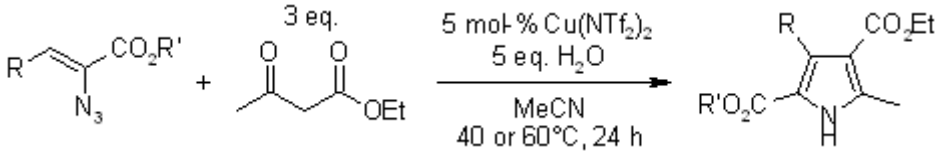
Two methods for the regioselective synthesis of tetra- and trisubstituted *N*-H pyrroles from starting vinyl azides have been developed: A thermal pyrrole formation via the 1,2-addition of 1,3-dicarbonyl compounds to 2H-azirine intermediates generated in situ from vinyl azides and a Cu(II)-catalyzed synthesis with ethyl acetoacetate through a 1,4-addition.[29] (*Scheme 18)*



Scheme 18

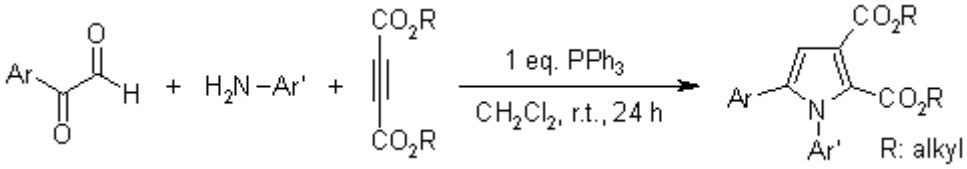
The synthesis of highly functionalized pyrroles is described. The sequence involves the preliminary preparation of α-aminohydrazones by Michael addition of primary amines to 1,2-diaza-1,3-butadienes. The treatment of these compounds with dialkyl acetylenedicarboxylates produces α-(N-enamino)-

hydrazones that were converted into the corresponding pyrroles by Lewis acid-catalyzed ring closure. A screening of several Lewis/Brønsted acid catalysts was also performed.[30] (*Scheme 19)*



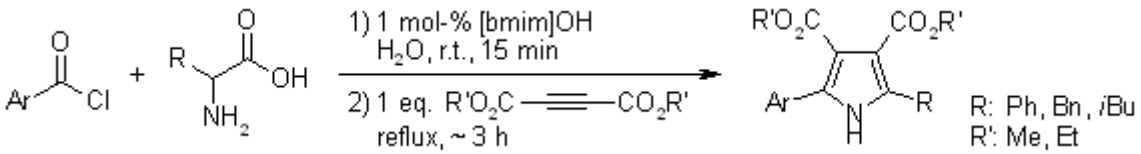
Scheme 19

A new and efficient three-component reaction between dialkyl acetylenedicarboxylates, aromatic amines, triphenylphosphine, and arylglyoxals afforded polysubstituted pyrrole derivatives in high yields. The reactions were performed in dichloromethane at room temperature and under neutral conditions.[31] (*Scheme 20)*



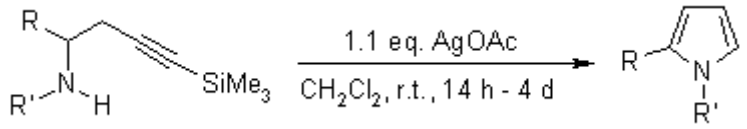
Scheme 20

A basic functionalized ionic liquid, 1-butyl-3-methylimidazolium hydroxide ([bmim]OH), catalyzed the three-component condensation reaction of acid chlorides, amino acids, and dialkyl acetylenedicarboxylates in water to afford functionalized pyrroles in high yields.[32] (*Scheme 21)*



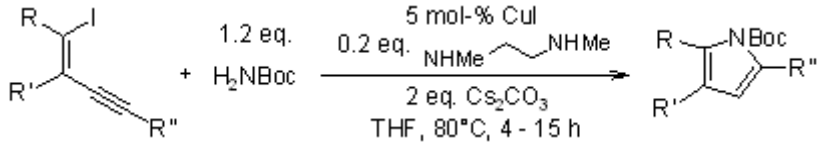
Scheme 21

A silver(I)-promoted oxidative cyclization of homopropargylamines at room temperature provides pyrroles. Homopropargylamines are readily available by the addition of a propargyl Grignard reagent to Schiff bases.[33] (*Scheme 22)*



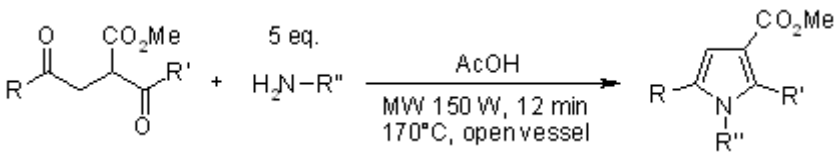
Scheme 22

A general, highly flexible Cu-catalyzed domino C-N coupling/hydroamination reaction constitutes a straightforward alternative to existing methodology for the preparation of pyrroles and pyrazoles.[34] (*Scheme 23*)



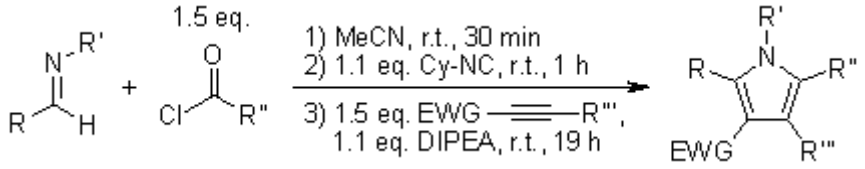
Scheme 23

An efficient and highly versatile microwave-assisted Paal-Knorr condensation of various 1,4-diketones gave furans, pyrroles and thiophenes in good yields. In addition, transformations of the methoxycarbonyl moiety, such as Curtius rearrangement, hydrolysis to carboxylic acid, or the conversion into amine by reaction with a primary amine in the presence of Me_3Al, are described.[35](*Scheme 24)*



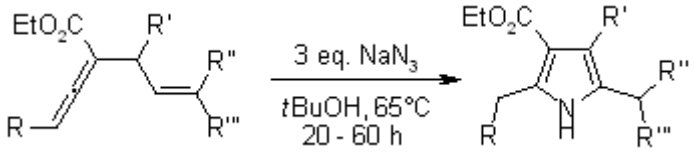
Scheme 24

A direct synthesis of pyrroles from imines, acid chlorides, and alkynes mediated by isocyanides proceeds with a range of substrates, providing a method to generate various pyrroles in high yield. Mechanistic studies suggest a generation of imino analogues of münchnones, which can undergo in situ coupling with alkynes to liberate isocyanate and form the pyrrole product.[36]*(Scheme 25)*



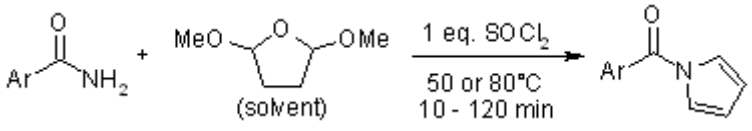
Scheme 25

The nucleophilic addition of sodium azide to 1,2-allenyl esters □egion- and stereoselectively generates vinyl azides in excellent yields. A sequential reaction for the synthesis of pyrroles using 1-allyllic 1,2-allenyl esters as substrates is developed on the basis of a domino process involving nucleophilic addition, cycloaddition, denitrogenation, and aromatization.[37]. *(Scheme 26)*



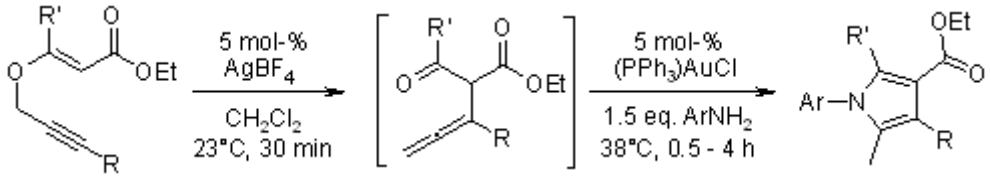
Scheme 26

The synthesis of N-acylpyrroles from primary aromatic amides and excess 2,5-dimethoxytetrahydrofuran in presence of one equivalent of thionyl chloride offers short reaction times, mild reaction conditions, and easy workup.[38](*Scheme 27)*



Scheme 27

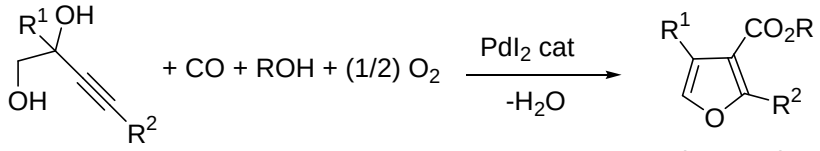
Propargyl vinyl ethers and aromatic amines are effectively converted into tetra- and pentasubstituted 5-methylpyrroles through a silver(I)-catalyzed propargyl-Claisen rearrangement, an amine condensation, and a gold(I)-catalyzed 5-exo-dig heterocyclization in a convenient one-pot process.[39](*Scheme 28)*



Scheme 28

1.6 Synthesis of furans

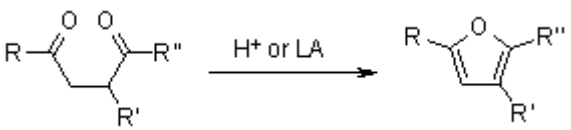
Gabriele et al. reported that a novel, convenient and atom-economical method for the preparation of this important class of furans derivatives, is based on direct oxidative carbonylation of readily available 3-yne-1,2-diols [40a] *(Scheme 29)*



R^1, R^2 = H, alkyl, aryl;
R = alkyl

(Scheme 29)

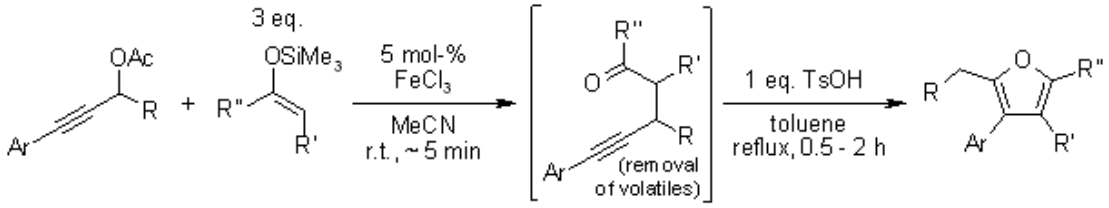
The acid-catalyzed cyclization of 1,4-dicarbonyl compounds known as the Paal-Knorr synthesis is one of the most important methods for the preparation of furans. As many methods for the synthesis of 1,4-diones have recently been developed, the synthetic utility of the Paal-Knorr reaction has improved.(*Scheme 30)*



Scheme 30

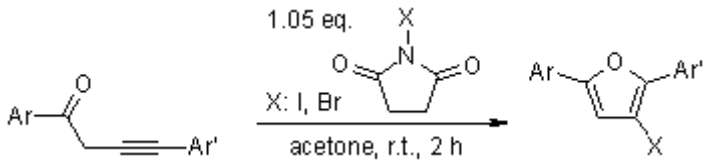
A comparison of the cyclizations of meso- and dl-3,4-diethyl-2,5-hexanediones showed that these compounds cyclize at unequal rates, and that the stereochemical configuration of unchanged dione is preserved during the reaction.[40b]

Recently in literature, an efficient $FeCl_3$-catalyzed substitution reaction of propargylic acetates with enoxysilanes under mild conditions affords corresponding γ-alkynyl ketones. A subsequent TsOH-catalyzed cyclization without purification of the γ-alkynyl ketone intermediates, offers a straightforward synthetic route to tri- or tetrasubstituted furans.(*Scheme 31)*.[41]



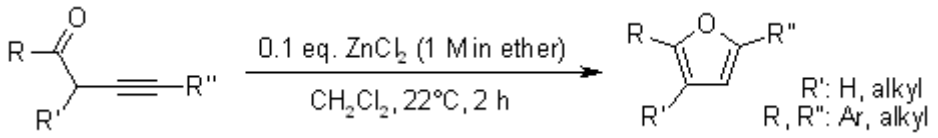
. ***Scheme 31***

Is also known that a 5-*Endo-dig* electrophilic cyclization of 1,4-diaryl but-3-yn-1-ones with NBS or NIS/acetone and ICl/CH_2Cl_2 provides 3-halo-2,5-diarylfurans with high yields. (*Scheme 32*)[42]



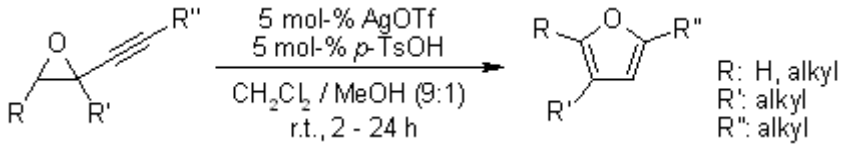
Scheme 32

Zinc chloride-catalyzed 5-endo-dig cycloisomerization of 1,4-di- and 1,2,4-trisubstituted but-3-yn-1-ones in dichloromethane at room temperature provides 2,5-di- and 2,3,5-trisubstituted furans in high yields. (*Scheme 33*) [43]



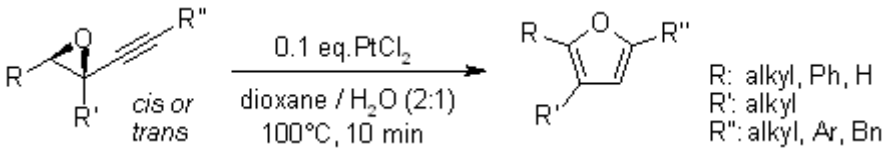
(*Scheme 33*)

A convenient, silver(I)-catalyzed reaction of alk-1-ynyl oxiranes in the presence of *p*-toluenesulfonic acid and methanol gives functionalized furans. Evidence supported a cascade mechanism. (*Scheme 34*) [44.]



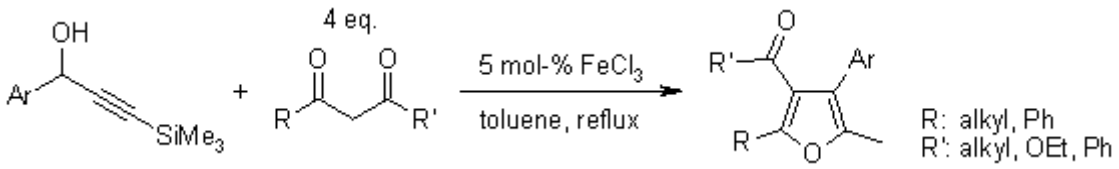
(*Scheme 34*)

Highly substituted furans were conveniently synthesized by the platinum-catalyzed reaction of propargylic oxiranes. Propargylic aziridines were also reacted with the platinum catalyst to produce the corresponding substituted furans in good yields. (*Scheme 35*) [45.]



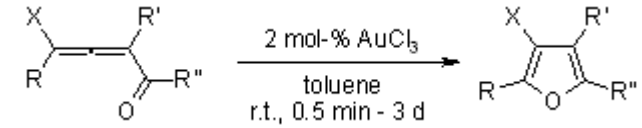
Scheme 35

An efficient $FeCl_3$-catalyzed tandem propargylation-cycloisomerization reaction of propargylic alcohols or acetates with 1,3-dicarbonyl compounds leads to highly substituted furans. (*Scheme 36*) [46].



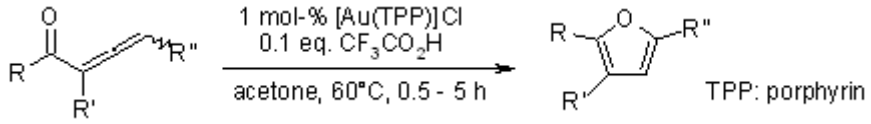
(*Scheme 36*)

Different gold catalysts effect either selective bromine migration or hydrogen shift in haloallenyl ketones, leading to the formation of 3- or 2-bromofurans, respectively. $AuCl_3$-catalyzed transformations include 1,2-halogen migrations via proposed halirenium intermediates and allow for mild and efficient synthesis of various types of 3-halofurans. (*Scheme 37*) [47]



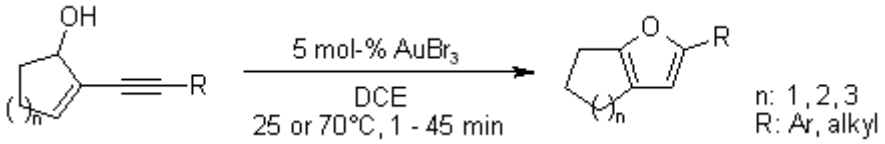
Scheme 37

Gold(III) porphyrin-catalyzed cycloisomerization of allenones gave the corresponding furans in good to excellent yields (up to 98%) and with quantitative substrate conversions. The Au(III) catalyst is recyclable (*Scheme 38*) [48].



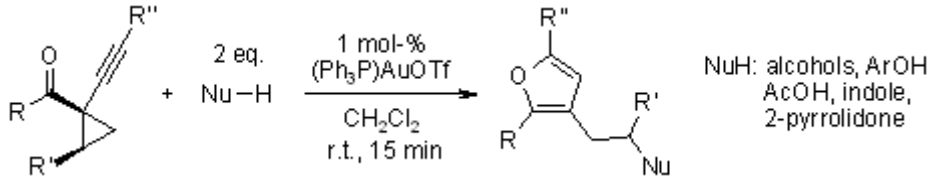
Scheme 38

An efficient synthesis of structurally diverse fused furans in good yields from 2-alkynylcycloalk-2-enols via gold(III) bromide catalyzed cycloisomerization was achieved under moderate reaction conditions (*Scheme 39*) [49].



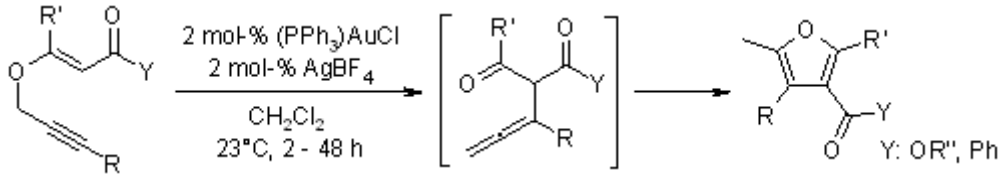
(*Scheme 39*)

A mild, gold-catalyzed cascade reaction provides efficient access to highly substituted furans. The substrates can be readily prepared from the corresponding enones through cyclopropanation.(*Scheme 40*).[50.]



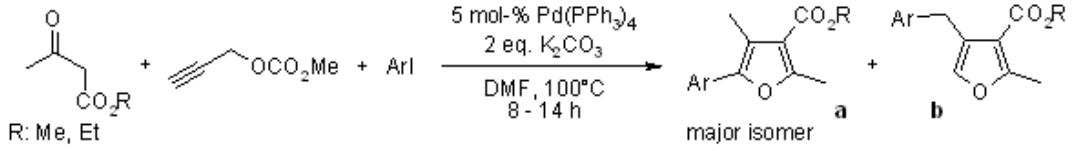
Scheme 40

Easily accessible propargyl vinyl ethers react in a cascade reaction of propargyl-Claisen rearrangement and heterocyclization catalyzed by cationic triphenylphosphine gold(I) to give tri- and tetrasubstituted furans.(*Scheme 41*).[51]



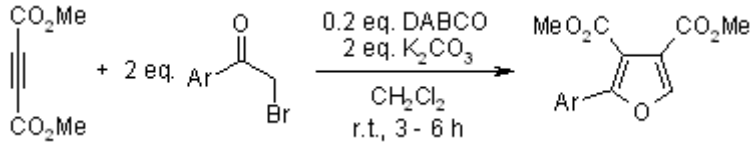
Scheme 41

A new three-component cyclization catalyzed by palladium produces polysubstituted furans in good yields from readily available substrates. (*Scheme 42*). [52]



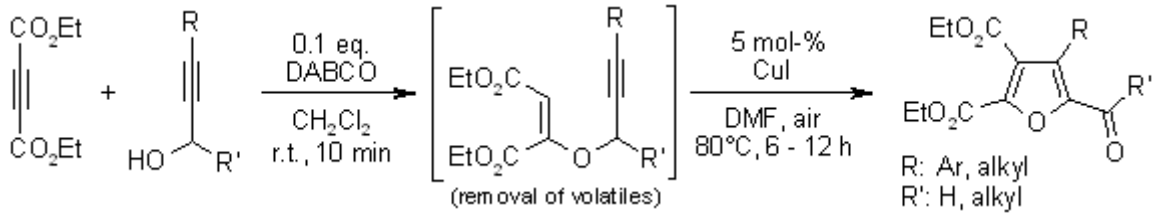
(*Scheme 42*)..

DABCO-catalyzed reactions of α-halo carbonyl compounds with dimethyl acetylenedicarboxylate (DMAD) at room temperature gave polysubstituted furans and highly functionalized 2*H*-pyrans in good yields. .(*Scheme 43*).[53]



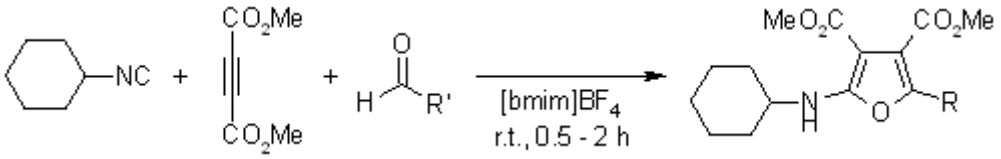
Scheme 43

A mild and efficient domino reaction allows a regiospecific synthesis of polysubstituted furans in moderate yields via a copper(I)-catalyzed rearrangement/dehydrogenation oxidation/carbene oxidation sequence of 1,5-enynes in situ formed from alkynols and diethyl but-2-ynedioate. .(*Scheme 44*).[54]



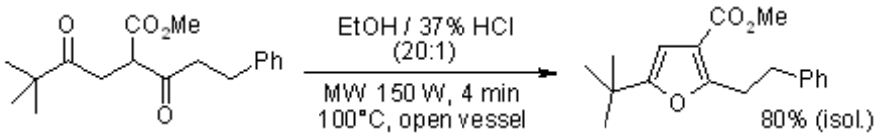
Scheme 44

The three-component coupling of aldehyde, dimethyl acetylenedicarboxylate (DMAD) and cyclohexyl isocyanide proceeds efficiently in [bmim]BF_4 ionic medium under extremely mild conditions to afford 2-aminofurans in high yields. The recovered ionic liquid was reused for five to six times with consistent activity (*Scheme 45*).[55]



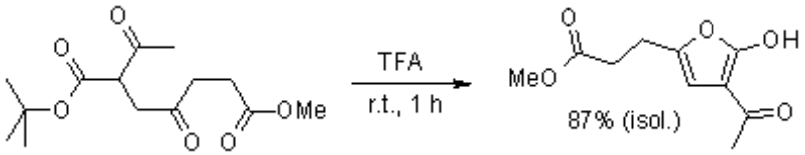
Scheme 45

An efficient and highly versatile microwave-assisted Paal-Knorr condensation of various 1,4-diketones gave furans, pyrroles and thiophenes in good yields. In addition, transformations of the methoxycarbonyl moiety, such as Curtius rearrangement, hydrolysis to carboxylic acid, or the conversion into amine by reaction with a primary amine in the presence of Me_3Al, are described. .(*Scheme 46*).[56].



Scheme 46

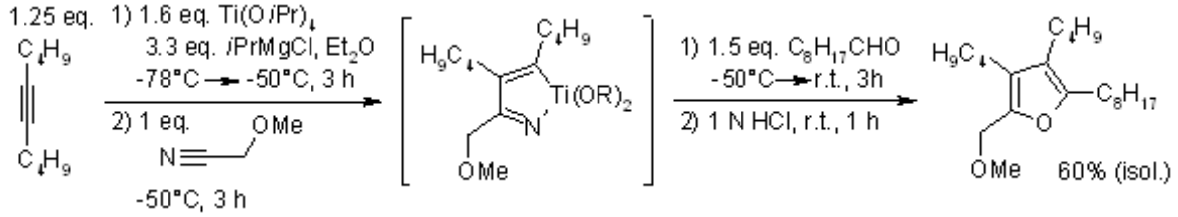
Substituted 2-hydroxy-3-acetylfurans are synthesized by alkylation of *tert*-butyl acetoacetate with an α-haloketone followed by treatment of the obtained intermediate with trifluoroacetic acid (TFA). A second alkylation of the intermediate followed by treatment with trifluoroacetic acid provides access to disubstituted 2-methylfurans. (*Scheme 47*).[57].



Scheme 47

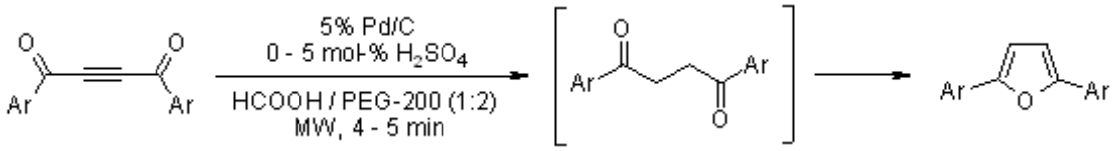
Coupling of acetylene, nitrile, and a titanium reagent generated new azatitanacyclopentadienes in a highly regioselective manner. The subsequent reaction with sulfonylacetylene and electrophiles gave substituted pyridines virtually as a single isomer. Alternatively, the reaction of azatitanacyclopentadienes with an aldehyde or another nitrile gave furans or

pyrroles having four different substituents again in a regioselective manner. (*Scheme 48*).[58]



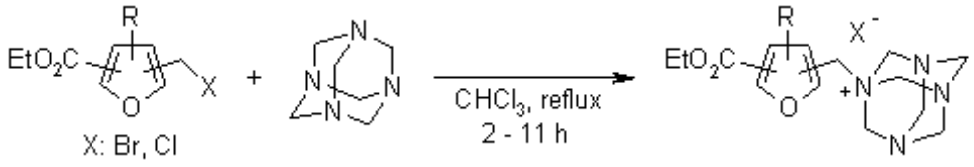
Scheme 48

Various di- and triarylfurans were prepared in high yields from but-2-ene-1,4-diones and but-2-yne-1,4-diones using formic acid in the presence of a catalytic amount of palladium on carbon in poly(ethylene glycol)-200 as solvent under microwave irradiation. (*Scheme 49*).[59]



Scheme 49

All isomers of (aminomethyl)furancarboxylic acids were prepared by the Delepine reaction from alkyl (halomethyl)furancarboxylates. Treatment of the initially formed quaternary salt with an ethanolic HCl solution gave the salts of the corresponding unstable amino acid esters. Hydrolysis of the crude esters yielded stable amino acid salts. (*Scheme 50*) [60]



(*Scheme 50*)

1.7 Conclusion

Heterocycles are especially important in chemical and pharmaceutical industries. It seems that industrial people have been using mostly the traditional and conventional transformations for the synthesis of heterocycles, perhaps because those reactions are reliable and robust and proceed generally at low cost. However, it is also true that some of those reactions are accompanied with waste byproducts. In this sense, transition-metal catalyzed reactions minimize such waste and are in general environmentally friendly.

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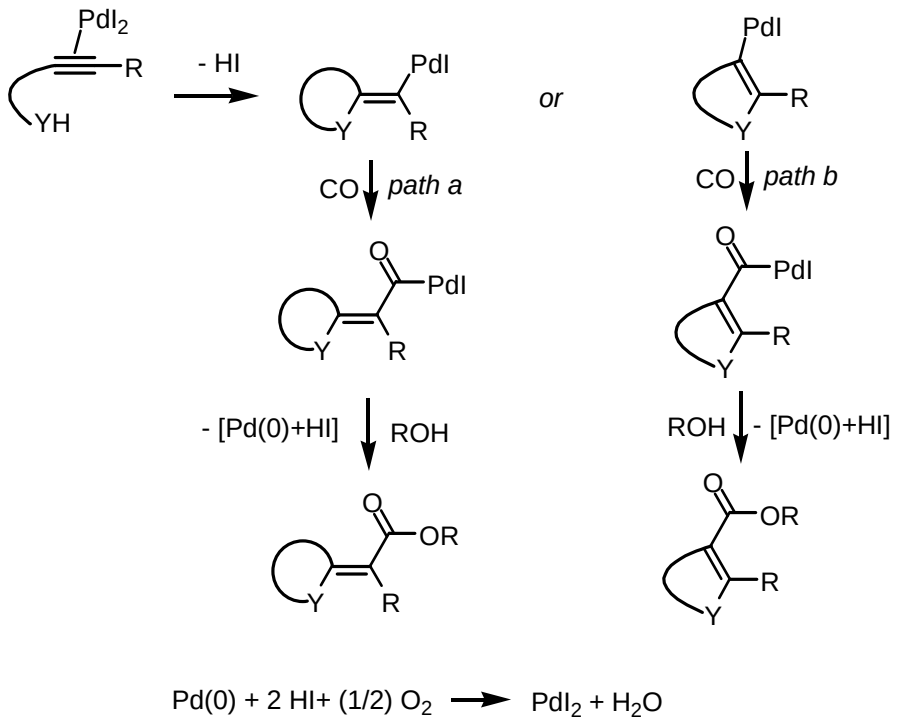
Chapter 2

2.1 Introduction

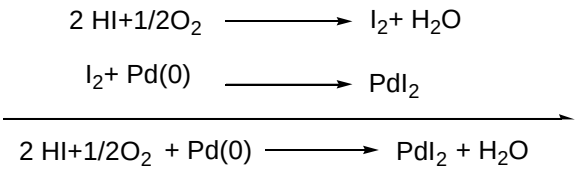
Carbonylation reactions represent a powerful tool for the direct preparation of carbonylated molecules starting from simple building blocks. In particular, carbonylation reactions of alkynes may be conducted under mild conditions using palladium catalysts (II). Recently, the catalytic system that has demonstrated a high degree of efficiency for these processes, is the PdI_2/KI [1]. This catalytic system allows the direct formation of heterocycles in excellent yields by cyclization-alkoxycarbonylation reactions starting from alkynes bearing a nucleophilic group in a suitable position. The general mechanism for these processes is shown in *Scheme 2.1* (anionic iodide ligands are omitted for clarity)



$$Pd(0) + 2\,HI + (1/2)\,O_2 \longrightarrow PdI_2 + H_2O$$

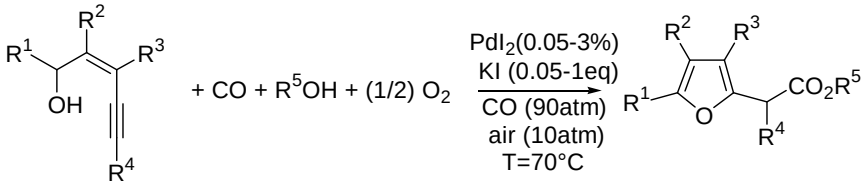
Scheme 2.1

The coordination of the triple bond to palladium allows the subsequent intramolecular nucleophilic attack. Two possible vinyl palladium species can be formed, according to the fact that attack is *exo* (mechanistic path a) or *endo* (mechanistic path b). The insertion of carbon monoxide in the vinyl-palladium species and subsequent nucleophilic attack of an alcohol give the product and Pd(0). Then, the Pd(0) is reoxidized by oxygen, present in the reaction mixture (Scheme 2.2).

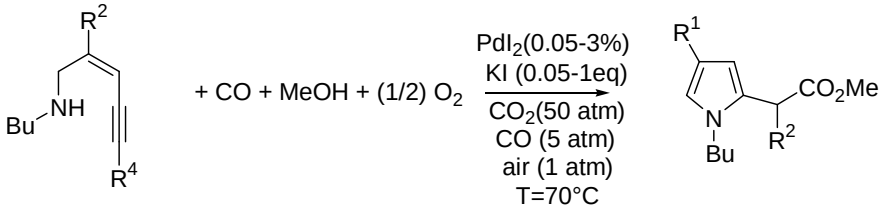


(Scheme 2.2)

Recently, several Pd-catalyzed oxidative cyclization-alkoxycarbonylation processes have been reported. For example, selective PdI_2- catalyzed synthesis of furan-2-acetic esters [2] and pyrrole-2-acetic esters [2] starting from 2-en-4-yn-ols (Eq. 2.1) and 2-en-4-ynyl-amines (Eq 2.2), respectively, were reported.

