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Aliphatic Nitro compounds as Key Starting Materials for the One-Pot Synthesis of Cyclic and Heterocyclic Fine Chemicals

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PhD candidate

Dr. Serena Gabrielli

Tutor

Prof. Roberto Ballini

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PREFACE

ORGANIC SYNTHESIS PAST, PRESENT & FUTURE

"Classical organic synthesis seems to be inefficient and is now under pressure because of increasing environmental awareness. How can it be improved?"

A reasonable way to define organic chemistry is the study of the relationship between the structure and properties of carbon compounds. The function of organic synthesis is to provide this study with access to these compounds in a pure form, either by extraction from natural resources or via synthesis, hence, 'Synthesis is the heart of chemistry'. The discipline of organic chemistry dates back to Berzelius who first used the term in 1807,[1] he also coined the word catalysis later, in 1835. Berzelius was a staunch believer in vitalism, the theory that organic substances derived from living matter were endowed with a mystical '*vital force*' (spiritus vitae) which preclude their synthesis in the laboratory from materials or mineral origin. The synthesis of urea in 1928 by Wholer starting from ammonia and cyanuric acid, heralded the demise of this theory. The final nail in its coffin was probably Kolbe's synthesis of acetic acid, from the elements, in 1845.[2] It is interesting to compare Kolbe's circuitous synthesize with how Nature produce acetic acid and the latest synthesis of it in the modern petrochemical technology, developed by Monsanto in which the key step is the rhodium-catalysed carbonylation of methanol. But, why did Kolbe synthesis acetic acid? Presumably to prove the theoretical point that vitalism was not tenable. As such it was the logic of synthesis rather than its practical use that was the issue. The next landmark in organic synthesis was Perkin's serendipitous synthesize of the first synthetic dye, mauveine, (aniline purple) in 1856.[3] This is generally regarded as the first industrial organic synthesis. Perkin was attempting to synthesis the drug quinine, by oxidizing allyltoluidine, bearing in mind that only the molecular formula, $C_{20}H_{24}N_2O_2$,

was known, but this attempt was doomed to failure. In subsequent experiments, using aniline that was contaminated with toluidines, Perkin obtained a low yield of a purple colored product. Fortunately, Perkin was not only a good chemist but also a very good businessman and he immediately recognized the commercial potential of his product. Further development of this process resulted in the commercialization of the first synthetic dye, which replaced the natural product Tyrian purple. At the time of Perkin's discovery this natural dye cost more per kilo than gold. Thus, the synthetic dye industry was born, the synthesis of natural dyes such as alizarin (1869)[4] and indigo (1878),[5] are clear examples. Further evolution of organic synthesis in the first half of the last century led to many elegant total syntheses of natural products, such as α-terpineol, tropinone and quinine. In these days, classical organic synthesis evolved almost into an art-form, culminating in the epochal synthesis of vitamin B12 by Wooward and Eschenmoser's group in 1970.[6] In the past twenty years organic synthesis has risen to even higher levels of sophistication with the advent of the more rational approach of computer-assisted retrosynthetic analysis.

For more than a century the main use of organic synthesis was as a final proof of structure. The structure of a natural product was finally accepted as proven when an ambiguous synthesis was planned, executed and a defined melting point taken. During the last decade, spectroscopic techniques have evolved to such levels of sophistication and reliability that they are more conclusive than total synthesis. So what others reasons for pursuing organic syntheses were there? First of all, it was necessary to demonstrate the existence of a molecule as a stable entity, for example, some molecules were synthesized not because they had a particular uses or properties, but just because it was a challenge, like a mountain waiting to be climbed. Another reason was to demonstrate the feasibility of yet another approach to the summit. Indeed, it is simple to understand that, application to the synthesis of a natural products is often used as a justification for studies of a particular reagent or reaction, in order to improve our knowledge about chemistry. Finally, the last but not the least, organic synthesis is also

undertaken with the goal of developing the most economic route for the industrial synthesis of a product for which there is a definite need. Nowadays, the green chemistry revolution is providing an enormous number of challenges to those who practice chemistry in industry, education and research. With these challenges however, there are an equal number of opportunities to discover and apply new chemistry and to enhance the much-tarnished image of chemistry.[7] In this context I would like to introduce you in this new image of chemistry, it is not the use of organic synthesis to reach new targets but the use of it to reach an innovative and cleaner processes.

In the word of Winston Churchill: *"Problems are just opportunities in disguise. The optimist sees opportunity in every danger, the pessimist sees danger in every opportunity"*

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CHAPTER 1

GREEN CHEMISTRY & ONE-POT PROCESSES

1.1 Introduction

Green chemistry, also called sustainable chemistry, is a philosophy of chemical research and engineering that encourages the design of products and processes that minimize the use and generation of hazardous substances. Whereas environmental chemistry is the chemistry of the natural environment, and of pollutant chemicals in nature, green chemistry seeks to reduce and prevent pollution at its source. In 1990 the *Pollution Prevention Act* was passed in the United States. This act helped to create a *modus operandi* for dealing with pollution in an original and innovative way. It aims to avoid problems before they happen. As a chemical philosophy, green chemistry applies to organic chemistry, inorganic chemistry, biochemistry, analytical chemistry, and even physical chemistry. While green chemistry seems to focus on industrial applications, it does apply to any chemistry choice. Domino processes, for example, are a style of chemical synthesis that is consistent with the goals of green chemistry. The focus is on minimizing the hazard and maximizing the efficiency of any chemical choice. It is distinct from environmental chemistry which focuses on chemical phenomena in the environment. Examples of applied green chemistry are supercritical water oxidation, on water reactions, and solvent-free reactions. In 2005 Ryōji Noyori identified three key developments in green chemistry: use of supercritical carbon dioxide as green solvent, aqueous hydrogen peroxide for clean oxidations and the use of hydrogen in asymmetric synthesis.[1] There still are some debates about green chemistry because of its principles and because if those principles cannot be applied, is not fair using the same term in order to explain the reduction of waste and the minimization of hazardous substances.

1.2 The 12 Principles of Green Chemistry

Paul Anastas, consituent of the United States Environmental Protection Agency (EPA), and John C. Warner, developed "The 12 principles of green chemistry",[2] which help to explain what the definition means in practice. The principles cover such concepts as:

- the design of processes to maximize the amount of raw material that ends up in the product;
- the use of safe, environment-benign substances, including solvents, whenever possible;
- the design of energy efficient processes;
- the best form of waste disposal: not to create it in the first place.

The 12 principles are:

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and, innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.

8. Reduce derivatives - Unnecessary derivatization (blocking group, protection/ deprotection, temporary modification) should be avoided whenever possible.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. Substances and the form of a substance used in a chemical process should be chosen to minimize potential for chemical accidents, including releases, explosions, and fires.

1.3 One-Pot Processes

The last decade has witnessed a change of paradigm in chemical synthesis.[3] The main goal now is the efficiency of a synthesis, which can be defined as the increase of complexity per transformation. Indeed, the question today is not only what can we prepare and the yield of transformation, but how do we do it in absence of a large amount of wastes? The challenge for chemists and others is to develop new processes that allow to achieve environmental benefits that are now required, in terms of safe chemistry. This requires a new approach which sets out to reduce the materials and energy intensity of chemical processes and products, minimize or eliminate the dispersion of harmful chemical in the environment, maximize the use of renewable resources and extend the durability and recyclability of the products. Some of the challenges for chemists include the discovery and development of new synthetic pathways using alternative feedstocks or more selective chemistry, identifying alternative reaction conditions and solvents (the preservation of resources and the avoidance of toxic reagents as well as toxic solvents.[4]) for improved selectivity and energy minimization and designing less toxic and inherently safer chemicals. In chemical synthesis, the ideal will be a combination of a number of environmental, health and safety, and economic targets (**Figure 1**).

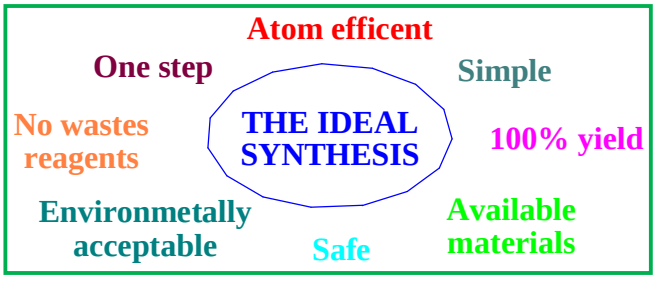


Figure 1. The ideal synthesis

That's why organic chemists are focusing on One-Pot procedures. Indeed, effective organic synthesis is predicated on site-isolation, the physical separation of reagents or catalysts from each other. Synthetic organic chemists typically achieve site-isolation by using separate flasks or reactors. The main problem, related to this kind of "multi-pots" processes is amenable to the waste of solvents, because each step requires an extraction, so, formation of an aqueous layer that must be treated at all. Beyond solvent, high-yielding reactions often produce salts (as explained before) and other impurities that must be removed to avoid deleterious effects on the downstream transformations. Serial reactions and purifications require massive amounts of solvents and materials. The average pharmaceutical syntheses yield 25-100 Kg (including solvent) of waste per kilogram of product, according to Sheldon.[5,6] Inputs used by the pharmaceutical industry are highly purified, processed and refined fine/bulk chemicals that are also wasteful to produce. Currently, inputs for pharmaceutical and fine chemical synthesis are plentiful, allowing synthesis to proceed at a reasonable price. However, as resources become more scarce and expensive, synthesis will become increasingly cost-prohibitive unless made sustainable. Biosynthesis, for example, offers an alternative to the organic chemist's current model of synthesis. In a cell myriad of incompatible reactions occur, but using enzymes and isolated catalyst compartment we can prevent fouling and cross-reactivity. The only problem is that biosynthesis is limited to natural substrates and structural motif. This field could be more efficient and environmentally benign than traditional synthesis, the only way should be to shift this behavior onto organic chemistry, so the question is: "How can we keep the best of organic synthesis and the biosynthetic behavior to create synthetic routes with excellent atom efficiency[7] or E-factor?[8-10] Until now, the "normal" procedure for the synthesis of organic compounds has been a stepwise formation of individual bonds in the target molecules, with workups after each transformation. In contrast, modern synthesis management must seek procedures that allow the formation of several bonds, whether C−C, C−O or C−N, in one process. This new approach is called *"One-Pot"* philosophy, it can be defined as, *a strategy to improve the*

efficiency of a chemical reaction whereby a reactant is subjected to successive chemical transformation in just one reactor. (**Figure 2**). The difference between these types of 'terminologies' as to be referred to the practical odds between them, in fact, in the One-Pot transformation we can add every reagent or reactant we need to get the target.

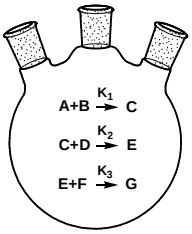
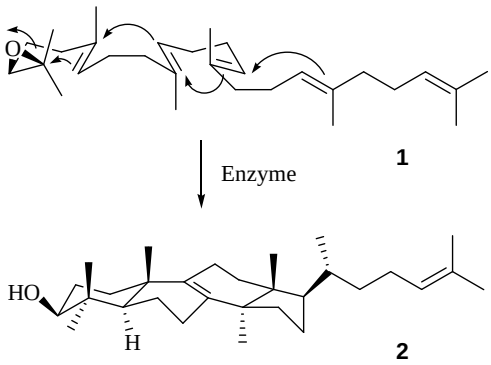


Figure 2. Coupled irreversible one-pot reactions.

The main task of this new philosophy is to avoid the generation of a large amount of wastes and the best way is to reduce a multi pots process to an easy one-pot proceeding. To be more precise, it's to carry out the reaction in the same flask even if the reaction counts different steps. The simplest example is related to a **Figure 2**, from how we can understand: if we go from A to G in three different steps, we will arrive at the end of the transformation with a lot of wastes, but if we realize a one-pot process we will able to pass directly from A to G in one way. One-Pot involves two different processes called, domino reaction and tandem reaction. In an ideal procedure, called "Domino Reaction" or *"Domino Process"*,[11] the entire transformation should be curried out without the addition of any further reagents or catalysts, and without changing the reaction conditions. This process *is defined as a process of two or more bond forming transformations under widely identical conditions in which the subsequent reactions take place at the functionalities obtained in the former transformation*. An excellent illustration being that of domino stones, where one stone tips over the next, which tips the two next, and the next . . . such that they all fall down in turn. In the literature, although the word *"Tandem"* is often used to describe this type of process, it is less appropriate as the encyclopedia *defines tandem as "locally, two after each other", is*

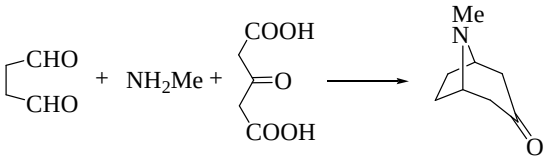
something like a synergy between two different processes that comes in the same way in the main time, in order to get the final product.

Although, domino reactions are not a new invention − indeed, Nature has been using this approach for billions of years! But, the quality of a domino reaction can be correlated to the number of bond-forming steps, as well as to the increase of complexity and its suitability for a general application. The greater is the number of steps − which usually goes hand-in-hand with an increase of complexity of the product, the more useful might be the process. An example of this type is the highly stereoselective formation of lanosterol **2** from (*S*)-2,3-oxidosqualene **1** in Nature, which seems not to follow a concerted mechanism (**Scheme 1**).[12]



Scheme 1. Synthesis of lanosterol **2**

The domino approach is also used by Nature for the synthesis of several alkaloids, the most prominent example being the biosynthesis of tropinone **6**. In this case, a biomimetic synthesis was developed before the biosynthesis had been disclosed. Shortly after the publication of a more than 20-step synthesis of tropinone by Willstätter,[13] Robinson[14] described a domino process (which was later improved by Schöpf [15]) using succinaldehyde **3**, methylamine **4** and acetonedicarboxylic acid **5** to give tropinone **6** in excellent yield without isolating any intermediates (**Scheme 2**).

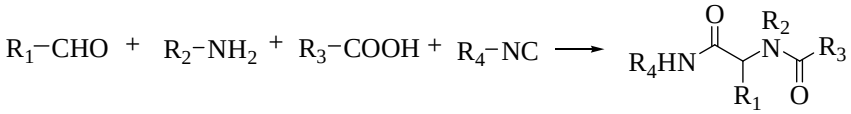


3 **4** **5** **6**

Scheme 2. Domino process for the synthesis of Tropinone **6**

Tropinone is a structural component of several alkaloids, including atropine. The synthesis is based on a double Mannich process with iminium ions as intermediate. The Mannich reaction in itself is a three-component domino process, which is one of the first domino reactions developed by humankind.

One very important aspect in modern drug discovery is the preparation of so called “substance libraries” from which pharmaceutical lead structures might be selected for the treatment of different diseases. An efficient approach for the preparation of highly diversified libraries is the development of multi-component reactions, which can be defined as a subclass of domino reactions. One of the most widely used transformations of this type was described by Ugi and coworkers using an aldehyde **7**, an amine **8**, an acid **9**, and an isocyanide **10** to prepare peptide-like compounds **11** showed in (**Scheme 3**).



7 **8** **9** **10** **11**

Scheme 3. Ugi four-component approach

As we can note, for all domino reactions, the substrates used must have more than two functionalities of comparable reactivity. For the design and performance of domino reactions it is important that the functionalities react in a fixed chronological order to allow the formation of defined molecules. There are several possibilities to determine the course of the reactions:

- One must adjust the reactivity of the functionalities, which usually react under similar reaction conditions;
- Another possibility, is to use entropic acceleration. In this way, it is possible to use a substrate that first reacts in an intramolecular mode to give an intermediate, which then undergoes an intermolecular reaction with a second molecule;
- It is also possible to avoid an intramolecular reaction as the first step, for example if the cycle being formed in this transformation would be somehow strained, as observed for the formation of medium rings. In such a case, an intermolecular process first takes place, followed by an intramolecular reaction.

A different situation exists if the single steps in a domino process follow different mechanisms. The difficulty is not the adjustment of the reaction conditions, but it is related to identify conditions that are suitable for both transformations.

1.4 Classification of Domino Processes

Domino reactions can be classified according to the mechanism of the single steps. Combination of the different reaction types as in **Table 1** allows the creation of a multitude of domino processes. Many of these permutations are already known, but there is plenty space for the development of new combinations. They can consist of the same but also of different reaction types. Most of the so far developed domino processes belong to the first category and may include two or more cationic, anionic, radical, pericyclic or transition metal-catalyzed transformations. The reactions with the same mechanism are note as *omo-domino* (cationic-cationic, anionic-anionic, etc.), while the sequence of reactions with different mechanisms are note as *etero-domino* (cationic-anionic, anionic-pericyclic).

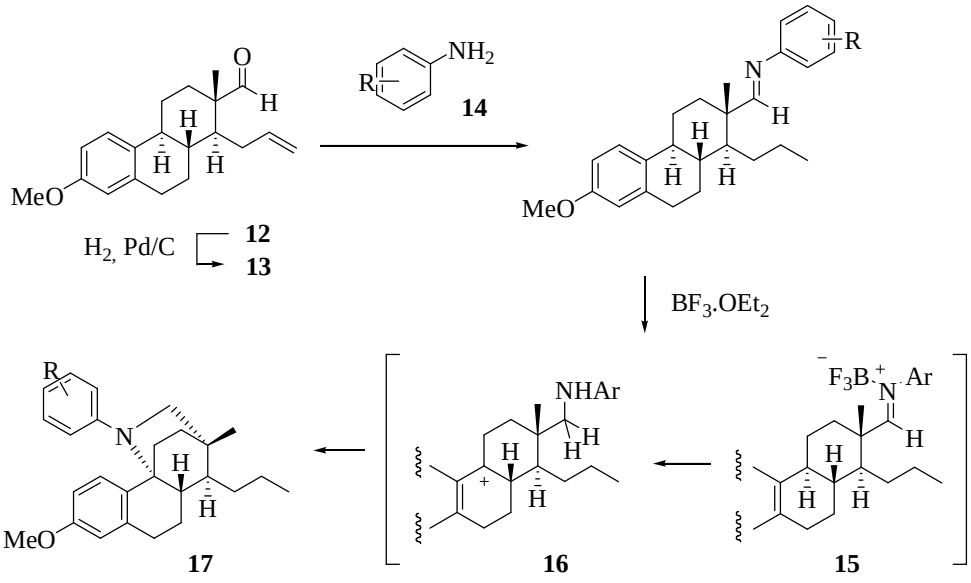
Table 1. Classification of Domino Processes

1. Step	2. Step etc.
1a cationic	2a cationic
1b anionic	2b anionic
1c radical	2c radical
1d pericyclic	2d pericyclic
1e photochemical	2e photochemical
1f transition metal-catalyzed	2f transition metal-catalyzed
1g oxidative/reductive	2g oxidative/reductive

Thus, based on our work, that undergoes through a domino steps, it is important to give a highlights about two different procedures as: cationic domino processes and anionic domino processes.

1.4.1 Cationic Domino Reactions

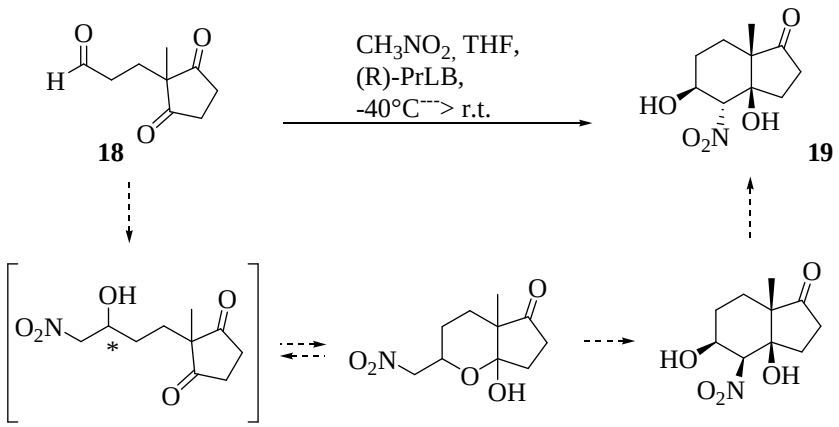
In the cationic domino processes which is a synonym for an electrophilic reaction a carbocation is formed first, either formally or in reality, which under bond formation reacts with a nucleophile to form a new carbocation. In most of the known domino processes of this type another cationic process follows where the final carbocation is either stabilized by elimination of a proton or by addition of another nucleophile to give the product. Recently it has been shown that iminium ions can induce a hydride shift to form a new carbocation which then reacts with a nucleophile. By this way the novel unusual bridged steroid alkaloids **17** were prepared from the secoestron derivative **12** (**Scheme 4**).[20] Treatment of **13** with aniline or aniline derivatives **14** containing an electron-withdrawing group in the presence of the Lewis acid $BF_3.OEt_2$ leads to the iminium ion **15**. This undergoes a 1,5-hydride shift to give **16**, which contains a secondary amine moiety and a carbocation. Finally, the last step allow to achieve **17** as a single diastereomer.



Scheme 4. Synthesis of bridged steroid alkaloids by a cationic domino 1,5 shift of a benzylic hydride

1.4.2 Anionic Domino Reactions

The anionic domino reaction is the most often encountered domino reaction in literature. In this process the primary step is the formation of an anion, which is a synonym for a nucleophile, mostly by deprotonation using a base. It follows a reaction with an electrophile to give a new anion which in the anionic-anionic process again reacts with an electrophile. The reaction is then completed either by addition of another electrophile as a proton or by elimination of an X^- group. A novel example of a catalytic anantioselective anionic domino process[16] is the inter-intramolecular nitro-aldol reaction described by Shibasaki et al. which generates substiutited indanones. As catalyst a praseodym-heterobimetallic complex with binaphthol as a chiral ligand is employed. Treatment of keto-aldehyde **18** with nitromethane in the presence of the catalyst at -40°C and successive warming to room temperature afford directly the product **19** in a good yield after several recrystallizations (**Scheme 5**).



Scheme 5. Enantioselective domino reaction for the formation of hydroindanones

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CHAPTER 2

ALIPHATIC NITRO COMPOUNDS: SYNTHESIS & UTILITY

2.1 Introduction

The nitro group, whether bonded to aromatic or aliphatic carbon, is probably the most widely studied among the functional groups and this is in part attributed to its use as an '*explosophore*' in many energetic materials.[1] But even if explosives have attracted a lot of unwanted publicity over the years for their misuse in the taking of life and the destruction of property, it should be known that, more explosives have been used in times of peace than in all the wars and conflicts put together. Explosives are in fact no more than a tool and remain as some of the most fascinating products of chemistry. Thus, nitro compounds can be considered, not only as explosives, but, much more important is their use and importance in organic synthesis, because of their use for a lot of synthetic strategies to achieve different fine chemicals. In fact, the nitro group can be transformed into others functionalities, so that, it can be obtained many other functions into the molecular structure (**Figure 1**).[2]

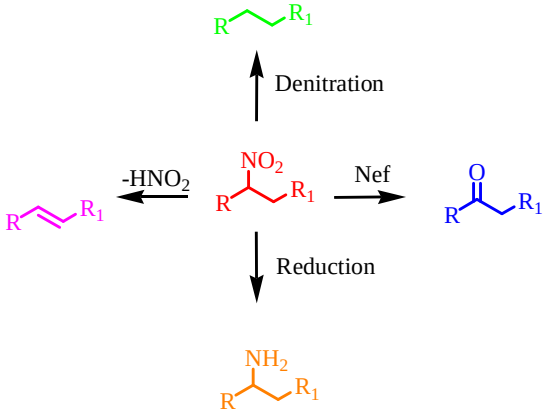
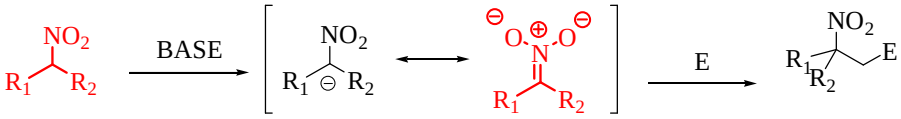


Figure 1. Conversion of nitro group into other functionalities.

This group appears to be one of the most important functional group in organic synthesis because, it is easy to synthesize and it is even easier to exploit its potential for the synthesis of complex target molecules. Nitro compounds can be easily synthesized, in a very large variety of methods, from the direct nucleophlic substitution of a primary halides with $NaNO_2$ or $AgNO_2$ etc… It must be taken into account that we can have different kind of nitro compounds, the most important are the aliphatic one. Most applications of aliphatic nitro compounds **1** in synthesis take advantage of an easy proton abstraction under basic conditions to form nitronate anion **2** followed by coupling with an electrophile (**Scheme 1**).[3]



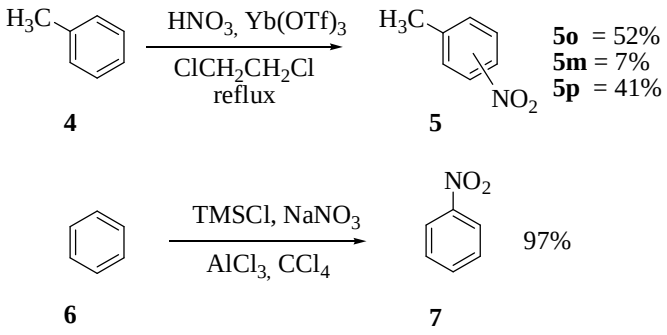
1 pKa = 10 **2** **3**

Scheme 1. Nitronate anion

2.2 Nitro compounds: Synthesis and applications as nucleophiles

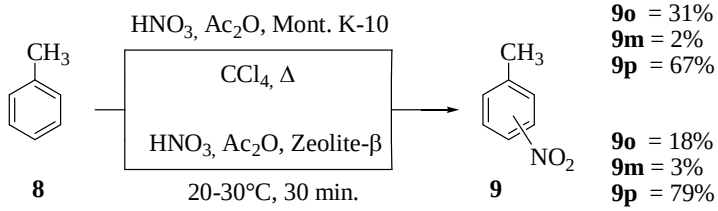
2.2.1 Synthesis of nitro compounds

The aliphatic nitro compounds, as aromatic too, are very important building blocks in organic synthesis. The main difference between them is that alkane derivatives are inert toward conventional nitrating agents used for the synthesis of aromatic tools in fact, the aromatic nitration can be easily promoted by large range of nitrating agents[2] such as: HNO_3, NO_2Cl, N_2O_5, $RONO_2$ under acidic catalysis; the most common catalysts are both Brønsted acid (H_2SO_4, H_2PO_4, CH_3SO_3H, HNO_3) and Lewis acid ($SnCl_4$, $AlCl_3$, $TiCl_4$, $Yb(OTf)_3$, BF_3) (**Scheme 2**).



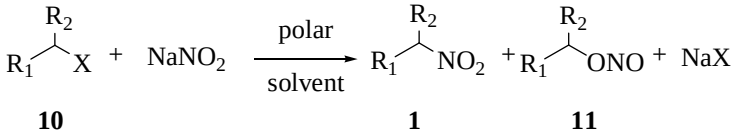
Scheme 2. Synthesis of aromatic nitro compounds

In the recent years new eco-friendly procedures have been developed by the use of solid acid catalysts, such as Nafion-H (polysulfonic acid resin),[4] Montmorillonite K-10 (acid clay)[5] or Zeolite β (**Scheme 3**).[6]



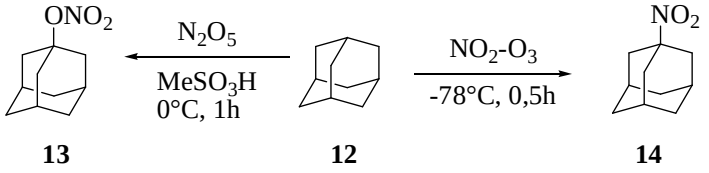
Scheme 3. Synthesis of aromatic nitro derivatives under heterogeneous conditions

Concerning aliphatic starting materials, the first procedure used for this reaction provided the nitration in gas phase producing nitromethane, nitroethane and other, at low molecular weight, derivatives.[2] Many other procedures have been reported for the synthesis of nitro compounds **1** and the most popular and most important is the reaction of primary and secondary alkyl halides **10** with metal nitrites. As metal nitrite, silver nitrite (Victor-Meyer reaction), potassium nitrite or sodium nitrite (Kornblum reaction) have been frequently used. Reactions with these nitrites provide the use of $AgNO_2$, KNO_2 or $NaNO_2$ in the presence of polar solvents, such as, DMF[7] or DMSO,[8] due to the SN_2 (nucleophilic substitutions) mechanism (**Scheme 4**).



Scheme 4. Synthesis of aliphatic nitro compounds

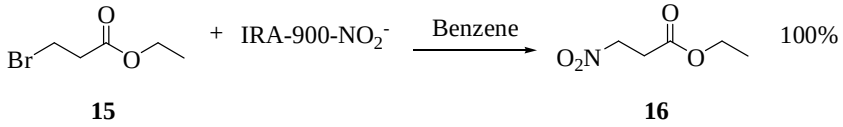
A further example is the nitration of adamantane **14** (alkane), with nitronium salts in aprotic solvents at room temperature.[9-10] This reaction proceeds by electrophilic substitution at the single bond. After that, many chemists tried to improve the yield of this reaction since that in 1996 Suzuky et al. reached 90% of the yield using nitrogen dioxide in presence of ozone at -78°C. Further, in the presence of methane sulfonic acid at 0°C, N_2O_5 reacts with the adamantane at the bridgehead position to give the nitrated products **13** and **14** (**Scheme 5**).[11-12]



Scheme 5. Synthesis of nitro adamantane

Thus, the reaction of alkyl halides and α-halo esters as well, with sodium nitrite, provides a very useful synthetic method for nitroalkane and α-nitro esters.[13]

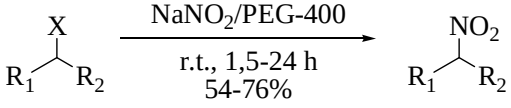
However, long reaction times, the use of cited toxic solvents and tedious work-up procedures are necessary and/or low yields are obtained. So, several new methods for the nitration process have been reported, for example, the use of nitrite ion bounded to macroporous quaternary ammonium amberlite resin (amberlite IRA-900-NO_2^-) improves the yield of the nitro compound avoiding the presence of a large amount of undesired alkyl nitrites (**Scheme 6**).[14-15]



15 **16**

Scheme 6. Synthesis of nitroesters with IRA-900-NO_2^-

Following the green chemistry philosophy, an important aspect which is receiving increasing attention is the use of alternative reaction media that circumvent the problems associated with many of the traditional volatile organic solvents (VOCs),[16] for example using PEG-400 as greener solvent. We developed a new alternative synthesis of nitro compounds using $NaNO_2$ in PEG-400 as reported in (**Scheme 7**)[17]

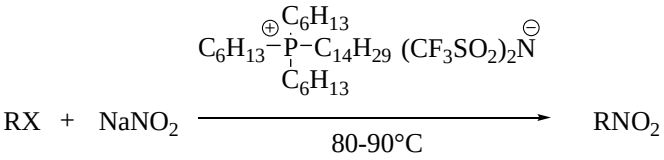


10 **1**

Scheme 7. Synthesis of nitro compounds using $NaNO_2$ in PEG-400

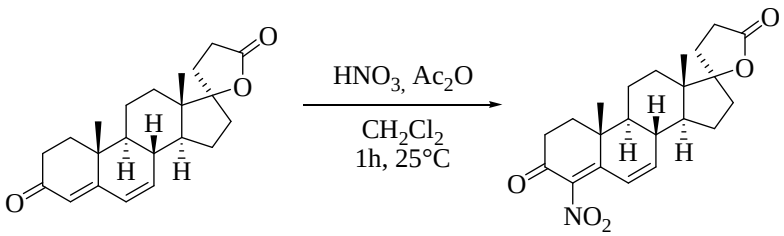
In alternative ionic liquids have been used as greener solvents, in fact, ILs may offer significant advantages in the development of environmentally benign chemical reactions by virtue of their non-flammability, thermal stability, and non-volatility.[18] Over the last few years, McNulty *et al.*[19] focused their attention on developing processes in phosphonium-salt-based

ILs with the view of exploring their general scope and exploiting their unique capabilities, in the synthesis of nitro derivatives (**Scheme 8**)



Scheme 8. ILs in the synthesis of nitro derivatives

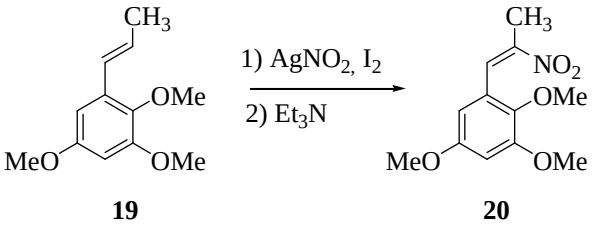
Nitration of alkenes gives conjugated nitroalkenes, which are useful and versatile intermediates in organic synthesis. The first known procedure to get nitroalkenes from conjugated derivatives provided a direct nitration of alkenes with HNO_3, but even its importance, it has never developed in the laboratory because of the lack of selectivity and decomposition of the alkene. However, one example has been reported about nitration of the steroid canrenone **17** using this preparative method in the presence of acetic anhydride obtaining good yield of the entire process (**Scheme 9**).[20-21]



17 **18**

Scheme 9. Nitration of alkenes

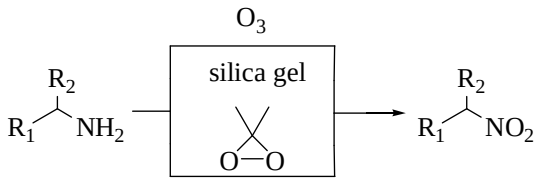
The regioselective addition of nitryl iodide to alkenes **19**, followed by base-induced elimination, give nitroalkenes as well. Nitryl iodide in fact is generally prepared in situ by the reaction of $AgNO_2$ and iodine. This method is very convenient for the synthesis of β-nitrostyrenes **20** with a large variety of functionalities (**Scheme 10**).[22-24]



19 **20**

Scheme 10. Synthesis of β-nitrosyrenes

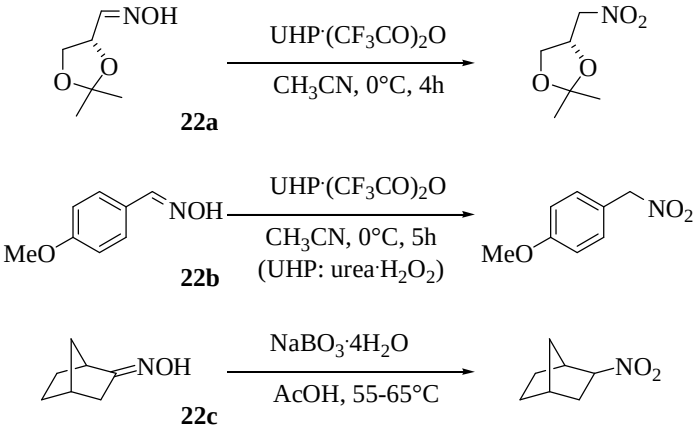
There are, different oxidation methods to get nitro derivatives from amines. Efficient synthetic procedures for the conversion of primary amines into the nitro compounds count for example, an oxidation reaction of primary amines by O_3[25-26] or dimethyldioxirane in acetone[27] or finally by oxidation using OXONE® (**Scheme 11**).[28]



21 acetone **1**

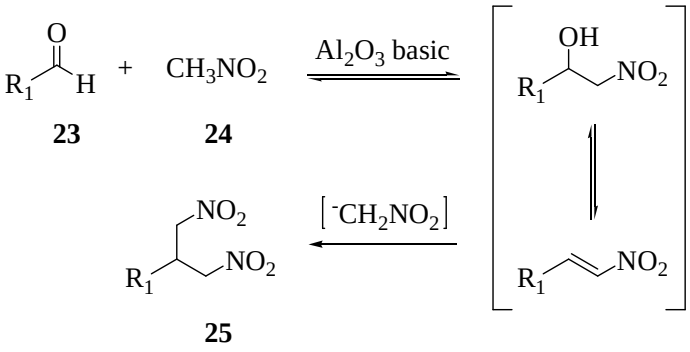
Scheme 11. Oxidation of amines to get nitro compounds

It is also possible the conversion of oximes or, well explained, the conversion of carbonyl to nitro group called retro Nef-reaction. Such conversion is generally effected via oximes using strong oxidants such as $(CF_3CO)_2O$ (**Scheme 12**).[29]



Scheme 12. Conversion of oximes into nitro derivatives

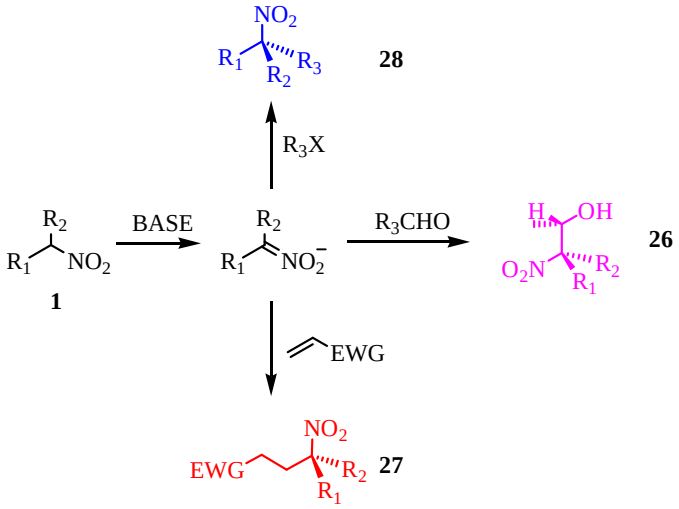
Finally, 1,3-dinitroalkanes are of e great interest because they serve as precursors of a variety of (i) 1,3-difuncionalzed molecules, (ii) omo- and hetrocycles[30] and (iii) potentially active energetic materials.[31] The standard procedure for the preparation of these compounds proceeds through the conjugated addition of nitroalkanes to pre-prepared nitroalkenes,[32] but, it is well known that the syntheses of nitrolefines are often intricate due to their reactivity and easy conversion into dimeric or polymeric derivatives. That's why, based on our experience and with the help of alumina as solid promoter, we performed the one-pot synthesis of dinitro compounds, starting from the opportune aldehydes and an excess of nitromethane, which act both, as a solvent and as nucleophile, giving the formation of nitroalkanols intermediates that convert to nitroolefines, by *in situ* dehydration. The second step is the nucleophilic attack of nitronate anion onto nitroalkenes generated, leads to the target **25** (**Scheme 13**).[33]



Scheme 13. Synthesis of dinitroalkanes

2.2.2 Reactivity of nitrocompounds

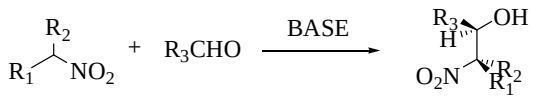
Nitroalkanes represent a formidable source of stabilized carbanions since the high electron-withdrawing power of the nitro group, which provides an outstandimg enhancement of the hydrogen acidity at the α-position.[2] Base-treatment of the nitroalkane **1** produces the corresponding nitronate anion which can be used as carbon nuchleophiles in reactions with carbonyl derivatives (Henry reaction),[34-35] Michael acceptors (Michael reaction),[36] and haloalkanes (only few methodologies are reported for the alkylation of nitronate anion, see referement),[37] leading to adducts, **26**, **27** and **28** (**Scheme 14**).



Scheme 14. Reactivity of nitro compounds

2.2.2.1 Henry reaction

Carbon-carbon bond formation is the essence of organic synthesis. The Henry reaction, the nitro-aldol reaction between aliphatic nitroalkanes **1** and carbonyl compounds (generally aldehydes) **29** to yield β-nitro alcohols **26**, discovered in 1895, represents one of the classical C-C bond-forming processes, and it has been used in many important syntheses.[38] The classical nitro-aldol reaction is routinely performed in presence of a base in an organic solvent. The reaction is generally conducted at room temperature in the presence of about 10% of base to give the desired product in good yield. The most popular bases and solvents used for this reaction are alkali metal hydroxide, carbonates, bicarbonates and alkoxids in water or ethanol[39] (**Scheme 15**).

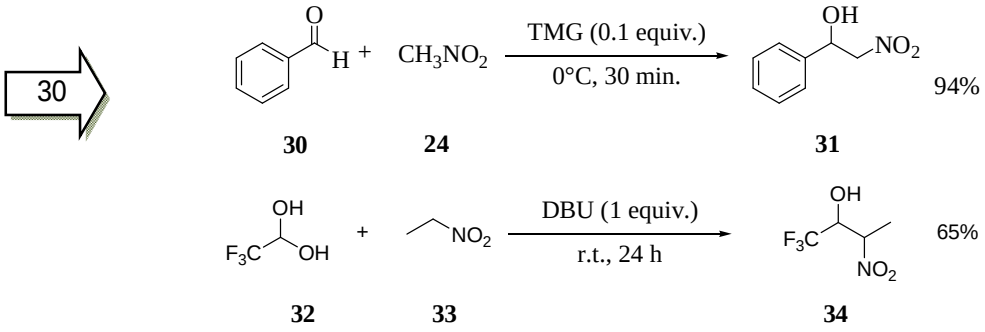


1 **29** **26**

Base: NaOR, $(Et)_3N$, DBU, DBN, TMG, Al_2O_3, KF-Al_2O_3 Amberlyst-A21, Amberlite IRA-420, NaOH+CTACl

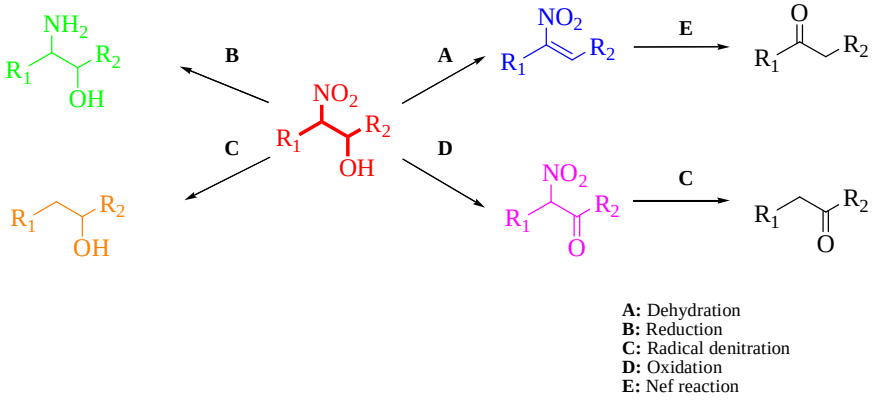
Scheme 15. General method to obtain β-nitro alcohols

Organic bases such as ammonia or various amines are very effective for the Henry reaction's. In fact, the reaction between nitro compound, an aldehyde in the presence of amine, followed by acidification, gives the desired product in good to excellent yield, examples are reported in (**Scheme 16**).



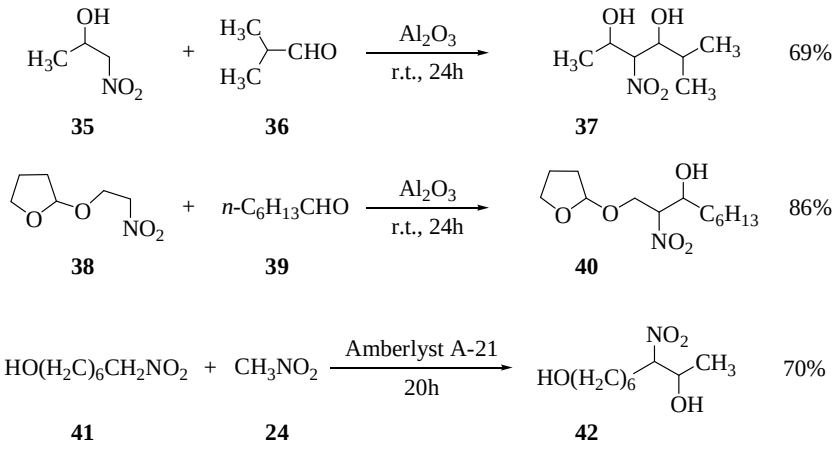
Scheme 16. Henry reaction with amines as base

As shown before, bases as tetramethylguanidine TMG,[40] 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)[41-42] in THF or acetonitrile are very effective for this kind of reaction. Since basic reagents are also catalysts for the aldol condensation and for the Cannizzaro reaction when aldehydes are used as carbonyl source, it is necessary to adopt experimental conditions to suppress these competitive reactions. This is possible with a careful control of the basicity of the reaction medium and leaving the reaction for a long time. So, it is nedeed opportune reaction conditions depending on the nature of nitro derivative and carbonyl source, for example, when aryl aldehydes are used, the β-nitro alcohol becomes an intermediate and may undergoes elimination of water to give nitroalkenes, that can be transformed later in a second step into a ketone, trough a Nef reaction. That's all is critical because the choice of reaction conditions is important to stop the reaction at the desired stage. The synthetic utility of the Henry reaction is shown in (**Scheme 17**), where β-nitro alcohols are converted into β-amino alcohols, amino sugars, ketones and other important compounds.



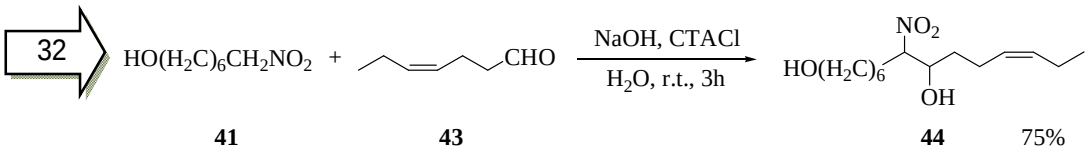
Scheme 17. Main derivatives of β-nitro alcohols

Sometimes, it is inconvenient to remove the base by acidification in the work-up procedure, because acidification may lead to the Nef reaction (as already reported). To avoid this inconvenience the reactions catalyzed in heterogeneous systems with Al_2O_3,[43-44] Al_2O_3-supported KF ,[45] and polymer-supported bases as Amberlyst A21,[46] have been developed (**Scheme 18**).



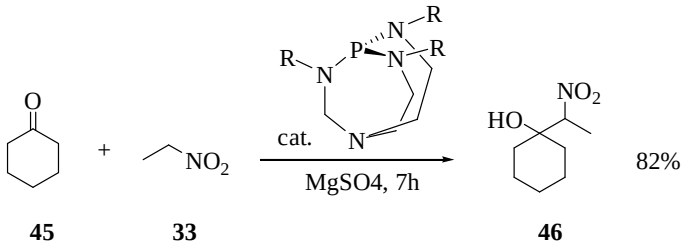
Scheme 18. Henry reaction under heterogeneous conditions

The nitro-aldol reaction can also be carry out in water using NaOH in the presence of cetyltrimethylammoniumchloride (CTACl), as a cationic surfactant (**Scheme 19**).[47]



Scheme 19. CTACl/NaOH as a cationic surfactant

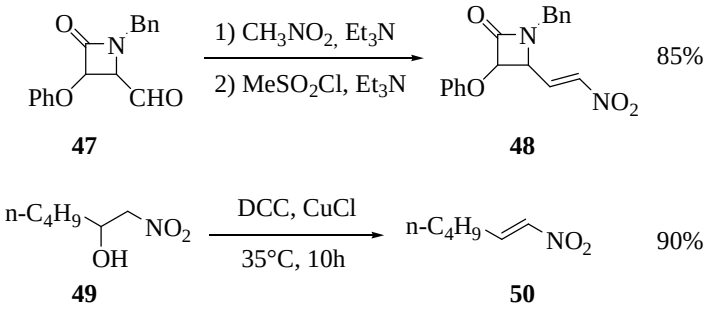
All these reactions are referred to aldehydes, just because the reaction with ketones is sensitive to steric factors and generally gives a complex mixture of products depending on the ratio of reactants, base, temperature and time. Nitroethane **33** is reactive enough toward ketones **45** to give the β-nitro alcohol **46** under various conditions (**Scheme 20**).[48]



Scheme 20. Henry reaction's with cyclohexanone **43**

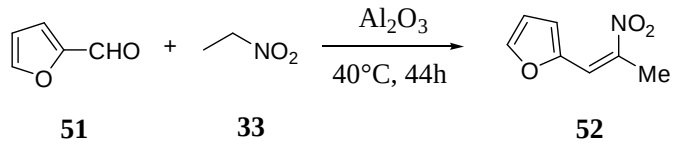
Main derivatives of β-nitro alcohols: **<u>Nitroalkenes</u>**

One of the most important method to prepare nitrolkenes is by dehydration of β-nitro alcohols, and is generally carried out by the following reagents, phthalic anhydride,[49] CH_3SO_2Cl-Et_3N, [50] dicyclohexylcarbodiimide (DCC),[51] Ac_2O-AcONa, Ph_3P-CCl_4,[52] TFFA-Et_3N.[53] Some examples are reported in (**Scheme 21**).