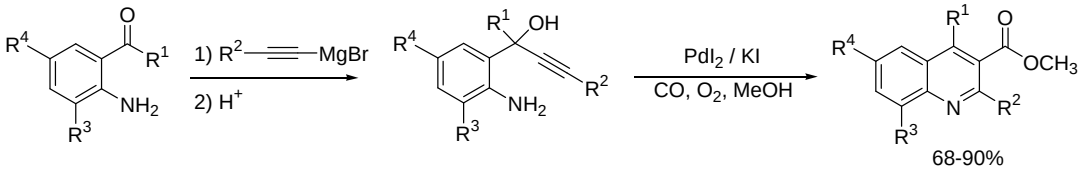


(50-81%) (2.1)



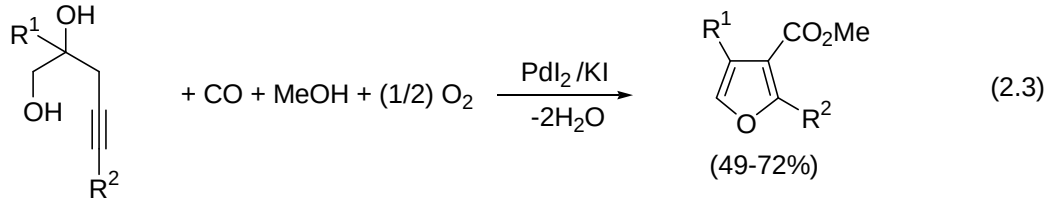
(62-65%) (2.2)

Another example is the synthesis of quinoline-3-acetic ester derivatives **3** by Pd-catalyzed heterocyclization-oxidative carbonylation-dehydration reaction of variously substituted 2-(1-hydroxy-2-alkynyl) anilines (Scheme 2.3). [3]



Scheme 2.3

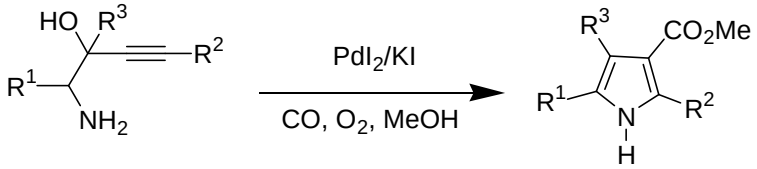
As a final example, an innovative synthesis of furan-3-carboxylic esters has been realized from 3-yn-1,2-diols (Eq 2.3):[4]



(2.3)

2.2 Synthesis of pyrrole-3-carboxylic esters

On the basis of the results obtained in the synthesis of heterocycles by cyclization-carbonylation processes described above, we have verified the possibility to extend this methodology to 1-amino-3-yn-2-ols for the synthesis of pyrrole-3-carboxylic esters (Eq 2.4).

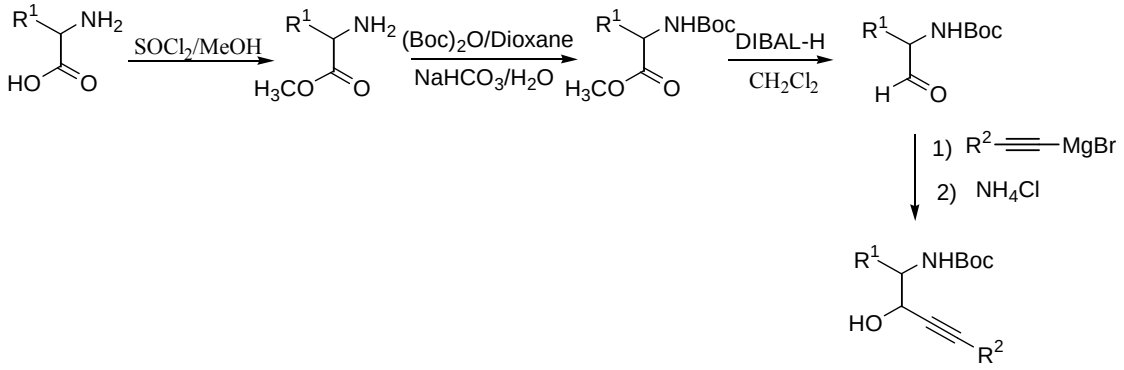


(2.4)

However, 1-amino-3-yn-2-ols with the free amino group are unstable, so it was necessary to protect it with the group *tert*-butoxycarbonyl (Boc). The *N*-Boc 1-amino-3-yn-2-ols were synthesized in two different ways:

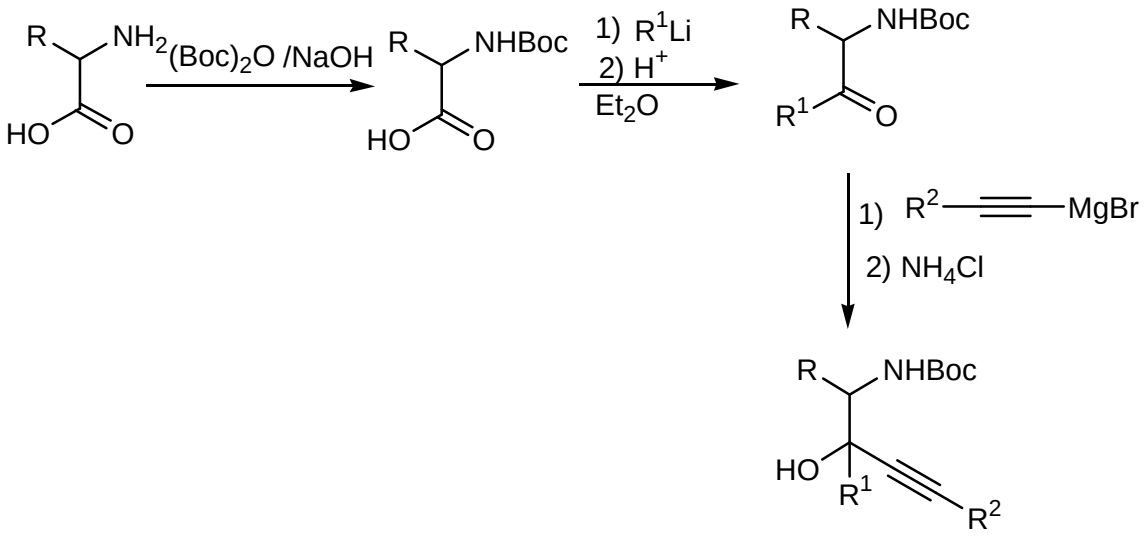
1) an α-amino acid ester, was protected by Boc and then reduced with DIBAL. The resulting product was allowed to react with the appropriate Grignard reagent,

finally leading to a mixture of diastereoisomers of *N*-Boc 1-amino-3-yn-2-ols. (Scheme 2.4).



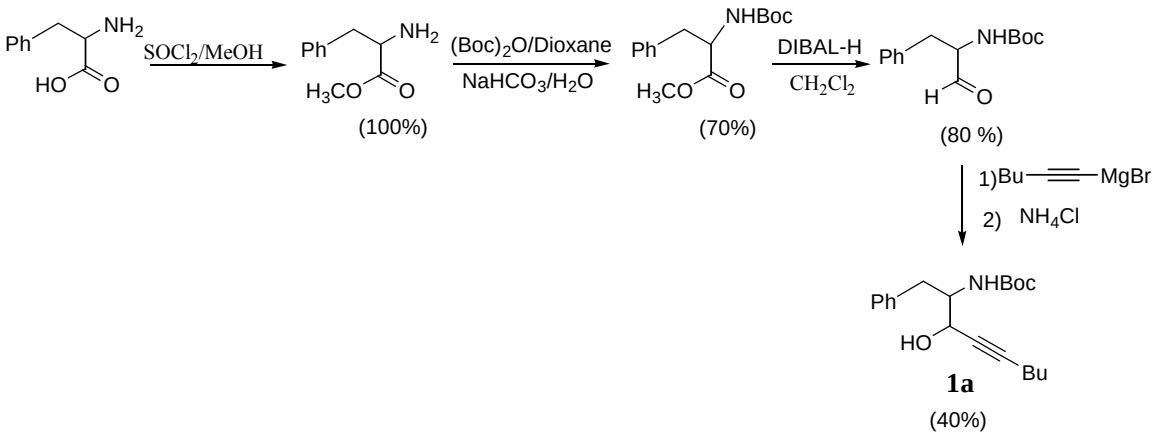
Scheme 2.4

2) In the second case, the starting amino acid was protected with Boc, then reacted with the appropriate organolithium reagent and finally with the appropriate Grignard reagent
(Scheme 2.5).



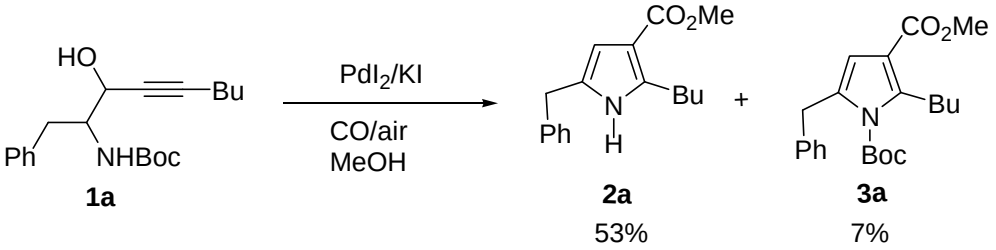
Scheme 2.5

The first substrate that has been studied is *N*-Boc-2-amino-1-phenyl-4-yn-3-ol (**1a**) according to Scheme 2.6.



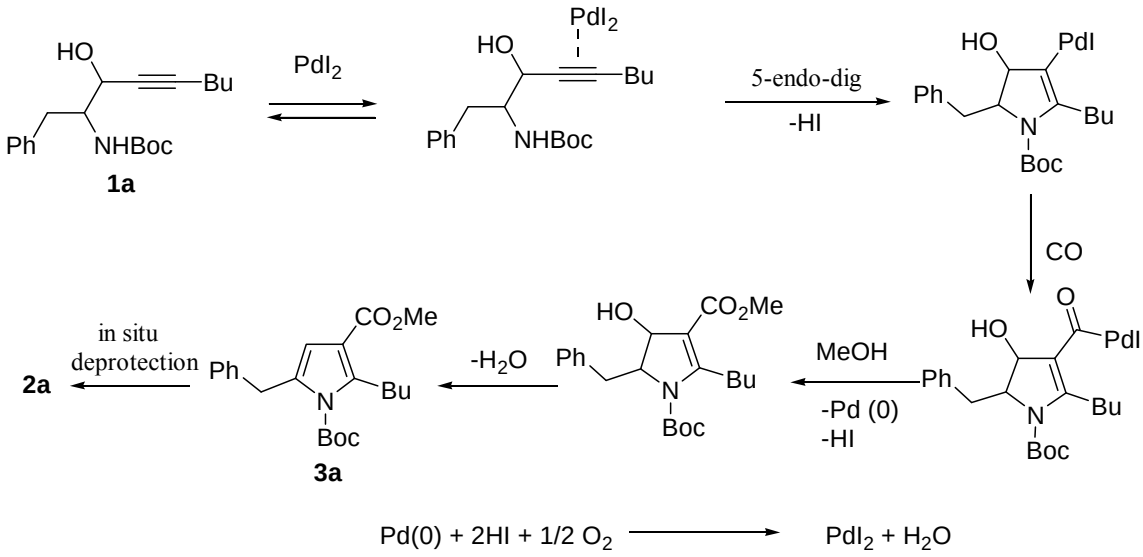
Scheme 2.6

N-Boc-2-amino-1-phenyl-non-4-yn-3-ol (**1a**) was introduced in an autoclave in the presence of KI and PdI_2 in a molar ratio PdI_2/KI/**1a**=1:10:50 and methanol (concentration of **1a** = 0.2 M). The autoclave was then pressurized with 16 atm of CO and 4 atm of air, and the mixture was let to react at a temperature of 80 ° C for 8h. After cooling, the autoclave was degassed, and the crude mixture purified by column chromatography using silica gel (SiO_2) as stationary phase and hexane / AcOEt (9:1), as eluent. Two products were isolated, which were characterized by mass spectrometry, IR and NMR spectroscopy. The most abundant product was identified as methyl 5-benzyl-2-butyl-1*H*-pyrrole-3-carboxylate (**2a**) and recovered with a yield of 53%. On the other hand, the less abundant product was identified as the corresponding Boc-protected carbonylated pyrrole, (**3a**) which that was obtained with a yield of 7% (Scheme 2.7).



Scheme 2.7

This result confirmed our initial hypothesis on the possibility to synthesize pyrrole-3-carboxylic esters by Pd-catalyzed cyclization-oxidative alkoxycarbonylation reaction. The plausible mechanism that may lead to compound **2a** is based on the coordination of the triple bond to PdI_2, followed by 5-endo-dig intramolecular nucleophilic attack of the nitrogen on the triple bond, to give a vinyl palladium iodide species. The latter undergoes insertion of CO, nucleophilic attack by MeOH and dehydration. Pd(0) is reoxidized by oxygen, present in the reaction mixture (Scheme 2.8).



Scheme 2.8

The carbonylation reaction of **1a** was then carried out for a shorter reaction time (3h) to verify whether, in these conditions, conversion of the substrate was complete. The result of the reaction showed a complete conversion and a higher selectivity towards the product (**2a**) (66% of the product **2a** and 8% of the product **3a**). This reaction was used as model in order to study in detail the effect of the variation of the reaction parameters on the behaviour of the process. The effect of the variation of the amount of KI was first studied. The results are shown in Table 2.1

Table 2.1 *Effect of the variation of the concentration of KI in the reaction of carbonylation of N-Boc-2-amino-1-fenilnon-4-in-3-ol. (1a)*[a]

PdI_2/KI/sub Molar Ratio	P_{CO}/P_{air} atm	T°C	t (h)	[*1a*] M	Conv %	Yield 2a[b] (%)	Yield 3a[b] (%)	Tot Yield (%)
1/10/50	16/4	80	3	0.2	100	66	8	74
1/100/50	16/4	80	3	0.2	100	42	12	54
1/2/50	16/4	80	3	0.2	100	52	22	74
1/50/50	16/4	80	3	0,2	100	42	15	57
1/5/50	16/4	80	3	0.2	100	60	15	75

[a]All reaction were carried out in MeOH as the solvent

[b]Isolated yield, based on starting **1a**

A PdI_2/KI ratio equal to 1 / 100 leads to a decrease of product **2a** and an increase of product **3a** with respect to the model-reaction (ratio of 1/10/50) and the same considerations can be made for the reactions carried out with PdI_2/KI ratios = 1 / 2 and 1 / 50.

On the other hand, using PdI_2 and KI in a molar ratio equal to 1 / 5, the yield of the product **2a** is comparable to the parent reaction, while the yield of product **3a** increases. This suggests that a ratio molar PdI_2/KI equal to 1 / 10 leads to better results.

The effect of the variation of the temperature on the reaction was then studied. Table 2.2 shows the reaction conditions and the results obtained by varying the temperature.

Table 2.2 *Effect of the variation of temperature in the reaction carbonylation of N-Boc-2-amino-1-phenyl-non-4-yn-3-ol* ***(1a)***[a]

PdI_2/KI/sub Molar Ratio	P_{CO}/P_{air} atm	T°C	t (h)	[*1a*] M	Conv(%)	Yield 2a[b](%)	Yield 3a[b](%)	Tot Yield (%)
1/10/50	16/4	80	3	0.2	100	66	8	74
1//10/50	16/4	100	3	0.2	100	14	18	32
1/10/50	16/4	60	3	0.2	70	38	-	38

[a] All reaction were carried out in MeOH as the solvent

[b] Isolated yield, based on starting **1a**

Carrying out the reaction at lower temperature (60° C), the conversion of the substrate and the yield of the **2a** decrease, while conducting the reaction at a temperature of 100 ° C, we observed the complete substrate conversion, but

reduced yields of product **2a** and **3a,** probably due to substrate or products decomposition under these conditions.

The effect of the variation of substrate concentration was also considered. Carrying out the reaction with a lower substrate concentration (0.05 M) leads to higher selectivity towards product **2a**, with slightly lower yields. On the other hand, carrying out the reaction at substrate concentration of 0.5 M leads to a selectivity comparable to that of the model reaction although with lower yields. The results are shown in Table 2.3

Table 2.3 *Effect of the variation of substrate concentration in carbonylation reaction of of N-Boc-2-amino-1-phenyl-non-4-yn-3-ol* ***(1a)***[a]

PdI_2/KI/sub Molar Ratio	P_{CO}/P_{air} atm	T°C	t (h)	[*1a*] M	Conv (%)	Yield 2a[b](%)	Yield 3a[b](%)	Tot Yield (%)
1/10/50	16/4	80	3	0.2	100	66	8	74
1//10/50	16/4	80	3	0.05	100	57	-	57
1/10/50	16/4	80	3	0.5	100	49	5	54

[a]All reaction were carried out in MeOH as the solvent

[b] Isolated yield, based on starting **1a**

Then, conducting the reaction under higher partial pressures of CO and air, but maintaining the CO/air ratio equal to 4, the exclusive formation of product **2a** was observed, with a yield comparable to the model reaction. However, in this case, a lower total yield is obtained. The results are shown in Table 2.4.

Table 2.4 *Effect of the variation of partial pressures of CO and air in the reaction of carbonylation of N-Boc-2-amino-1-phenyl-non-4-yn-3-ol* ***(1a)***[a]

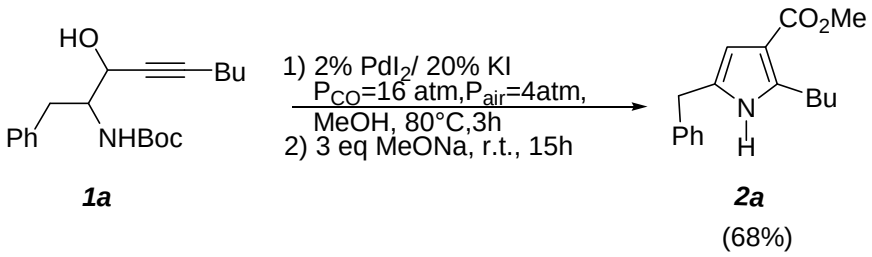
PdI_2/KI/sub Molar Ratio	P_{CO}/P_{air} atm	T°C	t (h)	[*1a*] M	Conv (%)	Yield 2a[b] (%)	Yield 3a[b] (%)	Tot Yield(%)
1/10/50	16/4	80	3	0.2	100	66	8	74
1//10/50	64/16	80	3	0.2	100	63	-	63

[a]All reaction were carried out in MeOH as the solvent

[b] Isolated yield, based on starting **1a**

We have found that product **3a** can be easily converted into **2a**, simply by adding to the crude reaction mixture 3 equiv of MeONa and then allowing the mixture to stir at room temperature for 15h. Under these conditions, the reaction

crude deriving from the model reaction led to the exclusive formation product **2a** with a yield of 68% (Scheme 2.9).



1a ***2a***

(68%)

Scheme 2.9

From the evaluation of the effects of the variation of the single reaction parameters, it was possible to determine the best operating conditions leading to a greater selectivity towards **2a** and simultaneously to a higher total yield of products. The optimized conditions are as follows:

-PdI_2 \ KI \ Sub: 1 \ 10 \ 50 Molar ratio;

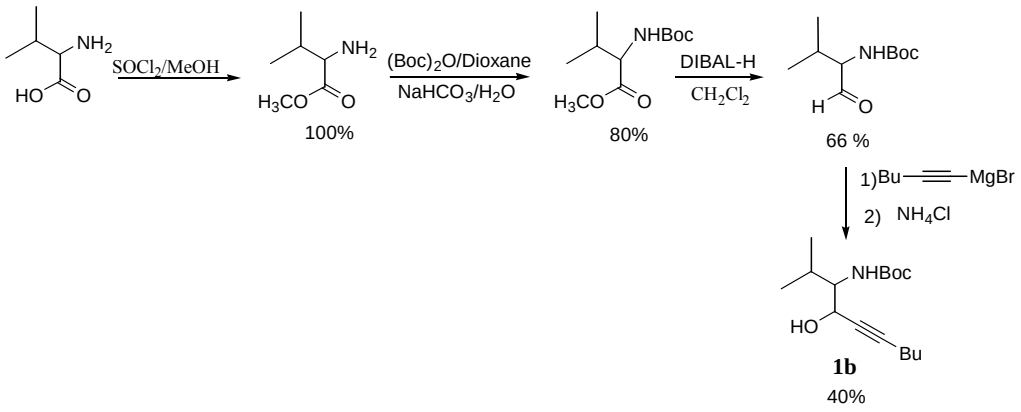
-Concentration of *N*-Boc-2-amino-1-fenilnon-4-in-3-ol (**1a**) 0.2 M in MeOH;

-Reaction temperature: 80 ° C;

-Reaction time: 3 h;

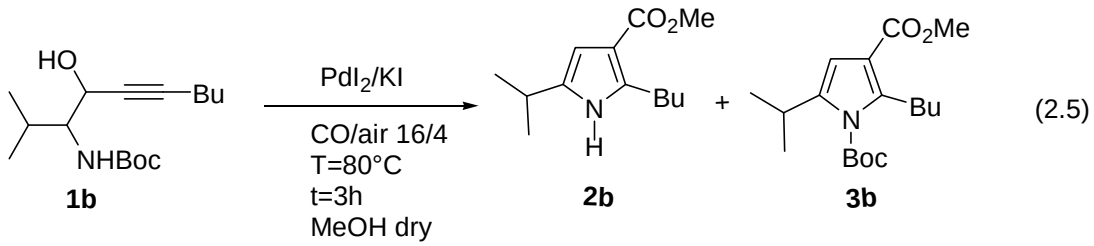
-P_{co} \ P_{air} atm = 16 \ 4 atm.

In view of the good results obtained with of *N*-Boc-2-amino-1-phenyl-non-4-yn-3-ol (**1a**), the study was continued with other substrates in order to access the generality of the process. Thus, a new substrate was synthesized, namely *N*-Boc-3-amino-5-methyildec-2-yn-4-ol (**1b**), bearing an isopropyl group on the α-carbon with respect to amino group. This substrate was prepared from L-Valine methyl ester hydrochloride that was protected with Boc group and then transformed into L-*N*-Boc-2-amino-3-metilbutanale by reduction with DIBAL (Yield = 66%). The aldehyde was reacted with hexynylmagnesium bromide to give substrate **1b** (as a mixture of diastereoisomers) with a yield of 40% (Scheme 2.10)

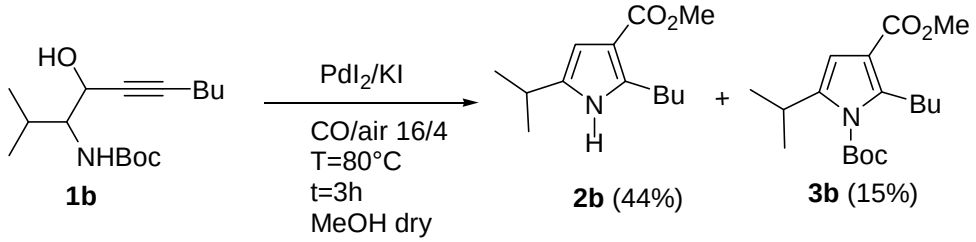


Scheme 2.10

Substrate **1b** was allowed to react in the optimized conditions shown before for the *N*-Boc-2-amino-1-phenyl-non-4-yn-3-ol (**1a**). (Eq. 2.5)



Comparing these results with those obtained with the substrate **1a** (66% product **2a** and **3a** 4% of the product) it can be observed that the desired unprotected product was not formed, while the Boc-protected pyrrole **3b** was obtained with a yield of 28%. Carrying out the reaction under similar conditions, but at a higher temperature (100 ° C), product **3b** was formed with a yield of 15% and the corresponding deprotected pyrrole **2b** with a yield of 44% (Scheme 2.11).



Scheme 2.11

To verify whether product **3b** could completely deprotect *in situ*, the reaction was conducted for a longer time. After 6h, the products **2b** and **3b** were obtained with 53% and 9% yields, respectively, while at 15h they were obtained in 50% and 7% yields. This clearly means that an increase in the reaction time does not lead to complete conversion of the protected product **3b** into **2b**. The results are summarized in Table 2.5.

Table 2.5 *Effect of the variation of time and temperature in the reaction of carbonylation of N-Boc-3-amino-5-methyildec-2-yn-4-ol (**1b**)*[a]

PdI_2/KI/sub Molar Ratio	P_{CO}/P_{air} atm	T°C	t (h)	Conv (%)	Yield 2b[b](%)	Yield 3b[b](%)	Tot Yield(%)
1/10/50	16/4	80	3	100	-	28	28
1//10/50	16/4	100	3	100	44	15	59
1/10/50	16/4	100	6	100	53	9	62
1/10/50	16/4	100	15	100	50	7	57

[a]All reaction were carried out in MeOH as the solvent, using 0.2 mmol of **1b** per mL of solvent

[b] Isolated yield, based on starting **1b**

To increase the total yield obtained, a reaction was carried out with a higher amount of catalyst. The results obtained are shown in Table 2.6

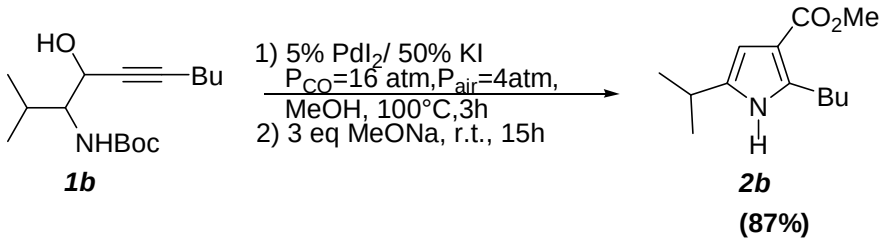
Table 2.6 *Effect of the variation of the substrates-to-catalyst molar ratio in the reaction of dicarbonyl N-Boc-3-amino-5-methyildec-2-yn-4-oll (**1b**)*[a]

PdI_2/KI/sub Molar Ratio	P_{CO}/P_{air} atm	T°C	t (h)	Conv(%)	Yield 2b[b](%)	Yield 3b[b](%)	Tot Yield(%)
1//10/50	16/4	100	3	100	44	15	59
1/10/20	16/4	100	3	100	53	34	87

[a]All reaction were carried out in MeOH as the solvent, using 0.2 mmol of **1b** per mL of solvent

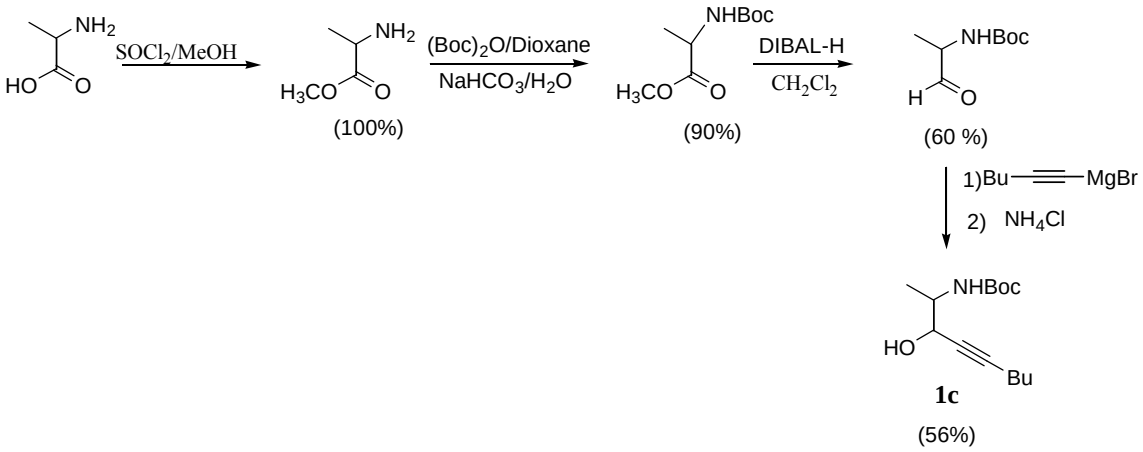
[b] Isolated yield, based on starting **1b**

Also for this substrate, it was verified the possibility to obtain product **2b** exclusively by adding to the crude reaction 3 equiv of MeONa and allowing the mixture to stir at room temperature for 15h. As expected, deprotected product **2b** was obtained exclusively with an isolated yield of 87% (Scheme 2.12).



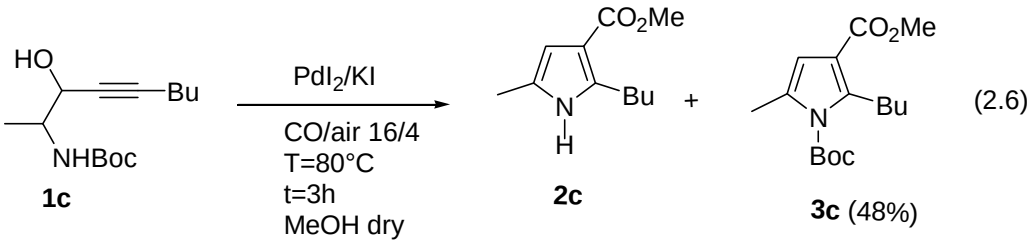
Scheme 2.12

The reaction works well also in the case of a substrate with a methyl group on the α-carbon. In particular, L-*N*-Boc-2-amino-4-ynenon-3-ol (**1c**) was synthesized via the procedure described before, in two steps: reduction with DIBAL of L-amino acid methyl ester BOC-protected and the reaction between L-*N*-Boc-2-amino propanal and hexynylmagnesium bromide with a yield of 56% (Scheme 2.13).

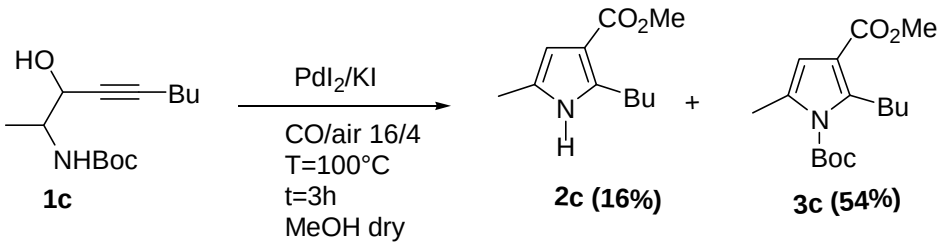


S***cheme 2.13***

The first reaction of *N*-Boc-3-amino-5-methyildec-2-yn-4-ol (**1c**) was conducted at T = 80 °C under the usual conditions. (Eq. 2.6)



Also in this case, the protected product **3c** was the only product formed, without formation of **2c**. Carrying out the reaction at a higher temperature (100 ° C), for 2h, a mixture of both was observed with a higher total yield (Scheme 2.14).



Scheme 2.14

The reaction was then carried out for a longer time (t = 15h), in order to verify whether the *N*-Boc-protected product **3c** could convert into the corresponding deprotected one **2c**. However, as observed in the case of the substrates previously discussed, conducting the reaction for a longer time afforded the deprotected product in lower yield (table 2.7).

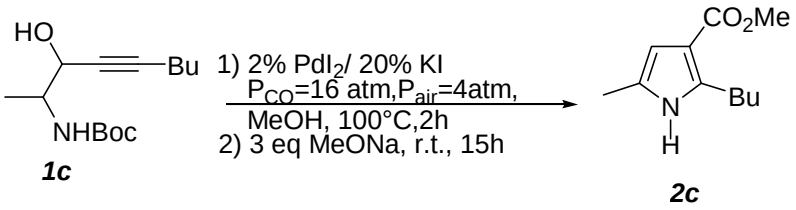
Table 2.7. *Effect of time and temperature in the carbonylation reaction of N-Boc-2-amino-4-yn-non-3-ol (**1c**)*[a]

PdI_2/KI/sub Molar Ratio	P_{CO}/P_{air} atm	T°C	t (h)	Conv (%)	Yield 2c[b](%)	Yield 3c[b] (%)	Tot Yield(%)
1/10/50	16/4	80	3	100	-	48	48
1/10/50	16/4	100	2	100	16	54	70
1/10/50	16/4	100	1	85	10	56	66
1/10/50	16/4	100	15	100	39	-	39

[a]All reaction were carried out in MeOH as the solvent, using 0.2 mmol of **1c** per mL of solvent

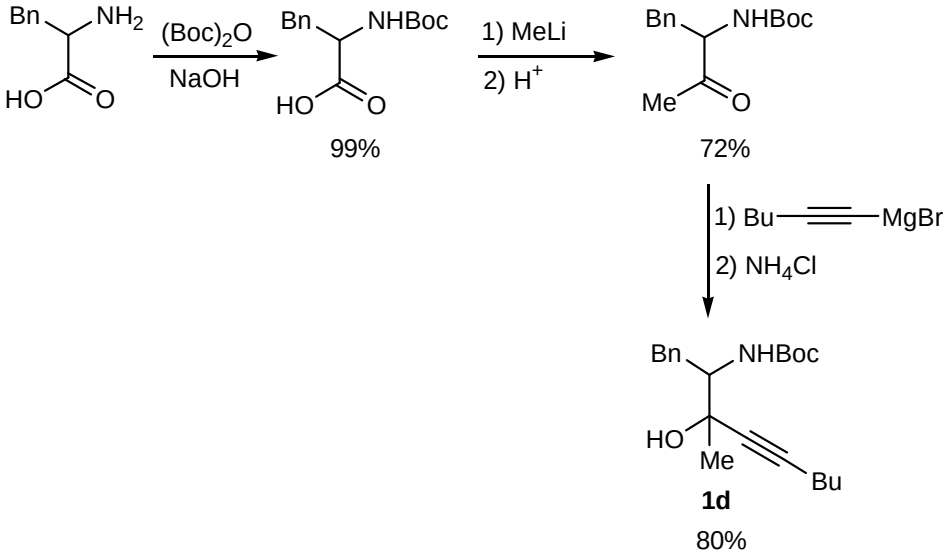
[b] Isolated yield, based on starting **1c**

Also for this substrate, it was verified the possibility to obtain product **2c** exclusively by adding to the crude reaction 3 equivalents of MeONa and allowing the mixture to stir at room temperature for 15h. As expected, the deprotected product **2c** was obtained exclusively with a yield of 70% (Scheme 2.15).



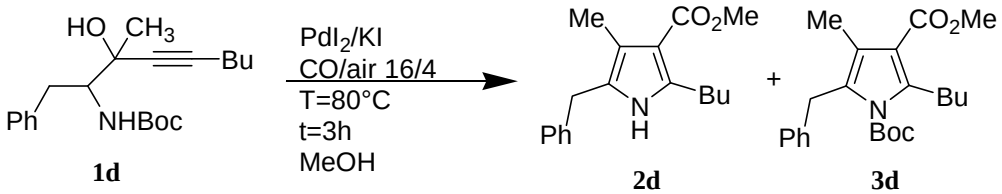
Scheme 2.15

A substrate substituted with a benzyl group, namely *N*-Boc-2-amino-3-methyl-1-phenyl-non-4-yn-3-ol (**1d**), was then synthesized (Scheme 2.16).



Scheme 2.16

This substrate was let to react under the optimized conditions at 80°C. A mixture of protected and deprotected pyrroles was obtained, with a total yield of 88% (Table 2.8, Scheme 2.17). On the other hand, carrying out the reaction at 100 ° C, the two products were obtained with a lower total yield, probably due to their partial decomposition.



Schema 2.17

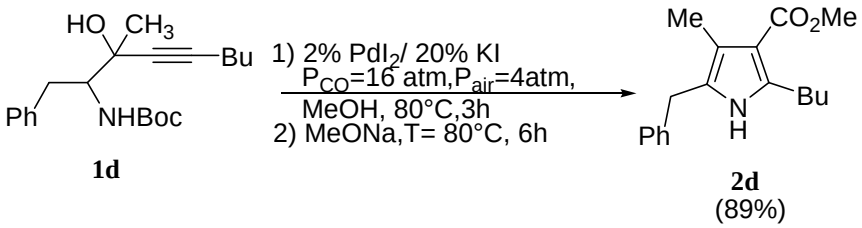
Table 2.8 *Effect of the variation of temperature in the reaction carbonylation of N-Boc-2-amino-3-methyl-1-phenyl-non-4-yn-3-ol (**1d**)*[a]

PdI_2/KI/sub Molar Ratio	P_{CO}/P_{air} atm	T°C	t (h)	Conv(%)	Yield 2d[b](%)	Yield 3d[b](%)	Tot Yield (%)
1/10/50	16/4	80	3	100	20	71	91
1//10/50	16/4	100	3	100	23	31	54

[a]All reaction were carried out in MeOH as the solvent, using 0.2 mmol of **1d** per mL of solvent

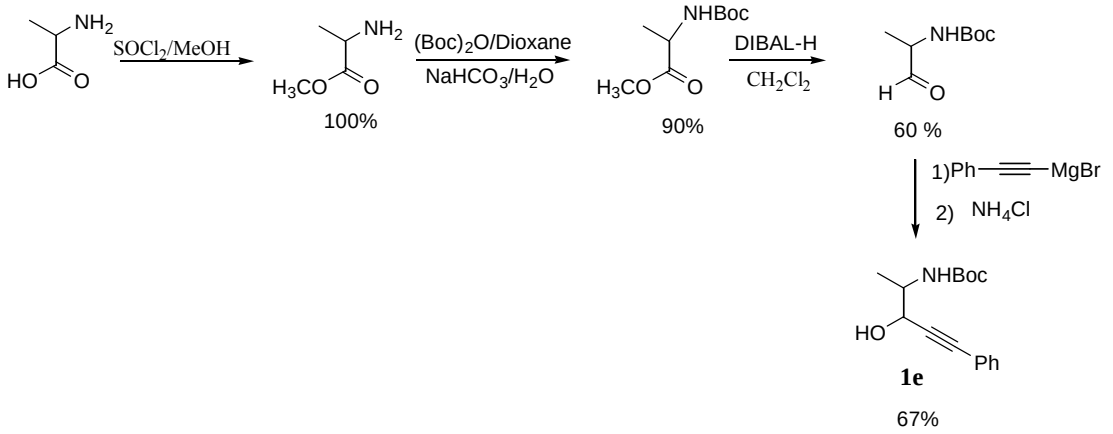
[b] Isolated yield, based on starting **1d**

Also for this substrate, it was possible to obtain exclusively product **2d** by adding to the crude reaction 3 equiv of MeONa and allowing the mixture to stir at 80°C for 6h. As expected, deprotected product **2d** was obtained exclusively with a yield of 89% (Scheme 2.18).

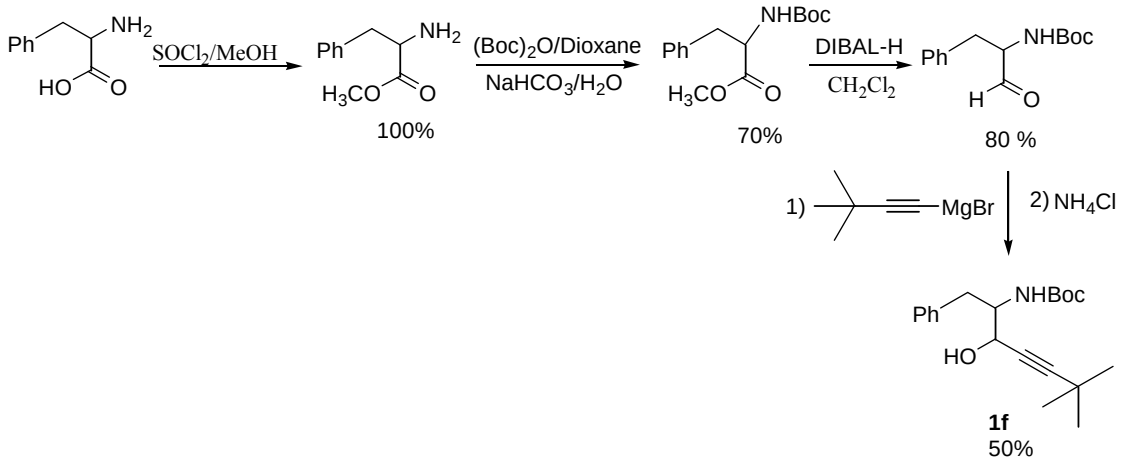


Schema 2.18

The effect of the nature of substituent on the triple bond was also studied. We accordingly prepared 2 substrates, with phenyl or *tert*-butyl group on the triple bond, namely: *N*-Boc-4-amino-1-phenyl-pent-1-yn-3-ol (**1e**) and *N*-Boc-2-amino-6,6-dimethyl-1-fenilept-4-in-3-ol (**1f**), respectively. These compounds were obtained by reaction with phenyl ethynyl magnesium bromide and 3,3-dimethylbutynylmagnesium bromide of the corresponding aldehydes (Scheme 2.19 and 2.20).



Schema 2.19



Schema 2.20

N-Boc-4-Amino-1-phenylpent-1-yn-3-ol (**1e**) was allowed to react at T = 80 ° C (eq. 2.7) and T = 100 ° C (see Table 2.9). At T = 80 ° C, only the Boc-protected compound **2e** was formed with a yield of 45%, while at T = 100°C a mixture of the protected and deprotected compounds was formed, with a similar total yield (Table 2.9). A 81% total yeld was obtained working for at 100°C for 2h.

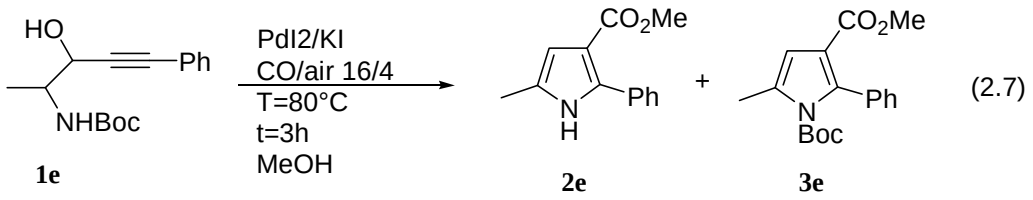


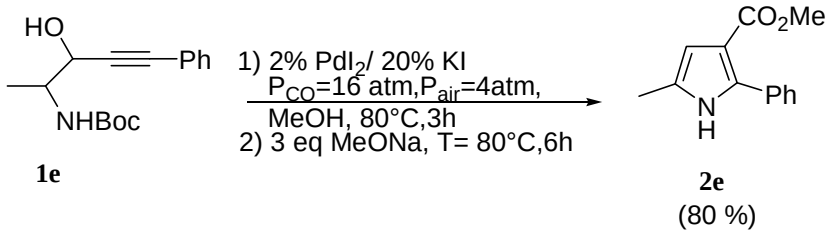
Table 2.9 *Effect of temperature and time in the reaction carbonylation of N-Boc-4-amino-1-phenylpent-1-yn-3-ol (**1e**)*[a]

PdI_2/KI/sub Molar Ratio	P_{CO}/P_{air} atm	T°C	t (h)	Conv(%)	Yield 2e[b](%)	Yield 3e[b](%)	Tot Yield (%)
1/10/50	16/4	80	3	100	-	45	45
1//10/50	16/4	100	3	100	29	23	52
1//10/50	16/4	100	2	100	34	47	81

[a] All reaction were carried out in MeOH as the solvent, using 0.2 mmol of **1e** per mL of solvent

[b] Isolated yield, based on starting **1e**

Also for this substrate, it was possible to obtain product **2e** exclusively by adding to the crude reaction 3 equiv of MeONa and allowing the mixture to stir at 80°C for 6h. As expected, deprotected product **2e** was obtained exclusively with a yield of 80% (Scheme 2.21).



Schema 2.21

N-Boc-2-amino-6 ,6-dimethyl-1-phenylept-4-yn-3-ol (**1f**) was reacted initially at T= 80 ° C under the optimized conditions. At this temperature, only traces of *N*-Boc-2-amino-6,6-dimethyl-1-phenylept-4-yn-3-ol (**3f**) were obtained (eq. 2.8) with no formation of corresponding deprotected compound. Conducting the reaction at T = 100 ° C, the formation of the deprotected compound (**2f**) was observed, but the total yield remained low. These results are probably due to the low reactivity of the substrate due to steric hindrance of the *tert*-butyl group. However, carrying out the reaction for a longer time (24h), it was possible to obtain a complete conversion of the substrate and a total yield of 54 %. (See Table 2.10)

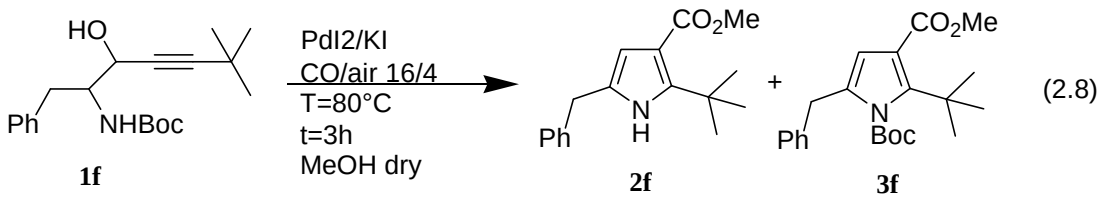


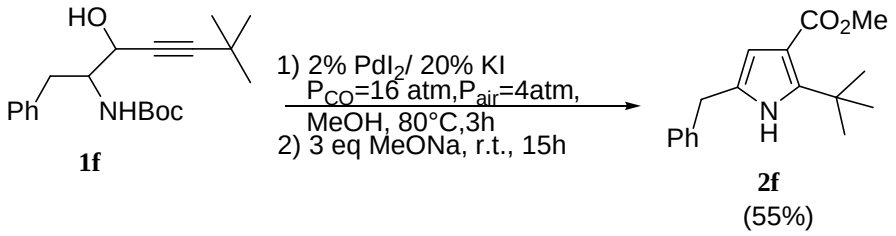
Table 2.10 *Effect of time and temperature in the reaction of carbonylation of N-Boc-2-amino-6 ,6-dimethyl-1-phenylept-4-yn-3-ol (**1f**)*[a]

PdI_2/KI/sub Ratio	Molar	P_{CO}/P_{air} atm	T°C	t (h)	Conv (%)	Yield 2f[b](%)	Yield 3f[b](%)	Tot (%)	Yield
1/10/50		16/4	80	3	50	-	8	8	
1//10/50		16/4	100	3	50	6	4	10	
1/10/50		16/4	100	6	50	5	15	20	
1/10/50		16/4	100	15	70	40	18	58	
1/10/50		16/4	100	24	100	45	9	54	

[a] All reaction were carried out in MeOH as the solvent, using 0.2 mmol of **1f** per mL of solvent

[b] Isolated yield, based on starting **1f**

Also for this substrate, it was possible to obtain exclusively product **2f** by adding to the crude reaction 3 equiv of MeONa and allowing the mixture to stir at room temperature for 15h. As expected, deprotected product **2f** was obtained exclusively with a yield of 55% (Scheme 2.22).

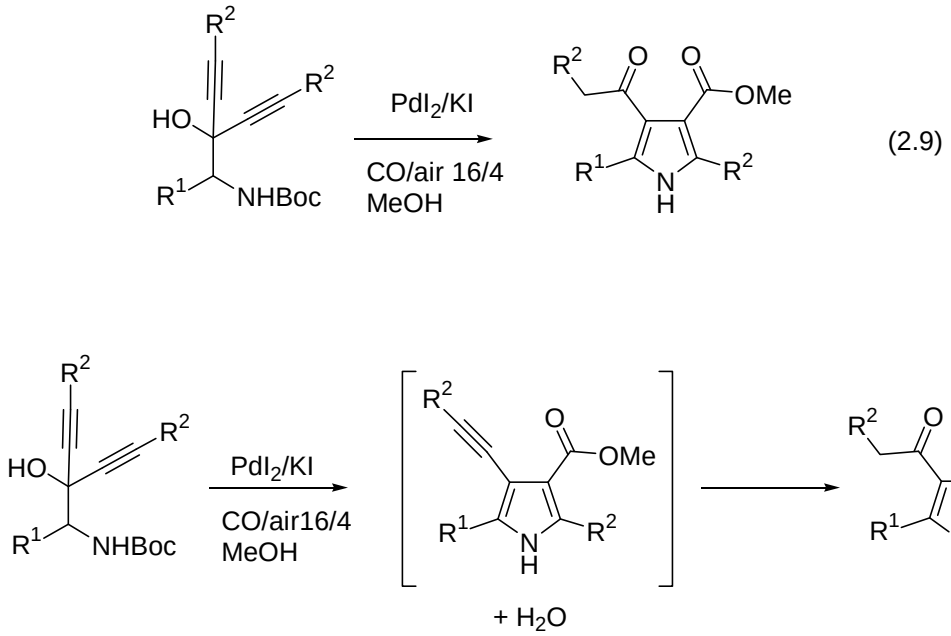


Schema 2.22

From our results it can be concluded that the studied process is general and can be applied to any *N*-Boc-2-amino-1-alkynyl-1-ols.

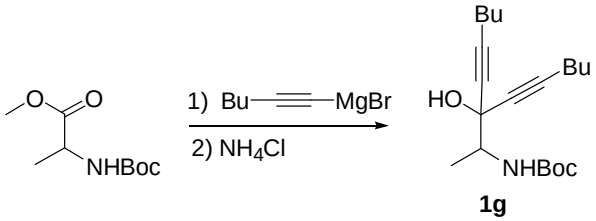
The method could be extended also to *N*-Boc-2-amino-1,1-dialkynyl-1-ols. In this case, the reaction leads to the direct formation of 3-alkoxycarbonyl-4-acylpyrrole derivatives (Eq. 2.9). Formation of this product occurs by in situ

hydration of the triple bond of the initially formed carbonylation product (Scheme 2.23):



Scheme 2.23

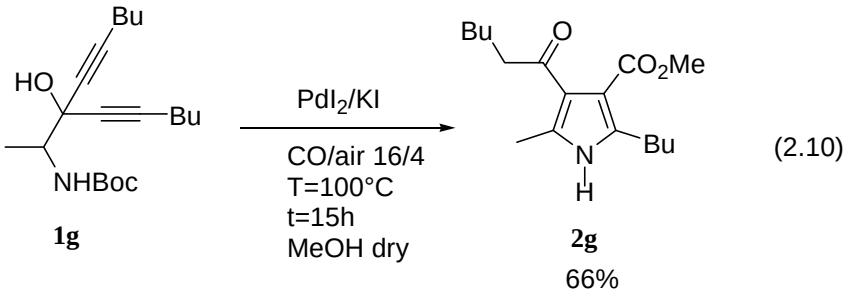
The first substrate of this class that has been studied was *N*-Boc 7-(1-Amino-ethyl)-trideca-5,8-diyn-7-ol **1g**. This substrate (**1g**), was synthesized by the reaction of hexynylmagnesium bromide and *N*-Boc-2 amino-propionic acid methyl ester (Scheme 2.24).



Scheme 2.24

By conducting the reaction under the same optimal conditions shown before for the monalkynyl substrates (T=100°C, t=3h), we observed a conversion of 30% with formation of the hydrated product with a yield of 20%. Carrying out the

reaction for a longer time (8 hours), conversion of substrate was still not complete, while at 15h, a total conversion of substrate was observed with a yield of the desired product to 66%.(Table 2.11)



(2.10)

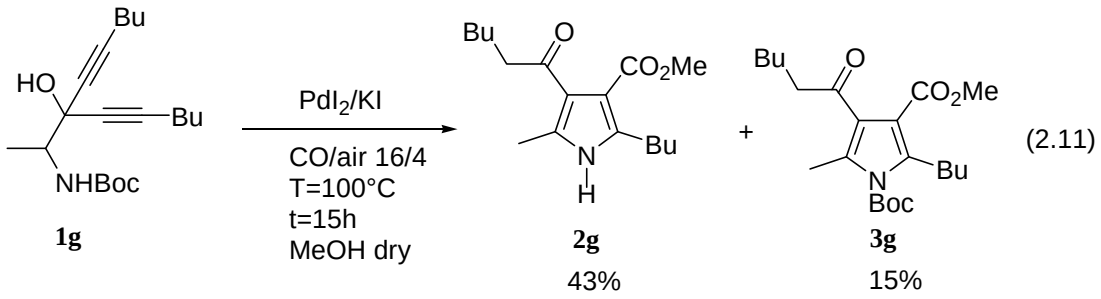
Table 2.11 *Effect of the variation of the time in the reaction of carbonylation of N-Boc 7-(1-Amino-ethyl)-trideca-5,8-diyn-7-ol (**1g**)*[a]

PdI_2/KI/sub	P_{CO}/P_{air} atm	T°C	t (h)	Conv (%)	Yield 2g[b] (%)	Tot Yield (%)
1/10/50	16/4	100	3	30	20	20
1//10/50	16/4	100	8	80	42	42
1/10/50	16/4	100	15	100	66	66

[a]All reaction were carried out in MeOH as the solvent, using 0.2 mmol of **1b** per mL of solvent

[b] Isolated yield, based on starting **1g**

Conducting the reaction under the optimal conditions but at 80°C a the mixture of *N*-Boc protected and *N*-Boc deprotected products is obtained (**2g** = 43%, **3g** =15%).

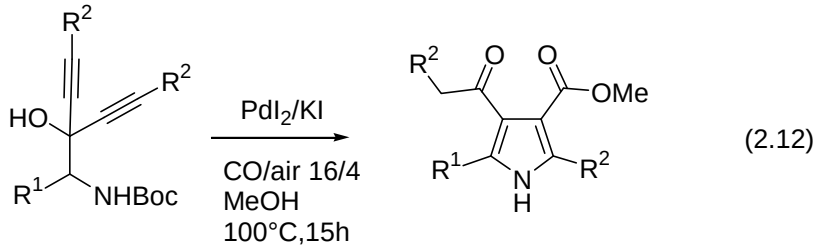


(2.11)

The reaction of this substrate has also been carried out under the same optimal conditions but using EtOH instead of MeOH as the solvent, obtaining the corresponding product (**2g'**) with an isolated yield of 33%; this is probably due to the lower nucleophilicity of EtOH with respect to MeOH.

This reaction was then applied to other 2-amino-1,1-dialkynyl-1-ols, and the best results were obtained by applying the following conditions: ratio PdI_2 \ KI \ Sub = 1 \ 10 \ 50, concentration of 1-amino-3-yn-2-ols 0.2 M MeOH, reaction temperature: 100 ° C, reaction time: 15 h, P_{co} \ P_{air}= 16 atm \ 4 atm (Table 2.12).

Table 2.12 *Synthesis of 3-alkoxycarbonyl-4-acylpyrrole derivatives* [a]



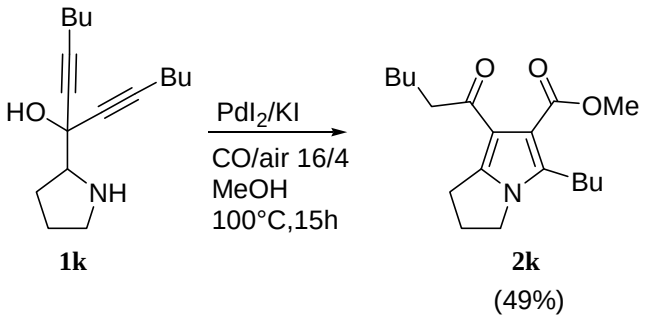
(2.12)

R^1	R^2	1	2	YIELD[b](%)
Me	Bu	**1g**	**2g**	66
i-Bu	Bu	**1h**	**2h**	75
Bn	Bu	**1i**	**2i**	68
i-Prop	Bu	**1j**	**2j**	63
Me	Ph	**1l**	**2l**	51
Me	*t*-Bu	**1m**	**2m**	62
i-Bu	*t*-Bu	**1n**	**2n**	56
i-Bu	$Si(CH_3)_3$	**1o**	**2o**	-

[a]All reaction were carried out in MeOH as the solvent, using 0.2 mmol per mL of solvent

[b] Isolated yield, based on starting substrates

A substrate with secondary amino group was also tested, without Boc-protection. The reaction of 7-pyrrolidin-2-yltrideca-5,8-diyn-7-ol (**1k**), carried out under the usual conditions, led to the formation of the corresponding 3-alkoxycarbonyl-4-acylpyrrole **2k** derivative with a yield of 49% (eq.2.13).



1k **2k** (49%) (2.13)

2.3 Conclusions

In the present work, a methodology for the synthesis of variously substituted pyrrole-3-carboxylic and 3-alkoxycarbonyl-4-acylpyrrole derivatives was developed, by Pd-catalyzed cyclization-alkoxycarbonylation reaction, starting from readily available substrates, *N*-protected-1-amino-3-in-2-ols and *N*-protected-2-amino-1,1-dialkynyl-1-ols.

References

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[3] Gabriele B.;Veltri L.; Mancuso, R.; Plastina P. Salerno G.; Costa M.; *J.Org.Chem*., **2008**, 73, 4971-4977.

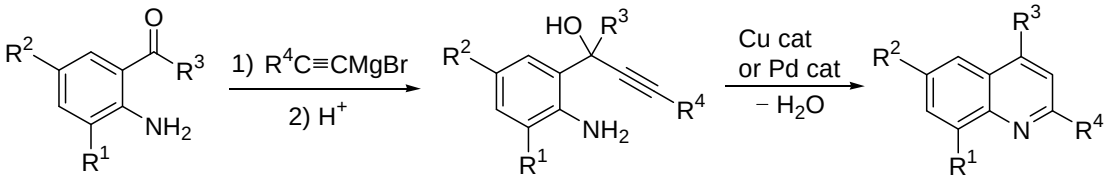
[4] Gabriele B.; Mancuso, R.; Salerno G.; Lupinacci,E; Ruffolo G.; Costa M.; *Tetrahedron Lett.* **2010**, 51, 1663-1665.

Chapter 3

3.1 Introduction

Metal-catalyzed reactions are some of the most attractive methodologies for synthesizing heterocyclic compounds, since they allow the direct construction of complex molecules starting from readily available starting materials under mild conditions.

In particular, copper catalysis has recently acquired an increasing importance, in view of the higher availability, lower toxicity, and lower environmental impact of copper-based catalysts when compared with other commonly employed transition metal catalysts.[1] We have recently reported several examples of synthesis of heterocyclic derivatives by heteroannulation reactions by using inexpensive $CuCl_2$ as the catalyst, under ligand-free conditions.[2] For example, a general and convenient synthesis of substituted quinolines by copper- or palladium-catalyzed cyclization-dehydration of 1-(2-aminoaryl)-2-yn-1-ols has been reported (scheme 12).[2b]

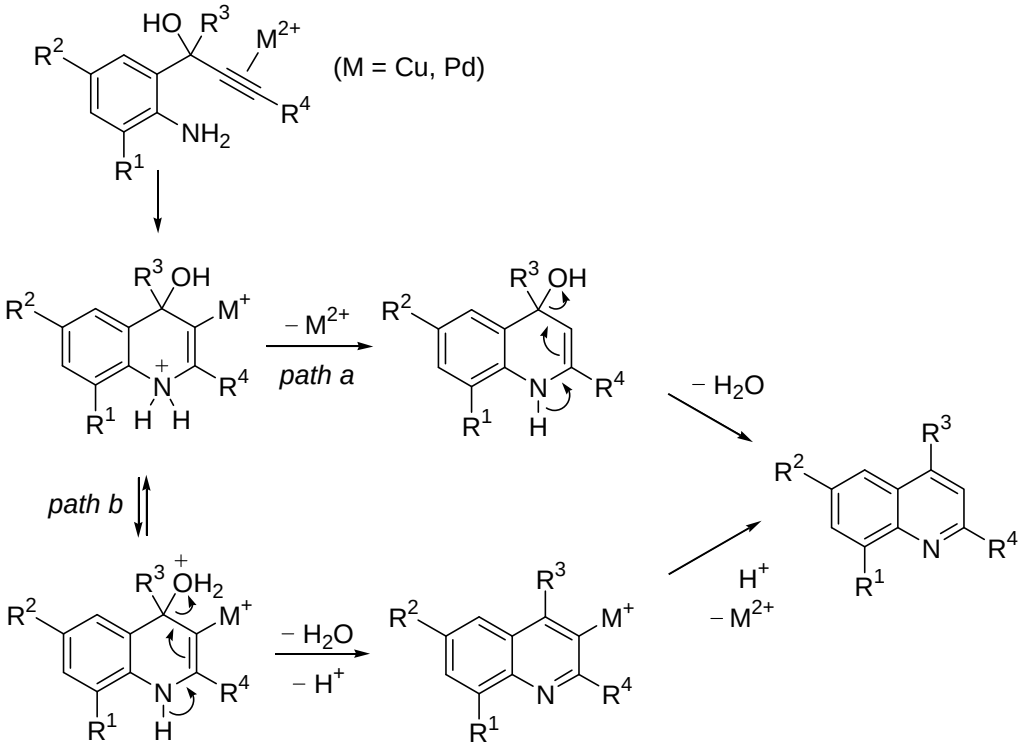


(crude product)

Scheme 3.1

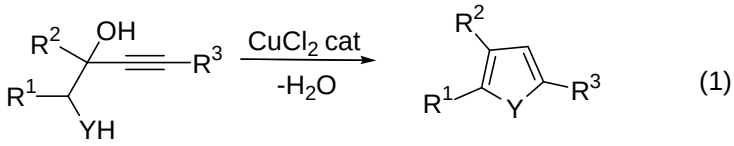
Substrates are easily obtained by Grignard reaction of the suitable alkynylmagnesium bromide and 2-aminoarylketones and can be used without further purification in the following cyclization step that can be promoted by copper or palladium species. Formation of quinolines occurs through a 6-*endo-dig* intramolecular attack by $–NH_2$ group on the metal-activated triple bond,

followed by protonolysis and dehydration (Scheme 3.2, path a) or vice versa (path b).



Scheme 3.2

We have now found that $CuCl_2$ is also an excellent catalyst for the heterocyclodehydration of readily available 3-yne-1,2-diols[3] and *N*-Boc- or *N*-tosyl-1-amino-3-yn-2-ols,[4] to produce substituted furans and pyrroles, respectively, in good to high yields (Eq. (1)).



1 **4 (53-99%)** (1)

R^1 = H, alkyl, aryl; R^2 = H, alkyl, alkynyl, aryl; R^3 = alkyl, aryl;
Y = O, NR, R = Boc or Ts

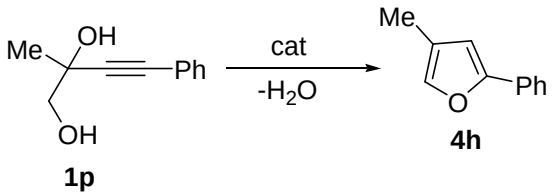
It is important to point out that the heterocyclodehydration of 3-yne-1,2-diols to give the corresponding furans was previously reported under Au,[5a,b] Ru,[5c] Ag,[5d,e] Mo,[5f,g] or Pd[5h,i] catalysis. In particular, mild and efficient reaction conditions have been recently developed under Au–Ag co-catalysis.[5a,b] To the best of our knowledge, however, no examples of copper-catalyzed formation of furans from 3-yne-1,2-diols have been reported so far in the literature. Also, the heterocyclodehydration of *N*-substituted 1-amino-3-yn-2-ols to give the corresponding pyrroles was previously reported to occur under palladium[5i] and gold catalysis.[5a,b]

However, no general method for the conversion of *N*-substituted 1-amino-3-yn-2-ols into pyrroles in the presence of catalytic amounts of copper has so far appeared in the literature.[6–8]

3.2 Synthesis of substituted furans and pyrroles by $CuCl_2$-catalyzed heterocyclodehydration of 3-yne-1,2-diols and N-Boc- or N-tosyl-1-amino-3-yn-2-ols

We began our investigations with 3-yne-1,2-diols. When 2-methyl-4-phenylbut-3-yne-1,2-diol **1p** (R^1 = H, R^2 = Me, R^3 = Ph, Y = O) was let to react at 80°C in MeOH for 1 h in the presence of 2 mol % of $CuCl_2$, we observed the formation of 4-methyl-2-phenylfuran **4h** in 37% GLC yield at 47% substrate conversion (Table 1, entry 1). Substrate conversion achieved 100% after 5 h, with a GLC yield of **4h** of 60% (55% isolated, Table 1, entry 2). The same reaction, carried out at 100 °C for 2 h, led to furan **4h** in 75% isolated yield (Table 3.1, entry 3). The reaction did not take place in aprotic solvents, such as 1,2-dimethoxyethane (DME), dioxane, or acetonitrile (Table 3.1, entries 4–6), or using CuI as the catalyst (Table 3.1, entry 7), while CuCl led to less satisfactory results (Table 3.1, entry 8).

Table 3.1 *Heterocyclodehydration reactions of 2-methyl-4-phenylbut-3-yne-1,2-diol* ***1p*** *under different conditions* [a]



1p **4h**

Entry	Catalyst	Solvent	T (C)	Time (h)	Conv of 1p [b] (%)	Yield of 4p [c] (%)
1	$CuCl_2$	MeOH	80	1	47	37
2	$CuCl_2$	MeOH	80	5	100	60(55)
3	$CuCl_2$	MeOH	100	2	100	80(75)
4	$CuCl_2$	DME	80	1	3	0
5	$CuCl_2$	Dioxane	80	1	1	0
6	$CuCl_2$	MeCN	80	1	3	0
7	CuI	MeOH	80	1	0	0
8	CuCl	MeOH	80	1	30	19

[a] All reactions were carried out in MeOH in the presence of the catalyst (2%), using 0.2 mmol of **1p** per mL of solvent (1 mmol scale based on **1p**).

[b] Calculated by GLC. GLC yield (isolated yield), based on starting **1p**.

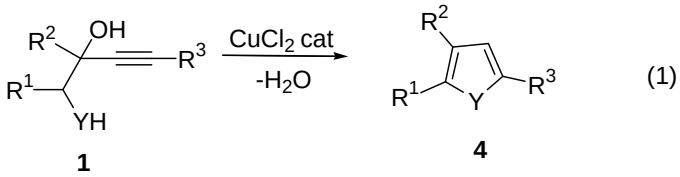
Once the possibility to realize the heterocyclodehydration of **1p** in MeOH with $CuCl_2$ as catalyst was established, we then tested the reactivity of differently substituted 3-yn-1,2-diols, in order to assess the generality of the method. The reactivity of 2,4-diphenylbut-3-yne-1,2-diol **1q** was similar to that of **1p**, with the corresponding furan **4i** being formed in 53% isolated yield (Table 3.2, entry 1). On the other hand, 2-phenyloct-3-yne-1,2-diol **1r**, bearing an alkyl rather than a phenyl group at C-4, turned out to be more reactive, and the reaction could be carried out at 80 °C for 2 h, with an isolated yield of furan **4j** of 80% (Table 3.2, entry 2). The reaction also worked nicely with substrates bearing an additional

phenyl group at C-1, as in the case of 1,2-diphenyloct-3-yne-2,3-diol **1s**, which was converted into the corresponding 5-butyl-2,3-diphenylfuran **4k** with an isolated yield as high as 81% working at 80 °C for 2 h (Table 3.2, entry 3). Good results were also obtained with substrates bearing an additional alkynyl group at C-2, as in the case of 2-hex-1-ynyl-oct-4-yne-1,2-diol **1t**, 3-hex-1-ynyl-non-4-yne-2,3-diol **1u**, 3-(3,3-dimethylbut-1-ynyl)-6,6-dimethylept-4-yne-2,3-diol **1v**, which were converted into the corresponding 3-alkynylfurans **4l-n** with isolated yields of 87, 91 and 81 %, respectively, working at 80 °C for 2 h (Table 3.2, entry 4-6). On the other hand, 5-phenyl-3-phenylethynylpent-4-yne-2,3-diol **1w** was converted into the corresponding 2-methyl-5-phenyl-3-phenylethynylfuran **4o** with an isolated yield of 84 %working at 100 °C for 3 h (Table 3.2, entry 7).