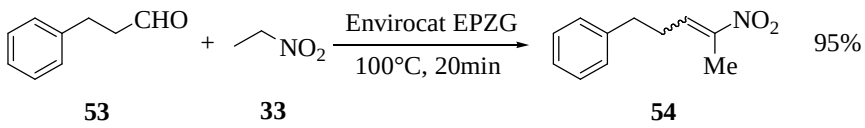
Scheme 21. Classical methods to obtain nitrolakenes

In recent years, there has been a considerable growth of interest in the catalysis in organic chemistry, in fact, other methods have been developed under heterogeneous conditions, for example, with alumina (Al_2O3) has been prepared the nitroalkene **52**, just mixing of phurfural **51** and nitroethane **33** with Al_2O_3 and subsequent warming at 40°C (**Scheme 22**).[54]



Scheme 22. Al_2O_3 as promoter for the dehydration reaction

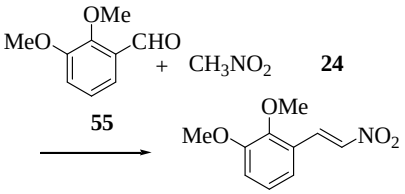
Further methods using supported reagents have also been reported, using Envirocat-EPZG, a new class of supported reagents, which exhibits both, Bronsted and Lewis acid character (**Scheme 23**).[55]



Scheme 23. Envirocat-EPZG, a new class of supported reagents

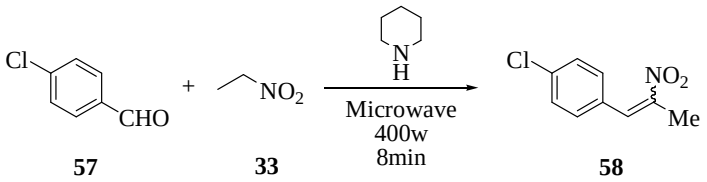
Application of ultrasound[56] and microwaves[57] permit the condensation reaction as shown in (**Scheme 24a** and **Scheme 24b**).

(a)



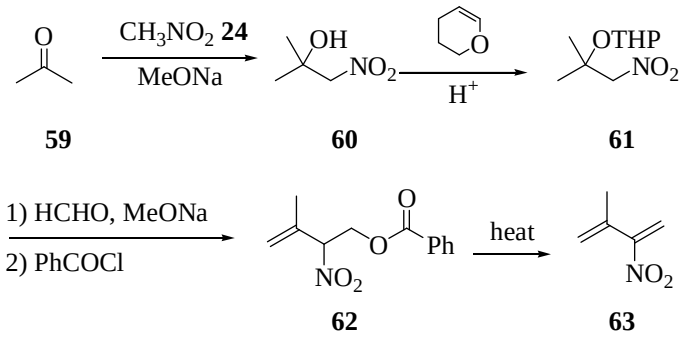
Conditions	Yield (%)
$NH_4OAc/AcOH$ 100°C, 3 h	35
$NH_4OAc/AcOH$ 22°C, 3 h))))	**99**

(b)



Scheme 24. (a) Ultrasounds and **(b)** microwave for the synthesis of nitroolefines

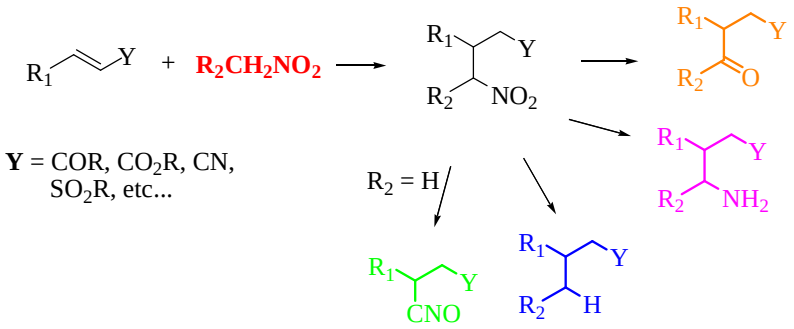
Finally, the nitro-aldol reaction followed by dehydration gives 2-nitro-1,3-dienes **63**, which are useful staring materials for cycloaddition reactions (**Scheme 25**).[58]



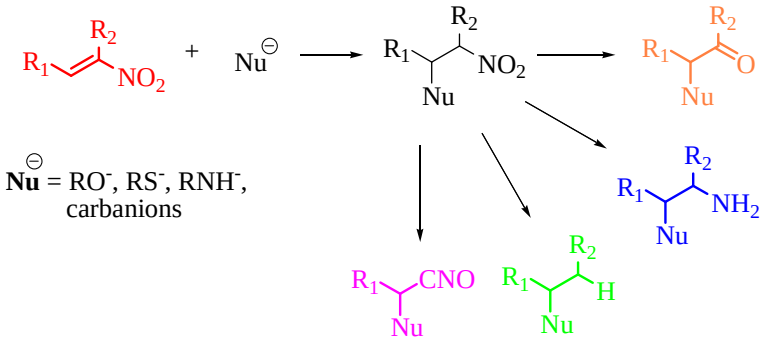
Scheme 25. Synthesis of 2-nitro-1,3-dienes

2.2.2.2 Michael reaction

The Michael reaction has attracted much attention as one of the most important carbon–carbon (C–C) bond-formation reactions in organic synthesis. Particularly, it is a completely atom-efficient procedure.[59] We can distingue two different types of this reaction, the one which provides the conjugated addition of nitroalkanes to electron-poor alkenes (**Scheme 26**) and the other one which provides the Michael addition of general nucleophiles to nitroalkenes (**Scheme 27**).



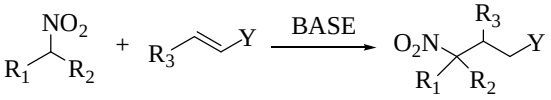
Scheme 26. Conjugated addition to electron-poor alkenes



Scheme 27. Conjugated addition to nitroalkenes

Conjugated addition of nitroalkanes to electron-poor alkenes

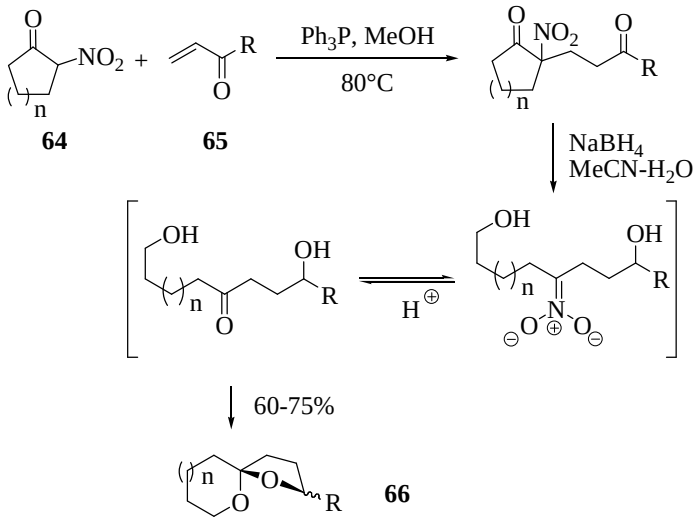
The Michael addition of nitroalkanes to electron-deficient alkenes provides a powerful synthetic tool in which it is perceived that the nitro group can be transformed into various functionalities. Various kind of bases have been used for this transformation in homogeneous solutions or, alternatively, there has been a growth interest about some heterogeneous catalysts. In general, bases used for the Henry reaction are effective also for this reaction (**Scheme 28**)[60]



Y = CO_2Et, C(O)R, CN, S(O)Ph, SO_2Ph, etc...
BASE = RO^-, F^-. $(R)_3N$. $(R)_3P$, TMG, DBU, etc...

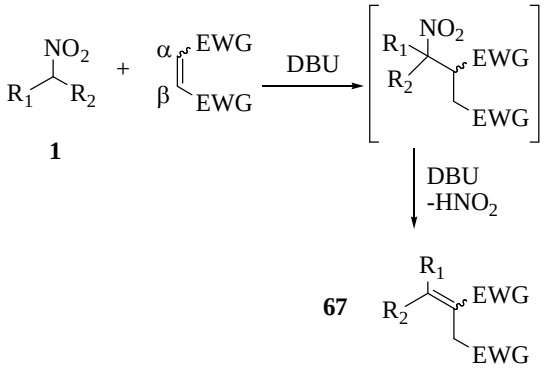
Scheme 28. Michael addition to electron-poor olefines

This behavior is very useful for the synthesis of spiroketals for example, in fact when electron-poor alkenes are very reactive, weak bases such as Et_3N or triphenylphosphine PPh_3 are reactive enough as base, so, spiro[4.5] and spiro[4.6] ketal systems **66**, can be efficiently prepared starting from α-nitro cycloalkanones **64**, commercially available or easily prepared by nitration of the corresponding ketones (**Scheme 29**).[61]



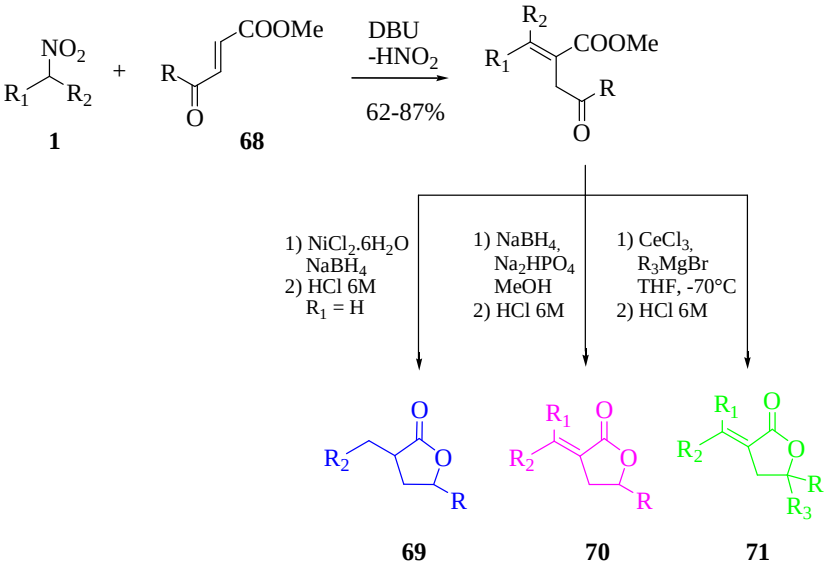
Scheme 29. Synthesis of spiroketals *via* Michael reaction

As we know, Michael reaction is one of the main approaches for the formation of a new carbon-carbon single bond, but, by the right choice of the electrophilic acceptors and the catalytic conditions, the formation of a new carbon-carbon double bond is also possible under homogeneous conditions, using TMG or DBU as bases (**Scheme 30**). It has been reported in fact, that nitroalkanes **1** react with electrophilic alkenes, having two electron-withdrawing groups in α- and β-positions, in a tandem Michael-elimination process giving unsaturated 1,4-difuntionalized derivatives **67** with enhanced *E* stereselectivity.[62,63]



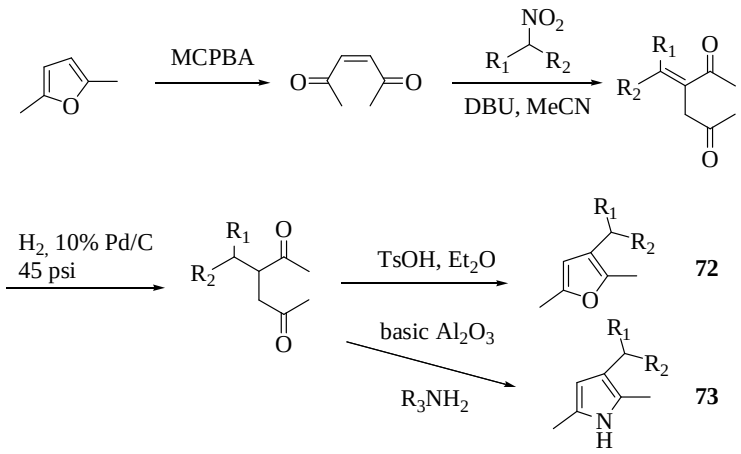
Scheme 30. Tandem Michael-elimination process

Using this strategy, a variety of important targets, such as γ-butyrolactones, furans, pyrroles, tetrahydrofurans (THFs), cyclopentadienones and nitrocyclopropanes have been prepared. γ-Butyrolactones are an important class of compounds and, of particular interest, are those having an exo-cyclic C-C double bond. Few years ago, in our laboratory have been performed the synthesis of three different γ-lactone systems **69**, **70**, **71**,[64-65] starting from the Michael addition of nitroalkanes to methyl (*E*)-4-oxopentenoate **68**, catalyzed by DBU (**Scheme 31**).



Scheme 31. Synthesis of γ-butyrolactones

Also aromatic structures can be achieved trough of this reaction, in fact trisubstituited furans[66] **72** and pyrroles[67] **73** have been obtained in homogeneous conditions (**Scheme 32**).

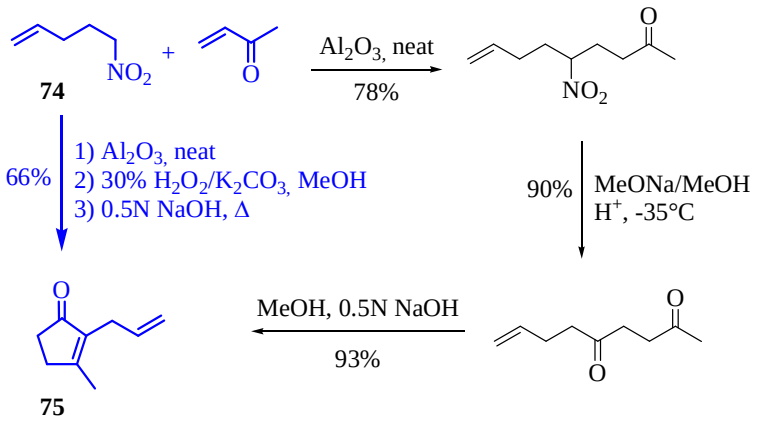


Scheme 32. Synthesis of furans and pyrroles

In the last years, it has been found that the reaction can be conveniently performed *via*:

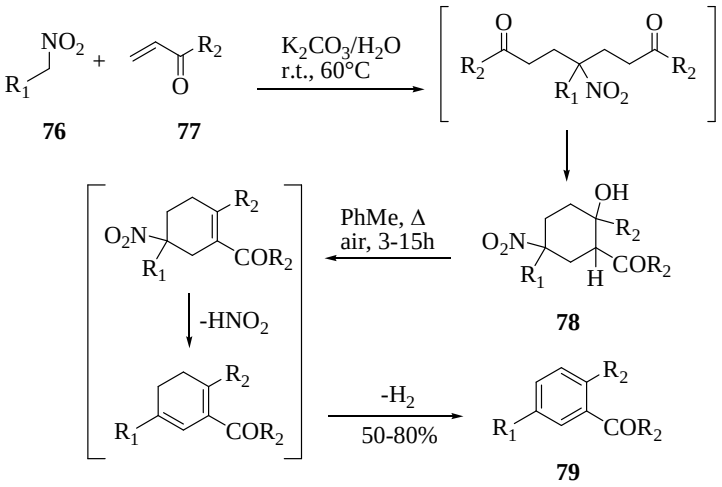
- heterogeneous catalysis, using solid catalyst, in the main cases avoiding organic solvents;
- aqueous medium, using water-diluted solution of sodium hydroxide or potassium carbonate, in the presence , or not, of catalytic amounts of surfactants.

Allylrethrone **75**, an important component of pyrethroids and a key building block for the synthesis of allethrolone and pyrethrins, has been prepared,[68] using 5-nitropent-1-ene **74** as key starting reagent, using alumina (Al_2O_3) as solid catalyst (**Scheme 33**).



Scheme 33. One-pot synthesis of allylrethrone (*blue*)

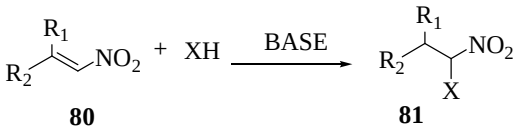
Finally, the conjugated addition of primary nitroalkanes **76** to α,β-unsaturated enones **77**, catalyzed by K_2CO_3/H_2O medium, afford the double Michael addition that undergoes an intramolecular cyclization, to get the nitrocyclohexanol **78** which can be converted at reflux on air, into the aromatic system **79** (**Scheme 34**).[69]



Scheme 34. Conjugated addition of primary nitroalkanes to α,β-unsaturated enones

Conjugated addition of nulceophiles to nitroalkenes

The use of the nitroalkenes **80** as Michael acceptors opens the way to synthetically useful C–C bond-forming reactions (**Scheme 35**).[70] Among the Michael acceptors, nitroalkenes are very attractive, because the nitro group is one of the most electron-withdrawing groups known (as already reported).[2]

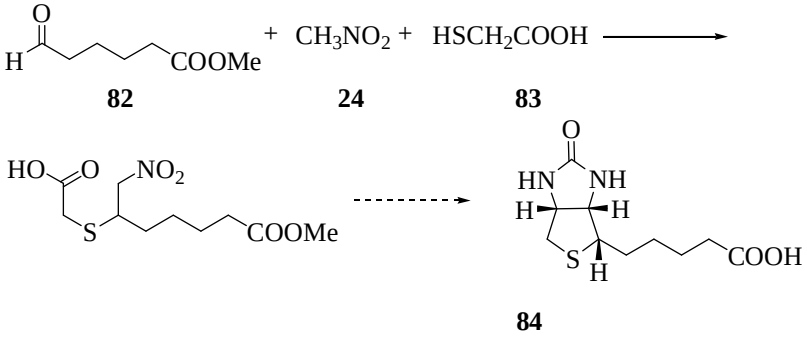


80 **81**

XH = ROH, RSH,
$(R)_2NH$, $(R)_2PH$

Scheme 35. Michael addition to nitroolefines

Many processes have been developed using nitroalkenes as intermediate for the synthesis of natural products, an example is the reaction of methyl 6-oxo-exanoate **82**, nitromethane **24** and 2-mercaptoacetic acid **83** in the presence of Et_3N.[71] β-Nitrosulfides has been obtained, which is used for the synthesis of δ-biotin **84** (**Scheme 36**).

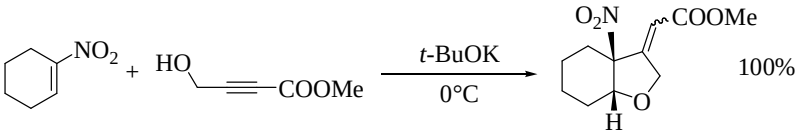


82 **24** **83**

84

Scheme 36. Synthesis of δ-biotin **84**

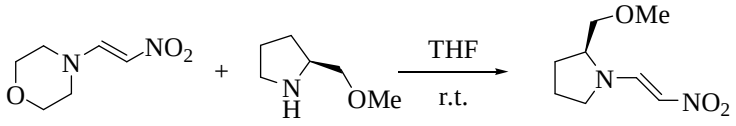
Recently, domino Michael addition initiated by oxygen nucleophiles have received much attention for the construction of octahydrobenzo[*b*]furans **87** (**Scheme 37**).[72]



85 **86** **87**

Scheme 37. Construction of octahydrobenzo[*b*]furans

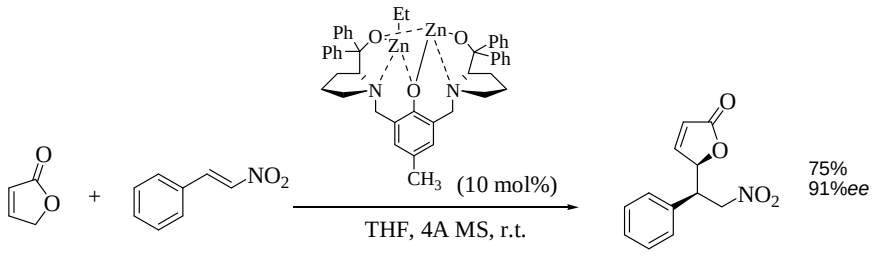
The conjugated addition of chiral nitrogen nucleophiles to nitralkenes provides access to chiral compounds having nitrogen functionalities on vicinal carbon atoms. Various natural products belong to this class of compounds, such as biotin, penicillin, and several amino acids that are components of the peptide antibiotics. Chiral nitrogen nucleophiles as (*S*)-2-methoxymethylpyrrolidine **90** and its enantiomer have been used for this reaction (**Scheme 38**).[73]



88 **89** **90**

Scheme 38. Syntheis of (S)-2-methoxymethylpyrrolidine

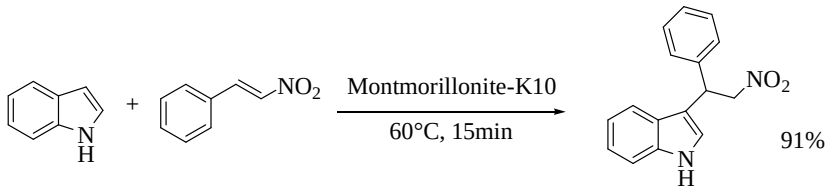
Recent efforts have been focused on the development of efficient methods to perform direct, asymmetric Michael addition reactions, and notable success has been achieved using transition metal catalysis.[74] The subsequent example is related to the reaction carried out between 2(5H)-furanone **91** as a donor, and β-nitrostyrene **92**, which permits to obtain the product **93** with a very high yield and a large enantiomeric excess (**Scheme 39**).



91 **92** **93**

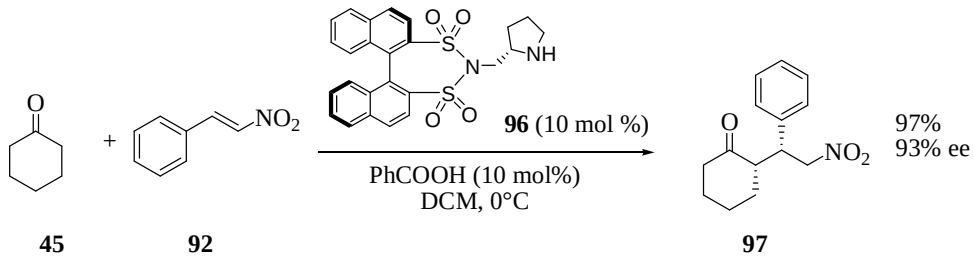
Scheme 39. Asymmetric Michael addition reaction

Also the use of heterogeneous catalyst have recived a growth interest. In (**Scheme 40**) is reported a new solvent-free process that uses Montmorillonite K10 as catalyst, concerning the reaction of indole **94** with β-nitrostyrene **92** and some other nitroolefines,[75] because the latter **95**is a versatile intermediate for the synthesis of many biologically active indole derivatives.[76-78]



Scheme 40. Michael reaction of indole and β-nitrostyrene, a new solvent-free process

Finally, a novel type of L-proline-based binaphthyl sulfonimides and sulfonamides have found to be efficient organocatalysts for the asymmetric Michael addition of ketones **45** to nitralkenes, in particular β-nitrostyrene **92**, to provide optically active γ-nitroketone derivatives **97** (**Scheme 41**).[79]



Scheme 41. Enantioselective Michael addition of ketones to nitroolefines[79]

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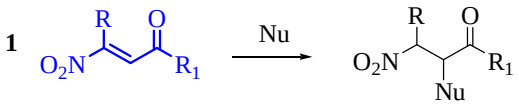
CHAPTER 3

β-NITROACRYLATES: SYNTHESIS & UTILITY

3.1 Introduction

As reported above, nitro compounds can be distingue between nucleophiles and electrophiles. Particular behavior have been demonstrated β-nitroacrylates **3** as electrophiles, in fact, they are a very useful source for the synthesis of a large variety of fine chemicals. β-Nitroacrylates[1] are a class of electron-poor alkenes having two electron-withdrawing groups in α- and β-positions. This peculiarity makes their chemical behavior more interesting with respect to the classical conjugated nitroalkenes and, in the last few years, there has been a growing interest in the chemistry of these molecules because they have been used as key building blocks for the synthesis of useful structures, including fragments of natural substances and biologically active compounds. The molecular structure presents an olefin conjugated with the nitro group, so, the carbon in the α position becomes more electropositive and it is subjected to a regioselective nucleophilic attack (**Scheme 1**).