The reaction was then extended to *N*-Boc-1-amino-3-yn-2-ols, for the synthesis of substituted pyrroles. Under the same conditions already optimized for 3-yne-1,2-diols **1p–w** (2 mol % of $CuCl_2$, in MeOH as the solvent at 80–100°C), *N*-Boc-2-amino-1-phenyl-non-4-yn-3-ol **1a** (Y = *N*Boc, R^1 = Bn, R^2 = H, R^3= Bu) turned out to be less reactive, as shown by the results reported in Table 2, entry 8 (to be compared with those reported in Table 3.2, entry 1). In any case, the formation of *N*-Boc-2-benzyl-5-butylpyrrole **4a** was indeed observed, thus confirming the possibility to obtain pyrroles by $CuCl_2$-catalyzed heterocyclodehydration of *N*-Boc-1-amino-3- yn-2-ols. In order to compensate for the lower reactivity of **1a** with respect to **1p–w**, we carried out the reaction with a lower substrate-to-catalyst ratio: with 5 mol % of $CuCl_2$ at 100°C, substrate conversion reached 100% after 15 h, with an isolated yield of **4a** of 70% (Table 3.2, entry 9). *N*-Boc-2-aminonon-4-yn-3-ol **1c** (Y = *N*Boc, R^1 = Me, R^2 = H, R^3 = Bu) behaved similarly, as shown in Table 2, entries 10 and 11 (to be compared with entries 8 and 9, respectively). On the other hand, a substrate bearing an additional alkynyl group at C-2, such as *N*-Boc-7-(1-aminoethyl)trideca-5,8- diyn-7-ol **1g** (Y = *N*Boc, R^1= Me, R^2= CCBu, R^3 = Bu), was significantly more reactive, leading to the corresponding pyrrole **4c** in practically quantitative yield after only 1 h reaction time at 80°C (Table 3.2, entry 12). Reactions of substrates **1l-1i** have been carried out at 80°C, with 2 mol

% of $CuCl_2$ substrate conversion reached 100% after 1 h, with an isolated yield of **4d, 4e** and **4f** of 82%, 78%, and 73%, respectively (Table 3.2, entries 13-15). *N*-Ts-1-amino-3-yn-2-ols could also be successfully used, as shown by the result obtained in the case of *N*-Ts-7-(1-aminoethyl)trideca-5,8-diyn-7-ol **1y** (Y = *N*Ts, R^1=Me, R^2 = CCBu, R^3 = Bu) (Table 3.2, entry 16).

Table 3.2 *$CuCl_2$-catalyzed synthesis of substituted furans and pyrroles **4** by 5-endo-dig heterocyclodehydration of 3-yne-1,2-diols and N-Boc- or N-tosyl-1-amino-3-yn-2-ols 1*[a]

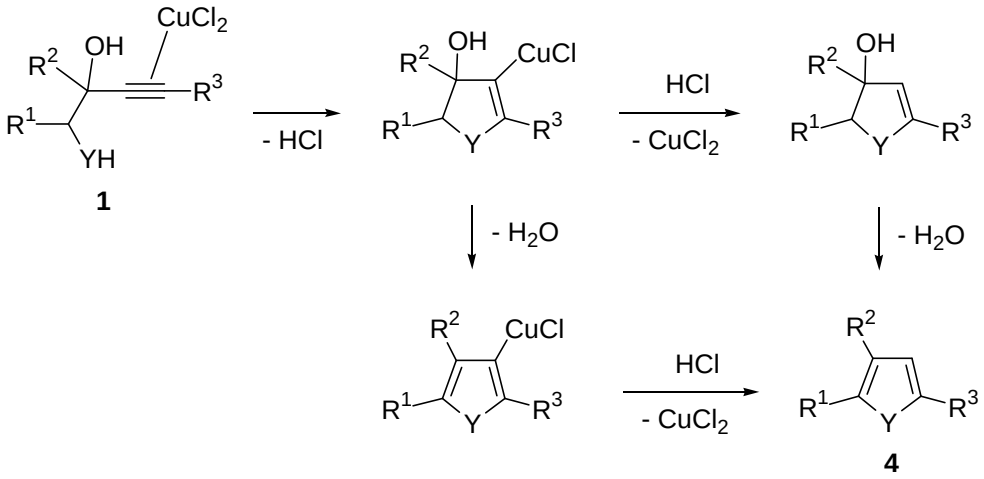


1 **4** (1)

Entry	1	Y	R^1	R^2	R^3	mmol % of $CuCl_2$	T (°C)	Time (h)	Conv. of 1[a] (%)	4	Yield of 4 [b](%)
1	**1q**	O	H	Ph	Ph	2	100	3	100	**4i**	53
2	**1r**	O	H	Ph	Bu	2	80	2	100	**4j**	80
3	**1s**	O	Ph	Ph	Bu	2	80	2	100	**4k**	81
4	**1t**	O	H	≡—Bu	Bu	2	80	2	100	**4l**	87
5	**1u**	O	Me	≡—Bu	Bu	2	80	2	100	**4m**	91
6	**1v**	O	Me	≡—*t*-Bu	*t*-Bu	2	80	2	100	**4n**	81
7	**1w**	O	Me	≡—Ph	Ph	2	100	3	100	**4o**	84
8	**1a**	*N*Boc	Bn	H	Bu	2	100	24	94	**4a**	42
9	**1a**	*N*Boc	Bn	H	Bu	5	100	15	100	**4a**	70
10	**1c**	*N*Boc	Me	H	Bu	2	100	24	95	**4b**	56
11	**1c**	*N*Boc	Me	H	Bu	5	100	15	100	**4b**	56
12	**1g**	*N*Boc	Me	≡—Bu	Bu	2	80	1	100	**4c**	99
13	**1l**	*N*Boc	Me	≡—Ph	Ph	2	80	1	100	**4d**	82
14	**1h**	*N*Boc	i-Bu	≡—Bu	Bu	2	80	1	100	**4e**	78
15	**1i**	*N*Boc	Bn	≡—Bu	Bu	2	80	1	100	**4f**	73
16	**1y**	*N*Ts	Me	≡—Bu	Bu	2	80	8	100	**4g**	83

[a] All reactions were carried out in MeOH in the presence of $CuCl_2$, using 0.2 mmol of **1** per mL of solvent (1 mmol scale based on **1**).
[b] Isolated yield, based on starting **1**.

The plausible mechanism for the formation of heterocyclic derivatives **4** starting from substrates **1** is shown in Scheme 1. It involves the intramolecular 5-*endo-dig* nucleophilic attack of the –YH group to the triple bond coordinated to $CuCl_2$, followed by protonolysis and dehydration or vice versa.



Scheme 3.3

3.3 Conclusions

In conclusion, we have developed a convenient, practical, and economical synthesis of substituted furans and pyrroles, by hetero-cyclodehydration of readily available 3-yne-1,2-diols and *N*-substituted 1-amino-3-yn-2-ols, catalyzed by $CuCl_2$ under ligand-free conditions. The possibility to obtain furan and pyrrole derivatives starting from readily available substrates and employing a simple and inexpensive catalyst appears particularly attractive, also in view of the importance of these classes of heterocyclic compounds.[9,10]

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[4] *N*-Substituted 1-amino-3-yn-2-ols **1e–h** were easily prepared by alkynylation, with an excess of $R_3CCMgBr$, of the appropriate *N*-Boc-α-amino aldehyde, *N*-Boc-α-amino ester, or *N*-tosyl-α-amino ester (*N*-Boc-2-amino-3-phenylpropionaldehyde in the case of **1e**; *N*-Boc-2-aminopropionaldehyde in the case of **1f**; methyl *N*-Boc-2-aminopropionate in the case of **1g**; methyl *N*-tosyl-2-aminopropionate in the case of **1h**).

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Chapter 4

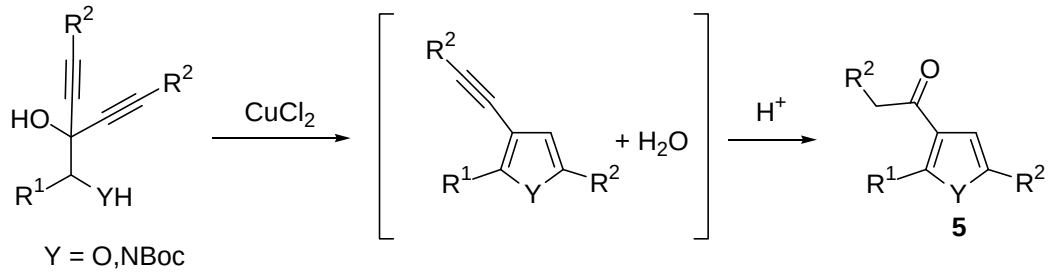
4.1 Introduction

The transition metal-catalyzed cycloisomerization is among the most important strategies for the synthesis of functionalized cyclic structures. The significance of this process stems from the rapid increase in structural complexity starting from relatively simple acyclic subunits containing yne fragments. Among a range of transition metal complexes capable of catalyzing cycloisomerizations, copper complexes are particularly important as they are capable of delivering a diverse array of cyclic products that are produced under mild conditions, in many cases with excellent chemoselectivity and high synthetic efficiency. While the pioneering work in this area goes back to the 1970s, there has been an explosive increase of interest in Cu and Pd catalysis during the last years. The diversity of cyclic structural motifs that can be efficiently accessed from a common yne precursor is remarkable. The process can furnish a six-membered or alternatively a five-membered heterocyclic products. The substitution pattern of the starting yne, as well as the nature of the catalyst, influences significantly the outcome of the cycloisomerization process.

4.2 Synthesis of pyrrole-3-alkyl-1-ones by a one-pot sequence of a $CuCl_2$-catalyzed heterocyclodehydration –acid or CO_2 promoted hydration of N-protected 2-amino-1,1- dialkynyl-1-ols

Acylpyrroles[1] and acylfurans[2] are compounds of considerable importance. In the previous chapter, it has been shown that 3-alkynylpyrroles and 3-alkynylfurans can be obtained using a $CuCl_2$-catalyzed reactions. The next step was to investigate whether they could be easily converted into 3-acylpyrroles and 3-

acylfurans, respectively. In particular, our hypothesis was to realize a one-pot procedure for the synthesis of 3-acylpyrroles and 3-acylfurans, through a sequence of reactions, namely: **a)** cyclodehydration of the substrate, as seen before, with formation of 3-alkynylpyrrole derivative; **b)** acid-promoted hydration of the triple bond of the latter, leading to 3-acylpyrrole and 3-acylfuran derivatives (Scheme 4.1).

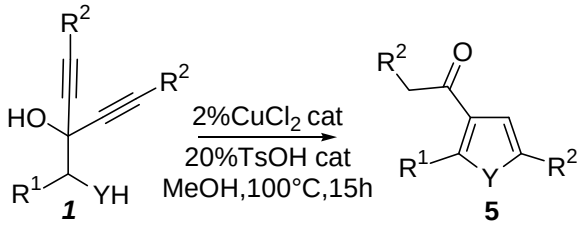


Scheme 4.1

The reaction of 3-hex-1-ynyl-non-4-yne-2,3-diol **1u** was initially conducted in the same experimental conditions as described in chapter 3, but in the presence of 20% of *p*-toluensulfonic acid monohydrate (with a molar ratio $CuCl_2$/TsOH/Sub=1:10:50), to promote the hydration of the triple bond.[3] Under these conditions, the reaction led to the direct and exclusive formation of 1-(5-butyl-2-methylfuran-3-yl)hexan-1-one **5a** with an isolated yield of 84 % (Table 1, entry 1), thus confirming the validity of the initial hypothesis. This reaction works well also in the case of other 1,1-dialkynyl-1,2-diols differently substituted on the triple bond (Table 1, entries 2,3). In particular, in the case of the substrate **1w** bearing a phenyl group on the triple bond, it was necessary to use a higher temperature and a longer reaction time, obtaining a good yield in the corresponding 3-acylfuran **5c**.

On the other hand, when *N*-protected 2-amino-1,1-dialkynyl-1-ols were allowed to react in the same conditions, with a molar ratio $CuCl_2$/TsOH/Sub=1:10:50, at 100°C, for 15h, at a concentration of 0.2 mmol/ mL of MeOH of *N*-protected-2-amino-1,1-dialkynyl-1-ol, we obtained lower yields in the corresponding *N*-Boc-3-acylpyrroles (Table 2, entries 4-8).

Table 4.1: ***Synthesis 3-acylfurans by $CuCl_2$-catalyzed cyclodehydration - p-TsOH promoted hydration***[a]



Entry	1	Y	R^1	R^2	T (°C)	t (h)	5	Yield 5(%)[b]
1	**1u**	O	Me	Bu	80	3	**5a**	84
2	**1v**	O	Me	*t*-Bu	80	3	**5b**	78
3	**1w**	O	Me	Ph	100	15	**5c**	75
4	**1g**	*N*Boc	Me	Bu	100	15	**5d**	54
5	**1h**	*N*Boc	*i*-Bu	Bu	100	15	**5e**	48
6	**1i**	*N*Boc	Bn	Bu	100	15	**5f**	59
7	**1l**	*N*Boc	Me	Ph	100	15	**5g**	19
8	**1m**	*N*Boc	Me	*t*-Bu	100	15	**5h**	56

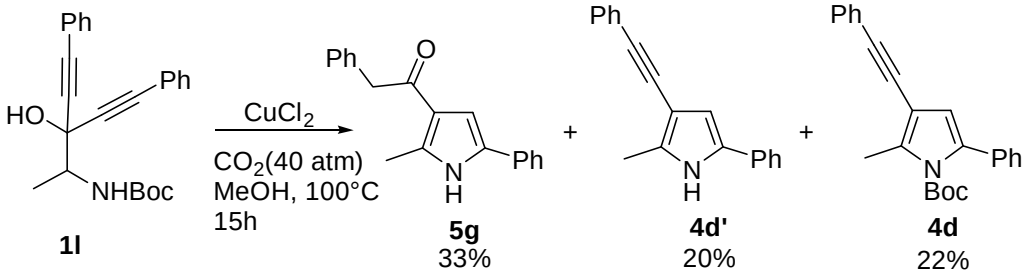
[a]All reaction were carried out in MeOH as the solvent, using 0.2 mmol of **1b** per mL of solvent

[b] Isolated yield, based on starting **substrates**

To improve the results with an Boc-2-amino-1,1-dialkynyl-1-ols, an alternative way to hydrate the triple bond was investigated. In particular, the use of carbon dioxide has been studied as promoter of the hydration step, instead of *p*-TsOH. We have in fact recently found that CO_2 can promote the hydration of the triple bond under certain conditions.[3]

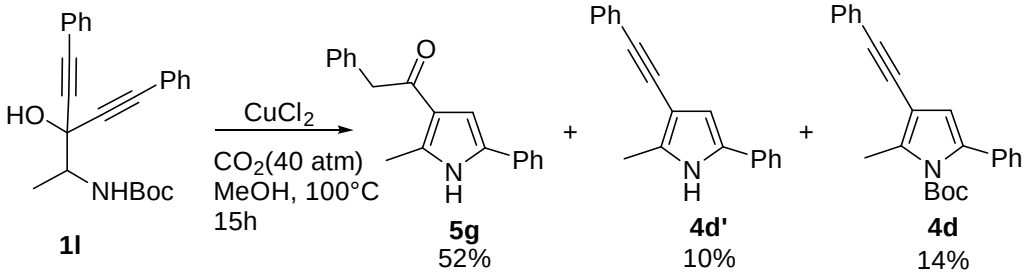
The first substrate used was *N*-Boc-3-(1-Amino-ethyl)-1,5-diphenyl-penta-1,4-diyn-3-ol **1l**, which was the less reactive under the acid-catalyzed conditions (see Tabel 4.1, entry 7). It was let to react in a stainless steel autoclave at 100 ° C with CO_2 (40 bar at room temperature) at a concentration of 0.2 mmol/ mL of MeOH

for 15 h with stirring and in the presence of $CuCl_2$, affording a mixture of three products, namely: the desired 3-acylpyrrole **5g**, with a yield of 33%, the cyclodehydration product **4d**, with a yield of 22%, and its deprotected derivative **4d'**, with a yield of 22% (total yield of 75%), as shown in Scheme 4.2 and Table 1, entry 1.



Scheme 4.2

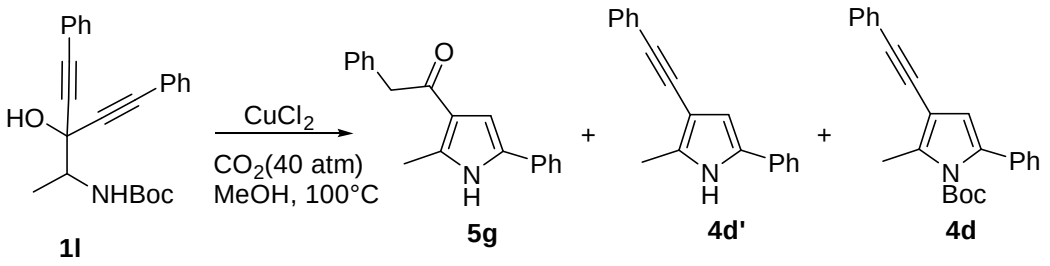
Carrying out the reaction for a longer time (24 h), the mixture of these products was obtained again, but the yield of the desired product **5g** turned to be higher (52%) as shown in Scheme 3 and Table 4.1, entry 2.



Scheme 4.3

To promote the hydration of the triple bond, it was investigated the possibility to add H_2O in the reaction mixture. The results obtained show that the optimal $CuCl_2$/substrate/CO_2 molar ratio is: 1:50:50 (Table 4.2, entry 3) and the optimal reaction time is 15h, even if a mixture of the three products was still obtained.

Table 4.2 **:** *Heterocyclohydratation - hydration reaction of N-Boc- 3-(1-Amino-ethyl)-1,5-diphenyl-penta-1,4-diyn-3-ol 1l under different conditions*[a]



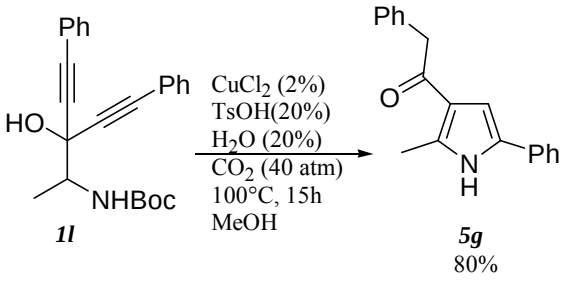
Entry	t(h)	Molar Ratio	Yield(%)[b] **5g**	Yield(%)[b] **4d'**	Yield(%)[b] **4d**	Yield(%) **Tot**
1	15	$CuCl_2$/Sub=1:50	33	20	22	75
2	24	$CuCl_2$/Sub=1:50	52	10	14	76
3	15	$CuCl_2$/Sub/H_2O=1:50:50	53	7	23	83
4	24	$CuCl_2$/Sub/H_2O=1:50:50	52	11	7	70
5	15	$CuCl_2$/Sub/H_2O=1:50:100	43	16	17	76
6	24	$CuCl_2$/Sub/H_2O=1:50:100	49	12	8	69
7	15	$CuCl_2$/Sub/H_2O=1:50:500	49	6	3	58
8	15	$CuCl_2$/Sub/H_2O=1:50:1000	49	4	2	55
9	8	$CuCl_2$/Sub/H_2O=1:50:1000	33	6	26	65

[a]All reaction were carried out in MeOH as the solvent

[b]Isolated yield, based on starting **1a**

In order to increase the acidity of the system, we used the above cited conditions, in the presence of *p*-TsOH. Thus, the reaction was conducted in autoclave at 100 ° C with CO_2 (40 bar at room temperature) at a concentration of 0.2 mmol/ mL of MeOH for 15 h and ratio molar equal to $CuCl_2$/TsOH/Sub/H_2O=1:10:50:50, affording exclusively the desired product **5g** with an isolated yield of 80 % (

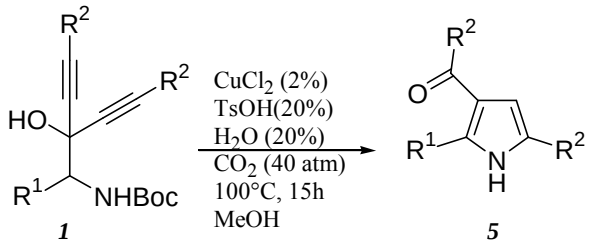
Schema 4.4).



Schema 4.4

Under these conditions, other *N*-protected-2-amino-1,1-dialkynyl-1-ols **1** were converted into their corresponding 3-acylpyrroles **5** in good yields (from 68% to 87%) (Table 4.3).

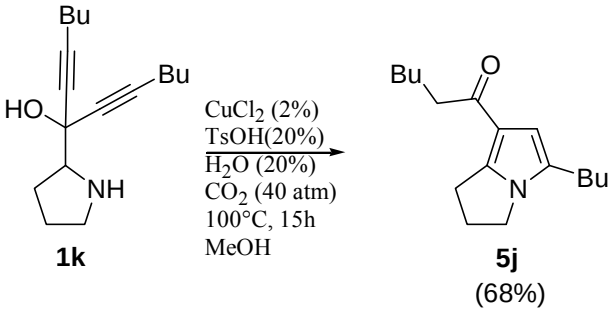
Table 4.3 *Synthesis of substituted Pirroles* ***5*** *by 5-endo-dig heterocyclodehydration of N-protected-2-amino-1,1-dialkynyl-1-ols* ***1*** *following by acid and CO_2 –promoted triple bond hydration*



Entry	**1**	R^1	R^2	**5**	Yield of **5** (%)[a]
1	**1g**	Me	Bu	**5d**	70
2	**1h**	*i*-Bu	Bu	**5e**	68
3	**1i**	Bn	Bu	**5f**	82
4	**1j**	*i*-prop	Bu	**5i**	71
5	**1l**	Me	Ph	**5g**	80
6	**1m**	Me	t-Bu	**5h**	87
7	**1n**	*i*-Bu	*t*-Bu	**5k**	78
8	**1o**	*i*-Bu	H	**5l**	42

[a]Isolated yield, based on starting substrates

A substrate with a secondary amino group was used without Boc-protection. The reaction of 7-pyrrolidin-2-yltrideca-5,8-diyn-7-ol **1k**, carried out in the conditions mentioned before, led to the formation of the corresponding 3-acylpyrrole derivative **5j** with an isolated yield of 68% (Schema 4.5).



Schema 4.5

4.3 Conclusions

In conclusion, we have developed a convenient, practical, and economical synthesis of substituted 3-acylfurans and 3-acylpyrroles, starting from *N*-protected 2-amino-1,1-dialkynyl-1-ols by a one-pot sequence of a $CuCl_2$-catalyzed heterocyclodehydration followed by acid- and CO_2- promoted triple bond hydration.

References

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[3] L. Hintermann, A. Labonne, *Synthesis* **2007**, 8, 1121–1150

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Chapter 5

5.1 General Experimental Methods

Melting points are uncorrected. 1H NMR and 13C NMR spectra were recorded at 25 °C in CDCl3 solutions at 300 MHz and 75 MHz, respectively, with Me4Si as internal standard. 1H NMR and 13C NMR spectra of products 2c, 2g and 2i were recorded at 25 °C in CDCl3 solutions at 500 MHz and 100 MHz, respectively, with Me4Si as internal standard Chemical shifts (□) and coupling constants (J) are given in ppm and in Hz, respectively. IR spectra were taken on an FT-IR spectrometer. ESI MS and MS/MS spectra were acquired on a API 2000 Triple Quadrupole Mass Spectrometer (AB Sciex Instruments, Toronto, Canada) equipped with a turbo-ion spray source. The mass spectrometer was operated in positive mode to obtain both the mass spectra (MS1) and the product ion spectra (MS2). Analytes (5 ug/mL concentration), dissolved in a 0.1% of acetic acid CH3OH solution, were introduced by direct infusion (10 μL/min) at the ion spray (IS) voltage of 5500 V. The source nitrogen (GS1) and the curtain gas (CUR) flows were set at pressures of 18 and 10 psi, respectively, whereas the declustering potential (DP), the focusing potential (FP), and the entrance potential (EP) were kept at 80, 400, and 10 V relative to ground, respectively. The MS2 spectra were acquired at a collision energy of 10-45 eV using N2 as the collision gas. Microanalyses were carried out with a Carlo Erba Elemental Analyzer Mod. 1106. All reactions were analyzed by TLC on silica gel 60 F254 and by GLC using a Shimadzu GC-2010 gas chromatograph and capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase (HP-5). Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh) or neutral alumina. Evaporation refers to the removal of solvent under reduced pressure. Mass spectra were obtained at 70 eV ionization voltage. Microanalyses were performed at our analytical laboratory. All reactions were

analyzed by TLC on silica gel 60 F254 and by GLC using capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase. Column chromatography was performed on silica gel 60. Evaporation refers to the removal of solvent under reduced pressure.

5.2 Preparation of Substrates

Starting *N*-protected-2-amino-1,1-dialkynyl-1-ols and 3-yne-1,2-diols **1** were prepared as described below. All other materials were commercially available and were used without further purification.

5.3 General Procedure for the preparation of N-Boc-2-amino-methyl ester

To a suspension of amino ester (60.5 mmol) in ice-cooled dry methanol (100 mL) was added dropwise thionyl chloride (10.0 g, 6.15 mL, 84.2 mmol) and the solution was stirred at room temperature overnight. Removal of the volatiles under reduced pressure gave amino methyl ester hydrochloride as a colorless crystalline solid quantitatively. To the mixture of the methyl ester hydrochloride (73.10 mmol) in 150 mL of aqueous $NaHCO_3$ (13.51 g, 160.8 mmol) was added dropwise a solution of $(Boc)_2O$ (17.55 g, 80.41 mmol) in dioxane (150 mL). The mixture was stirred at room temperature for 12 h, then concentrated to half of its original volume and extracted with ether (3x100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated, which was purified by chromatography on silica gel using ether/hexane (1:1, v/v) as eluent to give *N*-Boc-amino methyl ester[1].

5.4 General Procedure for reduction of N-Boc-2-amino-methyl ester

To a cold (-78 °C) solution of *N*-Boc-amino methyl ester (18.3 mmol) in CH_2Cl_2 (60 mL) was added dropwise a 1.0 M solution of DIBAL-H in hexane (40 mL, 40 mmol) over 1 h. After 2 h, the reaction mixture was quenched with AcOH (34 mL, 5 M in benzene) at -78°C and then warmed to room temperature. The mixture was poured into 10% aqueous tartaric acid (100 mL) and extracted with hexane/AcOEt (1:1) (3x60 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed to leave crude *N*-Boc-2-aminoaldehyde which usually was immediately used in the next step without further purification. After filtration and evaporation of the solvent, the product was purified by column chromatography on silica gel using 8:2 hexane-AcOEt as the eluent.

With this synthetic procedure were prepared the corrisponding aldehyde of following compounds[2]: *N*-Boc L-Phenylalanine methyl ester (white liquid, 80%), *N*-Boc L-Valine methyl ester (white liquid, 66%), *N*-Boc L-alanine methyl ester (white solid, 60%).

5.5 General Procedure for the preparation of N-Boc-2-amino-1-alkynyl-1-ols 1a, 1b, 1c

To a suspension of Mg turnings (0,6 g, 24,86 mmol) in anhydrous THF (3 mL), maintained under nitrogen and under reflux, was added pure ethyl bromide (0.5ml, 6.7 mmol) to start the formation of the Grignard reagent. The remaining bromide was added dropwise in THF solution (1,35mL, 18 mmol of EtBr in 12,3 mL of THF; total amount of EtBr added: 1,85mL, 24.86mmol). The mixture was then allowed to reflux for additional 20 min. After cooling, the resulting solution of EtMgBr was transferred under nitrogen to a dropping funnel and added dropwise under nitrogen to a solution of 1-hexyne (2.9 mL, 24.86mmol) in anhydrous THF (6 mL) at 0 °C with stirring. After additional stirring at 0°C for 15 min, the mixture was allowed to warm up to room temperature and then

maintained at 25 °C for 2 h. A solution of *N*-Boc protected aldehyde (9.943 mmol) in anhydrous THF (7 mL) was then added dropwise under nitrogen to the warm solution of 1-hexynylmagnesium bromide obtained as described before. The resulting mixture was allowed to stir at 25°C for additional 15 h. After cooling to room temperature, saturated NH_4Cl (100 mL) and AcOEt (40 ml) were sequentially added. Phases were separated, and the aqueous phase was extracted with AcOEt (3 × 100 mL). The collected organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the product was purified by column chromatography on silica gel using 8:2 hexane-AcOEt as the eluent to give pure *N*-protected-2-amino-1-alkynyl-1-ols; **1a** (yellow solid, m.p.=62-65°C ,40% based on aldehyde *N*-Boc protected); **1b** (yellow oil, 40% based on aldehyde *N*-Boc protected); **1c** (colorless oil, 56% based on adehyde *N*-Boc protected).

5.6 Procedure for the preparation of N-Boc-2-amino-3-methyl-1-phenyl-non-4-yn-3-ol (1d)

This procedure is general for all *N*-protected α-amino ketones[3]. A solution of *N*-Boc protected L-aminoacid (10.0 mmol) and THF (10.0 mL) was added dropwise, under nitrogen to a stirred, cooled (– 78°C) mixture of MeLi (22.9 mL of a 1.4 M solution in diethylether) in anhydrous THF (10 mL). This solution was cooled to -78°C . The addition was begun to the well-stirred amino acid solution such that the internal temperature did not exceed -65°C (approximately 1 mL/min). Upon completion of the addition, the reaction mixture was allowed to warm to room temperature and stirring was continued for an additional 2 h. In order to prevent racemization, the reaction mixture was poured into hydrochloric acid (50 mL, 1.0 N). Diethyl ether (50 mL) was added and the mixture was stirred at room temperature for 10 min. The aqueous layer was separated and extracted with diethyl ether (3 x 25 mL), and the combined organic extracts were dried over anhydrous magnesium sulfate. After filtration, the solvent was

removed by rotary evaporation. Purification was achieved by flash chromatography of silica gel and a solvent system of 4.5% methanol in chloroform to give pure *N*-Boc-2-amino-3-methyl-1-phenyl-non-4-yn-3-ol (**1d**)(white solid, m.p.=50-52, yield 72% based on *N*-Boc protected aldehyde).

5.7 Procedure for the preparation of N-Boc-4-amino-1-phenyl-pent-1-yn-3-ol (1e)

To a suspension of Mg turnings (0,6 g, 24,86 mmol) in anhydrous THF (3 mL), maintained under nitrogen and under reflux, was added pure ethyl bromide (0.5ml, 6.7 mmol) to start the formation of the Grignard reagent. The remaining bromide was added dropwise in THF solution (1,35mL, 18 mmol of EtBr in 12,3 mL of THF; total amount of EtBr added: 1,85mL, 24.86mmol). The mixture was then allowed to reflux for additional 20 min. After cooling, the resulting solution of EtMgBr was transferred under nitrogen to a dropping funnel and added dropwise under nitrogen to a solution of phenylacetylene (24.86mmol) in anhydrous THF (6 mL) at 0 °C with stirring. After additional stirring at 0°C for 15 min, the mixture was allowed to warm up to room temperature and then maintained at 25 °C for 2 h. A solution of of aldehyde *N*-Boc protected (9.943 mmol) in anhydrous THF (7 mL) was then added dropwise under nitrogen to the warm solution of phenylacetylmagnesium bromide obtained as described before. The resulting mixture was allowed to stir at 25°C for additional 15 h. After cooling to room temperature, saturated NH_4Cl (100 mL) and AcOEt (40 ml) were sequentially added. Phases were separated, and the aqueous phase was extracted with AcOEt (3 × 100 mL). The collected organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the product was purified by column chromatography on silica gel using 8:2 hexane-AcOEt as the eluent to give pure *N*-protected-2-amino-1-alkynyl-1-ols; **1e** (yellow solid, m.p.=62-65°C ,40% based on aldehyde *N*-Boc protected).

5.8 Procedure for the preparation of N-Boc-2-amino-6,6-dimethyl-1-phenyl-hept-4-yn-3-ol (1f)

To a suspension of Mg turnings (0,6 g, 24,86 mmol) in anhydrous THF (3 mL), maintained under nitrogen and under reflux, was added pure ethyl bromide (0.5ml, 6.7 mmol) to start the formation of the Grignard reagent. The remaining bromide was added dropwise in THF solution (1,35mL, 18 mmol of EtBr in 12,3 mL of THF; total amount of EtBr added: 1,85mL, 24.86mmol). The mixture was then allowed to reflux for additional 20 min. After cooling, the resulting solution of EtMgBr was transferred under nitrogen to a dropping funnel and added dropwise under nitrogen to a solution of 3,3-Dimethyl-1-butyne (24.86mmol) in anhydrous THF (6 mL) at 0 °C with stirring. After additional stirring at 0°C for 15 min, the mixture was allowed to warm up to room temperature and then maintained at 25 °C for 2 h. A solution of *N*-Boc protected aldehyde (9.943 mmol) in anhydrous THF (7 mL) was then added dropwise under nitrogen to the warm solution of 3,3-Dimethyl-1-butylmagnesium bromide obtained as described before. The resulting mixture was allowed to stir at 25°C for additional 15 h. After cooling to room temperature, saturated NH_4Cl (100 mL) and AcOEt (40 ml) were sequentially added. Phases were separated, and the aqueous phase was extracted with AcOEt (3 × 100 mL). The collected organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the product was purified by column chromatography on silica gel using 8:2 hexane-AcOEt as the eluent to give pure *N*-protected-2-amino-1-alkynyl-1-ols; **1f** (yellow solid, m.p.=62-65°C ,40% based on aldehyde *N*-Boc protected).

5.9 General Procedure for the preparation of N-Boc-2-amino-1,1-dialkynyl-1-ols 1g, 1h, 1i, 1j

To a suspension of Mg turnings (2.1 g, 86.4 mmol) in anhydrous THF (9 mL), maintained under nitrogen and under reflux, was added pure ethyl bromide (1.8 mL) to start the formation of the Grignard reagent. The remaining bromide was

added dropwise in THF solution (4.5 mL of EtBr in 48 mL of THF; total amount of EtBr added: 9.2 g, 6.3 mL 84.2 mmol). The mixture was then allowed to reflux for additional 20 min. After cooling, the resulting solution of EtMgBr was transferred under nitrogen to a dropping funnel and added dropwise under nitrogen to a solution of 1-hexyne (7.2 g, 10.08 mL, 88 mmol) in anhydrous THF (24 mL) at 0 °C with stirring. After additional stirring at 0°C for 15 min, the mixture was allowed to warm up to room temperature and then maintained at 45 °C for 2 h. A solution of *N*-Boc protected amino ester (22 mmol) in anhydrous THF (7 mL) was then added dropwise under nitrogen to the warm solution of 1-hexynylmagnesium bromide obtained as described before. The resulting mixture was allowed to stir at 35°C for additional 15 h. After cooling to room temperature, saturated NH_4Cl (100 mL) and AcOEt (40 ml) were sequentially added. Phases were separated, and the aqueous phase was extracted with AcOEt (3 × 100 mL). The collected organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the product was purified by column chromatography on silica gel using 8:2 hexane-AcOEt as the eluent to give pure *N*-protected-2-amino-1,1-dialkynyl-1-ols; **1g** (yellow oil, 5.0 g, 68% based on amino ester *N*-Boc protected); **1h** (yellow oil, 6.0 g, 73% based on amino ester *N*-Boc protected); **1i** (yellow solid, mp 61°-65°C, 6.2 g, 68% based on amino ester *N*-Boc protected); **1j** (yellow oil, 4.9 g, 61% based on amino ester *N*-Boc protected).

5.10 Procedure for the preparation of 7-Pyrrolidin-2-yl-trideca-5,8-diyn-7-ol (1k)

To a suspension of Mg turnings (2.1 g, 86.4 mmol) in anhydrous THF (9 mL), maintained under nitrogen and under reflux, was added pure ethyl bromide (1.8 mL) to start the formation of the Grignard reagent. The remaining bromide was added dropwise in THF solution (4.5 mL of EtBr in 48 mL of THF; total amount of EtBr added: 9.2 g, 6.3 mL 84.2 mmol). The mixture was then allowed to

reflux for additional 20 min. After cooling, the resulting solution of EtMgBr was transferred under nitrogen to a dropping funnel and added dropwise under nitrogen to a solution of 1-hexyne (7.2 g, 10.08 mL, 88 mmol) in anhydrous THF (24 mL) at 0 °C with stirring. After additional stirring at 0°C for 15 min, the mixture was allowed to warm up to room temperature and then maintained at 45 °C for 2 h. A solution of proline methyl ester hydrochloride (22 mmol) neutralized with NaOH 0,2 M in anhydrous THF (7 mL) was then added dropwise under nitrogen to the warm solution of 1-hexynylmagnesium bromide obtained as described before. While warm (ca 25-30 °C), the solution of 1-hexynylmagnesium bromide thus obtained was then added dropwise under nitrogen to a pre-heated (35 °C) solution of. The resulting mixture was allowed to stir at 35°C for additional 15 h. After cooling to room temperature, saturated NH_4Cl (100 mL) and AcOEt (40 ml) were sequentially added. Phases were separated, and the aqueous phase was extracted with AcOEt (3 × 100 mL). The collected organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the product was purified by column chromatography on silica gel using 8:2 hexane-AcOEt as the eluent to give pure *N*-protected-2-amino-1,1-dialkynyl-1-ols **1k** (brown oil, 3.1 g, 54% based on amino ester).

5.11 Procedure for the preparation of N-Boc-3-(1-Amino-ethyl)-1,5-diphenyl-penta-1,4-diyn-3-ol (1l)

To a suspension of Mg turnings (2.1 g, 86.4 mmol) in anhydrous THF (9 mL), maintained under nitrogen and under reflux, was added pure ethyl bromide (1.8 mL) to start the formation of the Grignard reagent. The remaining bromide was added dropwise in THF solution (4.5 mL of EtBr in 48 mL of THF; total amount of EtBr added: 9.2 g, 6.3 mL 84.2 mmol). The mixture was then allowed to reflux for additional 20 min. After cooling, the resulting solution of EtMgBr was transferred under nitrogen to a dropping funnel and added dropwise under nitrogen to a solution of phenylacetylene (9 g, 9,7 mL, 88 mmol) in anhydrous

THF (24 mL) at 0 °C with stirring. After additional stirring at 0°C for 15 min, the mixture was allowed to warm up to room temperature and then maintained at 45 °C for 2 h. A solution of amino ester (22 mmol) in anhydrous THF (7 mL) was then added dropwise under nitrogen to the warm solution of phenylacetylmagnesium bromide obtained as described before. The resulting mixture was allowed to stir at 35°C for additional 15 h. After cooling to room temperature, saturated NH_4Cl (100 mL) and AcOEt (40 ml) were sequentially added. Phases were separated, and the aqueous phase was extracted with AcOEt (3 × 100 mL). The collected organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the product was purified by column chromatography on silica gel using 8:2 hexane-AcOEt as the eluent to give pure *N*-protected-2-amino-1,1-dialkynyl-1-ols **1l** (yellow solid, 4.5 g, mp 127°-129°C, 55% based on *N*-Boc protected amino ester).

5.12 Procedure for the preparation of N-Boc-5-(1-Amino-ethyl)-2,2,8,8-tetramethyl-nona-3,6-diyn-5-ol (1m)

To a suspension of Mg turnings (2.1 g, 86.4 mmol) in anhydrous THF (9 mL), maintained under nitrogen and under reflux, was added pure ethyl bromide (1.8 mL) to start the formation of the Grignard reagent. The remaining bromide was added dropwise in THF solution (4.5 mL of EtBr in 48 mL of THF; total amount of EtBr added: 9.2 g, 6.3 mL 84.2 mmol). The mixture was then allowed to reflux for additional 20 min. After cooling, the resulting solution of EtMgBr was transferred under nitrogen to a dropping funnel and added dropwise under nitrogen to a solution of 3,3-Dimethyl-1-butyne (7.2 g, 10.8 mL, 88 mmol) in anhydrous THF (24 mL) at 0 °C with stirring. After additional stirring at 0°C for 15 min, the mixture was allowed to warm up to room temperature and then maintained at 45 °C for 2 h. A solution of *N*-Boc protected amino ester (22 mmol) in anhydrous THF (7 mL) was then added dropwise under nitrogen to the warm solution of 3,3-Dimethyl-1-butynylmagnesium bromide obtained as described before. The resulting mixture was allowed to stir at 35°C for additional

15 h. After cooling to room temperature, saturated NH_4Cl (100 mL) and AcOEt (40 ml) were sequentially added. Phases were separated, and the aqueous phase was extracted with AcOEt (3 × 100 mL). The collected organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the product was purified by column chromatography on silica gel using 8:2 hexane-AcOEt as the eluent to give pure *N*-protected-2-amino-1,1-dialkynyl-1-ols **1m** (white solid, mp 63°-66°C 5.4 g, 73% based on amino ester *N*-Boc protected).

5.13 Procedure for the preparation of N-Boc-5-(1-Amino-3-methyl-butyl)-2,2,8,8-tetramethyl-nona-3,6-diyn-5-ol (1n)

To a suspension of Mg turnings (2.1 g, 86.4 mmol) in anhydrous THF (9 mL), maintained under nitrogen and under reflux, was added pure ethyl bromide (1.8 mL) to start the formation of the Grignard reagent. The remaining bromide was added dropwise in THF solution (4.5 mL of EtBr in 48 mL of THF; total amount of EtBr added: 9.2 g, 6.3 mL 84.2 mmol). The mixture was then allowed to reflux for additional 20 min. After cooling, the resulting solution of EtMgBr was transferred under nitrogen to a dropping funnel and added dropwise under nitrogen to a solution of 3,3-Dimethyl-1-butyne (7.2 g, 10.8 mL, 88 mmol) in anhydrous THF (24 mL) at 0 °C with stirring. After additional stirring at 0°C for 15 min, the mixture was allowed to warm up to room temperature and then maintained at 45 °C for 2 h. A solution of *N*-Boc protected amino ester (22 mmol) in anhydrous THF (7 mL) was then added dropwise under nitrogen to the warm solution of 3,3-Dimethyl-1-butynylmagnesium bromide obtained as described before. The resulting mixture was allowed to stir at 35°C for additional 15 h. After cooling to room temperature, saturated NH_4Cl (100 mL) and AcOEt (40 ml) were sequentially added. Phases were separated, and the aqueous phase was extracted with AcOEt (3 × 100 mL). The collected organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the

solvent, the product was purified by column chromatography on silica gel using 8:2 hexane-AcOEt as the eluent to give pure *N*-protected-2-amino-1,1-dialkynyl-1-ols **1n** (white solid, mp 91°-95°C, 6.0 g, 72% based on amino ester *N*-Boc protected).

5.14 Procedure for the preparation of N-Boc-3-(1-Amino-3-methyl-butyl)-1,5-bis-trimethylsilanyl-penta-1,4-diyn-3-ol (1o)

To a suspension of Mg turnings (2.1 g, 86.4 mmol) in anhydrous THF (9 mL), maintained under nitrogen and under reflux, was added pure ethyl bromide (1.8 mL) to start the formation of the Grignard reagent. The remaining bromide was added dropwise in THF solution (4.5 mL of EtBr in 48 mL of THF; total amount of EtBr added: 9.2 g, 6.3 mL 84.2 mmol). The mixture was then allowed to reflux for additional 20 min. After cooling, the resulting solution of EtMgBr was transferred under nitrogen to a dropping funnel and added dropwise under nitrogen to a solution of Trimethylsilylacetylene (8.6 g, 12,4 mL, 88 mmol) in anhydrous THF (24 mL) at 0 °C with stirring. After additional stirring at 0°C for 15 min, the mixture was allowed to warm up to room temperature and then maintained at 45 °C for 2 h. A solution of *N*-Boc protected amino ester (22 mmol) in anhydrous THF (7 mL) was then added dropwise under nitrogen to the warm solution of 3,3-Trimethylsilylacetynylmagnesium bromide obtained as described before. The resulting mixture was allowed to stir at 35°C for additional 15 h. After cooling to room temperature, saturated NH_4Cl (100 mL) and AcOEt (40 ml) were sequentially added. Phases were separated, and the aqueous phase was extracted with AcOEt (3 × 100 mL). The collected organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the product was purified by column chromatography on silica gel using 8:2 hexane-AcOEt as the eluent to give pure *N*-protected-2-amino-1,1-dialkynyl-1-ols **1o** (white solid, mp 88°-89°C, 6.9 g, 77% based on amino ester *N*-Boc protected).

5.15 General Procedure for the Preparation of 3-Yne-1,2-diols 1p-1s

A solution of RC≡CH [R = Bu (3.66 g), Ph (4.55 g), 44.5 mmol] in anhydrous THF (6 mL) was added dropwise under nitrogen to a stirred, cooled (– 40°C) mixture of BuLi (28 mL of a 1.6 M solution in hexanes, 44.8 mmol) in anhydrous THF (16 mL). To the resulting mixture, maintained at – 40°C, was added, with stirring, a solution of LiBr (1.56 g, 18 mmol) in THF (6 mL). After 0.5 h, the appropriate α-hydroxy ketone (α-hydroxyacetone, 1.26 g, or α-hydroxyacetophenone, 2.55 g, 17.0 mmol), diluted in anhydrous THF (5 mL), was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 2 h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH_4Cl (20 mL), the mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with water (40 mL) and then dried over Na_2SO_4. After filtration, the solvent was evaporated to obtain crude **1p-s** . Crude 3-yne-1,2-diols **1p-s** were purified by column chromatography on silica gel: 2-methyl-4-phenylbut-3-yne-1,2-diol **1p** was a colorless solid (9:1 hexane-acetone, mp 105-106 °C, lit.[2] 109-110 °C, lit.[3] 105-106 °C, 2.56 g, 85% based on α-hydroxyacetone); 2,4-diphenyl-but-3-yne-1,2-diol **1q** was a colorless solid 107-108°C (6:4 hexane-AcOEt, 3.33 g, 90% based on α-hydroxyacetophenone); 2-phenyloct-3-yne-1,2-diol **1r** was a yellow oil (6:4 hexane-AcOEt, 3.33 g, 90% based on α-hydroxyacetophenone); 2,4-diphenylbut-oct-3-yne-1,2-diol **1s** was a colorless solid (6:4 hexane-AcOEt, mp 107-108 °C, lit.[4] 106 °C, 3.44 g, 85% based on α-hydroxyacetophenone).

5.16 General Procedure for the Preparation of 1,1-Dialkynyl-1,2-diols 1t-u

A solution of 1-hexyne (51.0 mmol) in anhydrous THF (12 mL) was added dropwise under nitrogen to a stirred, cooled (–40°C) mixture of BuLi (34 mL of a 1.6 M solution in hexanes, 54.4 mmol) in anhydrous THF (32 mL). To the resulting mixture, maintained at – 40°C, was added, with stirring, a solution of LiBr (2.13 g, 24.5 mmol) in THF (10 mL). After 0.5 h, the appropriate α-

hydroxyacetic acid ester (α-hydroxyacetic acid methyl ester, 1.53 g, or (*S*)-α-hydroxypropionic acid ethyl ester, 2.01 g, 17 mmol), diluted in anhydrous THF (7 mL) was slowly added unde nitrogen at the same temperature. The resulting mixture was stirred for additional 2 h, and then allowed to warm up to room temperature. After quenching with a saturated solution of NH_4Cl (20 mL), the mixture was extracted with Et_2O (3 × 50 mL). The combine organic layers were washed with water (40 mL) and then dried oven Na_2SO_4. After filtration and evaporation of the solvent, the crude products were purified by column chromatography: 2-hex-1-ynyloct-3-yne-1,2-diol **1t** was a yellow solid, m.p. 30-32°C (8:2 hexane-AcOEt, 2.80 g, 74% based on α-hydroxyacetic acid methyl ester); (*S*)-3-hex-1-ynylnon-4-yne-2,3-diol **1u** was a yellow oil [8:2 hexane-AcOEt, 3.21 g, 80% based on (*S*)-α-hydroxypropionic acid ethyl ester].

5.17 General Procedure for the Preparation of 1,1-Dialkynyl-1,2-diols 1v-w

A solution of 3,3-Dimethyl-but-1-yne or Ethynyl-benzene (51.0 mmol) in anhydrous THF (12 mL) was added dropwise under nitrogen to a stirred, cooled (–40°C) mixture of BuLi (34 mL of a 1.6 M solution in hexanes, 54.4 mmol) in anhydrous THF (32 mL). To the resulting mixture, maintained at – 40°C, was added, with stirring, a solution of LiBr (2.13 g, 24.5 mmol) in THF (10 mL). After 0.5 h, the (*S*)-α-hydroxypropionic acid ethyl ester (2.01 g, 17 mmol), diluted in anhydrous THF (7 mL) was slowly added unde nitrogen at the same temperature. The resulting mixture was stirred for additional 2 h, and then allowed to warm up to room temperature. After quenching with a saturated solution of NH_4Cl (20 mL), the mixture was extracted with Et_2O (3 × 50 mL). The combine organic layers were washed with water (40 mL) and then dried oven Na_2SO_4. After filtration and evaporation of the solvent, the crude products were purified by column chromatography: 3-(3,3-Dimethyl-but-1-ynyl)-6,6-dimethyl-hept-4-yne-2,3-diol **1v** was a yellow oil, (8:2 hexane-AcOEt, 2.80 g, 74% based on α-hydroxyacetic acid methyl ester); 5-Phenyl-3-phenylethynyl-

pent-4-yne-2,3-diol **1w** was a yellow oil [8:2 hexane-AcOEt, 3.21 g, 80% based on (*S*)-α-hydroxypropionic acid ethyl ester].

5.18 General Procedure for the Oxidative Carbonylation of N-Boc-2-amino-1-alkynyl-1-ols 1a-1f to Pyrrol-3-carboxylic Esters 2a-2f and 3a-3f

A 35 mL stainless steel autoclave was charged in the presence of air with PdI_2 (5.0 mg, 1.39×10^{-2} mmol), KI (23 mg, 13.9×10^{-2} mmol) and a solution of **1** [**1a** (232.5 mg), **1b** (198.4 mg), **1c** (178.8 mg), **1d** (241.8 mg), **1e** (192.7 mg), **1f** (232.0 mg),] in MeOH (3.5 mL). The autoclave was sealed and, while the mixture was stirred, the autoclave was pressurized with CO (16 atm) and air (up to 20 atm). After being stirred the autoclave was cooled, degassed and opened. The solvent was evaporated, and the products were purified by column chromatography on silica gel: **2a** was a yellow oil (8:2 hexane-AcOEt, 125.2 mg, 66% based on **1a**); **3a** was a yellow oil (8:2 hexane-AcOEt, 20.8 mg, 8% based on **1a**); **2b** was a yellow oil (8:2 hexane-AcOEt, 82.8 mg, 53% based on **1b**); **3b** was a yellow oil (8:2 hexane-AcOEt, 77 mg, 34% based on **1b**); **2c** was a yellow oil (8:2 hexane-AcOEt, 21.9 mg, 16% based on **1c**); **3c** was a white solid mp 36°C (8:2 hexane-AcOEt, 111.6 mg, 54% based on **1c**); **2d** was a white solid, m.p. = 80-82°C (8:2 hexane-AcOEt, 40 mg, 20% based on **1d**); **3d** was a yellow oil (8:2 hexane-AcOEt, 191.6 mg, 71% based on **1b**); **2e** was a brown oil (8:2 hexane-AcOEt, 51.2 mg, 34% based on **2e**); **3e** was a brown oil (8:2 hexane-AcOEt, 103.8 mg, 47% based on **2e**); **2f** was a yellow solid, m.p. = 112-114°C (8:2 hexane-AcOEt, 85.5 mg, 45% based on **1f**); **3f** was a yellow solid, m.p. = 112-114°C (8:2 hexane-AcOEt, 23.4 mg, 9% based on **1f).**

5.19 General Procedure for the Oxidative Carbonylation of N-Boc-2-amino-1,1-dialkynyl-1-ols 1g-1o to Pyrrol-3-carboxylic Esters 2g-2o and 2g'

A 35 mL stainless steel autoclave was charged in the presence of air with PdI_2 (5.0 mg, 1.39×10^{-2} mmol), KI (23 mg, 13.9×10^{-2} mmol) and a solution of **1** [**1g** (232.5 mg), **1h** (262.0 mg), **1i** (285.7 mg), **1j** (252.3 mg), **1k** (181.4 mg), **1l** (260.6 mg), **1m** (232.5 mg), **1n** (262.0), **1o** (284.4 mg) (0.69 mmol)] in ROH (R = Me or Et, 3.5 mL for **1g**). The autoclave was sealed and, while the mixture was stirred, the autoclave was pressurized with CO (16 atm) and air (up to 20 atm). After being stirred at 100°C for 15 h, the autoclave was cooled, degassed and opened. The solvent was evaporated, and the products were purified by column chromatography on silica gel: **2g** was a yellow oil (8:2 hexane-AcOEt, 134.2 mg, 66% based on **1g**); **2g'** was a colorless oil (8:2 hexane-AcOEt, 33% based on **1g**); **2h** was a yellow oil (8:2 hexane-AcOEt, 175 mg, 75% based on **1h**); **2i** was a colorless oil (8:2 hexane-AcOEt, 175 mg, 68% based on **1i**); **2j** was a yellow solid, mp 27-28 °C (8:2 hexane-AcOEt, 140.6 mg, 63% based on **1j**); **2k** was a yellow oil (8:2 hexane-AcOEt, 133.1mg, 49% based on **1k**); **2l** was a yellow oil (8:2 hexane-AcOEt, 118.0 mg, 51% based on **1l**); **2m** was a colorless oil (8:2 hexane-AcOEt, 126.0 mg, 62% based on **1m**); **2n** was a yellow oil (8:3 hexane-AcOEt, 130.4 mg, 56% based on **1n**); **2o** was a yellow oil (8:3 hexane-AcOEt, 81.3 mg, 60% based on **1o**).

5.20 Typical procedure for the $CuCl_2$-catalyzed heterocyclodehydration of 3-yne-1,2-diols 1p-w, N-substituted 1-amino-3-yn-2-ols 1a, 1c and N-sobstituted-2-amino-1,1-dialkynyl-1-ols, to the corresponding furans 4h–4o and pyrroles 4a-4g

To a solution of 1 (1.0 mmol) in anhydrous MeOH (5.0 mL) was added $CuCl_2$ (2.7 mg, 2.0×10^{-2} mmol, or 6.8 mg, 5×10^{-2} mmol, see Tables 1 and 2) under nitrogen in a Schlenk flask. The resulting mixture was stirred under nitrogen at 80°C or 100°C for the required time (see Tables 1 and 2, Chapter 3). The solvent

was evaporated, and the crude products were purified by column chromatography on silica gel (eluent: 99:1 hexane–acetone for **4h**, **4i**, and **4j**; hexane–AcOEt from 9:1 to 8:2 for **4k**, **4l**, **4m**, and **4n** ; hexane–AcOEt from 9:1 for **4a**-**4f**) or neutral alumina (for **4o**; eluent: 99:1 hexane–acetone) to give the pure products **4** (see yields, Chapter 3, Table 3.2).

5.21 General Procedure for the heterocyclodehydration -hydration of N-Boc-2-amino-1,1-dialkynyl-1-ols 1g-1o to 3-acylpyrroles 5d-5l

A 35 mL stainless steel autoclave was charged in the presence of air with $CuCl_2$ (3.0 mg, $22{,}3 \times 10^{-2}$ mmol), *p*-Toluenesulfonic acid monohydrate (42.4 mg, $22{,}3 \times 10^{-2}$ mmol), H_2O (20.0 mg, 1.11×10^{-2} mmol), and a solution of **1** [**1g** (374.3 mg), **1h** (419.1 mg), **1i** (457.0 mg), **1j** (403.5 mg), **1k** (290.2 mg), **1l** (416.8 mg), **1m** (372.4 mg), **1n** (419.1 mg), **1o** (454.8 mg), 1.11 mmol] in MeOH (5.6 mL). The autoclave was sealed and, while the mixture was stirred, the autoclave was pressurized with CO_2 (40 atm). After being stirred at 100°C for 15 h, the autoclave was cooled, degassed and opened. The solvent was evaporated, and the products were purified by column chromatography on silica gel: **5d** was a yellow solid (8:2 hexane-AcOEt, 188 mg, 70% based on **1g**); **5e** was a yellow oil (8:2 hexane-AcOEt, 211 mg, 68% based on **1h**); **5f** was a yellow oil (8:2 hexane-AcOEt, 280 mg, 82% based on **1i**); **5i** was a yellow oil,(8:2 hexane-AcOEt, 213 mg, 71% based on **1j**); **5j** was a yellow oil (8:2 hexane-AcOEt, 197 mg, 68% based on **1k**); **5g** was a brown solid (8:2 hexane-AcOEt 145 mg, 80 % based on **1l**); **5h** was a yellow solid (8:2 hexane-AcOEt, 225.0 mg, 87% based on **1m**); **5k** was a yellow solid (8:2 hexane-AcOEt, 206 mg, 78% based on**1n**); **5l** was a yellow oil (8:2 hexane-AcOEt, 250 mg, 82% based on **1o**).

5.22 Characterization products

***N*-Boc-2-amino-1-fenilnon-4-yn-3-ol (1a)** Yield: 8.02 g, starting from 60.5 mmol of amino ester (40%). Yellow solid. m.p. = 62-65°C; IR (KBr): ν/cm^{-1}= 3452 (br), 3379 (m), 2933 (m), 2230 (w), 1675 (s), 1531 (m), 1367 (m), 1250 (m), 1172 (m), 1041 (m), 759(w), 705 (m); Diastereoisomers mixture A and B, A / B = 1.1 determined by NMR. ^{1}H NMR: δ (300 MHz, $CDCl_3$)/ppm = 7.14-7.33 (m, 5H, Ph, [diastereoisomers A] + 5H, Ph, [diastereoisomers B]), 4.79-4.91 (m, 1H, N*H* [diastereoisomers A] + 1H, N*H* 50 [diastereoisomers B]), 4.37-4.42 (m, 1H, O*H* [diastereoisomers A]+ 1H, O*H* [diastereoisomers B]), 4.35 (dt, *J*= 4.5, 1.8 Hz, 1H, C*H*OH [diastereoisomers A] + 1H, C*H*OH [diastereoisomers B]), 4.01-4.12 (m, 1H, *CH*NH, diastereoisomers B), 3.87-4.00 (m, 1H, *CH*NH, diastereoisomers A), 3.04 (distorted dd, *J*= 14.0, 6.8 Hz, 2H, CH_2Ph diastereoisomers B), 2.92 (distorted dd, *J*= 14.0, 6.8 Hz, 2H, CH_2Ph diastereoisomers A), 2.27 (td, *J*= 7.0 , 1.8 Hz, 2H, CH_2C diastereoisomers B), 2.21 (td, *J*= 7.0 Hz, 1.8, 2H, CH_2C diastereoisomers A), 1.19-1.60 (m, 13H, C(CH_3)$_3$, CH_2CH_2 [diastereoisomers A] + 13H, C(CH_3)$_3$, CH_2CH_2 [diastereoisomers B]), 0.90 (t, *J*= 7.2 Hz, 3H, $CH_3CH_2CH_2$ Diastereoisomers A) , 0.94 (t, *J*= 7.2 Hz, 3H, $CH_3CH_2CH_2$ diastereosiomers B). ^{13}C NMR: δ (75 MHz, $CDCl_3$)/ppm = 156.3 (diastereoisomers B), 156.1 (diastereoisomers A), 138,2 (diastereoisomers B), 137, 8 (diastereoisomers A), 129.5 (diastereoisomers B), 129,3 (diastereoisomers A), 128.5 (diastereoisomers B), 128.5 (diastereoisomers A), 126.6 (diastereoisomers B), 126.4 (diastereoisomers A), 86.9 (diastereoisomers A + diastereoisomers B), 79.9 (diastereoisomers B), 79.6 (diastereoisomers A), 78.9 (diastereoisomers B), 77.8 (diastereoisomers A), 64.9 (diastereoisomers A + diastereoisomers B), 64.0 (diastereoisomers A + diastereoisomers B), 56.9 (distereoisomers B), 56.7 (diastereoisomers A), 37.6 (diastereoisomers B), 37.1 (diastereiosomers A), 30.8 (diastereoisomers B), 30.7 (diastereoisomers A), 28.3 (diastereoisomers A + diastereoisomers B), 22.1 (diastereoisomers B), 22.0 (diastereoisomers A), 18.5 (diastereoisomers B), 18.5 (diastereoisomers A), 13.6 (diastereoisomers A + diastereoisomers B). anal. calcd for $C_{20}H_{29}NO_3$ (331,45): C. 72.47; H. 8.82; N. 4.23; found C, 72.50; H, 8.79.

***N*-Boc-2-amino-2-methyildec-5-yn-4-ol (1b)** Yield: 6.9 g, starting from 60.5 mmol of amino ester (40%). Yellow oil; IR (film): ν/cm^{-1}= 3403 (br), 2962 (m), 2230 (w), 1696 (s), 1508 (m), 1366 (m), 1248 (m), 1172 (m), 1047 (m), 776(w). ^{1}H NMR**:** δ (300 MHz, $CDCl_3$)/ppm = 4.74-4.90 (m, 1H, N*H*), 4.40 (dt, *J*= 5.3, 2.0 Hz, 1H, C*H*OH), 4.15-4.30 (m, 1H, O*H*), 3.36-3.5 (m, 1H, *CH*NH), 2.20(td, *J*=6.9, 2.0 Hz , 2H, CH_2C≡), 1.99-2.12 (m, 1H, CH(CH_3)$_2$), 1.32-1.54 (m, 13H, C(*CH$_3$)$_3$, CH$_2$CH$_2$*), 0.98 (d, *J*=6.9Hz, 3H ,CH_3CH*CH$_3$*), 0.93 (d, *J*= 6.9 Hz, 3H, *CH$_3$*CHCH$_3$), 0.90 (t, *J*= 7.1 Hz, 3H, *CH$_3$*CH$_2$CH$_2$); ^{13}C NMR: δ (75 MHz, $CDCl_3$)/ppm = 156.9, 86.4, 79.4, 79.2, 63.9, 61.1, 30.7, 28.4, 22.0, 20.2, 18.5, 18.2, 13.6. anal. calcd for $C_{16}H_{29}NO_3$ (283,41): C. 67,81; H. 10,31; N. 4,94; found C, 67.79; H, 10.33.

***N*-Boc-2-aminonon-4-yn-3-ol (1c)** Yield: 8.7 g, starting from 60.5 mmol of amino ester (56%). Colorless oil; IR (film): ν/cm^{-1}= 3404 (br), 2934 (m), 2212 (w), 1695 (s), 1506 (m), 1367 (m), 1250 (m), 1169 (m), 1051 (m), 780(w). Diastereoisomers mixture A and B, A / B = 1.1 determined by NMR.^{1}H NMR: δ (300 MHz, $CDCl_3$)/ppm = 5.75-5.80 (m, 1H, N*H*, [diastereoisomers A] +1H, N*H*, [diastereoisomers B]) 4.13-4.28 (m, 1H, O*H* 54 [diastereoisomers [A] + 1H, O*H* [diastereoisomers [B]), 3.30-3.41 (m, 1H, *CH*OH [diastereoisomers A] + 1H, *CH*OH [diastereoisomers B]), 2.96 (q, *J*=6.6Hz, 1H, C*H*NH [diastereoisomers A] + 1H, C*H*NH [diastereoisomers B]), 2.18-2.26 (m, 2H, CH_2C [diastereoisomers A] + 2H, CH_2C [diastereoisomers B]), 2.15 (s, 9H, C(CH_3)$_3$ [diastereoisomers A] + 9H, C(CH_3)$_3$ [diastereoisomers B]), 1.27-1.58 (m, 4H, *CH$_2$CH$_2$*, [diastereoisomers A] + 4H, *CH$_2$CH$_2$*, [diastereoisomers B1.22 (d, *J*= 6.6 Hz, 3H, *CH$_3$*CH, [diastereosiomers A] + 3H, *CH$_3$*CH [diastereoisomers B]), 0.89 (t, *J*= 7.1 Hz, 3H, *CH$_3$*CH$_2$CH$_2$ diastereoisomers B) 0.89 (t, *J*= 7.1 Hz, 3H, *CH$_3$*CH$_2$CH$_2$ (diastereoisomers A)].^{13}C NMR: δ (75 MHz, $CDCl_3$)/ppm = 164.1 (diastereoisomers A + diastereoisomers B), 85.2 (diastereoisomers A + diastereoisomers B), 84.7 (diastereosiomers A + diastereoisomers B), 80.1 (diastereoisomers A+ diastereoisomers B), 56.8 (diastereoisomers A + diastereoisomers B), 30.9 (diastereoisomers B), 30.7

(diastereoisomers A), 30.7 (diastereoisomers B), 30.6 (diastereoisomers A), 22.0 (diastereoisomers A + diastereoisomers B), 18.4 (diastereoisomers A + diastereoisomers B), 18.3 (diastereoisomers A + diastereoisomers B), 13.6 (diastereoisomers A + diastereoisomers B), 13.5 (diastereoisomers A + diastereoisomers B). anal. calcd for $C_{14}H_{25}NO_3$ (255,35): C. 65.85; H. 9.87; N. 5.49; found C, 65.83; H, 9.90.

***N*-Boc-2-amino-3-methyl-1-fenil-non-4-yn-3-ol (1d)** Yield: 16.7 g, starting from 60.5 mmol of amino ester (80%). White solid**,** m.p.=50-52°C; IR (KBr): ν/cm^{-1}= 3444 (br), 3377 (m), 2933 (m), 2241 (w), 1676 (s), 1530 (m), 1366 (m), 1171 (m), 1073 (m), 753 (w), 699 (m). Diastereoisomers mixture A and B, A / B = 1.5 determined by NMR ^{1}H NMR: δ (300 MHz, $CDCl_3$)/ppm= 7.13-7.33 (m, 5H, Ph, [diastereoisomers A] + 5H, Ph, [diastereoisomers B]) 4.59-4.67 (m, 1H, N*H*, [diastereoisomers B]), 4.49-4.58 (m, 1H, N*H*, [diastereoisomers A]), 3.83-3.99 (m, 1H, C*H*NH, [diastereoisomers A] + 1H, , C*H*NH, [diastereoisomers B], 3.22-3.37 (m, 2H, CH_2Ph, [diastereoisomers A] + 2H, CH_2Ph, [diastereoisomers B], 2.86-2.94 (m, 1H, O*H*, [diastereoisomers A], 1H, O*H*, [diastereoisomers B]), 2,24 (t, *J*= 6.9 Hz, 2H, CH_2C, diastereoisomers B), 2.23 (t, *J*= 6.9 Hz, 2H, CH_2C, diastereoisomers A), 1.36-1.59 (m, 4H, CH_2CH_2 [diastereoisomers A] + 16H CH_2CH_2 , CH_3, C(CH_3)$_3$, [diastereoisomers B]), 1.24-1.34 (m , 12H, CH_3, C(CH_3)$_3$, diastereoisomers A), 0.95 (t, *J*= 7.1 Hz, 3H CH_3CH_2CH_2 ,diastereoisomers B), 0.93 (t, *J*= 7.1 Hz, 3H, CH_3CH_2CH_2, diastereoisomers A). ^{13}C NMR: δ (75 MHz, $CDCl_3$)/ppm = 156.1 (diastereoisomers A + diastereoisomers B), 138,6 (diastereoisomers A + diastereoisomers B), 129.28 (diastereoisomers B), 129,2 (diastereoisomers A), 128.3 (diastereoisomers A + diastereoisomers B), 126.3 (diastereoisomers B), 126.2 (diastereoisomers A), 85.6 (diastereoisomers A + diastereoisomers B), 71.4 (diastereoisomers A + diastereoisomers B), 60.31 (diastereoisomers B), 60.0 (diastereoisomers A), 37.4 (distereoisomers B), 36.7 (diastereoisomers A), 30.8 (diastereiosomers A + diastereoisomers B), 28.2 (diastereoisomers A + diastereoisomers B), 27.08

(diastereoisomers A + diastereoisomers B), 22.0 (diastereoisomers A + diastereoisomers B), 18.4 (diastereoisomers A + diastereoisomers B), 81.9 (diastereoisomers A + (diastereoisomers B), 13.6 (diastereoisomers A + diastereoisomers B); anal. calcd for $C_{21}H_{31}NO_3$ (345,48): C. 73.01; H. 9.04; N. 4.05; found C, 73.04; H, 9.01.