R_1 = Alkyl or OR

Scheme 1. β-Nitroacrylates

3.2 β-Nitroacrylates: Synthesis and applications as electrophiles

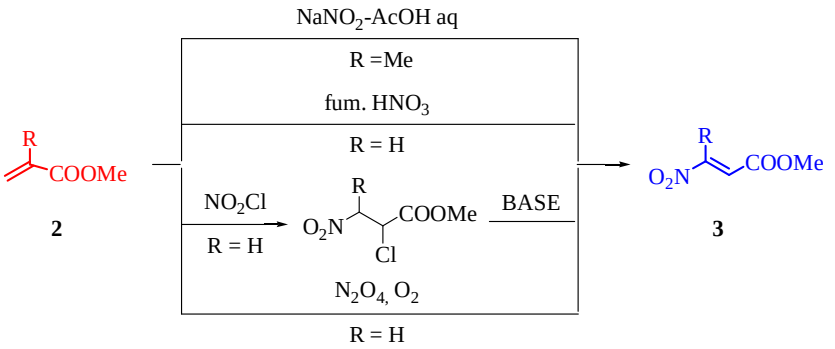
3.2.1 Synthesis of β-nitroacrylates

The synthesis of β-nitroacrylates has not been very large investigated during the last decade, in fact, although some preparations of them were reported, only recently their useful and very efficient synthesis was developed. However, we can distingue two different ways to make them:

- By nitration of acrylates;
- Via nitroaldol (Henry) reaction.

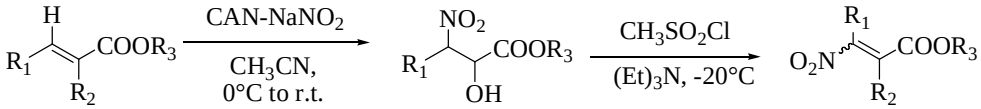
Nitration of acrylates

Initially, β-nitroacrylates were synthetized starting from acrylate systems and nitryl chloride.[2] After that other alternative processes were developed using different nitrating agents, such as, dinitrogen teroxide,[3] nitrous acid,[4] and fuming nitric acid,[5] (**Scheme 2**).



Scheme 2. β-Nitroacrylates starting from acrylate systems

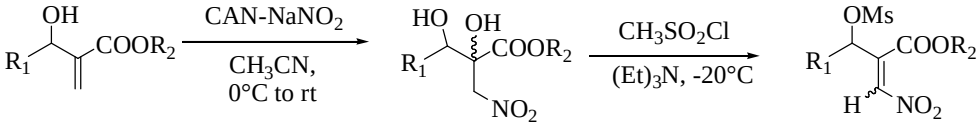
Recently, Vankar *et al.*[6] following their studies onto nitro compounds found that the system CAN ($NaNO_2$-ceric ammonium nitrate) could be a very efficient nitrating agent for a large variety of acrylic esters, in fact, as reported in (**Scheme 3**) several nitro derivatives can be obtained through out this way, being the starting material alkylic or cynnamic esters.



4 **5** **6**

Scheme 3. Nitration of acrylic esters using CAN

Furthermore, with the goal to extend their work, also acrylic esters derived from the Baylis-Hilman reaction were tested (**Scheme 4**). So, the corresponding diols were obtained, and then dehydrated into the corresponding β-nitroacrylates.



7 **8** **9**

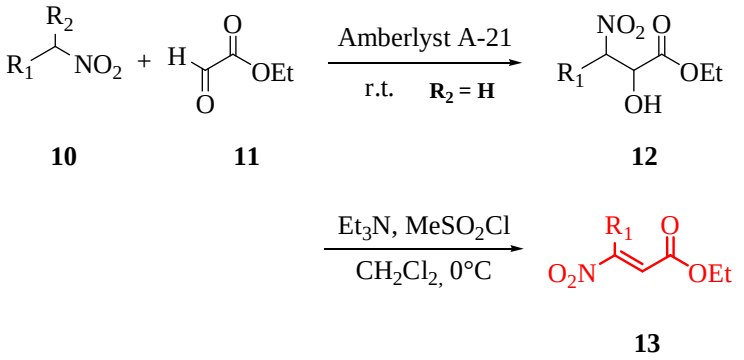
Scheme 4. Nitration of acrylic esters derived from the Baylis-Hilman reaction

Nitroaldol reaction (Henry reaction)

Taking into account that all these procedures were demonstrated to be a valuable source for the synthesis of β-nitroacrylates, it should be note that in our laboratory we developed a new method to synthesize these compounds in a very easier way. In fact, we exploited a well known reaction between carbonyl compounds and nitro compounds, in order to perform a new efficient two-step synthesis of β-nitroacrylates. The first step, is the reaction between nitroalkanes **10** and ethyl glyoxalate **11**, under heterogeneous conditions by using Amberlyst A-21 as a solid base,[7] followed by a dehydration step to nitroalkenes **13** (mainly as *E* isomer) by mesylation of

50

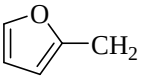
the hydroxyl group, and subsequent basic elimination of methanesulfonic acid (**Scheme 5**).[8]



Scheme 5. Synthesis of β-nitracrylates through the Henry-elimination two-step sequence

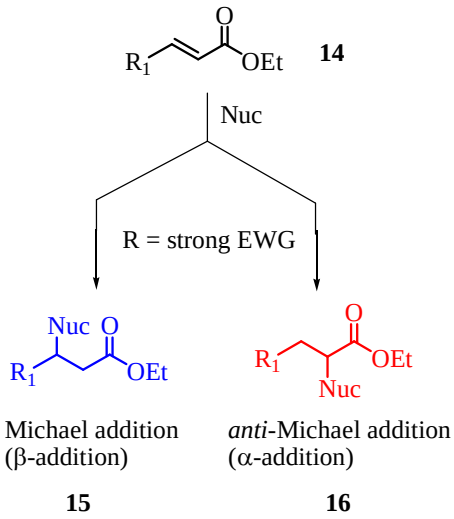
We tested different nitroalkanes as reported in **Table 1**, the yields are good (65-94%) even in the presence of other functional groups such as ketone, ketal, ester and heteroaromatic systems.

Table 1. Synthesis of β-nitroacrylates

R_1	Yield (%) of **12** (reaction time)	Yield (%) of **13**
Et	75(18)	85
n-Pr	70(16)	87
n-Bu	76(16)	86
$PhCH_2$	82(17)	71
	73(19)	87
$CH_3C(OCH_2)_2(CH_2)_2$	78(20)	73
	80(18)	94
Ph	87(21)	71

3.2.2 Reactivity of β-nitroacrylates

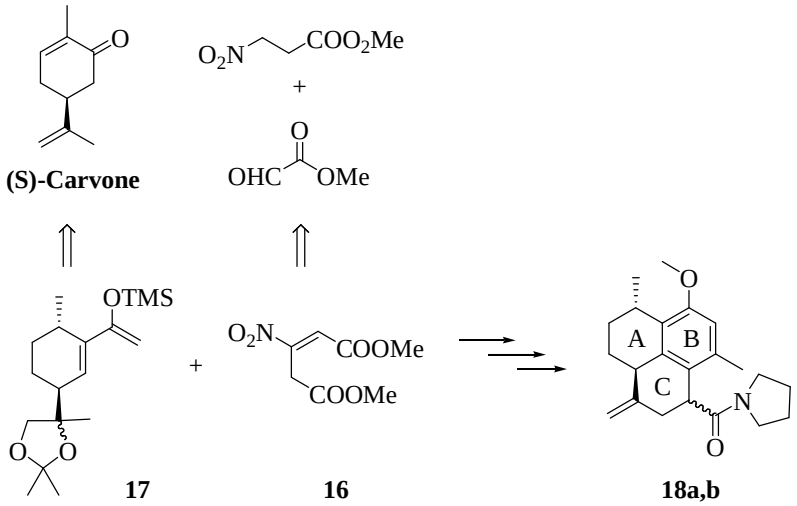
As reported in the last chapter, the conjugate addition of nucleophilic species to α,β-unsaturated compounds is a fundamental concept in organic chemistry. Among the large variety of C-C bond forming reactions, the Michael addition, also called 1,4-addition, is especially valuable for selectively creating a new bond at the β position of activated olefins **14**. When we take into account β-nitroacrylates, we will have the completely reverse of the medal, or else, in the presence of both the nitro group at the β position and the ester at the α position onto the alkene species, the regioselectivity of the nucleophilic attack is inverted, so the α position results activated. In this case we will get the product **16** (**Scheme 6**). This is known as *anti*-Michael reaction, *contra*-Michael addition, abnormal Michael reaction or simply, attack at α carbon.



Scheme 6. Regiospecific C-C (or C-heteroatom) bond formation of an activated olefin

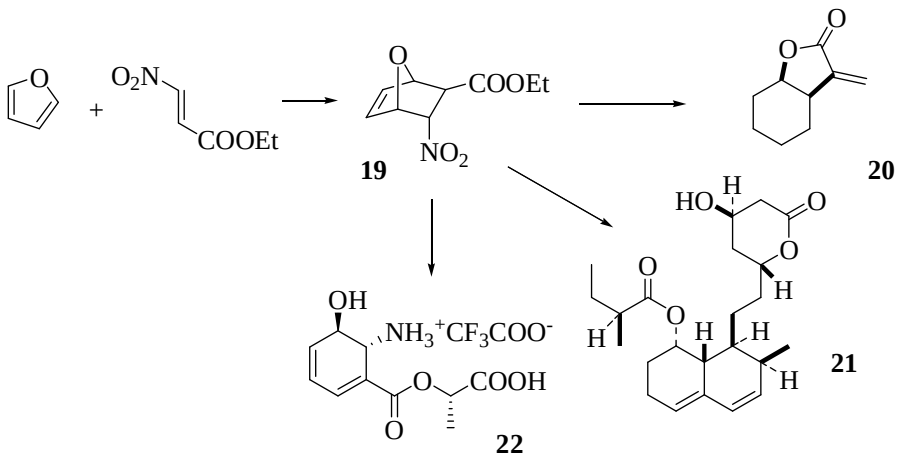
Dield-Alder reaction of β-nitroacrylates

One of the most important reactions of β-nitroacrylates is the cycloaddition with conjugated dienes, so, they are of special interest due to the presence of the ester functionality. In this context, Koz Kozikowski and Wu[9] developed an enantioselective approach to get analogues structures (**18a,b**) of the pseudopterosins family, that possess both potent *anti*-inflammatory and analgesic properties,[10-11] *via* the Diels-Alder reaction of β-nitroacrylate **16** with the diene **17** (**Scheme 7**).



Scheme 7. Syntheis of analogues structures (**18a,b**) of the pseudopterosins

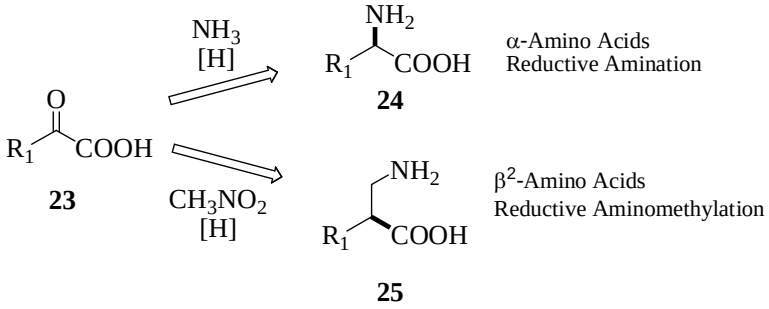
Furans have also been used as dienes, in the reaction with nitroacrylates, yielding a mixture of cycloadducts, favoring the *endo* nitro isomer **19** (**Scheme 8**), then this compound can be transformed into (i) α-methylenebutyrolactone **20** which constitutes the main fragment of a number of sesquiterpenes,[12] (ii) compactin **21** which is an important metabolite participating to the biosynthesis of cholesterol,[13] and (iii) oryzoxymycin **22** which exhibits antibacterial effects with respect to *Xanthomonas oryzae*.[14]



Scheme 8. Synthesis of cycloadducts **20, 21, 22**

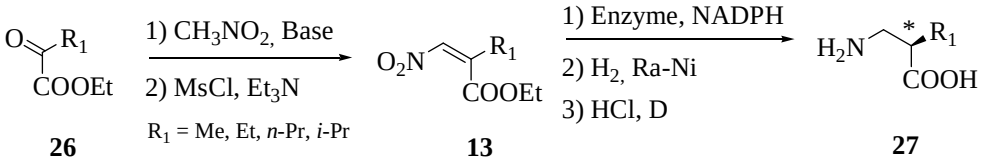
Synthesis of β²-amino acids and β-substituited α-amino acids

β²-Amino acids are a growing synthetic targets because peptides containing these residues can assume different structures than those of α-amino acids and their peptide bonds resist to protease degradation.[15] In contrast to α-amino acids, for which a variety of reliable, high-yielding methods have been devised, β²-amino acids remain challenging synthetic targets. In analogy to an enzymatic reductive amination of α-cheto acids **23** with ammonia, a hypothetic reductive amino-methylation with nitromethane should lead to β²-amino acids **25** (**Scheme 9**).



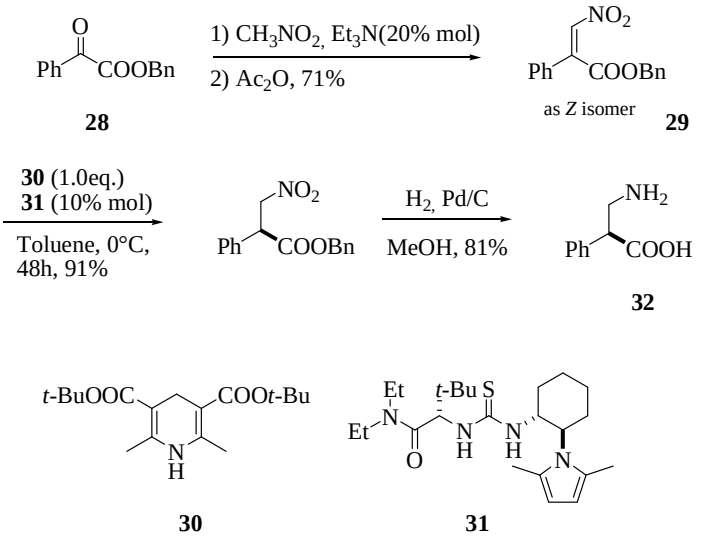
Scheme 9. Synthesis of α-amino acids and β²-amino acids

The reduction of β-nitroacrylates is one of the most important reaction, concerning these derivatives, because following this way we can prepare a collection of other functionalities in which the nitro group could be kept or coulde be transformed into an amino group. Stewart *at al.*[16] developed a reduction of β-nitroacrylates by *Saccharomyces carlsbergensis*-old yellow enzyme as reported in (**Scheme 10**).



Scheme 10. Reduction of β-nitroacrylates by *Saccharomyces carlsbergensis*

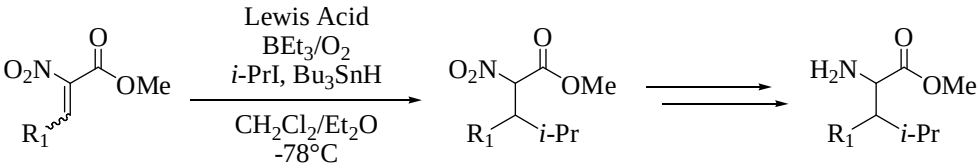
Further, a highly enantioselective conjugate reduction of β-nitroacrylates, has been performed, using Jacobsen-type thiourea **31** as a suitable catalyst.[17] The α-ketoester **28**, reacts first with nitromethane in the presence of Et_3N (20% mol) in order to get the nitroacrylates **29**, then treating **29** with Hantzsch ester **30** and thiourea **31**, and by subsequent reduction, we will have the desired product **32** (**Scheme 11**).



Scheme 11. Highly enantioselective conjugate reduction of β-nitroacrylates

β-Substituited α-amino acids are also very important, because they are present in several peptidic natural products,[18] Several methods have recently been devised for their preparation,[19] including some that employ conjugate additions to α,β-unsaturated amino acid precursors.[20-22]

Castle *et al.*[23] reported that α-substituted α,β-unsaturated α-nitro esters and amides are viable substrates in, Lewis acid promoted, radical conjugate additions,[24] as shown in (**Scheme 12**).

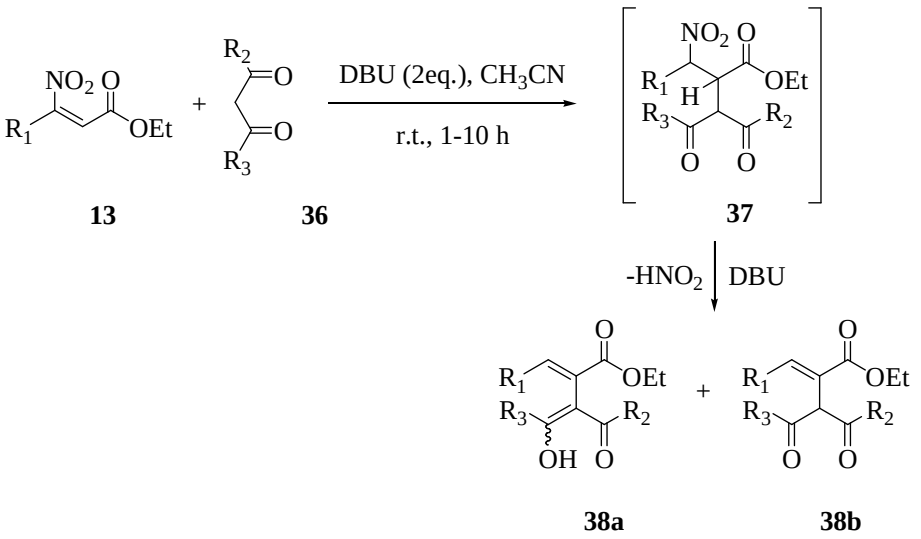


33 **34** **35**

Scheme 12. Radical conjugate addition, Lewis acid promoted, onto nitroacrylates

Carbanions as nucleophiles with β-nitroacrylates

With the aim to generate new C-C bonds and consequently, a wide variety of fine chemicals, consideration has been focused toward the reaction of β-nitroacrylates, as *anti*-Michael acceptors, with carbanions. The first example is relative to the synthesis of highly polyfuctionalized α,β-unsaturated esters, that are of a great importance in organic synthesis[25] since they can be further functionalized by the Michael or Diels-Alder reactions giving access to valuable molecules of considerable interest, especially in the synthesis of natural products.[26-27] The procedure[28] is based on a domino 'Michael addition-elimination' process and the key point is the simultaneous behavior of the nitro group as both an electron-withdrawing group and a good leaving group. The presence of (i) an acidic hydrogen in the α-position to the ester functionality, (ii) a nitro group in the vicinal position with respect to the acidic hydrogen and (iii) a base, induces the *in situ* elimination of nitrous acid, with the one-pot formation of polyfunctionalized α,β-unsaturated ester **38a,b** (**Scheme 13**)

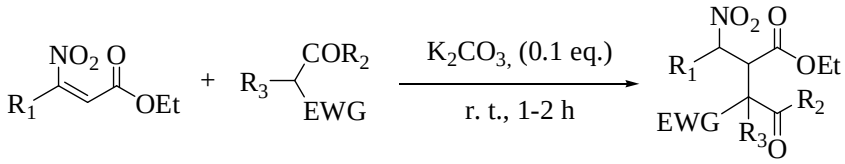


13 **36** **37** **38a** **38b**

Scheme 13. Synthesis of polyfunctionalized α,β-unsaturated esters

Another application of the 3-nitroalkenoates is also the synthesis of polyfunctionalized nitroalkanes. Nitroalkanes, as reported in the last chapter, are an important class of starting materials for the generation of both other functionalities and new C-C bonds.[29-31]

Thus, as reported in literature, in many processes happen that, the reaction conditions help the *in situ* elimination of the nitro group, and this behavior represent a loss of both, atom efficiency and also a loss due to the easy conversion of this group into important and useful other functionalities. Recently, in our laboratory, has been optimized a new method that permits the reaction between β-nitroacrylates **13** and active methylene compounds **39**, in the presence of catalytic amount of K_2CO_3 (**Scheme 14**).



13 **39** **40a-e**

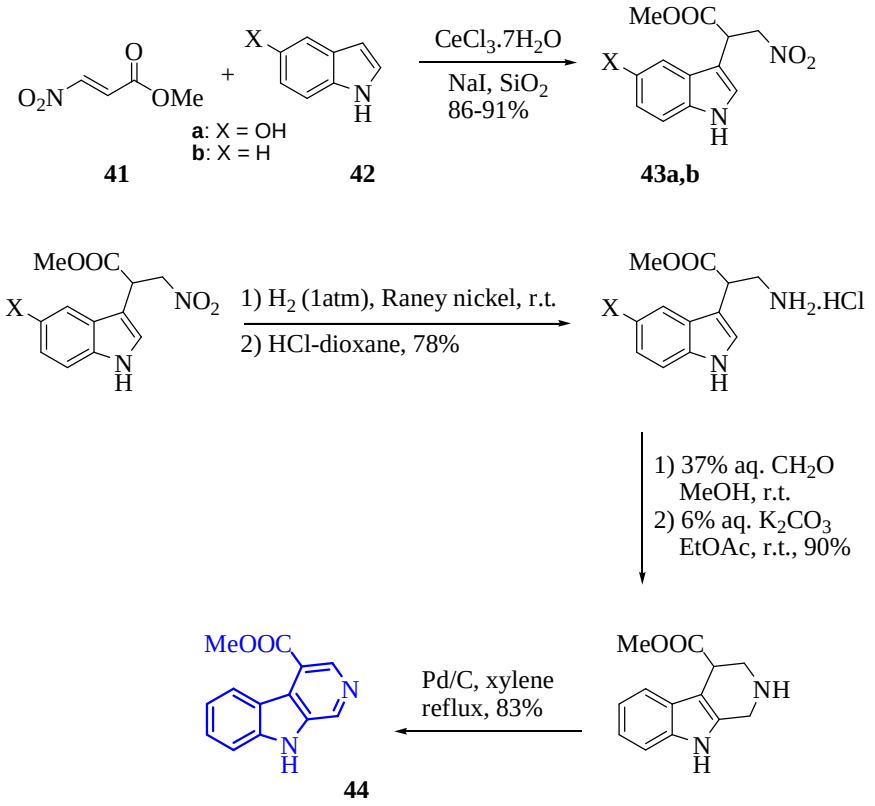
Scheme 14. Synthesis of polyfunctionalized nitroalkanes **40a-e**

Under these mild, solvent-free conditions various polyfunctionalized nitro derivatives **40a-e** are obtained in high yields (75-95%, **Table 2**), *via* an *anti* Michael reaction and with complete chemoselectivity since no elimination of nitrous acid from the adducts is observed.

Table 2. Synthesis of various polyfunctinalized nitro derivatives

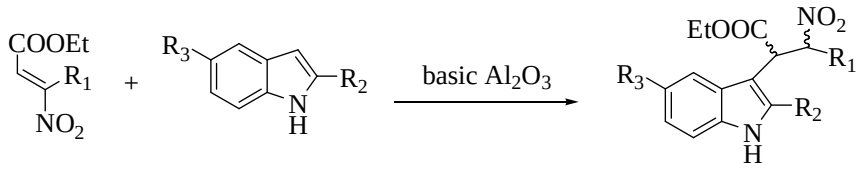
	R_1	R_2	R_3	EWG	Yield (%) of **40**
a	Et	Me	H	COMe	75
b	Me	EtO	H	COOEt	85
c	*n*-C_5H_{11}	EtO	H	CN	87
d	Ph	EtO	H	CN	84
e	$Ph(CH_2)_2$	EtO	H	CN	94

Also the reaction with indoles exploited by Bartoli *et al.*[32] is important because permits to incorporate functionalized substituents at the 3th position of this heterocycle. They studied the reactivity of indole with electron-poor olefins under $CeCl_3.7H_2O$-NaI-SiO_2 catalysis, and found that *trans*-β-nitroacrylate **41** reacts with indole **42** (**Scheme 15**) giving the adducts **43a,b**, then, this result has been applied to the synthesis of β-carbolines **44** which represent a large group of biologically active alkaloids widespread in nature.[33-35]



Scheme 15. Synthesis of β-carbolines

For this reason, due to the great importance of the target **43**, the study of this reaction allowed to perform a new method, under heterogeneous conditions, using basic alumina (basic Al_2O_3) as reported in (**Scheme 16**) and **Table 3**.



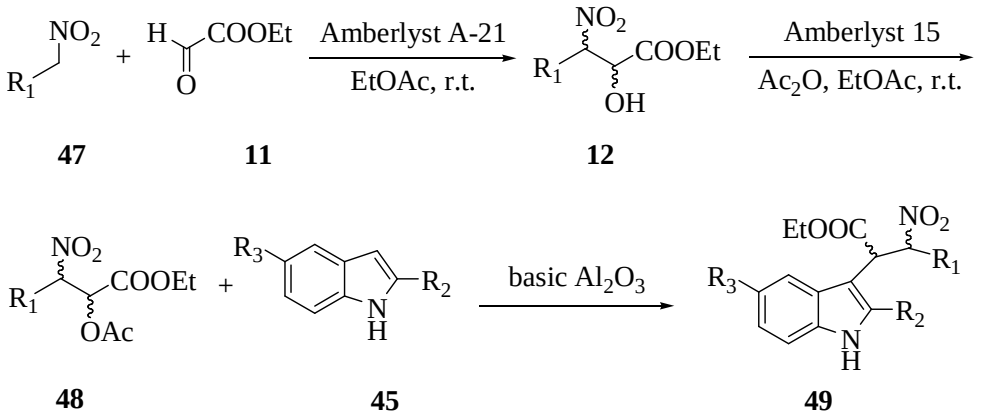
13 **45a-e** **46a-e**

Scheme 16. A new method, under heterogeneous conditions, to synthesize **46 a-e**

Table 3. Generality of the method

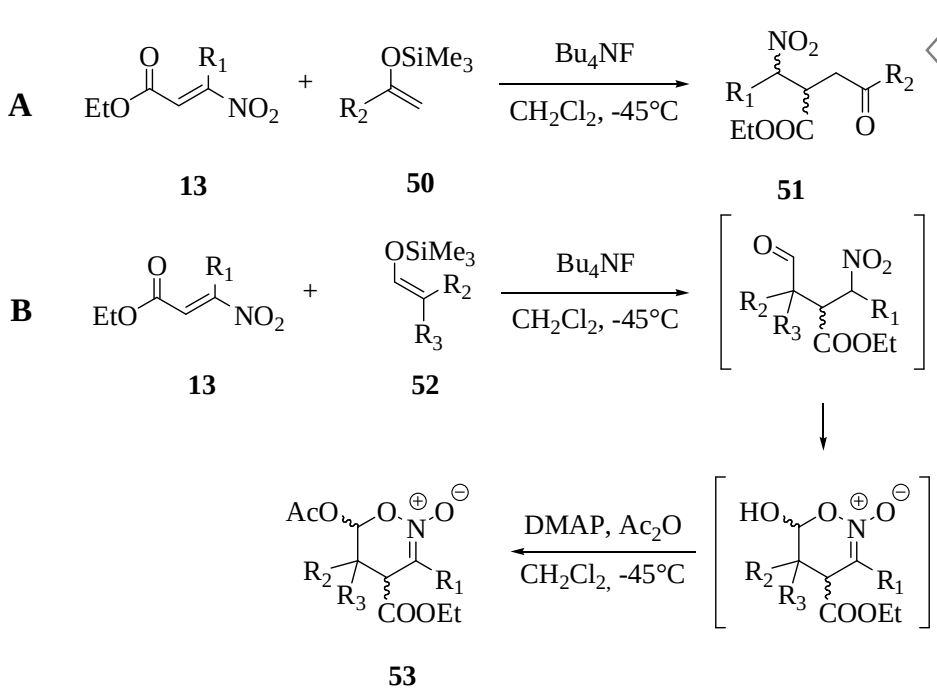
	R_1	R_2	R_3	Yield (%) of **46**
a	Me	H	H	90
b	*n*-Pr	H	OMe	88
c	*n*-Bu	H	H	94
d	*n*-Bu	Me	H	92
e	$AcO(CH_2)_3$	H	OMe	91

We reported further studies about the optimized overall procedure relative to the addition of β-nitroacrylates to indoles,[36] starting from the nitroaldol condensation of nitroalkanes **47** with ethylglyoxalate **11**, carried out under totally heterogeneous conditions with Amberlyst A-21 as basic promoter, the second step is carried out in acidic conditions with Amberlyst 15 (a macroreticular resin endowed with acid character, which is able to promoter the acetylation process) in the presence of Ac_2O, which is able to promote the acetylation process of **12** to **48**. The latter is then converted into the target **49**, under basic Al_2O_3 (**Scheme 17**).



Scheme 17. The optimized overall procedure relative to the addition of β-nitroacrylates to indoles

Finally, is important to take into account also the *anti*-Michael addition of silyl enol ethers to β-nitroacrylates, in fact, these compounds are an important class of stabilized carbanions very useful for the introduction of carbonyl functionalities. The useful reaction between them, permits to obtain both, polyfuctionalized β-nitro esters **53**, used as intermediates for the preparation of natural products[37-38] or 1,2-oxazine-2-oxide **55**, useful for the subsequent synthesis of pyrrolizidine, pyrrolidines, β-lactames-*N*-oxide, etc., the whole processes depending on the nature of the starting silyl enol ethers (**Scheme 18**).[39]

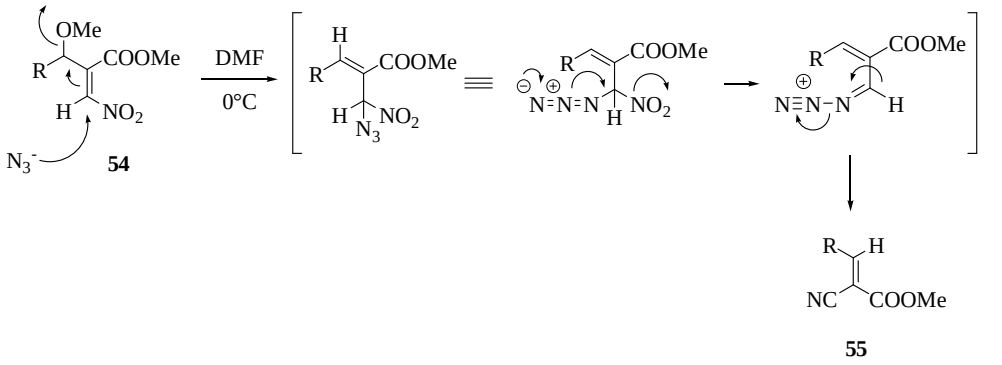


Scheme 18. *Anti*-Michael addition of silyl enol ethers to β-nitroacrylates

Heteroatoms as nucleophiles with β-nitroacrylates

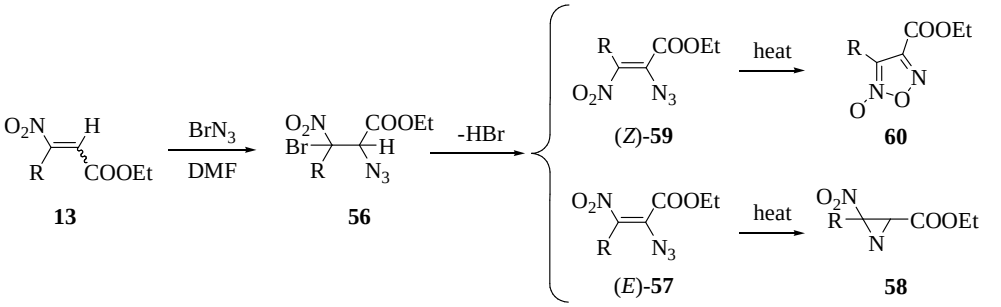
The *aza*-Michael reaction is generally perceived as one of the most important C-N bond-forming processes in organic synthesis, and β-nitroacrylates appear to be a very interesting class of nucleophilic acceptors. The only thing is that the common procedures require basic or acidic acvtivators,[40] however, to avoid the side reactions a large number of alternative methods have been developed.

The reaction between β-nitroacrylates and sodium azide (NaN_3) is the oldest method to obtain this kind of C-N bond that lead to the formation of the corresponding cyano derivatives **55** in a one-pot procedure and in a highly stereoselective (*E*-isomers) way.[41] The relative mechanism is shown in (**Scheme 19**).



Scheme 19. The reaction between β-nitroacrylates and sodium azide (NaN_3)

Bromine azide is also a useful nucleophile with β-nitroacrylates, because their reaction provides important synthetic opportunities such as the one-pot formation of 2-azido-3-nitro-2-alkenoates (*E*)-**57** and of oxadiazole 2-oxide **60** in moderate yields (**Scheme 20**).[42]

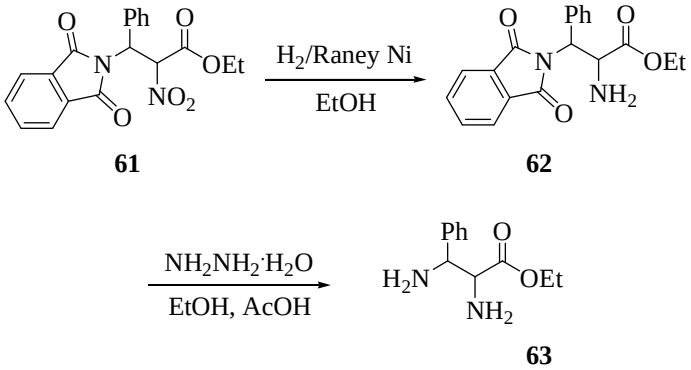


Scheme 20. BrN_3 as useful nucleophile with β-nitroacrylates

Thus, treating bromine azide with β-nitroacrylates, polyfunctinalized nitroalkenes, **57** and **59**, and heterocyclic derivatives, **58** and **60**, can be easly obtained.

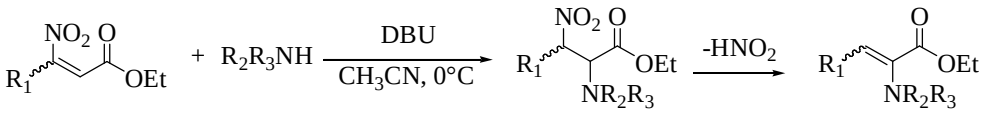
Further, the reaction of these derivatives with ammonia or amines developed in our laboratory, permits to achieve an excellent synthesis of β-nitro-α-amino esters. The latter, are an important class of building blocks for the synthesis of a large variety of targets such as (i) α,β-dehydro-α-amino acids, [43] which are common components of naturally occurring peptides[44] and (ii) β-nitro-α-amino acids that have been studied as enzyme inhibitor[45]

and as precursors in the synthesis of a variety of α-amino acids and diamino acids.[46-47] In order to extend the last work about β-nitro-α-amino esters, Lewandowska *et al.*[48] reported a new procedure on the nucleophilic addition of *N*-pronucleophiles to β-nitroacrylates as Michael acceptors in a new approach towards the synthesis of 2,3-diamino (**Scheme 21**) and 2,3-dehydroamino acid derivatives **63** and **65**(**Scheme 22**).



61 **62** **63**

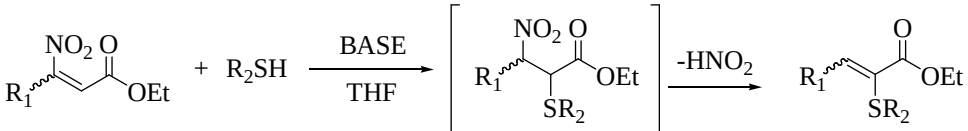
Scheme 21. Synthesis of 2,3-diamino acid derivative **63**



13 **64** **65**

Scheme 22. Synthesis of 2,3-dehydroamino acid derivative **65**

Finally, the α-addition of alkyl or aryl thionucleophiles to β-nitroacrylates, in the presence of TEA (triethylamine) or DBU, produce α-thio-α,β-unsaturated alkenoates. The α-thioacrylates have been used as Michael acceptors[49] and as nucleophiles in Diels-Alder reactions.[50] They usually have been synthesized by procedures that involves multistep reaction such as: (i) condensation of α-phenylthio acetate carbanions with aldehydes or ketoness,[51] or (ii) nucleophilic substitution-Wittig reaction of α-hypervalent iodine functionalized phosphonium yilide.[52] Thus, in this new one-pot way, it is important to note that, by choosing suitable reaction conditions, the *anti*-Michael reaction take place, and these conditions are able to drive the entire process to the thio nitro adducts **67** or the α-thio-α,β-unsaturated targets **68** (**Scheme 23**)



13 **66** **67** **68**

Schema 23. α-Addition of thionucleophiles to β-nitroacrylates

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CHAPTER 4

PhD WORK

ONE-POT SYNTHESIS OF HOMO- & HETEROCYCLE COMPOUNDS, NEW SYNTHETIC METHODOLOGIES

"RINGS IN MOLECULES MAKE THE DIFFERENCE"

4.1 Introduction

At the beginning of the new century, a shift in emphasis in chemistry is apparent with the desire to develop environmentally benign routes to a myriad of materials.[1] Green chemistry approaches hold out significant potential not only for reduction of waste formation and lowering of energy costs, but also in the development of new methodologies toward previously unobtainable materials by using existing technologies.[2,3] Of all the existing areas of chemistry, medicinal and pharmaceutical chemistry, with their traditionally large volume of waste/product ratio, are perhaps the most ripe for greening.[4] The synthesis of complex molecules is traditionally performed by a sequence of separate steps, each of which requires its own conditions, reagents, solvent, and promoter. After each reaction is complete, the solvent and the waste products are removed and discarded, and the intermediate product is separated and purified. Environmental and economic pressures are now forcing the chemical community to search for more efficient ways of performing chemical transformations.[5] These chapter can be addressed by the development of new synthetic methods, which, by bringing together simple components, can generate complex structures in one-pot way, as much as possible following the way that occurs in nature. We studied six different procedures concerning the development of new synthetic methodologies that lead to homo- and heterocyclic systems. This involvement about homo- and heterocycle derivatives is because they constitute the largest group of organic compounds and are becoming ever

more important in all aspects of pure and applied chemistry, further they are of immense importance biologically, industrially, and indeed to the functioning of any developed human society. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic, as are countless additives and modifiers used in industries as varied as cosmetics, information storage, and plastics.

Naturally occurring heterocyclic compounds are extremely common as, for example, most alkaloids, sugars, vitamins, DNA and RNA, enzymic cofactors, many of the components of coal tar, many natural pigments (such as indigo, chlorophyll, hemoglobin, and the anthocyanins), antibiotics (such as penicillin and streptomycin), and some of the essential amino acids (for example tryptophan), and many of the peptides (such as oxytocin). Some of the most important naturally occurring high polymers are heterocyclic, including starch and cellulose. Nevertheless, the major groups of natural products that are not mainly heterocyclic are the fats and most of the terpenes, steroids, and essential α-amino acids, though exceptions exist.

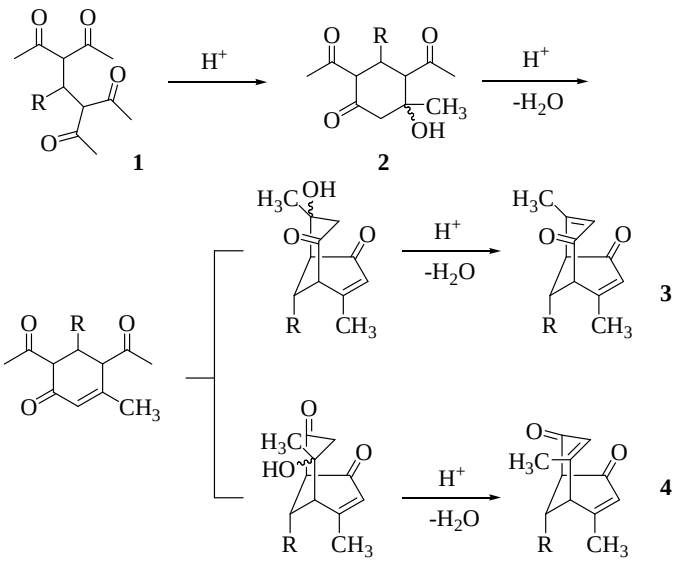
4.2 Classical bicyclo[3.3.1]nonanes synthesis & their applications

Polycarbocyclic compounds occupy a unique niche in the annals of synthetic organic chemistry. Compounds of this type collectively have been cataloged to the category of "natural products". Many derivatives possess high molecular symmetry, and the artist that resides in the soul of many synthetic chemists finds beauty and challenge therein.

Thus, an efficient construction of cyclic structures is an essential part of the biologically important natural products syntheses and various cyclization approaches[6] have been developed. That's why the chemistry of bicyclo[3.3.1]nonanes has received much attention from synthetic point of view. These compounds are of interest because of their relation with natural products (alkaloids) as well as with adamantanoid compounds. In particular 3- and 3,7-subsituted bicyclo[3.3.1]nonanes are potential precursors of adamantane derivatives. Particular attention is focused on 3,7-subsituted compounds, and the synthesis of these compounds can be easily classified into five general types, inherent to the structure of the basic system; namely:

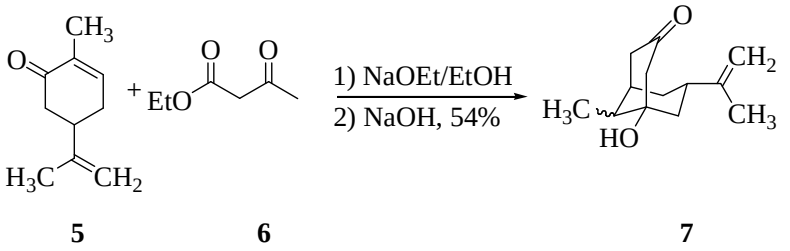
i) annulations of cyclohexane derivatives;
ii) annulations of cyclooctane derivatives;
iii) ring cleavage of adamantane derivatives;
iv) skeletal isomerization reaction;
v) synthesis starting from other bicyclo[3.3.1]nonanes.

Condensation of formaldehyde, acetaldehyde, or benzaldehyde with acetylacetone gives a product **1**, which upon acidic dehydration gives-probably *via* the cyclohexane derivative **2** the bicycle products **3** and **4** (**Scheme 1**).[7,8]



Scheme 1. Synthesis of bicyclo[3.3.1]nonanes *via* cyclohexanone derivative

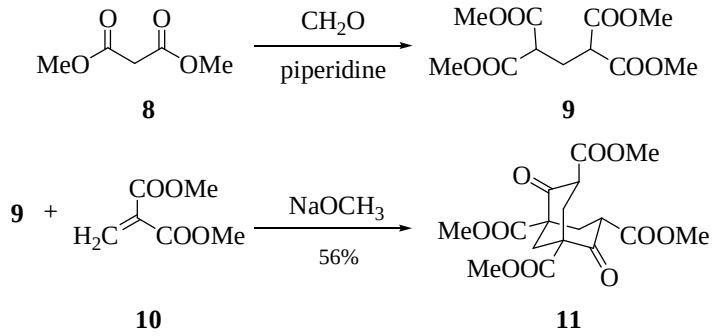
One of the first synthesis of a bicyclo[3.3.1]nonane, starting from a certain cyclohexane derivative, is the base catalyzed condensation of the terpene Carvone **5** with ethyl acetoacetate **6**.[9,10] The reaction proceeds via consecutive Michael addition, aldol condensation and decarboxylation (**Scheme 2**).



Scheme 2. Catalyzed condensation of the terpene Carvone

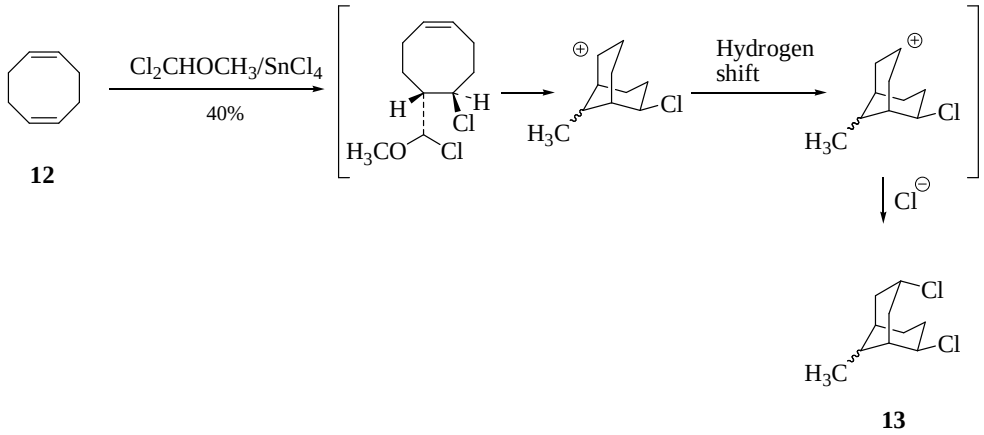
Another early representative of bicyclo[3.3.1]nonane compounds has been Meerwein ester **11**.[11] Meerwein ester has been a precursor in the syntheses of adamantane derivatives.[12] This ester can be synthesized from tetramethyl propane-1,1,3,3-tetracarboxylate **9** and dimethyl ethene-1,1-dicarboxylate

10, both of which can, in turn, be obtained from the condensation of dimethyl malonate **8** and formaldehyde (**Scheme 3**).[13,14]



Scheme 3. Meerwein ester **11**

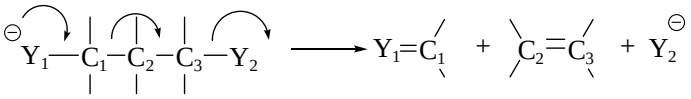
In 1978, an elegant synthesis of these compounds starting from 1,5-cyclooctane diene has been developed.[15] This reaction involves an electrophilic addition (*trans*) of dichloromethyl methyl ether to 1,5 cyclooctadiene **12**. Then, a transannular addition, probably followed by a hydride migration, takes place. Compounds **13** appears to be a valuable starting compound in the synthesis of several bicyclo[3.3.1]nonanes (**Scheme 4**).