***N*-Boc-4-amino-1-phenyl-1-yn-3-ol (1e)** Yield: 11.1 g, starting from 60.5 mmol of amino ester (67%). Yellow oil; IR (film): ν/cm^{-1}= 3353 (br), 2978 (m), 2226 (w), 1688 (m), 1504 (m), 1367 (m), 1166 (m), 1047 (m), 757 (m), 691 (m)Diastereoisomers mixture A and B, A / B = 1.6 determined by NMR; ^{1}H NMR: δ (300 MHz, $CDCl_3$)/ppm =7.40-7.47 (m, 5H, Ph, diastereoisomers B),7.27-7.34 (m, 5H, Ph, diastereoisomers A), 4.83-4,90 (m, 1H, N*H*, [diastereoisomers B]), 4.64 (d, *J*= 5.3 Hz, 1H, C*H*OH, [diastereoisomers B]), 4.57 (d, *J*= 5.3 Hz, 1H, C*H*OH, [dia stereoisomers A]), 3.85-4.09 (m, 1H, C*H*NH, [diastereoisomers A] + 1H, C*H*NH, [diastereoisomers B]), 3.39-3.60 (m, 1H, O*H*, [diastereoisomers B]), 3.0-3.35 (m, 1H, O*H*, [diastereoisomers A]), 1.46 (s, 9H, C(CH_3)$_3$, [diastereoisomers B]), 1.449 (s, 9H, C(CH_3)$_3$, [diastereoisomers A]), 1.31 (d, *J*= 6.9 Hz, 3H, CH_3, [diastereoisomers B]), 1.27 (d, *J*= 6.9 Hz, 3H, CH_3, [diastereoisomers A]). ^{13}C NMR: δ (75 MHz, $CDCl_3$)/ppm= 156.0 (diastereoisomers A + diastereoisomers B), 131.8 (diastereoisomers B), 131.8 (diastereoisomers A), 128.5 (diastereoisomers A + diastereoisomers B), 128.3 (diastereoisomers B), 128.3 (diastereoisomers A), 122.5 (diastereoisomers A + diastereoisomers B), 87.5 (diastereoisomers A + diastereoisomers B), 86.9 (diastereoisomers A + diastereoisomers B), 80.1 (diastereoisomers B), 79.9 (diastereoisomers A), 67.0 (diastereoisomers B), 66.6 (diastereoisomers A), 51.4 (diastereoisoemers B), 51.1 (diastereoisomers A), 28,4 (diastereoisomers A + diastereoisomers B), 16.4 (diastereoisomers A + diastereoisomers B), anal. calcd for $C_{16}H_{21}NO_3$ (275,34): C. 69.79; H. 7.69; N. 5.09; found C, 69.81; H, 7.66.

***N*-Boc-2-amino-6,6-dimethyl-1phenyl-4-yn-3-ol (1f).** Yield: 10.0 g, starting from 60.5 mmol of amino ester (50%). White solid. m.p.= 120-122°C. IR (KBr): ν/cm^{-1}= 3453 (br), 3397 (m), 2970 (m), 2241 (w), 1681 (s), 1527 (s), 1367 (m), 1250 (m), 1173 (m), 1024 (m), 702 (m), 579 (w). Diastereoisomers mixture A and B, A / B = 1.5 determined by NMR. ^{1}H NMR: δ (300 MHz, $CDCl_3$)/ppm = 7.11-7.42 (m, 5H, Ph, diastereoisomers A + 5H, Ph, diastereoisomers B), 4.70-4.88 (m, 1H, N*H*, diastereoisomers A + 1H, N*H*, diastereoisomers B), 4.38-4.46 (m, 1H, C*H*OH, diastereoisomers B), 4.26-4.37 (m, 1H, C*H*OH, diastereoisomers A), 4.01- 4.11 (m, 1H, C*H*NH, diastereoisomers B), 3.84-4.00 (m, 1H, C*H*NH, diastereoisomers A), 3.00 (distorted dd, *J*= 13.7, 6.5 Hz, 2H, CH_2Ph, diastereoisomers A + 2H, CH_2Ph, diastereoisomers B), 2.78-2.91 (m, 1H, O*H*, diastereoisomers B), 2.64 -2.72 (m, 1H, O*H*, diastereoisomers A), 1.39 (s, 9H , (CH_3)$_3$ diastereoisomers A + 9H , (CH_3)$_3$, diastereoisomers B), 1,27 (s, 9H, C(CH_3)$_3$, diastereoisomers B), 1.22 (s, 9H, C(CH_3)$_3$, diastereoisomers A). ^{13}C NMR: δ (75 MHz, $CDCl_3$)/ppm= 155.98 (diastereoisomers A + diastereoisomers B), 137.97 (diastereoisomers A + diastereoisomers B), 129.42 (diastereoisomers B), 129.24 (diastereoisomers A), 128.55 (diastereoisomers B), 128.49 (diastereoisomers A), 126.58 (diastereoisomers B), 126.45 (diastereoisomers A), 95.16 (diastereoisomers A + diastereoisomers B), 79.51 (diastereoisomers A + diastereoisomers B), 77.34 (diastereoisomers A + diastereoisomers B), 63.96 (diastereoisomers A + diastereoisomers B), 56.67 (diastereoisomers A + diastereoisomers B), 37.17 (diastereoisomers A + diastereoisomers B), 33.91 (diastereoisomers B), 33.31 (diastereoisomers A), 31.00 (diastereoisoemers B), 30.89 (diastereoisomers A), 28,32 (diastereoisomers B), 27.38 (diastereoisomers A) ; anal. calcd for $C_{20}H_{29}NO_3$ (331,45): C. 72.47; H. 8.82; N. 4.23; found C, 72.50; H, 8.79.

***N*-Boc-7-(1-Amino-ethyl)-trideca-5,8-diyn-7-ol (1g)**. Yield: 5.0 g, 68% based on amino ester *N*-Boc protected.Yellow oil. IR (KBr): *ν* = 3436 (s, br), 2874 (s), 2236 (w), 1701 (s), 1508 (s), 1556 (w), 1367 (m), 1247 (m), 1165 (m), 1052 (m), 861 (w), 756 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 4.76 (d, br, J=7.4, 1H,

NH), 4.05-3.86 (m, 1H, C*H*NH), 3.30 (s br, 1H, OH), 2.25 (t, J= 7.0, 2H, CH_2CH$_2$CH$_2$CH$_3$), 2.23 (t, J= 7.0, 2H, CH_2CH$_2$CH$_2$CH$_3$), 1.57-1.34 (m, 8H, 2 CH$_2$CH_2CH_2CH$_3$), 1.46 (s, 9H, C(CH$_3$)$_3$), 1.31 (d, J = 6.8, 3H, CHCH_3), 0.914 (t, J = 7.1, 3H, CH$_2$CH$_2$CH$_2$CH_3), 0.906 (t, J = 7.1, 3H, CH$_2$CH$_2$CH$_2$CH_3) ; ^{13}C NMR (75 MHz, CDCl$_3$): δ = 156.1, 85.1, 85.0, 79.7, 79.6, 78.9, 67.5, 67.1, 60.4, 55.7, 30.6, 30.5, 28.4, 27.5, 22.0, 18.4, 17.0, 13.5; anal. calcd for $C_{20}H_{33}NO_3$ (335.25): C, 71.60; H, 9.91; N, 4.18; found C, 71.58; H, 9.89.

***N*-Boc-7(1-ammino-3-methyl-butyl)-trideca-5,8-diyn-7-ol (1h)**. Yield: 6.0 g, 73% based on amino ester *N*-Boc protected. Yellow oil. IR (KBr): ν = 3439 (m, br), 3379 (m, br), 2958 (m), 2234 (w), 1716 (s), 1505 (m), 1436 (w), 1367 (m), 1251 (w), 1166 (s), 1049 (w), 875 (w), 779 (w) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 4.65 (d, br, J=10.1, 1H, NH), 4.18 (q d, J = 7.1, 1.6, 1H, C*H*NH), 3.90 (t, J= 10.9, 1H, C*H*(CH$_3$)$_2$), 3.30 (s br, 1H, OH), 2.23 (td, J= 6.9, 2.0, 4H, 2 CH_2CH$_2$CH$_2$CH$_3$), 1.74-1.62 (m, 2H, CH_2CH(CH$_3$)$_2$), 1.44 (d, J=1.61, 9H, C(CH_3)$_3$), 1.53-1.33 (m, 8H, 2 CH$_2$CH_2CH_2CH$_3$), 1.00-0.92 (m, 6H, CH(CH_3)$_2$), 0.91-0.84 (m, 6H, 2 CH$_2$CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$): δ =156.6, 85.1, 85.0, 79.7, 79.6, 78.7, 67.7, 61.2, 58.2, 40.1, 30.5, 30.4, 28.3, 25.0, 24.8, 23.9, 22.9, 22.0, 21.9, 21.6, 18.4, 14.1, 13.6; anal. calcd for $C_{23}H_{39}NO_3$ (377.56): C, 73.17; H, 10.41; N, 3.71; found C, 73.19; H,10.44.

***N*-Boc-7(1-ammino-2-phenyl-ethyl)-trideca-5,8-diyn-7-ol (1i)**. Yield: 6.2 g, 68% based on amino ester *N*-Boc protected Yellow solid. mp=61-65 °C; IR (KBr): ν = 3380 (m), 3290 (m, br), 2959 (m), 2230 (w), 1687 (s), 1603 (w), 1453 (w), 1366 (m), 1256 (w), 1170 (m), 1128 (m), 1061 (m), 1022 (w), 848 (w), 745 (m), 699 (m) cm^{-1};^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.41-7.10 (m, 5H on aromatic ring), 4.69 (d, J=9.7, 1H, NH), 4.13 (t d, J =10.9, 3.0, 1H, C*H*NH), 3.52 (s br, 1H, OH), 3.43-3.31 (m, 2H, CH$_2$Ph), 2.30-2.21 (m, 4H, 2 CH_2CH$_2$CH$_2$CH$_3$), 1.74-1.62 (m, 2H, CH$_2$CH(CH$_3$)$_2$), 160.137 (m, 8H, 2 CH$_2$CH_2CH_2CH$_3$), 1.31 (s, 9H, C(CH_3)$_3$), 0.92 (t, J= 7.0, 3H, CH$_2$CH$_2$CH$_2$CH_3), 0.90 (t, J= 7.0, 3H, CH$_2$CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$): δ =156.1,

138.3, 129.6, 129.2, 128.3, 126.2, 85.5, 85.4, 79.6, 79.5, 78.8, 67.2, 61.0, 37.1, 30.5, 30.4, 28.2, 27.9, 22.0, 18.4, 13.6. anal. calcd for $C_{26}H_{37}NO_3$ (411,28): C, 75.87; H, 9.06; N, 3.40; found C, 75.15; H, 9.06.

***N*-Boc-7-(1-ammino-2-methyl-propyl)-trideca-5,8-diyn-7-ol (1j)**. Yield: 4.9 g, 61% based on amino ester *N*-Boc protected. Yellow oil. IR (KBr): ν = 3440 (s, br), 2960 (m), 2234 (w), 1700 (s), 1505 (m), 1467 (w), 1392 (m), 1311 (m), 1239 (m), 1171 (s), 1094 (w), 1000 (w), 872 (w), 761 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.86 (d, br, J=10.5, 1H, NH), 4.12 (q, J=7.3, 1H, C*H*NH), 3.77 (dd, J= 10.5, 2.8, 1H, C*H*$(CH_3)_2$), 3.30 (s br, 1H, OH), 2.29-2.15 (m, 4H, 2 C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.55-1.35 (m, 8H, 2 CH$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.46 (s, 9H, C(C*H*$_3$)$_3$), 1.04-0.95 (m, 6H, CH(C*H*$_3$)$_2$), 0.91 (td, J = 7.3, 2.4, 6H, 2 CH$_2$CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.8, 85.5, 85.0, 79.9, 79.5, 79.4, 66.9, 64.4, 63..3, 60.5, 30.4, 29.2, 28.4, 22.2, 22.0, 21.0, 18.5, 17.0, 14.2, 13.6; anal. calcd for $C_{22}H_{37}NO_3$ (363,53): C, 72.69; H, 10.26; N, 3.85; found C, 72.70; H, 10.29.

7-Pyrrolidin-2-yl-trideca-5,8-diyn-7-ol (1k). Yield: 3.1 g, 54% based on amino ester. Brown oil. IR (KBr): ν = 3436 (m, br), 2956 (m), 2345 (w), 1648 (s), 1560 (w), 1522 (m), 1430 (w), 1385 (m), 1299 (w), 1189 (w), 971 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.88 (s, 1H, NH), 3.77 (t , J =7.1, 2H on pyrrolidine ring), 2.82(t, J =7.1, 2H on pyrrolidine ring), 2.44 (q, J=7.2, 4H, 2 C*H*$_2$CH$_2$CH$_2$CH$_3$), 2.35 (t , J =7.1, 1H, -NHCHCH$_2$-), 2.25-2.15 (m, 1H, OH), 1.60-1.29 (m, 10H, 2 CH$_2$C*H*$_2$C*H*$_2$CH$_3$ + 2H on pyrrolidine ring), 1.00-0.84 (m, 6H, 2 CH$_2$CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6, 127.8, 111.4, 94.8, 87.9, 75.9, 44.9, 31.4, 31.2, 27.4, 26.3, 24.1, 22.3, 22.0, 19.4, 13.9, 13.7; anal. calcd for $C_{17}H_{27}NO$ (261.40): C, 78.11; H, 10.41; N, 5.36; found C, 78.12; H, 10.38.

***N*-Boc-3-(1-ammino-ethyl)-1,5-diphenyl-penta-1,4-diyn-3-ol (1l)**. Yield: 4.5 g, 55% based on amino ester *N*-Boc protected; White solid. mp= 127-129°C. IR (KBr): ν = 3308 (m), 3206 (m, br), 3008 (w), 2230 (w), 1664 (s), 1598 (w), 1537

(s), 1490 (s), 1456 (w), 1384 (m), 1315 (m), 1257 (w), 1159 (s), 1112 (m), 1009 (m), 856 (w), 756 (m), 692 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51-7.44 (m, 3H on aromatic ring), 7.35-7.24 (m, 6H on aromatic ring), 4.95 (d, J=9.28, 1H, NH), 4.32-4.17 (m, 1H, $CHCH_3$), 4.10 (s, 1H, OH), 1.44 (s, 12H, $C(CH_3)_3$ + CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3, 132.0, 128.8, 128.3, 128.2, 122.2, 87.8, 87.0, 84.9, 84.7, 80.1, 68.6, 55.8, 28.4, 17.1; anal. calcd for $C_{24}H_{25}NO_3$ (375,46): C, 76.77; H, 6.71; N, 3.73; found C, 76.76; H, 6.70.

***N*-Boc-5-(1-ammino-ethyl)2,2,8,8-tetramethylnona-3,6-diyn-5-ol (1m)**. Yield: 5.4 g, 73% based on amino ester *N*-Boc protected. White solid. mp= 63-66°C. IR (KBr): ν = 3439 (m), 2972 (m), 2868 (w), 2247 (w), 1675 (m), 1513 (w), 1384 (s), 1165 (w), 1054 (w), 979 (w), 858 (w) cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.80-4.66 (m, 1H, NH), 3.48 (q, J=7.0, 1H, C*H*NH), 3.10 (s, 1H, OH), 1.46 (s, 9H, $OC(CH_3)_3$), 1.45 (s, 3H, Me), 1.22 (s, 9H, $C(CH_3)_3$), 1.13 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.0, 93.2, 92.9, 79.6, 78.4, 67.3, 65.8, 55.8, 30.8, 30.7, 28.5, 28.4, 27.4, 18.7, 17.2, 15.3, 14.2; anal. calcd for $C_{20}H_{33}NO_3$ (335,48): C, 71.60; H, 9.91; N, 4.18; found C, 71.59; H, 9.92.

***N*-Boc-5-(1-ammino-3-methyl-butyl)-2,2,8,8-tetramethylnona-3,6-diyn-5-ol (1n)**. Yield: 6.0 g, 72% based on amino ester *N*-Boc protected. White solid. mp=91.5-93.0 °C. IR (KBr): ν = 3449 (m), 2971 (m), 2930 (w), 2867 (w), 2244 (w), 1701 (s), 1511 (m), 1384 (s), 1175 (m), 1015 (w), 871 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.80-4.66 (m, 1H, NH), , 3.90 (t, J= 10.9, 1H, $CH(CH_3)_2$), 3.48 (q, J=7.0, 1H, C*H*NH), 3.10 (s, 1H, OH), 1.74-1.62 (m, 2H, $CH_2CH(CH_3)_2$), 1.46 (s, 9H, $OC(CH_3)_3$), 1.45 (s, y3H, Me), 1.13 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.0, 93.2, 92.9, 79.6, 78.4, 67.3, 65.8, 55.8, 30.8, 30.7, 28.5, 28.4, 27.4, 18.7, 17.2, 15.3, 14.2. anal. calcd for $C_{23}H_{39}NO_3$ (377,56): C, 73.17; H, 10.41; N, 3.71; found C, 73.116; H, 10.43.

***N*-Boc-3-(1-ammino-3-methyl-butyl)-1,5-bis-trimethylsilanyl-penta-1,4-diyn-3-ol (1o)**. Yield: 6.9 g, 77% based on amino ester *N*-Boc protected. White solid. mp= 88-89 °C . IR (KBr): ν = 3446 (m), 3369 (m, br), 2956 (m), 2172 (w), 1701 (s), 1510 (s), 1464 (w), 1368 (w), 1250 (s), 1178 (m), 1123 (w), 1044 (m), 841 (s), 761 (m), 701 (w) cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.55 (d, J=10.4, 1H, NH), 3.95 (t, J= 10.4, 1H, C*H*NH), 3.46 (s, 1H, OH), 1.68 (t, J= 5.2, 2H, $CH_2CH(CH_3)_2$), 0.96 (d, J= 6.0, 6H, $CH(CH_3)_2$) , 0.19 (s, 9 H, $C(CH_3)_3$) 0.18 (s, 18 H, $2Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.9, 104.0, 102.9, 89.9, 89.7, 80.2, 68.4, 58.3, 40.5, 28.7, 25.3, 24.1, 21.9; anal. calcd for $C_{21}H_{39}NO_3Si_2$ (409.71): C, 61.56; H, 9.59; N, 3.42; found C, 61.57; H, 9.61.

2-Methyl-4-phenyl-but-3-yne-1,2-diol (1p). Yield: 2.56 g, based on α-hydroxyacetone (85%); Colorless solid, mp 105-106 °C, IR (KBr): ν = 3399 (s, br), 2977 (w), 2931 (w), 2232 (w), 1491 (m), 1402 (m), 1231 (w), 1050 (s), 900 (s), 764 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45-7.30 (m, 5 H, Ph), 5.42 (s, 1 H, OH), 5.02 (t, J = 6.3, 1 H, OH), 3.52-3.35 (m, 2H, CH_2OH), 1.42 (s, 3 H, CH_3), ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.2, 128.5, 128.2, 122.7, 94.2, 81.9, 69.6, 67.7, 26.2, ; GC-MS (EI, 70 eV): *m/z* = 176 (3), 146 (18), 145 (100), 129 (11), 115 (11), 77 (10); anal. calcd for $C_{11}H_{12}O_2$ (176.21): C, 74.98; H, 6.86; found C, 75.01; H, 6.87.

2,4-Diphenyl-but-3-yne-1,2-diol (1q). Yield: 3.33 g, based on α-hydroxyacetophenone (90%), colorless solid, mp 107-108°C; IR (KBr): ν = 3352 (m, br), 3222 (m, br), 2215 (w), 1489 (w), 1412 (m), 1069 (m), 903 (m), 757 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60-7.64 (m, 2 H on phenyl ring), 7.51-7.45 (m, 2 H, on phenyl ring), 7.41-7.26 (m, 8 H, on phenyl ring), 3.88.3.68 (m, 2 H, CH_2OH), 3.54 (s, 1 H, PhCO*H*), 2.65 (s, 1 H, CH_2OH), 2.29 (t, J = 6.9, 2 H), 1.60-1.36 (m, 4 H), 0.92 (t, J = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.04, 141.0, 131.9, 128.8, 128.4, 128.4, 128.3, 126.0, 122.2, 89.5, 86.7, 74.2, 72.2, ; GC-MS (EI, 70 eV): *m/z* = 238 (M^+, absent), 208 (48), 207

(100), 191 (13), 189 (14), 178 (18), 130 (24), 129 (93), 105 (66), 77 (54), ; anal. calcd for $C_{16}H_{14}O_2$ (238.28): C, 80.65; H, 5.92; found C, 80.65; H, 5.92.

Phenyloct-3-yne-1,2-diol (1r). Yield: 3.33 g, starting from 2.55 g of α-hydroxyacetophenone (90%). Yellow oil. IR (film): ν = 3341 (m, br), 2931 (m), 2247 (w), 1588 (m), 1495 (m), 1385 (m), 1245 (s), 1074 (m), 1033 (m), 903 (m), 758 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65-7.58 (m, 2 H), 7.40-7.26 (m, 3 H), 3.69 (distorted dd, J = 10.9, 4.2, 1 H), 3.61 (distorted dd, J = 10.9, 6.3, 1 H), 3.23 (s, 1 H), 2.48-2.38 (m, 1 H), 2.29 (t, J = 6.9, 2 H), 1.60-1.36 (m, 4 H), 0.92 (t, J = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.5, 128.3, 128.0, 125.9, 87.8, 80.7, 73.9, 72.3, 30.7, 22.0, 18.5, 13.6; GC-MS (EI, 70 eV): *m/z* = 218 (M^+, absent), 188 (52), 187 (100), 141 (11), 128 (26), 115 (53), 109 (58), 105 (67), 91 (37), 79 (46), 77 (52), 66 (38); anal. calcd for $C_{14}H_{18}O_2$ (218.29): C, 77.03; H, 8.31; found C, 77.12; H, 8.29.

1,2-Diphenyl-oct-3-yne-1,2-diol (1s). Yield: 3.44 g, starting from 2.55 g of α-hydroxyacetophenone (85%). colorless solid; mp 107-108 °C; IR (KBr): ν = 3489 (m, br), 3451 (m,br) 2931 (w), 2858 (w), 2219 (w), 1491 (w), 1450 (m), 1384 (s), 1061 (m), 902 (w), 697 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.50-7.35 (m, 2 H, on phenyl ring), 7.30-7.00 (m, 8 H, on phenyl ring), 4.82 (s, 1 H, C*H*OH), 2.87 (s, 1 H, OH), 2.81 (s, 1 H, OH), 2.29 (t, J=7.3, 2 H $CH_2CH_2CH_2CH_3$), 1.60-1.35 (m, 4 H $CH_2CH_2CH_2CH_3$), 0.92 (t, J= 7.3 ,3 H CH_3), 0.92 (t, J = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =140.5, 137.7, 128.0, 127.9, 127.87,127.6, 127.25,126.7, 126.3; GC-MS (EI, 70 eV): *m/z* = 263 (M^+, absent), 163 (100), 105 (54), 77 (64); anal. calcd for $C_{20}H_{22}O_2$ (294.39): C, 81.60; H, 7.53; found C, 81.62; H, 7.54.

2-Hex-1-ynyl-oct-3-yne-1,2-diol (1t). Yield: 2.8 g, starting from 1.53 g of Hydroxy-acetic acid methyl ester (74%). Yellow solid, mp 30-32°C. IR (KBr): ν = 3339 (m, br), 2934 (m), 2241 (w), 1465 (w), 1382 (w), 1263 (m), 1175 (m), 1084 (m), 912 (w), 678 (m) cm^{-1}; ^1H NMR (300 MHz, CDCl3): δ = 3.70 (s, 2H,

C*H*$_2$OH), 3.00 (s br, 2 H, 2 OH), 2.24 (t, *J* = 6.9, 4 H, 2 C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.60-1.30 (m, 8 H, 2 CH$_2$C*H*$_2$C*H*$_2$CH$_3$), 0.91 (t, *J* = 7.1, 6 H, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, CDCl3): δ = 85.4, 78.5, 71.0, 64.5, 30.5, 22.0, 18.4, 13.6; GC-MS: m/z = 192 (15), 191 (100), 109 (6), 107 (5), 105 (7), 93 (5), 91 (17), 79 (20), 77 (12), 67 (7); anal. calcd for $C_{14}H_{22}O_2$ (222.16): C, 75.63; H, 9.97; found C, 75.55; H, 9.99.

(*S*)-3-Hex-1-ynylnon-4-yne-2,3-diol (1u). Yield: 3.21 g, 80% based on (*S*)-α-hydroxypropionic acid ethyl ester. Yellow oil. IR (film): *v* = 3399 (m, br), 2933 (m), 2237 (w), 1466 (w), 1378 (w), 1363 (w), 1270 (w), 1119 (m), 1012 (m), 889 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 3.90-3.77 (m, 1H), 3.37 (s, br, 1 H), 2.70 (s, br, 1H), 2.29-2.19 (m, 4 H), 1.58-1.33 (m, 8 H), 1.36 (d, *J* = 6.5, 3H), 0.96-0.87 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 85.9, 85.4, 79.1, 77.8, 74.4, 68.0, 30.5, 30.4, 22.00, 21.97, 18.44, 18.40, 17.5, 13.6; GC-MS (EI, 70 eV): *m/z* = 236 (M^+, absent), 191 (73), 150 (16), 131 (28), 121 (75), 117 (50), 108 (100), 107 (61), 91 (99), 79 (81); anal. calcd for $C_{15}H_{24}O_2$ (236.35): C, 76.23; H, 10.24; found C, 76.13; H, 10.25.

3-(3,3-Dimethyl-but-1-ynyl)-6,6-dimethyl-hept-4-yne-2,3-diol (1v). Yield: 2.41 g, 81% based on (*S*)-α-hydroxypropionic acid ethyl ester. Yellow oil. IR (film): *v* = 3333 (m, br), 2961 (s), 2238 (w), 1477 (m), 1340 (s), 1266 (s), 1206 (m), 1098 (m), 991 (s), 917 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 3.86-3.74 (m, 1H), 3.39 (s, br, 1 H, OH), 2.66 (s, br, 1 H, OH), 1.34 (d, *J* =, 3 H, CHC*H*$_3$), 1.24 [s, 9 H, C(CH$_3$)$_3$], 1.23 [s, 9 H, C(CH$_3$)$_3$]; ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 93.67, 93.11, 76.72, 76.51, 74.41, 67.83, 30.78, 30.70, 27.38, 27.32, 17.55; GC-MS (EI, 70 eV): *m/z* = 236 (M^+, absent), 191 (73), 150 (16), 131 (28), 121 (75), 117 (50), 108 (100), 107 (61), 91 (99), 79 (81); anal. calcd for $C_{15}H_{24}O_2$ (212.33): C, 76.23; H, 10.24; found C, 76.25; H, 10.27.

5-Phenyl-3-phenylethynyl-pent-4-yne-2,3-diol (1w). Yield: 2.82 g, 81% based on (*S*)-α-hydroxypropionic acid ethyl ester. Yellow solid.^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.0, 131.9, 128.9, 128.3, 121.8, 121.79, 87.1, 86.0, 85.5, 85.0, 74.5, 68.7, 17.8; GC-MS (EI, 70 eV): *m/z* = 276 (M^+, absent), 258 (18), 242 (12), 232 (63), 231 (100), 215 (42), 214 (62), 213 (44), 211 (11), 204 (24), 203 (38), 202 (44), 200 (13), 187 (12), 159 (11), 130 (11), 129 (83), 102 (25), 101 (19), 77 (19), 76 (12), 75 (21), 73 (11); anal. calcd for $C_{19}H_{16}O_2$ (276,33): C, 82.58; H, 5.84; found C, 82.60; H, 5.85.

***N*-Ts-7-(1-aminoethyl)trideca-5,8-diyn-7-ol (1y)**. Yield: 1.72 g, 71% based on N-Tos-amino ester. Colorless oil. IR (film): *v* = 3479 (m, br), 2934 (m), 2240 (w), 1430 (m), 1333 (s), 1165 (s), 1093 (m), 916 (w), 816 (w), 662 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82-7.77 (m, 2 H on phenyl ring), 7.33-7.28 (m, 2 H on phenyl ring), 4.92 (d, br, *J* = 8.9, 1 H, NH), 3.54-3.43 (m, 1 H, C*H*NH), 2.99 (s, br, 1 H, O*H*), 2.42 (s, 3 H, Me on Ts), 2.18 (t, *J* = 7.1, 2 H, ≡CCH_2), 2.16 (t, *J* = 7.1, 2 H, ≡CCH_2), 1.53-1.29 (m, 8 H, 2 CH_2CH_2CH_3), 1.22 (d, *J* = 6.5, 3 H, CHCH_3), 0.90 (t, *J* = 7.1, 3 H, CH_2CH_3), 0.88 (t, *J* = 7.1, 3 H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.5, 137.7, 129.7, 127.2, 86.3, 85.9, 78.3, 77.6, 66.8, 58.9, 30.4, 30.3, 22.00, 21.97, 21.6, 18.3, 17.8, 15.3, 13.6; MS (ESI, 45 eV): *m/z* = 412 [$(M+Na)^+$, 100], 394 (21), 216 (21); anal. calcd for $C_{22}H_{31}NO_3S$ (389.55): C. 67,83; H. 8,02; N. 3,60; S. 8,23; found C. 67,63; H. 8,02; N. 3,62; S. 8,24

Methyl-5-benzil-2-butyl-1*H*-pyrrole-3-carboxyc acid methyl ester (2a). Yield: 125.2 mg, starting from 232.0 mg of **1a** (66%). Yellow oil. IR (film): ν/cm^{-1}= 3405 (br), 2955 (m), 1751 (s), 1710(s), 1541 (m), 1370 (m), 1303 (m), 1213 (m), 1055 (m), 848 (m), 784 (m). ^{1}H NMR: δ (300 MHz, $CDCl_3$)/ppm = 8.07-8.28 (m, 1H, N*H*), 7.07-7.38 (m, 5H, Ph), 6.23-6.29 (m, 1H, C*H*), 3.87 (s, 2H, CH_2Ph), 3.73 (s, 3H, CO_2CH_3), 2.85 (t, *J*= 7.7 Hz, 2H, CH_2CH), 1.46-1.62 (m, 2H, CH_2CH_2), 1,22-1.43 (m, 2H, C$H_2$$CH_2$), 0.88 (t, *J*= 7.2 Hz, 3H, C$H_3$$CH_2$$CH_2$).^{13}C NMR: δ (75 MHz, $CDCl_3$)/ppm = 165.9, 140,04, 139.03,

129.08, 128.71, 128.66, 126.62, 110.01, 108.47, 50.54, 33.85, 31.71, 27.00, 22.48, 13.77. GC/MS: m\z 272 (M+1, 7), 271(M+38), 240 (6), 228 (100), 196(6), 120(6), 91 (26), 78 (8), 65 (8), 41 (9). anal. calcd for $C_{17}H_{21}NO_2$ (271.35): C. 75.25; H. 7.80; N. 5.16; found C, 72.28; H, 7.83.

***N*-Boc-5-benzil-2-butyl-pyrrole-3-carboxylic acid methyl ester (3a).** Yield: 20.8 mg, starting from 232.0 mg of **1a** (8%). Yellow oil. IR (film): ν/cm^{-1}= 2956 (m), 1712.40 (s), 1676.8 (s), 1456 (m), 1224 (m), 1075 (m), 782 (m), 701 (m).^{1}H NMR: δ (300 MHz, $CDCl_3$)/ppm = 7,01-7.32 (m, 5H, Ph), 6.17 (s, 1H, C*H*=), 4.11 (s, 2H, CH_2Ph), 3.76 (s, 3H, CO_2CH_3), 3.21 (t, *J*= 7.7 Hz, 2H, CH_2C=), 0.92 (t, *J*=7.2 Hz, 3H, C$H_3CH_2CH_2$), 1.30- 1.64 (m, 9H, C(CH_3)$_3$ + 4H CH_2CH_2); ^{13}C NMR: δ (75 MHz, $CDCl_3$)/ppm = 165.21, 149.69, 143.31, 140.13, 139.32, 132.47, 128.43, 126.27, 113.59, 112.17, 84.90, 50.84, 34.91, 32.49, 29.72, 26.27, 22.77, 13.87.anal. calcd for $C_{22}H_{29}NO_4$ (371.47): C. 71.13; H. 7.87; N. 3.77; found C, 71.15; H, 7.83.