Scheme 4. Synthesis of bicyclo[3.3.1]nonanes starting from 1,5-cyclooctane diene

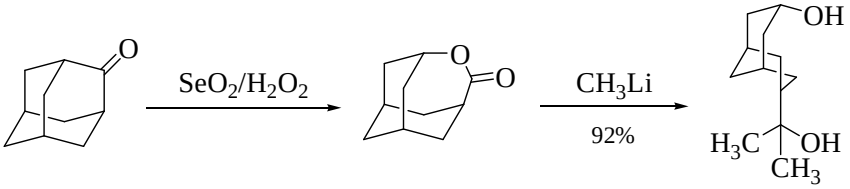
Another application is relative to the ring cleavage of adamantane derivatives, to give 3- and 3,7-disubtituted bicyclo[3.3.1]nonanes, as a crucial synthetic route. Several cleavage reactions of adamantanes are based

on the Grob fragmentation, which can be characterized by the following general reaction **Scheme 5**.[16]



Scheme 5. Schematic Grob's fragmentation

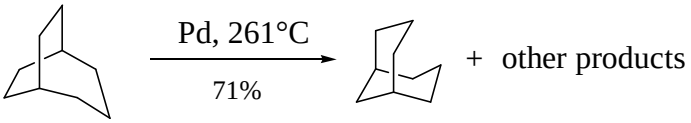
An attractive approach to 3,7-disubstituted bicycle-nonanes is the oxidative cleavage of adamantane compounds. Baeyer-Villiger reaction of adamantanone **14** gave 4-oxohomoadamantan-5-one **15**, which yielded diol **16** upon treatment with methyllitium (**Scheme 6**).[17,18]



14 **15** **16**

Scheme 6. An attractive approach to 3,7-disubstituted bicyclo nonanes

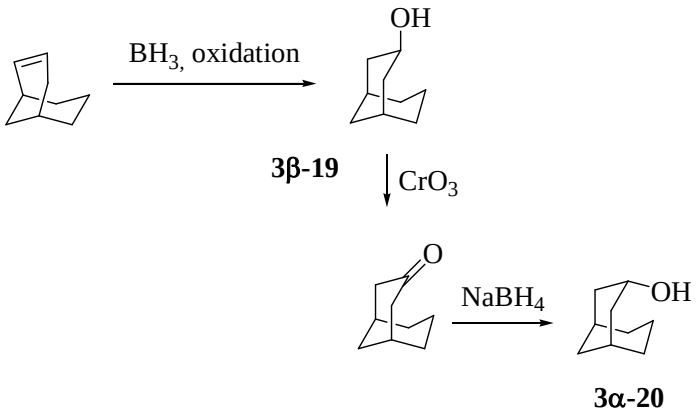
Bicycle[3.3.1]nonane **17** can be also obtained by palladium-catalyzed isomerization of bicycle[3.3.2]nonane **18** as reported in **Scheme 7**.[19]



17 **18**

Scheme 7. Palladium-catalyzed isomerization of bicycle[3.3.2]nonane **17**

Finally, there are numerous examples of syntheses of 3- and 3,7-substituted bicycle[3.3.1]nonanes by modification of other bicycle[3.3.1]nonanes derivatives. An easy demonstration is the reaction sequence yielding 3β- and 3α-hydroxybicyclo[3.3.1]nonanes **19** and **20** (**Scheme 8**).[20]



Scheme 8. Sequence yielding 3β- and 3α-hydroxybicyclo[3.3.1]nonanes

Thus, being this framework quite common in nature as a constituent of many natural and biologically active products or their metabolites,[21] biosynthetic pathway of many sesquiterpenoids and other naturally occurring materials involve the formation of bicycle[3.3.1]nonanes.[22] Hyperforin (**Figure 1**) was isolated as a metabolite from St. John's wort (*Hypericum perforatum* L.), a medicinal plant traditionally used to treat depression and superficial wounds, burns and dermatitis.[23,24]

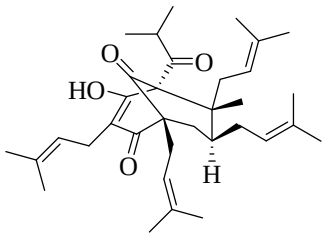


Figure 1. Hypericum perforatum L.

Further, (+)-Upial, isolated from the sponge Dysidea fragilis of Kaneohe Bay (Hawaii), was found to be a non-isoprenoid sesquiterpene aldehyde lactone containing the rare bicycle[3.3.1]nonane skeleton (**Figure 2**).[25,26]

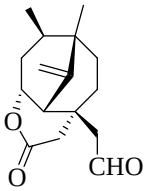
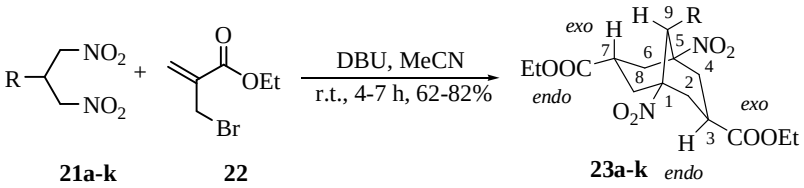


Figure 2. (+)-Upial

4.2.1 One-Pot synthesis of polyfunctionalized bicyclo[3.3.1] nonanes[27]

We focused our attention in an innovative procedure for the synthesis of polyfunctionalized bicyclo[3.3.1]nonanes **23** from 1,3-dinitroalkanes **21** and the commercially available ethyl(2-bromomethyl)acrylate **22** (**Scheme 9**).



21a-k **22** **23a-k**

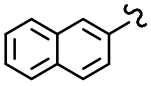
Scheme 9. One-pot synthesis of bicyclo[3.3.1]nonanes

It is evident that this type of reaction would allow the minimization of waste, making its management much easier, since, compared with stepwise reactions, the amount of solvent, reagents, adsorbents, and energy would be dramatically decreased, as well as the amount of work.

Optimizing work

The reactions were performed simply by adding the acrylate **22** (2 equiv.) to a solution of dinitroalkane **21** (1–1.2 equiv., **Table 1**) under basic conditions (1,8-diazabicyclo[5.4.0]undec-7-ene, DBU), in acetonitrile, and at room temperature. The multistep process occurs with good overall yields (62–82%, **Table 1**) for compounds **23**, as a one-pot procedure and under short reaction times (4–7 h), through an anionic domino process. The method works well with a variety of dinitroalkanes, including those possessing other functionalities, such as (*Z*)-C=C double bond (**21c**), ether group (**21g**), or heterocyclic compounds (**21k**) which are preserved under our mild reaction conditions. Most of the bicyclo[3.3.1]nonanes **23** were obtained exclusively as the *exo*-3,*endo*-7-diastereoisomer, only for compounds **23f**, **23g**, and **23k** was an *exo*-3,*endo*-7/*exo*-3,*exo*-7-diastereomeric mixture was obtained (80:20, 65:35 and 85:15, respectively).

Table 1. Bicyclo[3.3.1]nonanes **23a-k** prepared

Entry	R	ratio **21**/**22**	Reaction time (h)	Yield (%)	*Exo*-3,*endo*-7: *exo*-3,*exo*-7
a	*n*-Pr	0.5/1	4	78	
b	$Ph(CH_2)_2$	0.5/1	4	62	
c	*(Z)*-$Me(CH_2)_4CH{=}CH(CH_2)_2$	0.5/1	6	66	
d	*c*-C_6H_{11}	0.5/1	6	73	
e	*n*-C_5H_{11}	0.5/1	6	76	
f	Ph	0.6/1	4	82	80:20
g	*p*-$MeOC_6H_4$	0.6/1	6	80	65:35
h	*p*-MeC_6H_4	0.6/1	7	79	
i	*p*-PhC_6H_4	0.6/1	6	76	
j		0.6/1	7	64	
k	Pyr	0.6/1	6	70	85:15

The structure of compounds **23** were elucidated by 1D and 2D NMR spectroscopy, including NOESY-1D experiments for the relative stereochemistry. The assigned structures for **23f** and **23g** were confirmed by X-ray analysis.[28] In particular, *exo*-3,*endo*-7-**23f** and *exo*-3,*exo*-7-**23f** could be separated by column chromatography, and *exo*-3,*endo*-7-**23f** gave suitable crystals for X-ray analysis (**Figure 3**).

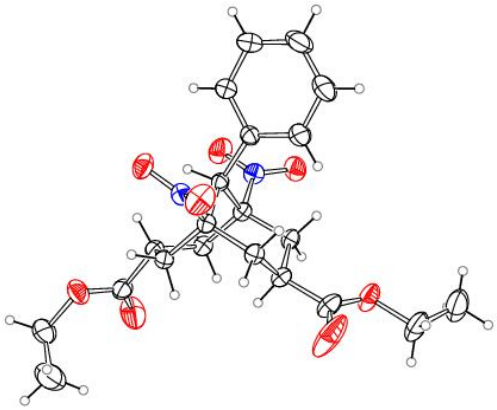


Figure 3. X-ray structure of compounds **23f** (*exo*-3,*endo*-7 form)

In the case of **23g**, the two inseparable diastereoisomers obtained by column chromatography co-crystallized in a 1:1 ratio, permitting the simultaneous determination of the two forms (**Figure 4**).

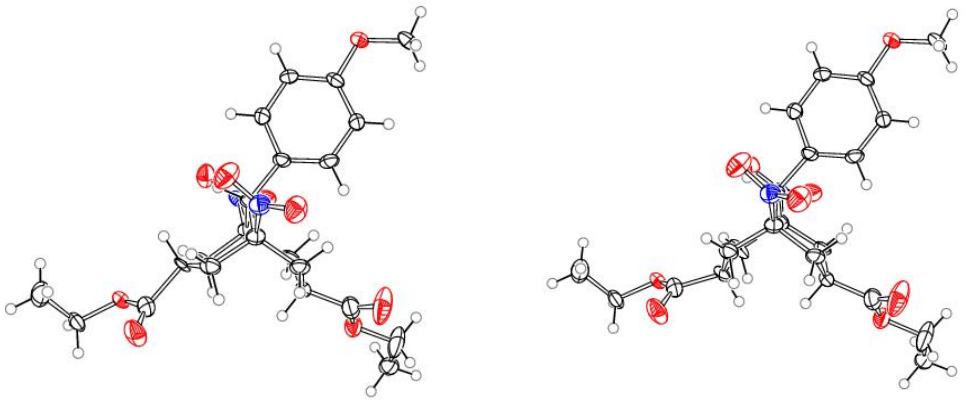
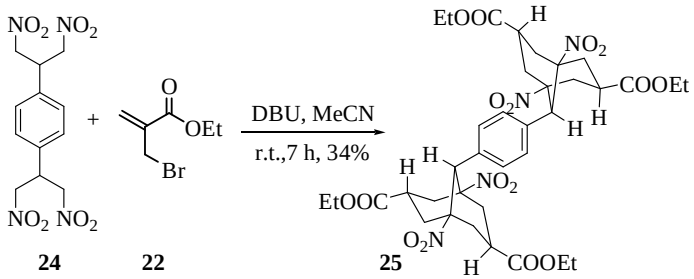


Figure 4. X-ray structure of compound **23g** in its two *exo*-3,*endo*-7 and *exo*-3,*exo*-7 forms

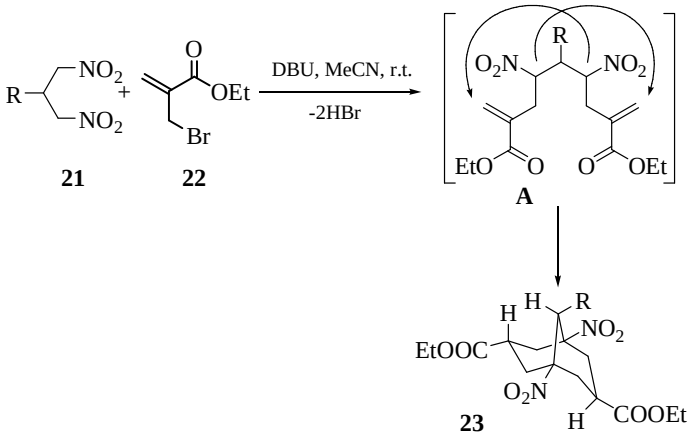
Moreover, it is important to note that the target compounds **23** were obtained as polyfunctionalized bicyclo[3.3.1]nonanes, since two tertiary nitro groups (1- and 5-positions) an two esters (3- and 7-positions) are still present, giving the opportunity for further transformations. In fact, tertiary nitro groups can be converted into other strategic functionalities, such as amino, thiols,[29] hydroxylamines,[30] or can be replaced with hydrogen[31] giving the corresponding denitrated products, while esters can be converted into an array of other derivatives, including carboxilic acids and primary alcohols.[32] From our procedure, a large collection of alkyl or aryl groups can be easily introduced in the 9-position, independent of their nature (acyclic, cyclic, aromatic, polyaromatic, heterocyclic), by making an appropriate choice of the starting 1,3-dinitroalkanes **21**.

In addition, a structurally unique *bis*-bicyclic compound **25** can be obtained in a one-pot reaction starting from the tetranitro derivative **24** and four equivalents of ethyl(2-bromomethyl)acrylate **22**, in 34% overall yield (**Scheme 10**).



Scheme 10. Synthesis of the *bis*-bicyclic compound **25**

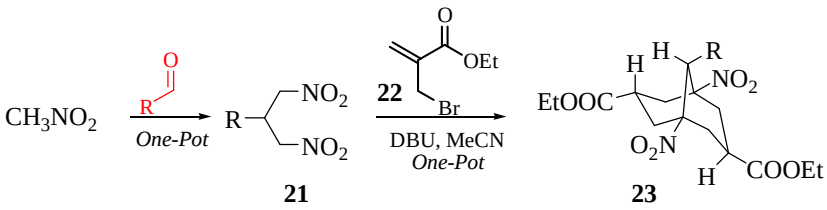
Taking into account that nitroalkanes easily add to Michael acceptors under the present conditions,[33] we suggest a plausible mechanism as reported in **Scheme 11**.



Scheme 11. Possible mechanism for the formation of **23**

Thus, a double Michael reaction of the dinitro compound **21** with two equivalents of ethyl(2-bromomethyl)acrylate **22** and the elimination of two molecules of bromide acid,[34] allows the intermediate **A**, which is prone to give a further double internal conjugate addition to the formed electron-poor alkenes, allowing the synthesis of bicyclo3.3.1]nonanes **23** by means of an anionic domino process. Thus, the one-pot synthesis of **23** proceeds through the *in situ* diastereo controlled generation of four new C-C bonds (including the elimination of two molecules of bromide acid), at room temperature

under very mild reaction conditions and in very good overall yields, while the compound **25** has been obtained through the one-pot generation of eight new C-C bonds in 34% overall yield! It is important to note that, since the 1,3-dinitroalkanes used as the key starting materials for the present synthesis were in turn prepared in a one-pot reaction of nitromethane and the appropriate aldehydes,[35] the polyfunctionalized bicyclo[3.3.1]nonanes **23** and **25** can actually be obtained from a very simple molecule, such as nitromethane, just by two "one-pot" sequences (**Scheme 12**).

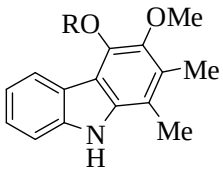


Scheme 12. Two step sequence for the synthesis of **23** from nitromethane

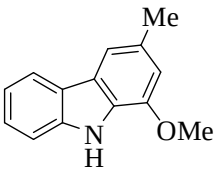
4.3 Classical synthesis of carbazoles & their applications

A long-standing goal of organic synthesis is the development of new methods that access aromatic nitrogen heterocycles,[36] as carbazoles. The tricyclic carbazole ring system is the core structure for a wide range of alkaloids displaying a variety of biological activities,[37] and are important building blocks for the construction of polymers with special thermal,[38] electrical,[39] and photoelectrical properties,[40] and polymer-blend additives for the fabrication of photorefractive,[41] charge-transporting,[42] and light-emitting materials.[43] From a synthetic standpoint, the formation of the carbazole system can be carried out exploiting two main general procedures. The first one is based on the direct formation of the tricyclic system starting from functionalized benzene precursors. The second approach employs indole derivatives as substrates on which the third benzene ring is built up. Metal-catalyzed coupling reactions of anilines with functionalized arenes, followed by an oxidative ring closure, belong to the former approach.[44] Similarly, reductive ring closures of nitrogenated biphenyl derivatives[45] and cycloaddition reactions of diene compounds,[46] allow the preparation of carbazoles from functionalized benzene systems. Thus, the unique importance of these organic materials has attracted considerable interest and the development of simple, mild, efficient and general methods to synthesize the carbazole ring system from easily available starting materials are of current interest.

One of the most important class of compounds containing the carbazole core is Carbazomycins because, they are an unprecedented class of antibiotics with a carbazole framework.[47] Carbazomycins A and B (**Figure 5**) inhibit the growth of phytopathogenic fungi and have antibacterial and *anti*-yeast activities.



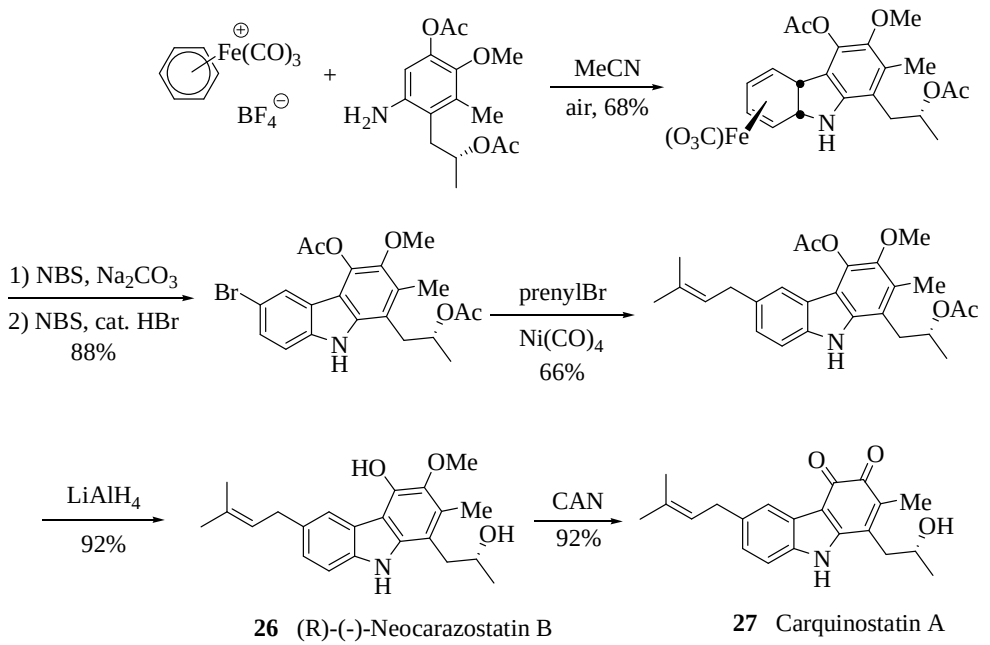
Carbazomycin A, R = Me
Carbazomycin B, R = H



Murrayafoline A

Figure 5. Carbazomycin A & B, and Murrayfoline A

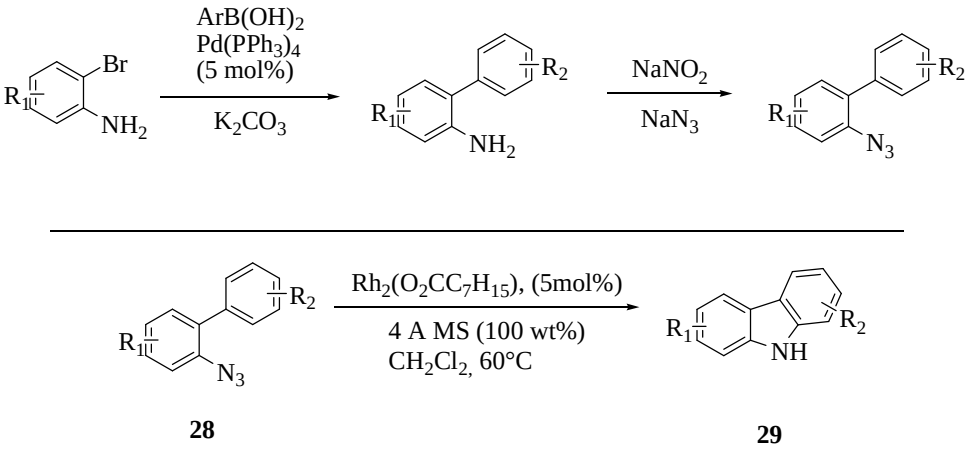
Further, a series of carbazole derivatives with promising pharmacological properties has been prepared using either an iron-mediated or a palladium-catalyzed synthetic approach. Both routes offer the advantage of functionalized building blocks, which can be combined by exploitation of transition-metal-mediated or catalyzed coupling reactions. The carbazole alkaloid Carquinostatin A **27**, for example, is an antioxidant, acting as free-radical scavenger. It represent potential lead compound for the development of novel drugs against diseases initiated by oxygen derived free radicals. It is structurally related to Neocarazostatin B **26** which has been isolated from the culture of Streptomyces sp. strainGP 38 (Kato et al., 1991). Thus using the iron-mediated carbazole construction, a straightforward synthesis of both alkaloids has been developed (**Scheme 13**).[48]



26 (R)-(-)-Neocarazostatin B **27** Carquinostatin A

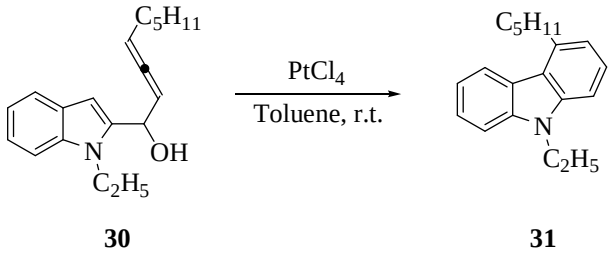
Scheme 13. Synthesis of the Carquinostatin A alkaloid

Dirhodium(II) complexes are well-known atom-transfer catalysts.[49] They are particularly effective in aliphatic C-N bond formation,[50] enabling access to nitrogen heterocycles efficiently. Employing azides **28** as substrates would complement these existing technologies as well as related deoxygenation methods,[51,52] as azides are easily obtained,[53] intrinsically prone to decomposition,[54] and produce N_2 as the only byproduct (**Scheme 14**).



Scheme 14. Dirhodium(II) complexes catalyzed reaction

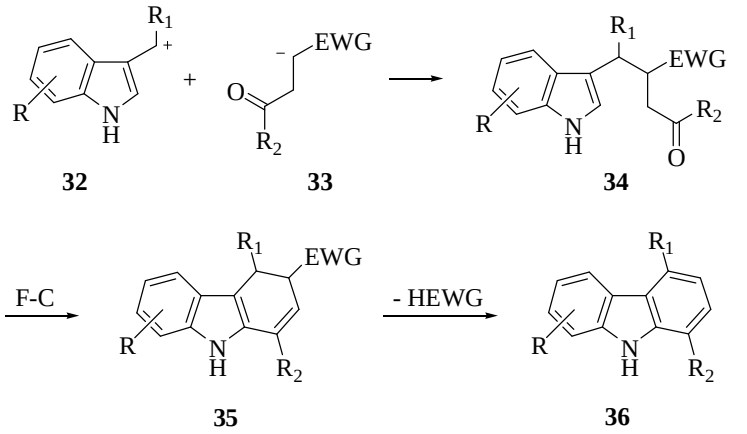
Finally, Kong *et. al.*,[56] reported an efficient synthesis of carbazoles from indoles. They observed that $PtCl_4$ catalyze an intramolecular cyclization of β-allenol to 2-substituted indoles, then, the reaction of 1-(indol-2-yl)-2,3-allenol **30** in the presence of the catalyst, either $PtCl_4$, afford to the carbazole **31** (**Scheme 15**).



Scheme 15. $PtCl_4$ catalyzed intramolecular cyclization to carbazole **31**

4.3.1 Synthesis of unsymmetrical 1,4-disubstituted carbazoles from sulfonylindoles[57]

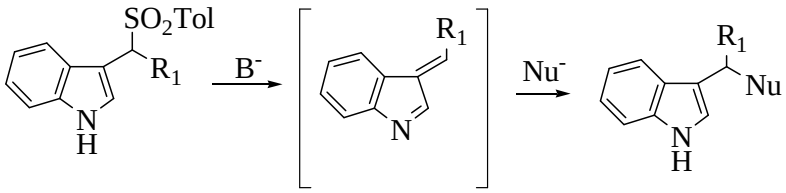
Following our knowledge, we started to study the conversion of indoles to carbazole. In a first attempt, we observed that carbazole derivatives can be achieved exploiting the Friedel–Crafts reaction, in particular for the synthesis of 3- substituted indoles and this process, carried out using 1,4-dicarbonyl derivatives on indoles, is effective for the preparation of 1,4-dialkylcarbazoles.[58] Unfortunately, this approach is only useful for the synthesis of symmetrical carbazole derivatives. In order to circumvent this drawback, the carbon-carbon bond connection at the indole ring would be done in two distinct steps, with final aromatization of the resulting partially unsaturated carbacycle. Thus, a suitable indole system with a reactive electrophilic benzylic position, e.g., **32**, could react with a stabilized carbanion **33** leading to the first carbon-carbon bond connection (**Scheme 16**).