5-Benzil-5-isopropyl-1*H*-pyrrole-3-carboxylic acid methyl ester (2b). Yield: 82.8 mg, starting from 198.4 mg of **1b** (53%). Yellow oil. IR (film): ν/cm^{-1}= 3333,6 (br), 2959 (m), 1671 (s), 1457 (m), 1456.86 (m), 1280 (m), 1199 (m), 757 (m); ^{1}H NMR: δ (300 MHz, $CDCl_3$)/ppm = 7.9-8.1 (m, 1H, N*H*), 6.10-6.26 (m, 1H, C*H*=), 3.78 (s, 3H, CO_2CH_3), 2.91 (t, 2H, *J*=7.7 Hz, CH_2C=), 2.83 (ept, *J*= 6.9 Hz, 1H, $(CH_3)_2CH$), 1.51-1.66 (m, 2H, CH_2CH_2), 1.29-1.46 (m, 2H, CH_2CH_2), 1.23 (d, *J*= 6.9 Hz, 6H, $(CH_3)_2CH$), 0.92 (t, *J*= 7.3 Hz, 3H, C$H_3CH_2CH_2$); ^{13}C NMR: δ (75 MHz, $CDCl_3$)/ppm = 166.06, 139.18, 136.87, 129.29, 104.54, 50.64, 31.72, 27.02, 26.76, 22.57, 22.37, 13.89; GC/MS: m/z 223 (M+1), 222 (M+ 95), 192 (11), 120 (4), 73 (19), 59 (38); anal. calcd for $C_{13}H_{21}NO_2$ (223.31): C.69.92; H. 9.48; N. 6.27; found C, 69.95; H, 9.45.

***N*-Boc-5-Benzil-5-isopropyl-pyrrole-3-carboxylic acid methyl ester (3b).** Yield: 77 mg, starting from 198.4 mg of **1b** (34%). Yellow oil. IR (film):ν/cm^{-1}= 2961 (m), 1675 (s), 1595 (m), 1463 (m), 1243 (m), 1070 (m), 782 (m); ^{1}H NMR: δ (300 MHz, $CDCl_3$)/ppm = 6.26-6.28 (m, 1H, C*H*=), 3.79 (s, 3H, CO_2CH_3), 3.28 (ept, *J*=7.7 Hz, 1H, $(CH_3)_2CH$), 3.16 (t, *J*=7.7 Hz, 2H, CH_2C=), 1.47-1.66 (m, 2H, CH_2CH_2 + 9H, $C(CH_3)_3$), 1.31-1.46 (m, 2H, CH_2CH_2), 1.21 (d, *J*= 6.5 Hz, 6H, $(CH_3)_2CH$), 0.93 (t, *J*= 7.3 Hz, 3H, $CH_3CH_2CH_2$); ^{13}C NMR: δ (75 MHz, $CDCl_3$)/ppm = 165.40, 150.0, 142.4, 140.9, 112.9, 107.0, 84.9, 50.9, 32.4, 29.7, 27.8, 26.4, 26.2, 22.9, 14.0; anal. calcd for $C_{13}H_{21}NO_2$ (323.43): C.66.84; H. 9.04; N. 4.33; found C, 66.87; H, 9.07

5-Butyl-5-methyl-1*H*-pyrrole-3-carboxylic acid methyl ester (2c). Yield: 21.9 mg, starting from 178.8 mg of **1c** (16%). Yellow oil. IR (film): ν/cm^{-1}= 3319 (br), 2955 (m), 1676 (s), 1459 (m), 1224 (m), 1097 (m), 1075 (m), 781 (m); ^{1}H NMR: δ (300 MHz, $CDCl_3$)/ppm = 7.90- 8.08 (m, 1H, N*H*), 3.75 (s, 3H, CO_2CH_3), 6.18-6.29 (m, 1H, C*H*=), 2.92 (t, *J*= 7.3 Hz, 2H, CH_2C=), 1.55- 1.69 (m, 2H, CH_2CH_2), 1.33- 1.54 (m, 2H, CH_2CH_2 + 3H, CH_3C=), 0.94 (t, *J*=7.3 Hz, 3H, $CH_3CH_2CH_2$); ^{13}C NMR: δ (75 MHz, $CDCl_3$)/ppm = 13.9, 22.4, 26.8, 27.0, 31.7, 50.6, 104.6, 110.4, 136.8, 139.1, 166.0; GC/MS: m\z 196 (M+1,3), 195(M+27), 152 (100), 138 (9),120 (28), 93(16), 65 (8), 41 (10). anal. calcd for $C_{13}H_{21}NO_2$ (195.26): C.67.66; H. 8.78; N. 7.17; found C, 67.69; H, 8.75.

***N*-Boc-5-Butyl-5-methyl-pyrrole-3-carboxylic acid methyl ester (3c).** Yield: 111.6 mg, starting from 178.8 mg of **1c** (54%). White solid; m.p. =36°C. IR (KBr): ν/cm^{-1}= 2931 (m), 1748 (s), 1712 (s), 1546 (m), 1437 (m), 1216 (m), 1059 (m), 783 (m); ^{1}H NMR: δ (300 MHz, $CDCl_3$)/ppm = 6.19-6.25 (m, 1H, C*H*=), 3.79 (s, 3H, CO_2CH_3), 3.21 (t, *J*= 7.7 Hz, 2H, CH_2C=), 2.89 (s, 3H, CH_3C=), 1.47-1.66 (m, 2H, CH_2CH_2 + 9H, $C(CH_3)_3$), 1.31-1.46 (m, 2H, CH_2CH_2), 0.92 (t, *J*= 7.3 Hz, 3H, $CH_3CH_2CH_2$); ^{13}C NMR: δ (75 MHz, $CDCl_3$)/ppm = 165.3,

149.8, 142.9, 130.0, 113.5, 110.7, 84.6, 51.0, 32.5, 27.9, 26.4, 22.8, 15.7, 14.0; anal. calcd for $C_{16}H_{25}NO_4$ (295.37): C.65.06; H. 8.53; N. 4.74; found C, 65.09; H, 8.57.

5-benzyl-2-butyl-4-methyl-1*H*-pyrrole-3-carboxylic acid methyl ester (2d). Yield: 40 mg, starting from 241.8 mg of **1d** (20%). White solid; m.p. = 80-82°C. IR (KBr): ν/cm^{-1}= 3289 (s, br), 2956 (m), 2929 (m), 1659 (s), 1455 (m), 1260 (m), 1121(m), 1082 (m), 1030 (m); ^{1}H NMR: δ (300 MHz, $CDCl_3$)/ppm = 7.61-7.70 (m, 1H, N*H*), 7.17- 7.36 (m, 3H, Ph), 7.08-7.16 (m, 2H, Ph), 3.87 (s, 2H, C*H*$_2$Ph), 3.79 (s, 3H, CO_2CH_3), 2.82 (t, *J*= 7.7 Hz, 2H, C*H*$_2$C=), 2.23 (s, 3H, =C-C*H*$_3$), 1.58 -1.23 (m, 4H, C*H*$_2$C*H*$_2$CH$_3$), 0.89 (t, *J*= 7.3 Hz, 3H, C*H*$_3$CH$_2$CH$_2$); ^{13}C NMR: δ (75 MHz, $CDCl_3$)/ppm = 166.7, 139.3, 128.7, 128.6, 128.4, 126.5, 124.7, 117.1, 110.2, 50.3, 31.7, 31.4, 27.6, 22.5, 13.8, 11.1; GC/MS: m\z 286 (M+1,5), 285(M+32), 242 (100), 167 (8),91 (22), 65 (14), 41 (10); anal. calcd for $C_{18}H_{23}NO_2$ (285.38): C.75.76; H. 8.12; N. 4.91; found C, 75.79; H, 8.15.

***N*-Boc-5-benzyl-2-butyl-4-methyl-pyrrole-3-carboxylic acid methyl ester (3d).** Yield: 191.6 mg, starting from 241.8 mg of **1d** (71%). Yellow oil. IR (film): ν/cm^{-1}= 2956 (m), 1748 (s), 1707 (s), 1436 (m), 1384 (m), 1249 (m), 1132 (m), 758 (m); ^{1}H NMR: δ (300 MHz, $CDCl_3$)/ppm = 7.10-7.28 (m, 3H, Ph), 6.96-7.1 (m, 2H, Ph), 4.15 (s, 2H, C*H*$_2$Ph), 3.83 (s, 3H, CO_2CH_3), 3.12 (t, *J*= 7.7 Hz, C*H*$_2$C=), 2.22 (s, 3H, =C-C*H*$_3$), 1.47-1.63 (m, 2H, CH_2CH_2), 1.24-1.44 (m, 2H, C*H*$_2$CH$_2$ + 9H, C(C*H*$_3$)$_3$), 0.92 (t, *J*= 7.3 Hz, 3H, C*H*$_3$CH$_2$CH$_2$); ^{13}C NMR: δ (75 MHz, $CDCl_3$)/ppm = 166.3, 149.7, 142.1, 139.9, 128.3, 127.8, 127.5, 125.9, 119.7, 113.8, 84.2, 50.8, 32.5, 30.8, 27.4, 26.4, 22,8, 14.0, 11.2; anal. calcd for $C_{23}H_{31}NO_4$ (385.50): C.71.66; H. 8.11; N. 3.63; found C, 71.69; H, 8.14;

5-Methyl-2-phenyl-1*H*-pyrrole-3-carboxylic acid methyl ester (2e). Yield: 51.2 mg, starting from 192.7 mg of **1e** (34%). Brown oil. IR (film): ν/cm^{-1}= 3309 (br), 2948 (m), 2741 (m), 1680 (s), 1592 (m), 1075 (m), 943 (m); ^{1}H NMR: δ (300 MHz, CDCl3)/ppm = 8.41- 8.55 (m, 1H, N*H*), 7.47-7.59 (m, 2H, Ph), 7.22-7.41 (m, 3H, Ph), 6.31-6.39 (m, 1H, C*H*=), 3.67 (s, 3H, CO_2CH_3), 2.22 (s, 3H, CH_3C=); ^{13}C NMR: δ (75 MHz, $CDCl_3$)/ppm = 165.6, 136.2, 132.3, 128.8, 128.1, 127.9, 127.8, 111.7, 109.6, 50.80, 12.61; GC/MS: m\z 216 (M+1,11), 215(M+78), 184 (100), 128 (13),77 (17), 63 (8). GC/MS: m\z 216 (M+1,11), 215(M+78), 184 (100), 128 (13),77 (17), 63 (8). anal. calcd for $C_{13}H_{13}NO_2$ (215.25): C.72.54; H. 6.09; N. 6.51; found C, 72.57; H, 6.12.

***N*-Boc-5-Methyl-2-phenyl-pyrrole-3-carboxylic acid methyl ester (3e).** Yield: 103.8 mg, starting from 192.7 mg of **1e** (47%). Yellow solid. m.p. = 112-114°C. IR (KBr): ν/cm^{-1}= 2986 (m), 1721 (s), 1717 (s), 1237 (m), 1090 (m), 782 (m), 699 (m); ^{1}H NMR: δ (300 MHz, $CDCl_3$)/ppm = 7.21-7.50 (m, 5H, Ph), 6.3-6.48 (m, 1H, C*H*=), 3.63 (s, 3H, CO_2CH_3), 2.38-2.53 (m, 3H, , CH_3C=), 1.17 (s, 9H, $C(CH_3)_3$); ^{13}C NMR: δ (75 MHz, $CDCl_3$)/ppm = 164.5, 149.6, 138.2, 133.7, 131.6, 130.0, 127.9, 127.5, 115.4, 110.7, 84.0, 51.0, 27.2, 14.7; anal. calcd for $C_{18}H_{21}NO_4$ (315.36): C.68.55; H. 6.71; N. 4.44; found C, 68.58; H, 6.75.

5-Benzyl-2-*tert*-butyl-1*H*--pyrrole-3-carboxylic acid methyl ester (2f). Yield: 85.5 mg, starting from 232.0 mg of *N*-Boc-2-amino-6,6-dimethyl-1phenyl-4-yn-3-ol **(1f)** (45%). White solid. m.p. = 116-118°C**.** IR (KBr) : ν/cm-1= 3359 (br), 2953 (m), 1687 (s), 1444(m), 1069 (m), 782 (m), 698 (m); ^{1}H NMR: δ (300 MHz, $CDCl_3$)/ppm = 8.48-8.52 (m, 1H, N*H*), 7.04-7.16 (m, 5H, Ph), 6.25-6.31 (m, 1H, C*H*=), 3.88 (s, 3H, CO_2CH_3), 3.82-3.86 (m, 2H, CH_2Ph), 1.30-1.35 (m, 9H, $C(CH_3)_3$); ^{13}C NMR: δ (75 MHz, $CDCl_3$)/ppm = 167.0, 137.7, 132.0, 130.0, 129.2, 128.4, 125.5, 109.0, 108.0, 50.0, 36.0, 32.3, 30.2; GC/MS: m\z 272 (M+1,6), 271(M+46), 256 (9), 240 (15),224 (100), 120(3), 91 (85), 77 (18), 65

(15), 41 (16). anal. calcd for $C_{17}H_{21}NO_2$ (271.35): C.75.25; H. 7.80; N. 5.16; found C, 75.28; H, 7.83.

***N*-Boc-5-Benzyl-2-*tert*-butyl--pyrrole-3-carboxylic acid methyl ester (3f).** Yield: 23.4 mg, starting from 232.0 mg of **1f** (9%). Yellow oil. IR (film): ν/cm^{-1}= 2920 (s), 1604(s) ,1602 (s), 1594 (m), 1480 (m), 1258 (m), 1070 (m), 782 (m), 656 (m); ^{1}H NMR: δ (300 MHz, $CDCl_3$)/ppm = 7.06-7.14 (m, 5H, Ph), 5.92-5.98 (m, 1H, C*H*=), 3.90-3.95 (s, 2H, CH_2Ph), 3.75 (s, 3H, CO_2CH_3), 1.45-1.49 (m, 9H, OC(CH_3)$_3$), 1.38- 1.42 (m, 9H, C(CH_3)$_3$); ^{13}C NMR: δ (75 MHz, $CDCl_3$)/ppm = 166.7, 161.2, 138.2, 130.5, 128.8, 128.7, 128.6, 126.5, 111.8, 110.8, 76.6, 51.4, 33.4, 29.4, 28.6, 22.7; anal. calcd for $C_{22}H_{29}NO_4$ (371.47): C.71.13; H. 7.87; N. 3.77; found C, 71.15; H, 7.84.

2-Butyl-4-hexanoyl-5-methyl-1*H*-pyrrole-3-carboxylic acid methyl ester (2g). Yield: 134.2 mg, 66% based on **1g**. Yellow oil. IR (film): *v* = 3289 (s), 2957 (m), 2927 (m), 2872 (m), 1705 (s), 1675 (m), 1646 (m), 1528 (w), 1448 (m), 1169 (w), 1110 (w), 1072 (w), 787 (w), 736 (w)cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 9.28 (s, br, 1 H, NH), 3.78 (s, 3 H, OMe), 2.77 (t, *J* = 7.7, 2 H, $CH_2(CH_2)_2CH_3$ e/o $CH_2(CH_2)_3CH_3$), 2.70 (t, *J* = 7.7, 2 H, $CH_2(CH_2)_2CH_3$ e/o $CH_2(CH_2)_3CH_3$), 2.17 (s, 3H, CH_3 on aromatic ring), 1.71-1.48 (m, 4 H, $CH_2(CH_2)_2CH_3$ e/o $CH_2(CH_2)_3CH_3$), 1.40-1.29 (m, 6 H, $CH_2(CH_2)_2CH_3$ e/o $CH_2(CH_2)_3CH_3$), 0.95-0.78 (m, 6H, $CH_2(CH_2)_2CH_3$ e/o $CH_2(CH_2)_3CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 202, 9, 165.8, 138.7, 129.9, 123.3, 110.5, 51.0, 43.5, 31.8, 31.7, 26.6, 24.7, 22.5, 22.4, 13.9, 13.8, 12.1; GC-MS: *m/z* = 293 (M^+, 10), 232 (11), 223 (12), 222 (100), 218 (16), 205 (26), 192 (13), 163 (10), 121 (11), 93 (30); anal. calcd for $C_{17}H_{27}NO_3$ (293,40): C, 69.59; H, 9.28; N, 4.77; found C, 69.60; H, 9.30.

2-Butyl-4-hexanoyl-5-isobutyl-1*H*-pyrrole-3-carboxylic acid methyl ester (2h). Yield: 175 mg, 75% based on **1h**. Yellow solid. mp= 40.0-42.0 °C. IR (KBr): *v* = 3295 (m), 2957 (m), 2927 (m), 2871 (m), 1708 (s), 1675 (s), 1525 (m), 1449 (m), 1368 (m), 1193 (w), 1166 (m), 1091 (m), 1066 (w), 787 (w), 750

(w) cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.14 (s, br, 1 H, NH), 3.76 (s, 3 H, OMe), 2.81 (t, J= 7.7, 2H, $CH_2(CH_2)_2CH_3$ e/o $CH_2(CH_2)_3CH_3$) , 2.69 (t, J= 7.7, 2H, $CH_2(CH_2)_2CH_3$ e/o $CH_2(CH_2)_3CH_3$), 2.40 (d, J= 7.7, 2H, $CH_2CH(CH_3)_2$ e/o $CH_2(CH_2)_3CH_3$), 1.90-1.79 (m, 1H, CH_3CHCH_3), 1.70-1.51 (m, 4 H, $CH_2(CH_2)_2CH_3$ e $CH_2(CH_2)_3CH_3$), 1.41-1.26 (m, 6H, $CH_2(CH_2)_2CH_3$ e/o $CH_2(CH_2)_3CH_3$), 0.94-0.86 (m, 6H, $CH_2(CH_2)_2CH_3$ e $CH_2(CH_2)_3CH_3$), 0.82 (d, J=6.5, 6H, CH_3CHCH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.0, 165.7, 138.8, 133.1, 123.9, 110.2, 50.9, 43.9, 35.3, 31.8, 31.7, 29.3, 26.7, 24.6, 22.6, 22.3, 22.4, 13.9, 13.8; GC-MS: *m/z* = 335 (M^+, 21), 304 (15), 303 (36), 292 (17), 288 (22), 274 (10), 265 (16), 264 (100), 260 (50), 247 (18), 246 (11), 232 (17), 93 (27); anal. calcd for $C_{20}H_{33}NO_3$ (335,25): C, 71.60; H, 9.91; N, 4.18; found C, 71.61; H, 9.94.

2-Benzyl-2butyl-4-hesanoyl-1*H*-pyrrole-3-carboxylic acid methyl ester (2i). Yield: 175 mg, 68% based on **1i**. Yellow solid. mp= 94-96 °C. IR (KBr): *v* = 3287 (m), 2956 (m), 2930 (m), 1704 (s), 1673 (s), 1525 (w), 1495 (m), 1456 (s), 1367 (w), 1199 (m), 1160 (w), 1110 (w), 1076 (w), 755 (w), 696 (w) cm^{-1} ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.75 (s, br, 1 H, NH), 7.23-7.10 (m, 5H on aromatic ring), 6.20 (d, J= 2.31, 2H; CH_2Ph), 4.29 (s, 3 H, OMe), 2.69 (t, J= 7.6, 2H, $CH_2(CH_2)_2CH_3$ e/o $CH_2(CH_2)_3CH_3$) , 2.44 (t, J= 7.7, 2H, $CH_2(CH_2)_2CH_3$ e/o $CH_2(CH_2)_3CH_3$), 1.65 (q, J= 7.6, 2H, $CH_2CH(CH_3)_2$ e/o $CH_2(CH_2)_3CH_3$), 1.52 (q, J= 7.6, 2H, $CH_2CH(CH_3)_2$ e/o $CH_2(CH_2)_3CH_3$), 1.36-1.27 (m, 6H, $CH_2(CH_2)_2CH_3$ e/o $CH_2(CH_2)_3CH_3$), 0.87 (t, J=7.1, 6H, $CH_2(CH_2)_2CH_3$ e $CH_2(CH_2)_3CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.2, 138.81, 138.80, 136.2, 131.6, 128.9, 128.6, 126.4, 120.2, 106.6, 40.6, 33.70, 33.67, 33.6, 31.8, 31.4, 27.0, 24.7, 22.6, 22.3, 14.0, 13.8; GC-MS: *m/z* = 369 (M+, 37), 338 (35), 337 (100), 308 (15), 298 (34), 295 (22), 294 (50), 281 (30), 279 (23), 278 (39), 267 (15), 266 (57), 253 (11), 252 (13), 238 (21), 238 (11), 196 (17), 195 (10, 168 (34), 167 (21), 91 (23), 73 (19); anal. calcd for $C_{23}H_{31}NO_3$ (369,23): C, 74.76; H, 8.46; N, 3.79; found C, 74.75; H, 8.47.

2-Butyl-4-hexanoyl-5-isopropyl-1*H*-pyrrole-3-carboxylic acid methyl ester (2j). Yield: 140.6 mg, 63% based on **1j**. Yellow solid. mp= 68-71°C. IR (KBr): ν = 3217 (m), 2962 (m), 2934 (m), 1711 (s), 1647 (s), 1529 (m), 1464 (m), 1384 (m), 1362 (m), 1257 (w), 1206 (m), 1160 (w), 1110 (m), 1077 (m), 959 (w), 792 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 9.05 (s, br, 1 H, NH), 3.77 (s, 3 H, OMe), 3.25-3.12 (m, 1H, CH_3CHCH_3), 2.88-2.79 (m, 2 H, $CH_2(CH_2)_2CH_3$ e/o $CH_2(CH_2)_3CH_3$), 2.74-2.76 (m, 2H, $CH_2(CH_2)_2CH_3$ e/o $CH_2(CH_2)_3CH_3$), 1.71-1.52 (m, 4 H, $CH_2(CH_2)_2CH_3$ e/o $CH_2(CH_2)_3CH_3$), 1.41-1.24 (m, 6 H, $CH_2(CH_2)_2CH_3$ e/o $CH_2(CH_2)_3CH_3$), 1.20 (dd, J=7.3, 2.4, 6H, CH_3CHCH_3), 0.97-0.83 (m, 6H, $CH_2(CH_2)_2CH_3$ e $CH_2(CH_2)_3CH_3$) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.9, 165.7, 139.2, 138.7, 121.9, 109.6, 51.0, 44.2, 31.9, 31.6, 26.8, 25.5, 24.8, 22.6, 22.48, 22.51, 14.0, 13.8; GC-MS: *m/z* = 321 (M^+, 20), 260 (11), 251 (17), 250 (100), 247 (12), 246 (38), 233 (25), 232 (14), 218 (16), 148 (10), 132 (11), 120 (17), 107 (17), 106 (24), 79 (10); anal. calcd for $C_{19}H_{31}NO_3$ (321,45): C, 70.99; H, 9.72; N, 4.36; found C, 71.0; H, 9.75.

2-Butyl-1-hexanoyl-6,7-dihydro-5*H*-pyrrolizine-2-carboxylic acid methyl ester (2k). Yield: 133.1 mg, 49% based on **1k**. Yellow solid. mp= 59-62°C. IR (film): ν = 3747 (m, br), 2983 (w), 1744 (s), 1487 (w), 1384 (s), 1327 (m), 1291 (w), 1136 (w), 756 (w), 691 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.89 (t, J= 7.3, 2 H, 2H prolina), 3.80 (s, 3H, OMe), 3.02 (t, J= 7.4, 2H, prolina), 2.81-2.68 (m, 2H,prolina), 2.62-2.45 (m, 2H, $CH_2(CH_2)_2CH_3$ e $CH_2(CH_2)_3CH_3$), 1.78-1.25 (m, 12H, $CH_2(CH_2)_2CH_3$ e $CH_2(CH_2)_3CH_3$), 1.10-0.70 (m, 6H, $CH_2(CH_2)_2CH_3$ e $CH_2(CH_2)_3CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.8, 166.1, 141.6, 134.9, 117.3, 114.4, 51.2, 45.1, 41.7, 31.76, 31.72, 26.5, 26.0, 15.7, 24.4, 22.6, 22.4, 14.0, 13.8; GC-MS: *m/z* = 319 (M^+, 19), 288 (11), 319 (19), 288 (11), 276 (14), 263 (18), 258 (14), 249 (16), 248 (100), 244 (11), 231 (17), 218 (10), 189 (26), 160 (11), 119 (28), 91 (11); anal. calcd for $C_{19}H_{29}NO_3$ (319,21): C, 71.44; H, 9.15; N, 4.38; found C, 71.45; H, 9.13.

5-Methyl-2-phenyl-4-phenylacetyl-1H-pyrrole-3-carboxylic acid methyl ester (2l). Yield: 118.0 mg, 51% based on **1l**. Yellow oil. IR (film): ν = 3496 (s, br), 1701 (s), 1641 (s), 1525 (w), 1493 (m), 1437 (s), 1381 (w), 1263 (w), 1170 (w), 1040 (w), 986 (w), 761 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 9.28 (s, br, 1H, NH), 7.44-7.35 (m, 2 H on aromatic ring), 7.33-7.24 (m, 4 H on aromatic ring), 7.24-7.16 (m, 2 H on aromatic ring), 7.16-7.10 (m, 2 H on aromatic ring), 4.00 (s, 2H, CH_2Ph), 3.68 (s, 3H, OMe), 2.14 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.6, 166.6, 135.1, 134.0, 133.6, 131.0, 129.6, 128.4, 128.3, 128.15, 128.22, 126.6, 122.6, 112.0, 51.7, 49.2, 12.7; GC-MS: *m/z* = 333 (M^+, 5),243 (16), 242 (100), 212 (16), 128 (4), 104 (5), 91 (5); anal. calcd for $C_{21}H_{19}NO_3$ (333,38): C, 75.66; H, 5.74; N, 4.20; found C, 75.67; H, 5.76.

2-*tert*-Butyl-4-(3,3-dimethyl-butyl)-5-methyl-1*H*-pyrrole-3-carboxylic acid methyl ester (2m). Yield: 126.0 mg, 62% based on **1m** Yellow oil. IR (film): ν = 3334 (m, br), 2956 (m), 1711 (s), 1647 (m), 1522 (w), 1432 (m), 1366 (w), 1270 (w), 1218 (w), 1165 (w), 1065 (w), 756 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.92 (s, br, 1H, NH), 379, (s, 3H, OMe), 2.51 (s, 2H, $CH_2C(CH_3)_3$, 2.35 (s, 3H, Me), 1.34 (s, 9H, $C(CH_3)_3$), 1.00 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.9, 168.6, 140.1, 129.4, 124.0, 111.2, 53.9, 51.9, 32.5, 31.6, 29.7, 29.5, 13.4, 13.3; GC-MS: *m/z* = 293 (M^+, 14), 246 (26), 223 (13), 222 (100), 206 (15), 205 (42), 204 (12), 190 (58), 121 (20), 120 (11); anal. calcd for $C_{17}H_{27}NO_3$ (293,40): C, 69,59; H, 9.28; N, 4.77; found C, 69.60; H, 9.31.

2-tert-Butyl-4-(3,3-dimethyl-butyryl)-5-isobutyl-1*H*-pyrrole-3-carboxylic acid methyl ester (2n). Yield: 130.4 mg, 56% based on **1n**. Yellow solid. mp=127-129°C. Yellow oil. IR (film): ν = 3369 (s), 2963 (s), 1712 (s), 1652 (s), 1512 (w), 1438 (m), 1366 (m), 1270 (w), 1222 (w), 1168 (m), 1062 (m), 794 (w), 710 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.14 (s, br, 1H, NH), 3.79 (s, 3H, OMe), 2.60-2.54 (m, 2H, CH_2CHC$(CH_3)_3$), 2.52-2.48 (m, 3H, CH_2C$(CH_3)_3$ e CHC$(CH_3)_3$), 1.37 (s, 9H, CC(C$H_3)_3$), 1.01 (s, 9H, CH_2C(C$H_3)_3$); 0.96-0.88 (m, 6H, CH_3CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.1, 167.8, 140.5, 131.9,

124.9, 111.1, 54.5, 51.6, 35.9, 32.5, 31.4, 30.7, 30.65, 29.9, 29.5, 29.4, 28.4, 22.5; GC-MS: *m/z* = 335 (M^+, 28),304 (15), 303 (44), 292 (11), 289 (13), 288 (43), 265 (16), 264 (83), 248 (13), 247 (37), 246 (100), 236 (28), 232 (36), 120 (10); anal. calcd for $C_{20}H_{33}NO_3$ (335.25): C, 71.60; H, 9.91; N, 4.18; found C, 71.59; H, 9.88.

***N*-Boc-2-Benzyl-5-butylpyrrole (4a)**. Yield: 220.4 mg, starting from 331.9 mg of **1a** (70%) (Table 2, entry 5). Yellow oil. IR (film): *v* = 3019 (m), 2928 (w), 1734 (s), 1496 (m), 1456 (w), 1371 (m), 1336 (m), 1216 (s), 1126 (w), 755 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.30-7.08 (m, 5 H, Ph), 5.84 (d, br, *J* = 3.2, 1 H, H-4), 5.68 (d, br, *J* = 3.2, 1 H, H-3), 4.16 (s, 2H, C*H*$_2$Ph), 2.83-2.74 (m, 2 H, C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.65–1.50 (m, 2 H, CH$_2$C*H*$_2$CH$_2$CH$_3$), 1.48-1.33 (m, 2 H, CH$_2$CH$_2$C*H*$_2$CH$_3$), 1.42 (s, 9 H, *t*-Bu), 0.93 (t, *J* = 7.3, 3 H, CH$_2$CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.3, 140.2, 136.8, 133.4, 128.5, 128.2, 125.9, 111.5, 108.9, 83.4, 35.7, 31.3, 29.2, 27.7, 22.6, 14.0; MS (ESI, 10 eV): *m/z* = 336 [$(M+Na)^+$, 67] 280 (100), 236 (50); anal. calcd for $C_{20}H_{27}NO_2$ (313.43): C. 76,64; H. 8,68; N. 4,47; found C. 76,49; H. 8,70 .

***N*-Boc-2-Butyl-5-methylpyrrole (4b)**. Yield: 130.8 mg, starting from 254.8 mg of **1c** (55%) (Table 2, entry 7). Yellow oil. IR (film): *v* = 2958 (m), 1720 (s), 1531 (m), 1435 (w), 1364 (w), 1283 (m), 1228 (m), 1084 (m), 750 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.82-5.78 (m, 2 H, H-3 + H-4), 2.82-2.72 (m, 2 H, C*H*$_2$CH$_2$CH$_2$CH$_3$), 2.37 (s, br, 2 H, Me at C-5), 1.64-1.50 (m, 2 H, CH$_2$C*H*$_2$CH$_2$CH$_3$), 1.59 (s, 9 H, *t*-Bu), 1.45-1.31 (m, 2 H, C*H*$_2$CH$_3$), 0.93 (t, *J* = 7.3, 3 H, C*H*$_2$CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.5, 136.1, 131.2, 110.1, 109.0, 83.2, 31.4, 29.4, 28.1, 22.6, 16.5, 14.1; MS (ESI, 20 eV): *m/z* = 260 [$(M+Na)^+$, 19], 204 (60), 160 (100); anal. calcd for $C_{14}H_{23}NO_2$ (237.34): C. 70,85; H. 9,77; N. 5,90; found C. 70,80; H. 9,75; N. 5,91

***N*-Boc-5-Butyl-3-hex-1-ynyl-2-methylpyrrole (4c)**. Yield: 315.5 mg, starting from 335.0 mg of **1g** (99%) (Table 2, entry 8). Pale yellow oil. IR (film): ν = 2968 (m), 2878 (m), 2229 (w), 1752 (s), 1548 (w), 1459 (w), 1338 (s), 1171 (m), 1108 (m), 856 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.87 (t, J = 0.9, 1 H, H-4), 2.77-2.69 (m, 2 H, =CCH_2), 2.43 (s, 3 H, Me at C-2), 2.39 (t, J = 7.0, 2 H, ≡CCH_2), 1.62-1.30 (m, 8 H, 2 $CH_2CH_2CH_2CH_3$), 1.58 (s, 9 H, *t*-Bu), 0.93 (t, J = 7.1, 3 H, $CH_2CH_2CH_2CH_3$), 0.92 (t, J = 7.1, 3 H, $CH_2CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.1, 135.3, 134.4, 111.8, 106.4, 91.6, 83.7, 74.9, 31.3, 29.0, 28.1, 22.5, 22.0, 19.3, 14.8, 14.0, 13.6; MS (ESI, 10 eV) : *m/z* = 340 [$(M+Na)^+$, 35], 284 (19), 240 (100); anal. calcd for $C_{20}H_{31}NO_2$ (317.47): C. 75,67; H. 9,84; N. 4,41; found C. 75,75; H. 9,81; N. 4,43.

***N*-Boc-2-Methyl-5-phenyl-3-phenylethynylpyrrole (4d)**. Yield: 292.7 mg, starting from 357 mg of **1l** (82%). Yellow solid. mp= 81-83°C IR (KBr): ν = 3014 (w, br), 2981 (w), 2925 (w), 2211 (w), 1743 (s), 1598 (w), 1484 (w), 1443 (w), 1370 (w), 1327 (s), 1283 (m), 1154 (m), 1154 (m), 1007,4 (w) 960 (w), 756 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.52-7.48 (m, 2 H, on phenyl ring), 7.37-7.24 (m, 8 H on phenyl ring), 6.24 (s, 1 H, H-4), 2.61 (s, 3 H, CH_3), 1.25 (s, 9 H, *t*But); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.6, 137.0, 134.5, 134.3, 131.3,128.5, 128.3, 127.8, 127.7, 127.1, 123.9, 114.1, 106.0, 91.4, 84.1, 83.8, 27.3, 14.1; 13.6; GC-MS: *m/z* = 246 (28), 214 (22), 187 (41), 186 (87), 156 (18), 155 (90), 143 (24), 129 (14), 128 (100), 127 (42), 126 (12), 115 (17), 77(11); anal. calcd for $C_{24}H_{23}NO_2$ (357,44): C, 80.64; H, 6.49; N, 3.92; found C, 80.61; H, 6.46

***N*-Boc-5-Butyl-3-hex-1-ynyl-2-isobutylpyrrole (4e)**. Yield: 279 mg, starting from 377.0 mg of **1h** (78%). Pale yellow oil. IR (film): ν = 3386 (m,br), 2960 (s), 2925 (s), 2873 (m), 2225(w), 1716 (s), 1467 (m), 13569 (s), 1320 (m), 1161 (m), 848 (w), 756(w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.88-5.85 (m, 1 H, H-4), 2.79 (d, J = 7.3, 2 H, $CH_2CH(CH_3)_2$), 2.75-2.68 (m, 2 H, =CCH_2), 2.38 (t, J = 6.7, 2 H, ≡CCH_2), 1.92–1.78 (m, 1 H, $CH(CH_3)_2$), 1.63-1.32 (m, 8 H, 2

$CH_2CH_2CH_2CH_3$), 1.59 (s, 9 H, *t*-Bu), 0.97-0.87 (m, 12 H, 2 $CH_2CH_2CH_2CH_3$ + 2 $CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.1, 138.0, 135.3, 111.6, 107.4, 91.3, 83.6, 75.6, 36.4, 31.32, 31.26, 29.5, 29.0, 28.0, 22.4, 22.5, 22.0, 19.3, 13.9, 13.6; anal. calcd for $C_{23}H_{37}NO_2$ (359.55): C. 76,83; H. 10,37; N. 3,90; found C. 77,01; H. 10,36; N. 3,91.

***N*-Boc-2-Benzyl-5-butyl-3-hex-1-ynylpyrrole (4f)**. Yield: 284.4 mg starting from 411 mg **1i**. Yellow oil. IR (film): ν = 3407 (m, br), 2960 (s), 2931 (s), 2873 (m), 2225 (w), 1743 (s), 1624 (w), 1495 (w), 1456 (m), 1369 (s), 1325 (s), 1257 (m), 1161 (s), 1102 (m), 848 (w), 757 (m), 703 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.26-7.03 (m, 5 H,aromatic), δ = 5.96 (s, 1 H,*CH*-), δ = 4.32 (s, 2 H,CH_2Ph), δ = 2.76-2.68 (m, 2H,=CCH_2), δ = 2.35, (s, J=6.9 2H, CCH_2), 1.67-1.21 (m, 8 H, 2$CH_2CH_2CH_2CH_3$), δ=*1.31* (s, 9 H, *t*Bu), δ =0.92 (t, J= 7.3, 3 H, $CH_2CH_2CH_2CH_3$); δ =0.88 (t, J = 7.3, 3 H $CH_2CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.6, 140.5, 135.9, 135.6, 128.2, 127.9, 125.7, 111.4, 108.0, 91.7, 83.8, 74.7, 33.1,31.1, 28.8, 27.5, 22.5, 22.0, 19.3, 14.0, 13.6. calcd for $C_{26}H_{35}NO_2$ (393,56): C, 79.35; H, 8.96; N, 3.56; found C, 79.38; H, 8.93

***N*-Tosyl-5-Butyl-3-hex-1-ynyl-2-methylpyrrole (4g)**.Yield: 309.3 mg, starting from 389.9 mg of **1y** (83%) (Table 1, entry 9). Brown oil. IR (film): ν = 2931 (m), 2872 (m), 2232 (w), 1739 (s), 1597 (w), 1457 (w), 1366 (s), 1251 (m), 1106 (m), 1092 (m), 813 (m), cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.55-7.48 (m, 2 H on phenyl ring), 7.29-7.21 (m, 2 H on phenyl ring), 5.94 (s, br, 1 H, H-4), 2.80-2.70 (m, 2 H, =CCH_2), 2.44 (s, 3 H, Me at C-2), 2.38 (s, 3 H, Me on Ts), 2.37 (t, J = 6.9, 2 H, ≡CCH_2), 1.63-1.28 (m, 8 H, 2 $CH_2CH_2CH_2CH_3$), 0.92 (t, J = 7.1, 3 H, $CH_2CH_2CH_2CH_3$), 0.89 (t, J = 7.1, 3 H, $CH_2CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.6, 137.2, 136.6, 135.3, 130.0, 126.2, 113.1, 108.1, 92.9, 73.9, 31.1, 31.0, 28.3, 22.4, 22.0, 21.5, 19.2, 14.1, 13.9, 13.6; MS (ESI, 30 eV): *m/z* = 394 [$(M+Na)^+$, 89], 239 (100), 216 (30), 179 (46); anal. calcd for $C_{22}H_{29}NO_2S$ (371.54): C. 71,12; H. 7,87; N. 3,77; S. 8,63; found C. 71,32; H. 7,86; N. 3,78; S. 8,61

4-Methyl-2-phenylfuran (4h). Yield: 118.4 mg, starting from 176.3 mg of **1p** (75%). Colorless solid mp 37-39 °C, lit.[11] 38-40 °C; IR (KBr): ν = 2960 (m), 1601 (w), 1495 (w), 1449 (w), 1266 (m), 1116 (w), 739 (m), 702 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65-7.57 (m, 2 H on phenyl ring), 7.37-7.28 (m, 2 H on phenyl ring), 7.23-7.15 (m, 2 H, 1 H on phenyl ring + H-5), 6.48 (s, 1 H, H-3), 2.02 (d, J = 1.2, 3 H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.0, 138.9, 131.2, 128.6, 127.1, 123.7, 122.0, 107.8, 9.8; GC-MS (EI, 70 eV): *m/z* = 158 (M^+, 100), 129 (70), 128 (43), 127 (21), 115 (39), 102 (11), 89 (5), 77 (20); anal. calcd for $C_{11}H_{10}O$ (158.20): C. 83,51; H. 6,37; found C. 83,74; H. 6,36

2,4-Diphenylfuran (4i). Yield: 115.9 mg, starting from 239.5 mg of **1q** (53%) (Table 3.2, entry 1). Colorless solid, mp 108-110 °C, lit.[12] 110-111 °C; IR (KBr): ν = 3062 (m), 1610 (w), 1538 (w), 1492 (w), 1453 (m), 1200 (w), 914 (m), 809 (m), 749 (m), 691 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.75-7.65 (m, 3H, 2 H on phenyl ring + H-5), 7.55-7.47 (m, 2 H on phenyl ring), 7.43-7.32 (m, 4 H on phenyl ring), 7.31-7.21 (m, 2 H on phenyl ring), 6.94 (s, 1 H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.8, 137.9, 132.3, 130.6, 128.8, 128.7, 128.4, 127.6, 127.1, 125.8, 123.8, 104.0; GC-MS (EI, 70 eV): *m/z* = 220 (M^+, 100), 192 (29), 191 (85), 190 (10), 189 (32), 165 (26), 139 (5), 115 (12), 94 (11), 63 (10); anal. calcd for $C_{16}H_{12}O$ (220.27): C. 87,25; H. 5,49; found C. 87,16; H. 5,48

2-Butyl-4-phenylfuran (4j). Yield: 160.8 mg, starting from 217.3 mg of **1r** (80%) (Table 3.2, entry 2). Colorless solid, mp 32-34 °C; IR (KBr): ν = 2958 (m), 1601 (w), 1495 (w), 1449 (m), 1266 (w), 1116 (m), 948 (w), 738 (m), 690 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.55 (s, 1 H, H-5), 7.46-7.35 (m, 2 H on phenyl ring), 7.34-7.24 (m, 2 H on phenyl ring), 7.22-7.12 (m, 1 H on phenyl ring) 6.27 (s, 1 H, H-3), 2.61 (t, J = 7.7, 2 H, $CH_2CH_2CH_2CH_3$), 1.69-1.57 (m, 2 H, $CH_2CH_2CH_3$), 1.44-1.30 (m, 2 H, CH_2CH_3), 0.92 (t, J = 7.3, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.7, 136.6, 133.0, 128.7, 127.0, 126.7, 125.7, 104.0, 30.1, 27.8, 22.3, 13.8; GC-MS (EI, 70 eV): *m/z* = 200 (M^+, 55), 171 (7),

158 (29), 157 (100), 141 (6), 129 (53), 128 (61), 127 (24), 115 (15), 102 (7), 77 (9); anal. calcd for $C_{14}H_{16}O$ (200.28): C. 83,96; H. 8,05; found C. 83,90; H. 8,06.

5-Butyl-2,3-diphenylfuran (4k). Yield: 223 mg, starting from 296 mg of **1s** (80%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53-7.47 (m, 2 H on phenyl ring), 7.42-7.36 (m, 2 H on phenyl ring), 7.34-7.12 (m, 6 H on phenyl rings), 6.14 (s, 1 H, H-4), 2.68 (t, J = 7.6, 2 H $CH_2CH_2CH_2CH_3$), 1.76-1.63 (m, 2 H, $CH_2CH_2CH_2CH_3$), 1.50-1.36 (m, 2 H, $CH_2CH_2CH_2CH_3$), 0.95 (t, J = 7.6, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.7, 146.6, 134.8, 131.6, 128.6, 128.5, 128.3, 127.0, 126.9, 125.9, 123.0, 109.3, 30.1, 27.8, 22.4, 13.9; GC-MS: *m/z* = 276 (70), 234 (21), 233 (100), 203 (9), 189 (8), 105 (26), 77 (20); anal. calcd for $C_{20}H_{20}O$ (276.37): C, 86.92; H, 7.29; found C, 86.90; H, 7.28.

2-Butyl-4-hex-1-ynyl-furan (4l). Yield: 286 mg, starting from 380 mg of **1t** (87%). Yellow oil; IR (film): v = 2958(s), 2933(s), 2872 (s), 1768 (m), 1466 (m), 1133 (m), 944 (w)cm^{-1}; GC-MS: *m/z* =204 (63), 189 (11), 162 (18), 161 (100), 147 (14), 133 (11), 119 (32), 115 (12), 105 (30), 103 (11), 91(54), 89 (13), 79 (15), 77(23), 65 (18), 63 (11), 55 (11); anal. calcd for $C_{14}H_{20}O$ (204,31): C, 82.30; H, 9.87; found C, 82.32; H, 9.89.

5-Butyl-3-hex-1-ynyl-2-methylfuran (4m). Yield: 199.1 mg, starting from 236.6 mg of **1u** (91%) (Table 2, entry 3). Pale yellow oil. IR (film): v = 2932 (m), 2862 (m), 2230 (w), 1580 (m), 1465 (m), 1232 (m), 1124 (w), 951 (w), 799 (w), 734 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.87 (s, 1 H, H-4), 2.51 (t, J = 7.7, 2 H, $=CCH_2$), 2.37 (t, J = 6.9, 2 H, $C\equiv CCH_2$), 2.28 (s, 3 H, Me at C-2), 1.63-1.24 (m, 8 H, 2 $CH_2CH_2CH_2CH_3$), 0.93 (t, J = 7.4, 3 H, Me), 0.91 (t, J = 7.4, 3 H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.0, 153.5, 107.6, 103.7, 92.0, 72.9, 31.1, 30.1, 27.5, 22.2, 22.0, 19.2, 13.8, 13.7, 12.5; GC-MS (EI, 70 eV): *m/z* = 218 (M^+, 28), 176 (14), 175 (100), 145 (4), 133 (11), 117 (4), 105 (5), 91 (8), 77 (6); anal. calcd for $C_{15}H_{22}O$ (218.33): C. 82,52; H. 10,16; found C. 82,32; H. 10,19

5-tert-Butyl-3-(3,3-dimethyl-but-1-ynyl)-2-methyl-furan (4n). Yield: 224 mg, starting from 299 mg of **1v** (81%). Yellow oil. IR (film): ν = 2968 (m), 2869 (m), 2217 (w), 1783 (w), 1683 (w), 1575 (w), 1362 (m), 1293 (m), 1099 (m), 943 (w), 802 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* = 218 (M^+, 28), 176 (14), 175 (100), 145 (4), 133 (11), 117 (4), 105 (5), 91 (8), 77 (6); anal. calcd for $C_{15}H_{22}O$ (218,33): C, 82.52; H, 10.16; found C, 82.53; H, 10.19.

2-Methyl-5-phenyl-3-phenylethynyl-furan (4o). Yield: 298 mg, starting from 380 mg of **1w** (84%). Colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63-7.58 (m, 2 H on phenyl ring), 7.52-7.46 (m, 2 H on phenyl ring), 7.38-7.17 (m, 6 H on phenyl rings), 6.64 (s, 1 H, H-4), 2.47 (s, 3 H *CH_3*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9, 151.9, 131.4, 130.3, 128.7, 128.3, 128.0, 127.4, 123.6, 107.6, 105.4, 92.1, 81.6, 12.9; GC-MS: *m/z* = 258 (100), 257 (12), 229 (9), 216 (9), 215 (46), 213 (20), 189 (6), 129 (6), 77 (8); anal. calcd for $C_{19}H_{14}O$ (258,31): C, 88.34; H, 5.46; found C, 88.32; H, 5.45.

1-(5-Butyl-2-methyl-furan-3-yl)-hexan-1-one (5a). Yield: 199 mg, starting from 237 mg of **1u** (84%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.19 (s, 1 H, H-4), 2.70-2.50 (m, 4 H CO*CH_2* + *CH_2*$CH_2CH_2CH_3$), 2.54 (s, 3 H, =CCH_3), 1.73-1.55 (m, 4 H, $COCH_2$*CH_2* + CH_2*CH_2*CH_2CH_3), 1.45-1.29 (m, 6 H, $COCH_2CH_2$*CH_2CH_2*CH_3 + CH_2CH_2*CH_2*CH_3), 1.00-0.85 (m, 6 H, $COCH_2CH_2CH_2CH_2$*CH_3* + $CH_2CH_2CH_2$*CH_3*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.9, 156.7, 154.4, 121.7, 105.0, 41.3, 31.7, 30.1, 27.5, 23.9, 22.6, 22.3, 14.3, 13.9, 13.8; GC-MS: *m/z* = 236 (21), 193 (22), 181 (10), 180 (78), 166 (11), 165 (100), 137 (41), 123 (16), 95 (8), 81 (10), 55 (12); anal. calcd for $C_{15}H_{24}O$ (236,35): C, 76.23; H, 10.24; found C, 76.21; H, 10.27.

1-(5-Isopropyl-2-methyl-furan-3-yl)-3,3-dimethyl-butan-1-one (5b). Yield: 157 mg, starting from 202 mg of **1v** (78%). Yellow oil. IR (film): ν = 2957 (m), 2869 (w), 1668 (s), 1565 (s), 1463 (m), 1392 (m), 1364 (m), 1230 (m), 1108 (w), 902 (w) cm^{-1}; GC-MS: *m/z* = 236 (35), 222 (12), 221 (80), 180 (61), 166 (18),

165 (100), 57 (18); anal. calcd for $C_{14}H_{21}O$ (221,32): C, 75.98; H, 9.56; found C, 76.00; H, 9.59.

1-(2-Methyl-5-phenyl-furan-3-yl)-2-phenyl-ethanone (5c). Yield: 285 mg, starting from 380 mg of **1w** (75%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64-7.59 (m, 2 H on phenyl ring), 7.40-7.19 (m, 8 H on phenyl rings), 6.90 (s, 1 H, H-4), 4.03 (s, 2 H, *C*H_2), 2.63 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.0, 159.0, 151.7, 134.3, 129.9, 129.5, 128.7, 128.6, 127.8, 126.9, 123.7, 122.4, 104.8, 48.0, 14.5; GC-MS: *m/z* = 276 (21), 186 (13), 185 (100), 157 (22), 115 (26), 77 (100), 136 (34), 122 (15), 107 (24), 94 (18), 93 (44), 92 (10); anal. calcd for $C_{19}H_{16}O$ (276,33): C, 82.58; H, 5.84; found C, 82.56; H, 5.83.

1-(5-Butyl-2-methyl-1*H*-pyrrol-3-yl)-hexan-1-one (5d). Yield: 188 mg, starting from 380 mg of *N*-Boc-7-(1-Amino-ethyl)-trideca-5,8-diyn-7-ol (70%). Yellow solid. mp=48-49° C IR (film): *v* = 3299 (s), 3299(s), 2952 (m), 2929 (m), 2860 (w), 1636 (s), 1585 (m), 1522 (w), 1468 (m), 1384 (s), 1192 (s), 961 (m), 804 (w), 728 (w)cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.84 (s,br 1 H,N*H*), 6.20-6.14 (m, 1 H, H-4), 2.71 (t, *J* = 7.6, 2 H *CH*$_2$CO), 2.56-2.48 (m, 5 H, =C*CH*$_2$+ =C*CH*$_3$), 1.75-1.52 (m, 4 H, CH_2*CH*$_2$$CH_2CH_3$ +$COCH_2$*CH*$_2$$CH_2CH_2CH_3$), 1.43-1.25 (m, 6 H, CH_2CH_2*CH*$_2$$CH_3$ +$COCH_2CH_2$*CH*$_2$ *CH*$_2$$CH_3$), 0.95-0.84 (m, 6 H, $CH_2CH_2CH_2$*CH*$_3$ +$COCH_2CH_2CH_2CH_2$*CH*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.1, 134.0, 130.9, 120.6, 106.5, 40.6, 31.9, 31.6, 27.1, 24.7, 22.6, 22.4, 13.95, 13.91, 13.8 ; GC-MS: *m/z* = 235 (7), 192 (14), 179 (22), 165 (13), 164 (100), 136 (34), 122 (15), 107 (24), 94 (18), 93 (44), 92 (10); anal. calcd for $C_{15}H_{25}NO$ (235,37): C, 76.55; H, 10.71; N, 5.95; found C, 76.58; H, 10.68.

1-(5-Butyl-2-isobutyl-1*H*-pyrrol-3-yl)-hexan-1-one (5e). Yield: 211 mg, starting from 421 mg of *N*-Boc-7-(1-Amino-3-methyl-butyl)-trideca-5,8-diyn-7-ol(68%). Yellow oil. IR (KBr): *v* = 3278 (m), 2957 (s), 2925 (s), 2871 (m), 1634 (s), 1588 (m), 1516 (m), 1466 (s), 1394 (m), 1288 (w), 961 (w), 797 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.26 (s,br 1 H,N*H*), 6.22-6.16 (m, 1 H, H-4), 2.81

(d, *J* = 7.1, 2 H,CH_2CH(CH_3)$_2$), 2.72 (t, *J* = 7.6, 2 H, CH_2CO), 2.54 (t, J=7.6, 2 H, =CCH_2), 2.07-1.92 (m, 1 H, $CH_2CH(CH_3)_2$), 1.74-1.54 (m, 4 H, $CH_2CH_2CH_2CH_3$ +$COCH_2CH_2CH_2$ CH_2CH_3), 1.42-1.23 (m, 6 H, $CH_2CH_2CH_2CH_3$ +$COCH_2CH_2CH_2CH_2CH_3$), 0.94-0.85 (m, 12 H, $CH_2CH_2CH_2CH_3$ +$COCH_2CH_2CH_2CH_2CH_3$ + $CH_2CH(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.1, 138.2, 130.6, 120.3, 106.6, 40.7, 36.8, 31.8, 31.6, 28.9, 27.1, 24.9, 22.6, 22.5, 22.4, 13.9, 13.8; GC-MS: *m/z* = 277 (18), 234 (67), 221 (15), 206 (55), 179 (11), 178 (63), 164 (72), 162 (10), 150 (10), 136 (23), 135 (29), 134 (23), 122 (11), 120 (16), 118 (16), 107 (19), 106 (18), 94 (16), 93 (50), 69 (14), 43 (100); anal. calcd for $C_{18}H_{31}NO$ (277,44): C, 77.92; H, 11.26; N, 5.05; found C, 77.94; H, 11.29.

1-(2-Benzyl-5-butyl-1*H*-pyrrol-3-yl)-hexan-1-one (5f). Yield: 280 mg, starting from 452 mg of *N*-Boc-7-(1-Amino-2-phenyl-ethyl)-trideca-5,8-diyn-7-ol (82%). Yellow oil. IR (KBr): *v* = 3365 (m, br), 2956 (s), 2930 (s), 2859 (m), 1631 (s), 1588 (m), 1516 (m), 1461 (s), 1396 (w), 1190 (w), 959 (w), 725 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.97 (s,br 1 H,N*H*), 7.23-7.16 (m, 5H on phenyl ring), 6.22-6.17 (m, 1 H, H-4), 2.68 (t, *J* = 7.6, 2 H, CH_2CO), 2.44 (t, J=7.6, 2 H, =CCH_2), 1.71-1.46 (m, 4 H, $CH_2CH_2CH_2CH_3$ + $COCH_2CH_2CH_2CH_2CH_3$), 1.37-1.19 (m, 6 H, $CH_2CH_2CH_2CH_3$ + $COCH_2CH_2CH_2CH_2CH_3$), 0.92-0.82 (m, 6H, $CH_2CH_2CH_2CH_3$ +$COCH_2CH_2CH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.1, 138.9, 136.1, 131.6, 128.9, 128.6, 126.4, 120.5, 106.6, 40.6, 33.7, 31.8, 31.5, 27.1, 24.7, 22.6, 22.3, 13.9, 13.8; GC-MS: *m/z* = 311 (36), 268 (38), 255 (25), 254 (11), 241 (20), 240 (100), 213 (13), 212 (47), 196 (19), 184 (33), 183 (89), 182 (23), 181 (10), 180 (24), 170 (27), 169 (28), 168 (92), 167 (47), 166 (14), 165 (14), 164 (53), 154 (21), 141 (11), 115 (14), 93 (10), 91 (46), 77 (14), 65 (13); anal. calcd for $C_{21}H_{29}NO$ (311,46): C, 80.98; H, 9.38; N, 4.50; found C, 81.0; H, 9.35.

1-(2-Methyl-5-phenyl-1*H*-pyrrol-3-yl)-2-phenyl-ethanone (5g). Yield: 145 mg, starting from 279 mg of *N*-Boc-3-(1-Amino-ethyl)-1,5-diphenyl-penta-1,4-diyn-3-ol (80%). Brown solid. mp= 176-178°C IR (KBr): ν = 3273 (m), 3024 (w), 1622 (s), 1605 (m), 1475 (m), 1448 (m), 1384 (m), 1197 (m), 1144 (w), 1071 (w), 988 (w), 814(m), 765 (m) ,729 (m), 692 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 9.04 (s,br 1 H,N*H*), 7.48-7.42 (m, 2H on pheyl ring), 7.38-7.15 (m, 8H on phenyl ring) 6.86-6.83 (m, 1 H, H-4), 4.10 (s, 2 H CH_2CO), 2.53 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.8, 137.3, 135.5, 131.7, 130.0, 129.5, 129.0, 128.5, 126.7, 126.6, 123.8, 121.4, 107.1, 47.2, 14.1; GC-MS: *m/z* = 275 (8), 185 (13), 184 (100), 129 (17), 128 (12), 91 (10), 77 (7); anal. calcd for $C_{19}H_{17}NO$ (275,34): C, 82.88; H, 6.22; N, 5.09; found C, 82.90; H, 8.27.

1-(5-*tert*-Butyl-2-methyl-1*H*-pyrrol-3-yl)-3,3-dimethyl-butan-1-one (5h). Yield: 225 mg, starting from 360 mg of *N*-Boc-5-(1-Amino-ethyl)-2,2,8,8-tetramethyl-nona-3,6-diyn-5-ol (87%).Yellow solid. mp= 202-204 °C. IR (KBr): ν = 3283 (s, br), 2959 (s), 2967 (w), 1628 (s), 1576 (m), 1515 (m), 1474 (m), 1385 (m), 1362 (m), 1241 (m), 1003 (w), 974(m), 903 (s), 794 (m) $cm^{-}1$; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.51 (s,br 1 H,N*H*), 6.16-6.12 (m, 1 H, H-4), 2.60 (s, 1 H CH_2CO), 2.51 (s, 3H, CH_3), 1.29 (s, 9 H, =C$(CH_3)_3$), 1.06 (s, 9 H, $COCH_2(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.6, 139.3, 133.8, 121.8, 104.7, 31.3, 31.1, 30.7, 30.4, 30.3, 28.4, 14.1; GC-MS: *m/z* = 235 (25), 220 (43), 179 (23), 178 (10), 165 (13), 164 (100), 121 (15); anal. calcd for $C_{15}H_{25}NO$ (235,37): C, 76,55; H, 10.71; N, 5.95; found C, 76.54; H, 10.69

1-(5-Butyl-2-isopropyl-1*H*-pyrrol-3-yl)-hexan-1-one (5i). Yield: 213 mg, starting from 406 mg of *N*-Boc-7-(1-Amino-2-methyl-propyl)-trideca-5,8-diyn-7-ol(71%). Yellow oil. IR (KBr): ν = 3265 (m, br), 2957(s) 2930 (s), 2959 (m), 1631 (s), 1588 (w), 1516 (m), 1461 (s), 1396 (w), 1191 (w), 958 (w), 725 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 9.32 (s,br 1 H,N*H*), 6.23-6.15 (m, 1 H, H-4), 3.98-3.81 (m, 1 H, $CH(CH_3)_2$), 2.74 (t, *J* = 7.6, 2 H, CH_2CO), 2.55 (t, J=7.6, 2 H, =CCH_2), 1.76-1.54 (m, 4 H, $CH_2CH_2CH_2CH_3$ + $COCH_2CH_2CH_2CH_2CH_3$),

1.44-1.29 (m, 6 H, $CH_2CH_2\mathit{CH_2}CH_3$ +$COCH_2CH_2\mathit{CH_2CH_2CH_3}$) 1.25 (d, J=6.8, 6H $CH(\mathit{CH_3})_2$, 0.95-0.84 (m, 6 H, $CH_2CH_2CH_2\mathit{CH_3}$ +$COCH_2CH_2CH_2CH_2\mathit{CH_3}$) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.0, 144.3, 130.9, 118.9, 106.6, 40.9, 31.9, 31.6, 27.2, 26.4, 24.9, 22.6, 22.5, 21.8, 14.0, 13.9; GC-MS: *m/z* = 263 (17), 220 (21), 207 (20), 193 (13), 192 (100), 164 (21), 150 (12), 120 (16), 106 (35); anal. calcd for $C_{17}H_{29}NO$ (263.42): C, 77.51; H, 11.10; N, 5.32; found C, 77.49; H, 11.07.

1-(3-Butyl-6,7-dihydro-5*H*-pyrrolizin-1-yl)-hexan-1-one (5j). Yield: 197 mg, starting from 290 mg of 7-Pyrrolidin-2-yl-trideca-5,8-diyn-7-ol (68%). Yellow oil . IR (film): *v* = 3419 (w, br), 2957 (s), 2931(s), 2872(s), 1722 (w), 1652 (m), 1558 (w), 1520 (m), 1431 (m), 1299 (w), 754 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.30-6.26 (m, 1 H, H-4), 3.85 (t, J=7.2, 2 H, $CH_2CH_2CH_2\mathit{CH_2}N$), 3.09 (t, J=7.6, 2H, $\mathit{CH_2}CH_2CH_2CH_3$), 2.64 (t, *J* = 7.6, 2 H $\mathit{CH_2}CO$), 2.56-2.46 (m, 4 H, $\mathit{CH_2CH_2}CH_2CH_2N$), 1.73-1.52 (m, 4 H, $CH_2\mathit{CH_2}CH_2CH_3$ +$COCH_2\mathit{CH_2}CH_2CH_2CH_3$), 1.45-1.27 (m, 6 H, $CH_2CH_2\mathit{CH_2}CH_3$ +$COCH_2CH_2\mathit{CH_2}$ $\mathit{CH_2}CH_3$), 0.97-0.84 (m, 6 H, $CH_2CH_2CH_2\mathit{CH_3}$ +$COCH_2CH_2CH_2CH_2\mathit{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.2, 142.0, 129.4, 116.9, 109.1, 44.9, 39.9, 31.9, 31.1, 27.0, 26.5, 26.2, 24.8, 22.6, 22.4, 14.0, 13.8 ; GC-MS: *m/z* = 261 (34), 218 (49), 205 (58), 191 (14), 190 (100), 162 (35), 120 (12), 119 (20); anal. calcd for $C_{17}H_{27}NO$ (261,40): C, 78.11; H, 10.41; N, 5.36; found C, 78.13; H, 10.43.

1-(5-*tert*-Butyl-2-isobutyl-1*H*-pyrrol-3-yl)-3,3-dimethyl-butan-1-one (5k). Yield: 206 mg, starting from 359 mg of *N*-Boc-5-(1-Amino-3-methyl-butyl)-2,2,8,8-tetramethyl-nona-3,6-diyn-5-ol (78%).Yellow solid. mp= 126-128°C IR (KBr): *v* = 3299 (s), 3289 (s), 2958 (s), 2868(m), 1628 (s), 1580 (m), 1469 (m), 1384 (s), 1232 (m), 1003 (w), 794 (m), 731 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (s,br 1 H,N*H*), 6.16-6.12 (m, 1 H, H-4), 2.60 (s, 1 H $\mathit{CH_2}CO$), 2.81 (d, *J* = 7.1, 2 H,$\mathit{CH_2}CH(CH_3)_2$), 1.29 (s, 9 H, =C$\mathit{(CH_3)_3}$), 1.06 (s, 9 H, $COCH_2\mathit{(CH_3)_3}$; GC-MS: *m/z* = 277 (49), 262 (50), 234 (100), 221 (27), 220 (45),

207 (12), 206 (76), 179 (12), 178 (72), 164 (14), 163 (14), 162 (13), 135 (13), 122 (11), 121 (12), 120 (14);; anal. calcd for $C_{18}H_{31}NO$ (277,44): C, 77.92; H, 11.26; N, 5.05; found C, 77.90; H, 11.29

1-(2-*Isobutyl*-5-trimethylsilanyl-1*H*-pyrrol-3-yl)-2-trimethylsilanyl-ethanone (5l). Yield: 116 mg, starting from 250 mg of *N*-Boc-3-(1-Amino-3-methyl-butyl)-1,5-bis-trimethylsilanyl-penta-1,4-diyn-3-ol (82%). Yellow oil. IR (film): ν = 3264 (m, br), 3110 (w), 1637 (s), 1560 (m), 1464 (m), 1389 (m), 1292 (w), 938 (w), 896 (w), 719 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 9.95 (s,br 1 H,N*H*), 6.62-6.58 (m,1H, H-5), 6.55-6.53 (m, 1 H, H-4), 2.86 (d, J=7.1, 2H, $CH_2CH(CH_3)_2$), 2.44 (s, 3 H, CH_3CO), 2.10-1.96 (m, J = 7.1, 1 H,$CH_2CH(CH_3)_2$), 0.90 (d, J = 6.5, 6 H, $CH_2CH(CH_3)_2$) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.7, 139.5, 120.4, 116.0, 110.8, 36.7, 28.8, 28.5, 22.5; GC-MS: *m/z* = 246 (28), 214 (22), 187 (41), 186 (87), 156 (18), 155 (90), 143 (24), 129 (14), 128 (100), 127 (42), 126 (12), 115 (17), 77(11); anal. calcd for $C_{10}H_{15}NO$ (165.23): C, 72.69; H, 9.15; N, 8.48; found C, 72.70; H, 9.13

References

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ALLEGATO F al verbale del Collegio di dottorato di ricerca in Metodologie per lo Sviluppo di Molecole di Interesse Farmacologico del 20 Ottobre 2010

Relazione del collegio dei docenti sull'attività svolta durante il corso dal dottorando Mabel Valeria VETERE

La candidata ha usufruito di una borsa aggiuntiva di dottorato di ricerca MIUR – Bando Fondo Sostegno Giovani). Il Collegio dei Docenti ha valutato l'attività di ricerca della candidata che si è sviluppata nel campo "Nuove sintesi di eterocicli mediante processi metallo-catalizzati", e ha preso in esame i risultati conseguiti, riportati in n° 2 lavori a stampa o in corso di stampa su riviste internazionali con referee a buon IF medio (3.46), n° 2 comunicazioni in congressi internazionali e n° 5 comunicazioni in congressi nazionali.

Il Collegio ha inoltre valutato:

- l'attività formativa della candidata che si è realizzata attraverso la partecipazione a n° 1 Convegno internazionale e n° 3 Convegni nazionali
- l'attività formativa della candidata che si è realizzata a seguito della assidua frequenza all'attività didattica proposta dalla Scuola di Dottorato.

Con riferimento a quanto sopra richiamato, il Collegio dei Docenti del corso di Dottorato di Ricerca in *Metodologie per lo Sviluppo di Molecole di Interesse Farmacologico*, giudica l'attività della Dr.ssa Mabel V. VETERE ampiamente positiva e la presenta con piena soddisfazione al giudizio della Commissione.

Il coordinatore