Scheme 16. Reactivity of indoles

The resulting intermediate **34** undergoes a Friedel–Crafts (F-C) reaction by which the tricyclic skeleton **35** is formed. Aromatization of the latter cycle occurs upon elimination of the activating electron-withdrawing group (EWG) leading to the carbazole compound **36**.[59] The depicted synthetic strategy requires a three-step process that, however, could be shortened if

the ring closure and the aromatization steps are joined in a tandem operation. Among carbanion stabilizing groups, the nitro group occupies a prominent position since its formidable electron-withdrawing power allows the generation of the corresponding nitronate anions under mild conditions.[60] Moreover, reactive indolyl intermediates of type **32** are readily available starting from stable precursors having a good leaving group at the benzylic position.[61] Recently, we have introduced a new class of indole derivatives, namely 3-(1-arylsulfonylalkyl)indoles **37**, that have been demonstrated to be efficient precursors of alkylideneindolenines **38**, or their parent iminium ions, for the synthesis of 3-substituted indoles **39** by reaction with suitable nucleophiles (**Scheme 17**).[62]



37 **38** **39**

Scheme 17. Utility of 3-(1-arylsulfonylalkyl)indoles **37**

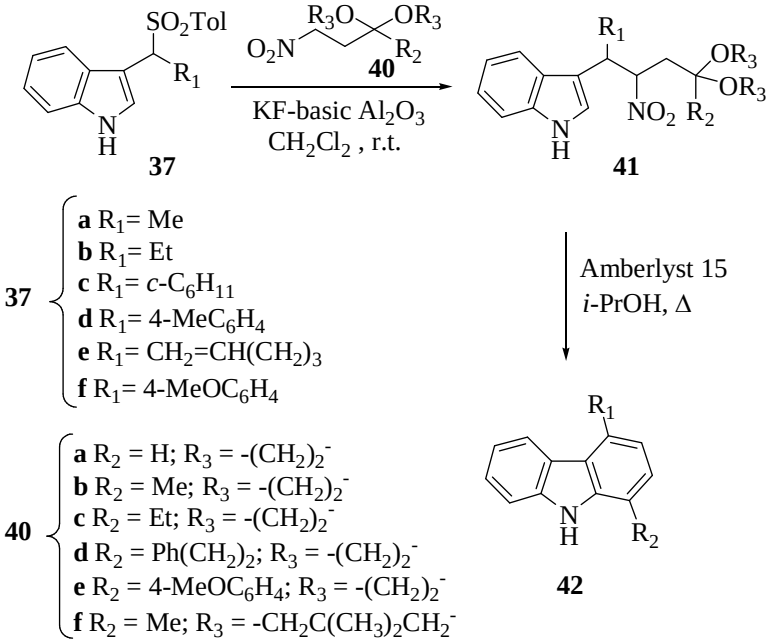
In a recent work we have demonstrated that these sulfonyl derivatives react with nitroalkanes, in the presence of a basic promoter, leading to the corresponding 3-(2-nitroalkyl)indoles,[63] but, although a large variety of functionalized nitroalkanes successfully react with sulfonylindoles **37**, β-nitro ketones **33** (EWG=NO_2, R_2=Me, Et) gave disappointing results in the same reaction under different solvent/base combinations. The failure is probably due to a preliminary retro-Michael reaction suffered by β-nitro ketones under basic conditions which leads to a decomposition of the nitro derivative.[64] This unwanted side process could be avoided by a suitable protection of the carbonyl group that prevents the retro-Michael process. In fact, conversion of β-nitro ketones into the corresponding nitro acetals **40**[65] and their reaction with sulfonylindoles **37** in the presence of KF-basic alumina generate adducts **41** in good yield (**Table 2**). The subsequent

transformation of 3-(2-nitroalkyl)indoles **41** into carbazoles **42** cover three different transformations:

1. Acetal cleavage,
2. Friedel–Crafts cyclization,
3. Final aromatization by elimination of nitrous acid.

In principle, all these synthetic operations could be performed under acidic conditions so that different promoters have been tested. Furthermore, working under heterogeneous conditions allows an easy recovery of the solid acid and a considerable speeding up in the subsequent work-up operations. The best conditions for this process have been found in the utilization of Amberlyst 15 as proton source in isopropyl alcohol at reflux as evidenced by the satisfactory results displayed in **Table 2**.

Table 2. Synthesis of Carbazoles **42**

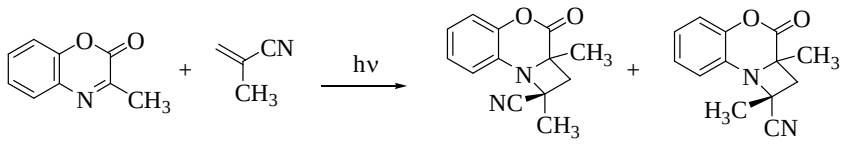


entry	indole **37**	nitro alkane **40**	nitro indole **41** yield (%)	carbazole **42**	yield (%)
1	**a**	**b**	**a** – (3.0)	**a**	55 (1.5)
2	**a**	**d**	**b** – (7.0)	**b**	54 (2.0)
3	**b**	**b**	**c** 89 (3.5)	**c**	64 (1.5)
4	**b**	**b**	**c** – (3.5)	**c**	61 (1.5)
5	**b**	**a**	**d** 83 (3.5)	**d**	68 (1.5)
6	**b**	**a**	**d** – (3.5)	**d**	62 (1.5)
7	**b**	**d**	**e** – (9.0)	**e**	56 (2.0)
8	**c**	**c**	**f** 78 (16)	**f**	65 (1.5)
9	**c**	**c**	**f** – (16)	**f**	62 (1.5)
10	**d**	**c**	**g** 90 (5.0)	**g**	56 (2.5)
11	**d**	**c**	**g** – (5.0)	**g**	53 (2.5)
12	**d**	**e**	**h** – (5.0)	**h**	44 (4.5)
13	**d**	**f**	**i** 84 (7.0)	**i**	58 (2.0)
14	**d**	**f**	**i** – (7.0)	**i**	55 (2.0)
15	**e**	**c**	**j** – (9.0)	**j**	47 (6.0)
16	**f**	**f**	**k** – (9.0)	**k**	68 (1.5)

Although the intermediate adducts **41** can be isolated, we have observed that crude products, obtained by simple filtration of the solid basic promoter and solvent evaporation, are suitable for the next cyclization step. This simplified procedure has a beneficial effect on the overall waste reduction and allows us to record a better chemical yield over the two-step process involving purification of intermediate compounds **41**. We also changed the nature of the acetal protection from 1,3-dioxolanyl to 5,5-dimethyl-1,3-dioxanyl without pointing out any substantial advantage (**Table 2**, entries 13, 14, 16).

4.4 Synthesis of benzoxazin-2-ones & their application

Benzoxazines constitute a class of compounds of important biological interest,[66] particularly 1,4-benzoxazinone structures, usually synthesized by the reaction between *o*-aminophenols with α-keto esters[67-69] or alkyl propriolates,[70] are of great interest due to their both photochemical activity[71] and their presence in many important products such as cephalandole alkaloids,[72] analogues of squamocin,[73] drugs (such as Psoralen plus UVA).[69] Concerning their photochemical behavior, Nonell *et al*.[71] reported that benzoxazinone derivatives exhibit spectral and photophysical properties of great interest such as broad first absorption band, emission in the red, intense fluorescence in both organic solutions and crystalline state, large dipole moment increase in the excited state, and short fluorescence lifetimes.[74-77] However, few studies addressing the photochemistry of aryloxazinones have been carried out. Light induced reactions of 1,4-benzoxazin-2-ones with electron-deficient olefins have been described by Nishio *et al*.,[78] in fact, irradiation of a mixture of 3-methyl-1,4-benzoxazin-2-one **43** and an excess of methacrylonitrile **44** under nitrogen atmosphere gave two stereoisomeric azetidine derivatives **45a,b**. (**Scheme 18**).

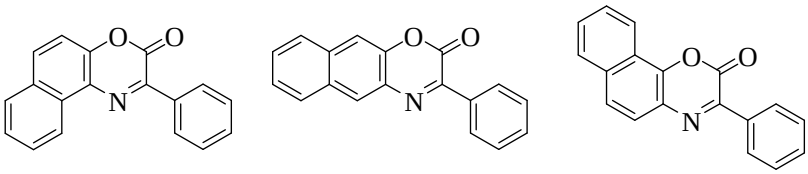


43 **44** **45a** **45b**

Scheme 18. Synthesis of stereoisomeric azetidine **45a,b**

Based on the fact that the benzoxazinone excited states have substantial charge-transfer character, has been demonstrated that, substitution of the benzo- with a naphtho-group, substantially affected the photophysical and photochemical properties of these compounds. Thus, all these naphthoxazinones differing in the position where the oxazinone ring is fused to the naphtho group and in their relative orientation, have shown significant

changes in the photophysical properties. The properties evaluated for these compounds suggest that they are valuable candidates for technological applications, such as dyes, quantum counters, or fluorescent probes (**Figure 6**).



46 **47** **48**

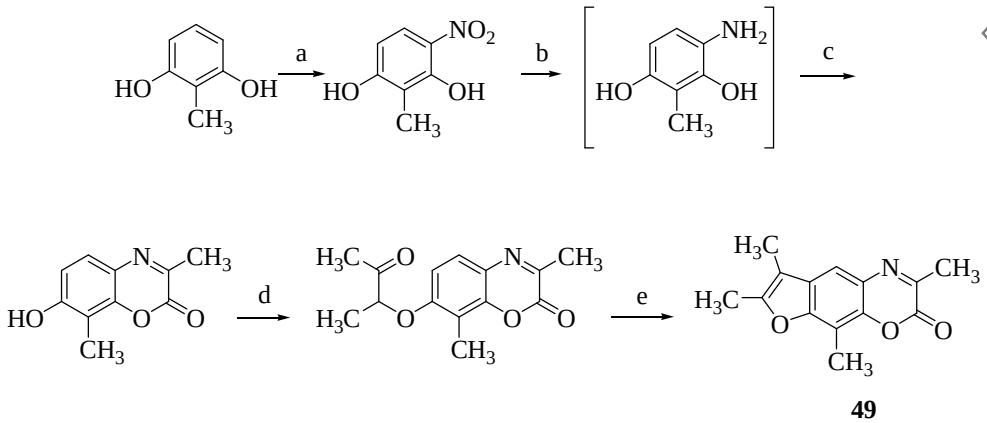
Figure 6. Naphthoxazinones derivatives

2H-1,4-Benzoxazine-2-ones can also be considered as 4-azacoumarins, in fact, some of these compounds reported by Moffett in 1966,[68] gave indication of antitumoral activity (**Figure 7**).

Coumarins **2H-1,4-benzoxazine-2-ones**

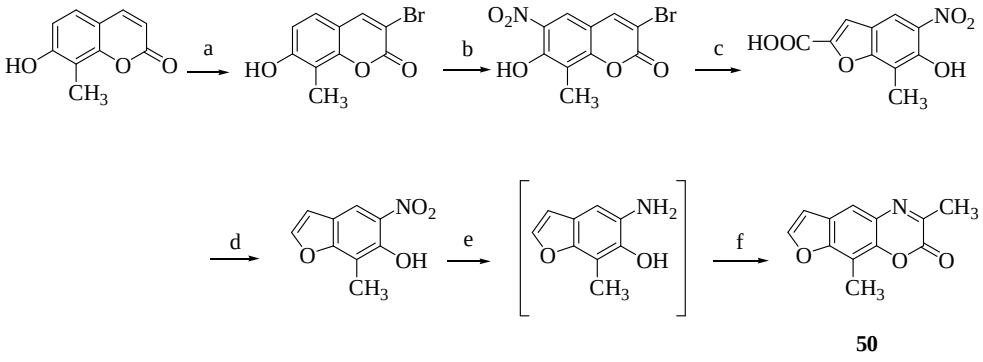
Figure 7. 2H-1,4-Benzoxazine-2-ones considered as 4-azacoumarins

Recently Chilin *et al.*[71] shown how changing the molecular structure of psoralens, (Psoralens are well-known natural and/or synthetic drugs currently used in PUVA (Psoralen plus UVA) therapy for various skin diseases.)[79] introducing a banzoxazinone core, both the photochemical behaviour of these psoralen isosters in terms of their ability to photobind to DNA thymine, and their photobiological properties, are deeply modified.[80-82] They exploited two different and straightforward routes: the first route consisted of condensing a furan ring onto a preconstituted 1,4-benzoxazinone nucleus **49** (**Scheme 19**), and the other in condensing a 1,4-oxazine ring onto the appropriate benzofuran system obtained from coumarin by ring contraction **50** (**Scheme 20**).



49

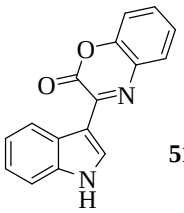
Scheme 19. Reagents and conditions: (a) *n*-pentyl nitrite, diethyl ether, room temp., 1 h; (b) Pd/C 10%, H_2, abs. EtOH, room temp., 24 h; (c) methyl pyruvate, room temp., 5 h; (d) 3-chlorobutan-2-one, anhydrous K_2CO_3, acetone, reflux, 7 h; (e) conc. H_2SO_4, room temp., 3 h.



50

Scheme 20. Reagents and conditions: (a) Br_2, glacial AcOH, 60 °C, 30 min; (b) HNO_3, H_2SO_4, 0 °C; (c) KOH, di(-ethylene glycol) ethyl ether; (d) quinoline, Cu, reflux, 30 min; (e) Pd/C 10%, H_2, abs. EtOH, room temp., 2 h; (f) methyl pyruvate, room temp., 12 h.

Finally, it is important to take in consideration that 1,4-benzoxazinones are constituents of several indole alkaloids, including Chephalandoles A **51** extract of the Taiwanese orchid *Cephalanceropsis gracilis* (Orchidaceae). In **Figure 8** it is shown the real Chephalandoles A, which represents the first example of a natural product featuring a 3-substituted 2*H*-1,4-benzoxazin-2-one core, although there are many examples of other naturally occurring benzoxazinoids.[83]

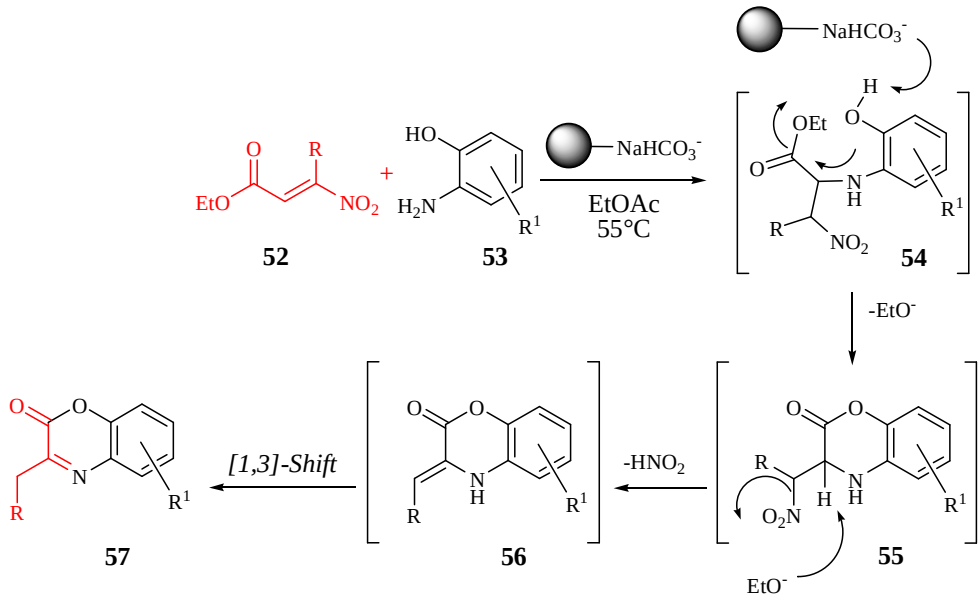


51

Figure 8. The real **s**tructure of Chephalandoles A **51**

4.4.1 Synthesis of 2H-1,4-benzoxazin-2-one derivatives under heterogeneous conditions[85]

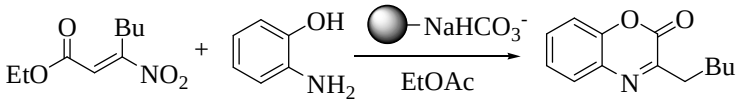
Following our studies on the application of solid heterogeneous catalysis in combination with the chemistry of aliphatic nitro compounds,[86] we have found that commercially available carbonate on polymer support promotes the reaction between β-nitroacrylates **52** and *o*-aminophenols **53** giving a direct synthesis of 2H-1,4-benzoxazin-2-one derivatives **57** (**Scheme 21**). A plausible mechanism of our reaction consists in a domino process in which four different transformations are involved: (i) hetero-Michael addition of the amine functionality to nitroolefins giving the intermediates **54**, (ii) intramolecular transesterification with formation of **55**, (iii) elimination of a molecule of nitrous acid affording the intermediates **56**, and (iv) [1,3]-proton shift with the formation of target products **57**, as previously reported in the literature.[87]



Scheme 21. A plausible mechanism for the synthesis of 2H-1,4-benzoxazin-2-one derivatives **57**

With the aim to optimize the process, we investigated the reaction using stoichiometric amounts of β-nitroacrylate **52a** and 2-aminophenol **53a**, in ethyl acetate as eco-friendly solvent,[88] under different conditions. Thus, as reported in **Table 3**,[(a)] the best result was obtained in the presence of an equimolar amount of carbonate on polymer, at 55 °C for 5.5 h.

Table 3. The best amount of carbonate on polymer

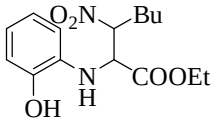


52a **53a** **57a**

Entry	Carbonate on polymer (mol%)	T°C	Yield [%] of **57a**	T [h]
a	100	35	72	24
b	100	55	77	5.5
c	50	55	23	24
d	200	55	51	5.5

[a]The catalyst can be recycled (**52a** and **53a** to **57a** was chosen as model reaction) with similar yields (reaction 77%; 1st recycle 75%, 2nd recycle 75%, 3rd recycle 74%) after its reactivation, following the reported procedure.[89]

Later, in order to verify the importance of the promoter, we examined the reaction both in the absence and under different amounts of SSR. The synthesis in the absence of carbonate on polymer, after one day, provided both the starting materials and the adduct **58** due to the hetero-Michael addition of the amine to β-nitroacrylate (**Figure 9**).

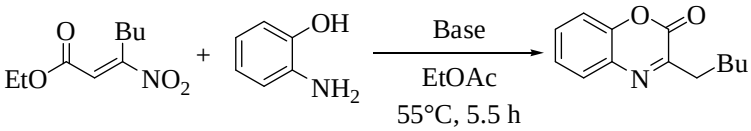


58

Figure 9. Synthesis due to the hetero-Michael addition of the amine to β-nitroacrylate

On the other hand, the presence of 50 mol% of carbonate on polymer gave, after one day, **57a** in poor yield (23%), while the presence of 200 mol% of the promoter afforded **57a** in 51% yield. Then, the efficiency of the carbonate on polymer support was compared with other standard promoters, and the sample reaction was investigated in the presence of a variety of other bases. However, as showed in **Table 4**, the best yield was still obtained in the presence of carbonate on polymer.

Table 4. Choosing the best basic conditions



52a **53a** **57a**

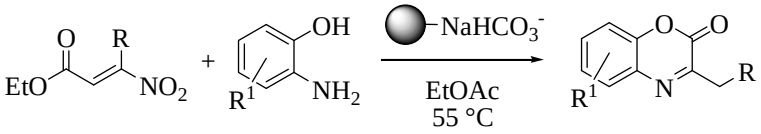
Entry	Base	Yield [%] of **57a**
a	Carbonate on polymer support[a]	77
b	K_2CO_3[a]	51
c	Amberlyst A21[b]	43
d	TBD[a]	40
e	Basic alumina[b]	13

[a] 1 eq. of base was used

[b] 1 g of base per each mmol of **2a** was used

Finally, with the purpose to enlarge the potential of our procedure, we extended the methodology to a variety of β-nitroacrylates and *o*-aminophenols, as reported in **Table 5**.

Table 5. Generality of the method



52 **53** **57**

Entry	R	R_1	Yield [%] of **57**	*T* [h]
a	Bu	H	77	5.5
b	$Me(CH_2)_4$	H	85	5.5
c	$NC(CH_2)_4$	H	65	2.5
d	$Ph(CH_2)_2$	H	82	5.5
e	$Me(CH_2)_6$	H	75	7
f	Me	H	51	5.5
g	$(Me)_2CH(CH_2)_2$	7-Me	75	5
h	$MeOCO(CH_2)_4$	7-Me	68	6
i	Me	7-Me	63	5.5
j	$CH_2=CH(CH_2)_8$	7-Me	66	7
k	$Me(CH_2)_4$	7-Me	90	5.5
l	Me	6-Cl	45	5.5
m	$(Me)_2CH(CH_2)_2$	6-Cl	55	6

4.5 Synthesis of dihydroquinoxalinones & their applications

In the family of biologically active heterocyclic templates, quinoxalinone system has its own identity. Quinoxalinone core is of interest as an important pharmacophore in numerous biologically active compounds. They are reported to possess significant biological properties[90-92] including utility as inhibitors of aldose reductase **59**, partial agonists of *c*-aminobutyric acid (GABA)/benzodiazepine receptor complex **61** and kinase inhibitors **60** (**Figure 10**).

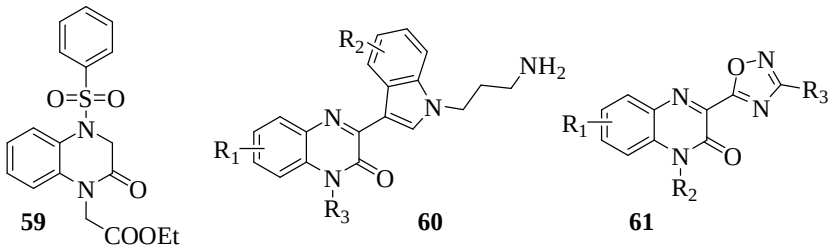
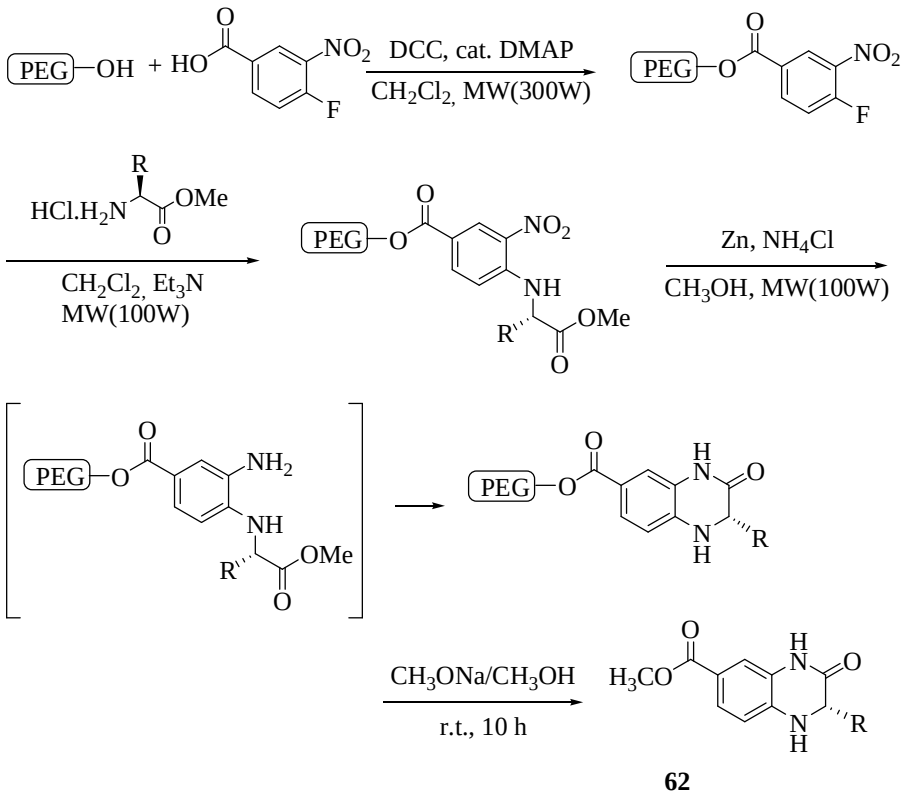


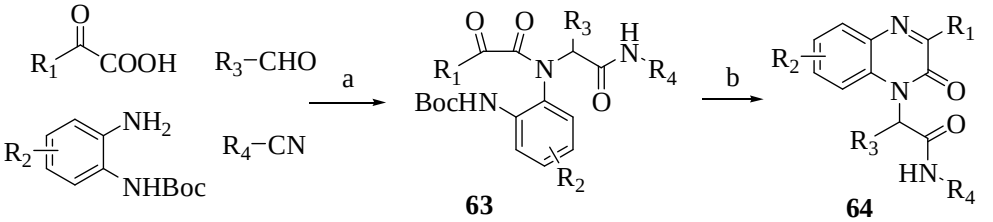
Figure 10. Significant biological derivatives

Quinoxalinone skeleton is also used as an intermediate in designing different quinoxaline derivatives, which are shown to have antimicrobial,[93] antifungal[94] and anticancer[95] activities. Thus, due to the importance of these derivatives, there are rich literatures concerning synthetic methods for dihydroquinoxalin-2-ones and derivatives, which include, soluble polymer-supported organic synthesis and aromatic substitution of *o*-fluoronitrobenzene with amino acid followed by reductive cyclization.[96-98] Soluble polymer-supported organic synthesis is recognized as a convenient method to deliver vast number of small molecule libraries in mild reaction conditions.[99] Chemically robust polyethylene glycol (CH_3O–PEG–OH) is the soluble polymeric support where homogeneous reaction conditions are maintained. In **Scheme 22** is reported an easy procedure for the synthesis of chiral quinoxalinones **62** by microwave irradiation using PEG as supporting polymer.



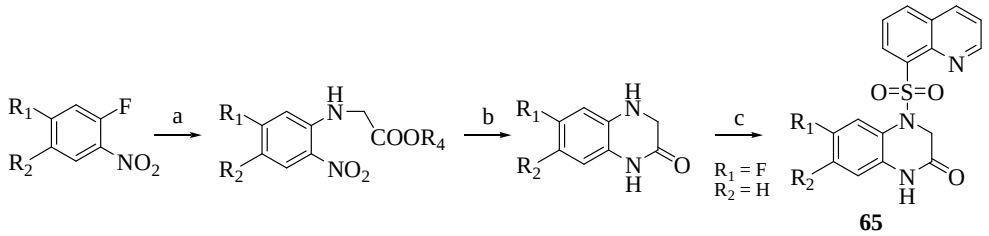
Scheme 22. Synthesis of chiral quinoxalinones **62** by microwave irradiation using PEG as supporting polymer

Another important example, a novel quinoxalinones synthesis utilizing a UDC (Ugi/de-Boc/cyclize) strategy, is reported by Nixey *et al.* (**Scheme 23**).[100]



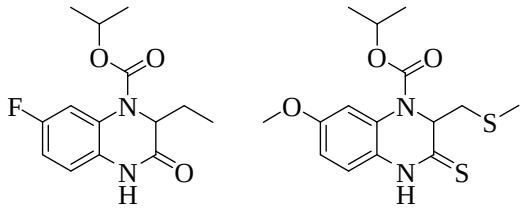
Scheme 23. Reagents and conditions: (a) PS-tosylhydrazine (3 equiv.), THF:CH_2Cl_2, 1:1, 24 h; (b) 10% TFA,CH_2Cl_2, 18 h.

N^4-(hetero)arylsulfonylquinoxalinones result as HIV-1 reverse transcriptase inhibitors. Xu et al.[101] reported that 6-fluoro-N^4-(quinoline-8-sulfonyl)-3,4-dihydroquinoxalin-2(1H)-one **65** was identified with *anti*-HIV activity at micromolar level (**Scheme 24**).



Scheme 24. Reagents and conditions: (a) amino acid ester/DIEA, CH_3CN; (b) $Na_2S_2O_4/K_2CO_3$/ethanol/water; (c) $ArSO_2Cl$, pyridine, CH_2Cl_2.

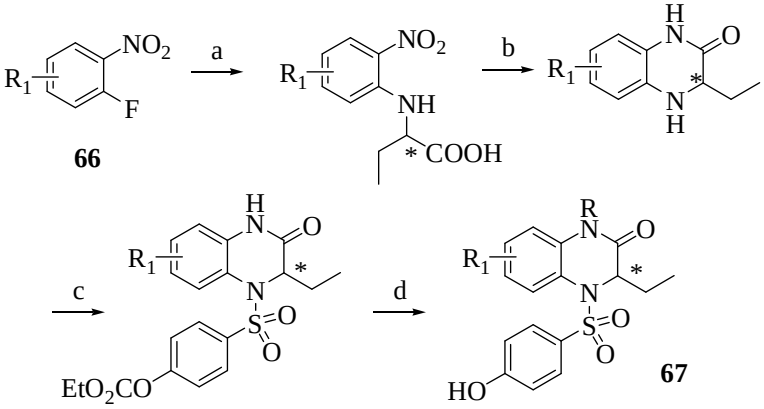
The lead compound **65** is a quinoxaline-based chemical entity, and this subunit also was presented in the potent NNRTIs (non-nucleoside reverse-transcriptase inhibitors (NNRTIs), clinic drugs which interact with a specific allosteric non-substrate binding site on HIV-1 reverse transcriptase) such as GW420867x[102,103] and HBY097 (**Figure 11**).[104]



GW420867x **HBY097**

Figure 11. Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)

Finally, concerning the aromatic substitution of *o*-fluoronitrobenzene **66** with amino acid followed by reductive cyclization, we report a lecture about Mahaney's work, USA, which realized a new class of pathway-selective estrogen receptors ligands **67**,[105] based on the peculiarity of (4-hydroxyphenyl)sulfonyl-3,4-dihydroquinoxalin-2(1H)-ones (**Scheme25**).



Scheme 25. Reagents and conditions: (a) (*R*)- or (*S*)-2-aminobutyric acid, K_2CO_3, DMF, 100 °C; (b) 10% Pd/C, H_2 (50 psi), EtOH; (c) ethyl (4-chlorosulfonyl)phenyl carbonate, pyridine, CH_2Cl_2; (d) RI, Cs_2CO_3, acetone, Δ; then 2 N NaOH.

4.5.1 Synthesis of polyfunctionalized dihydroquinoxalinone derivatives, via an *anti*-Michael reaction[106]

During our studies devoted to explore the chemical potential of β-nitroacrylates we discovered an innovative procedure for the synthesis of polyfunctionalized dihydroquinoxalinone derivatives in a one-pot way under uncatalysed reaction conditions. Thus, taken into account the importance of quinoxalinone derivatives, and considering that, as previously reported, their synthetic routes are mainly based on nucleophilic aromatic substitution of *o*-halonitrobenzene followed by cyclization of the obtained *o*-nitroamine,[107] or the reaction of *o*-phenylenediamines with α-bromoesters,[108] we focused our attention on the reaction of *o*-phenylenediamine **68** with β-nitroacrylates **69**, which allows the *anti*-Michael adducts **70** that, *in situ*, convert to the target dihydroquinoxalinones **71** (**Scheme 26**).

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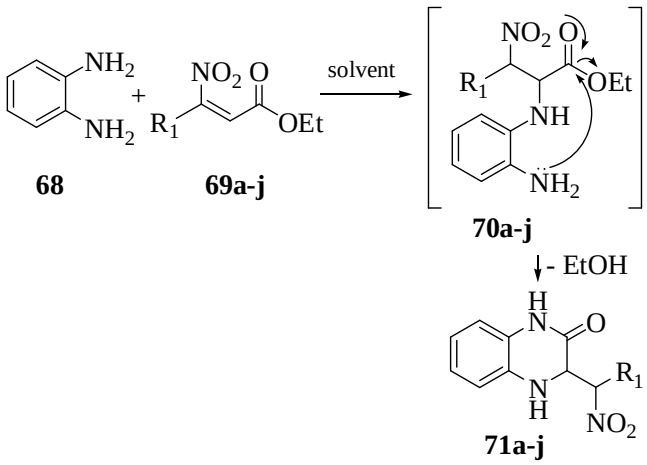
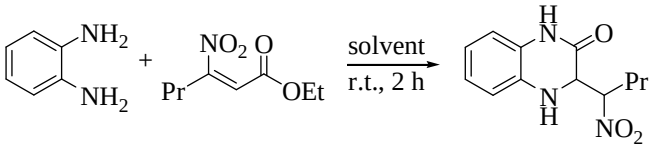


68 **69a-j** **70a-j** **71a-j**

Scheme 26. Reaction of *o*-phenylenediamine **68** with β-nitroacrylates **69**

In order to optimize the reaction conditions, we firstly examined, as a representative conversion, the preparation of compound **71c** starting from the *o*-phenylenediamine with the β-nitroacrylate **69c**. As reported in the **Table 6**, the best yield was obtained after 2 hours at room temperature, using 1.25 equivalents of diamine and ethyl acetate as solvent.

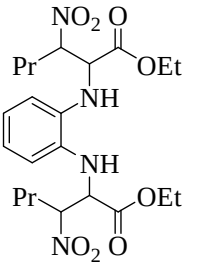
Table 6. Optimization of the reaction



68 **69c** **71c**

Eq. of **68**	solvent	Yield (%) of **71c**
1.0	EtOAc	59
1.25	EtOAc	84
1.5	EtOAc	78
1.25	CH_2Cl_2	68
1.25	Toluene	60

Use of 1 eq. of diamine, results in formation of the target dihydroquinoxalinone **71c** accompanied by a moderate amount of the bis adduct **72** (**Figure 12**). Thus, the formation of **72** can be minimize by using a slight excess of diamine.

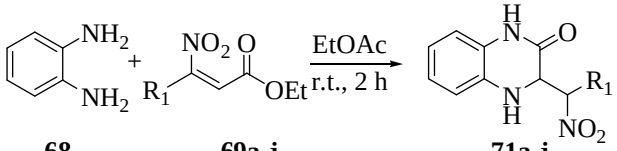


72

Figure 12. The bis adduct **72**

Finally, with the purpose to test the generality of our method, we examined a variety of β-nitroacrylates obtaining good to excellent yield (70-90%) of **71** (**Table 7**).

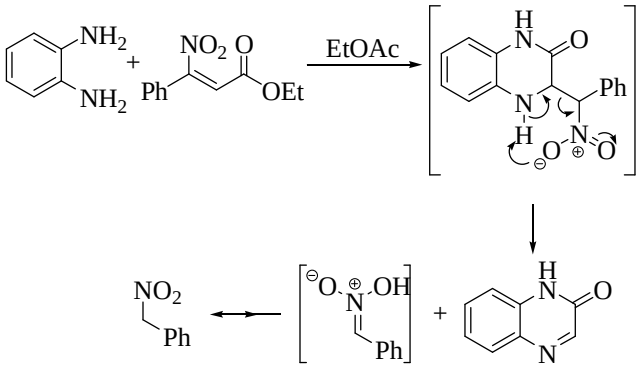
Table 7. Preparation of dihydroquinoxalinones **71a-j**



68 **69a-j** **71a-j**

Entry	R	Yield (%) of **71**	Diasteromeric ratio
a	Me	83	65:35
b	Et	79	73:27
c	Pr	84	70:30
d	$MeO(O)C(CH_2)_4$	80	50:50
e	$PhCH_2CH_2$	82	65:35
f	$CH_3(OCH_2CH_2O)CCH_2$	85	75:25
g	$CH_2=CH(CH_2)_8$	70	50:50
h	$N\equiv C(CH_2)_4$	90	70:30
i	$CH_3(CH_2)_6$	71	65:35
j	$(CH_3)_2CHCH_2CH_2$	82	60:40

A particular behaviour was observed with β-nitroacrylate **69k** (R = Ph), since the crude product **71k** (obtained after 1h, **Scheme 27**) was unstable during the purification step (chromatography), giving the quinoxalin-2(1H)-one **73** (confirmed by NMR spectroscopy).

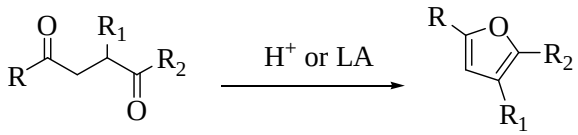


Scheme 27. Probable mechanism in which **71k** is amenable

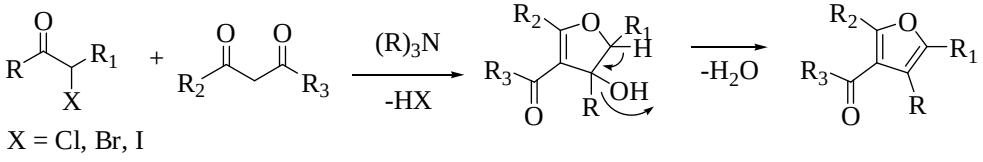
The probable mechanism consists of an intramolecular deprotonation of **71k** and simultaneous cleavage of C-C bond in 4- and 3-positions respectively, affording **73** and the nitronic acid (stabilized by the high conjugation with the aromatic system), that tautomerizes into the more stable phenylnitromethane.

4.6 Synthesis of furan derivatives & their applications

Furan, as one of the representative five-membered heterocycles, can be found in many naturally occurring compounds. Polysubstituted furans play an important role in organic chemistry not only due to their presence as key structural units in many natural products[109] and in important pharmaceuticals,[110] but they can also be employed in synthetic chemistry as building blocks and a lot of transformation reactions. For this reason, the syntheses of polysubstituted furans continue to attract the interest of many synthetic chemists. Although a number of reviews on the synthesis of furans have appeared in the literature,[111,112] only very few of them deal with the regioselective methods for preparing furans. Therefore, a tremendous number of synthetic methods to approach substituted furans is known.[113] The most frequently used methods include the cyclocondensation of 1,4-dicarbonyl compounds (Paal–Knorr synthesis, **Scheme 28**),[114] and the classical Feist–Benary synthesis (**Scheme 29**).[115]



Scheme 28. Paal-Knorr cyclococndensation



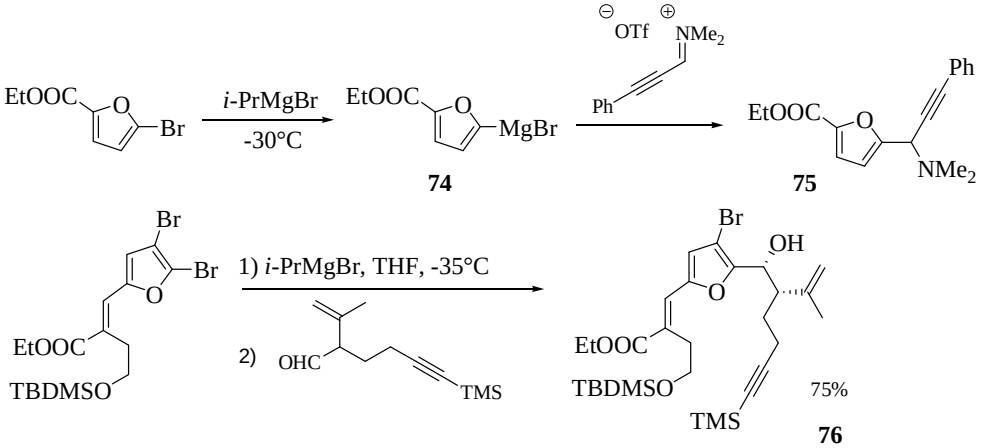
Scheme 29. Feist-Benary synthesis

Although these methods have proven to be very useful for the synthesis of furan derivatives, there are some limitations, including the difficulty in accessing furans that contain sensitive functional groups and the inability to provide furans with high flexibility regarding their substitution pattern. For these reasons, the development of even newer and more efficient methods

for the synthesis of highly functionalized furans under mild conditions remains an area of ongoing interest. Most, but not all furan syntheses can be generally divided into two categories: the first, functionalization of existing furan-containing precursors by introduction of new substituents, and the second, construction of the heterocyclic core by cyclization of acyclic substrates.[116]

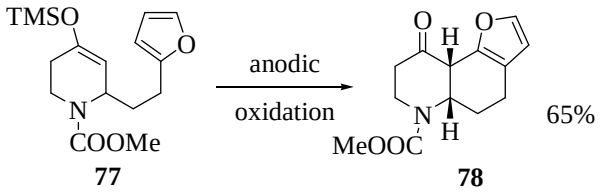
Funtionalization of existing furans

The methods based on functionalization of existing furan precursors are typically not general. For example, derivatization of furans *via* electrophilic substitution is sometime restricted due to the low stability of furans under acidic and aerobic conditions.[109] Methods involving the metalation of furan derivatives followed by quenching with various electrophiles are mostly limited to basestable furans.[117] An interesting metalation protocol that partially overcomes the latter limitation is reported by Knochel and coworkers.[118] Therein, halogen–magnesium exchange becomes an attractive method to generate positionally stable functionalized furylmagnesium compounds **74** under mild conditions tolerating various functional groups such as esters, nitriles or amides (**Scheme 30**).



Scheme 30. Functionalized furans by halogen–Mg exchange

Recent investigations by Wright and co-workers[119] examined an electro-oxidative coupling of furans and silyl enol ethers for the assembly of annulated furans (**Scheme 31**).



77 **78**

Scheme 31. Electro-oxidative synthesis of annulated furans

Synthesis of furans via cyclization reactions

The vast majority of the routes to multiply substituted furans have involved cyclization approaches starting from acyclic precursors. A particularly effective approach is through transition metal catalyzed cycloisomerization of unsaturated acyclic precursors, which usually proceeds under rather mild conditions. Many different strategies involve allenyl ketones as starting materials for furan synthesis mostly using, for example, Au(III) compounds as catalysts for 5-*endo-trig* cyclizations.[120] An alternative strategy involves catalyzed cyclization of alkynyl ketones,[121,122] alcohols,[123] or epoxides.[124] Alkynes are typically considered to be more attractive starting materials than allenes, since practical routes to allenes that contain sensitive functional groups are sometime limited. Furthermore, transition metal catalyzed cyclization of alkynyl or allenyl substrates has been typically used to prepare di- and trisubstituted furans, while tetrasubstituted furans are not readily accessed. That's why the need of new and more efficiently routes to obtain tetrasubsituted furans are in coming.

Intresting base- and acid-catalyzed reactions of alkynyl ketones have been reported to yield furans.[125,126] These approaches are rather incongruous with sensitive functional groups. Relevant reactions have also been reported with the aid of transition-metal catalysts.[127] In general, gold, mainly as $AuCl_3$, is the most effective catalyst for cycloisomerizations leading to furans (**Figure 13**).[128]

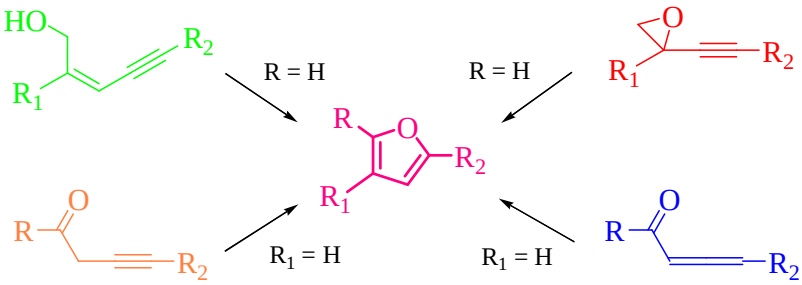
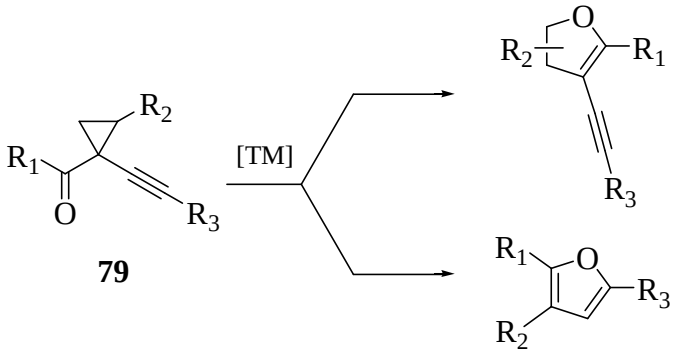


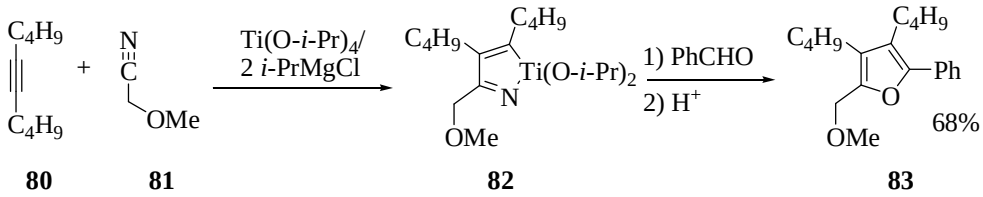
Figure 13. Representative gold-catalyzed cycloisomerizations leading to furans

A specific example is reported by Zhang *et al.*,[129] a mild and efficient method for the synthesis of multiply substituted furans starting from compounds of type **79** (**Scheme 32**).



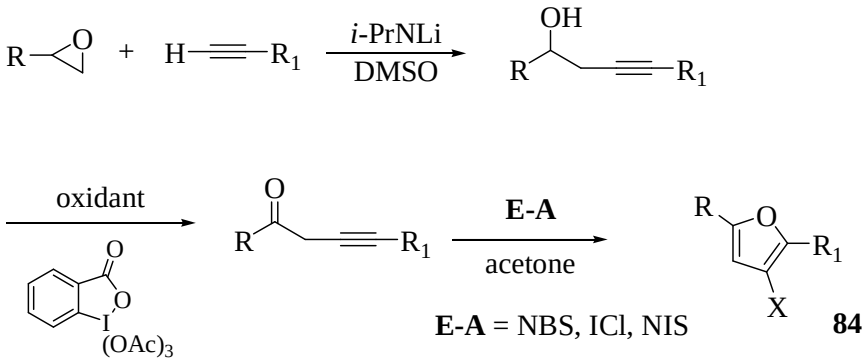
Scheme 32. Two possible modes of reaction for the cyclization of **79**. [TM]=Transition Metal reagent

Coupling of acetylene **80**, nitrile **81**, and a titanium reagent, Ti(O-*i*-Pr)$_4$/2 i-PrMgCl, generates new azatitanacyclopentadienes **82** in a highly regioselective manner, and, if the latter is prepared from an unsymmetrical acetylene which reacts with an aldehyde, gives furans having four different substituents **83** (**Scheme 33**).[130]



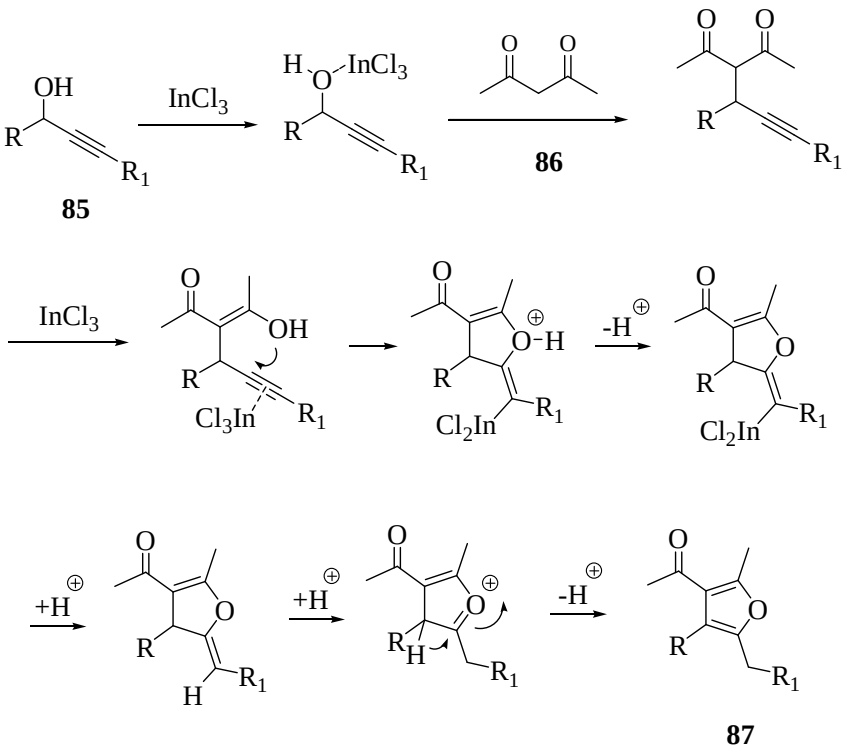
Scheme 33. Coupling of acetylene, nitrile, and Ti(O-*i*-Pr)$_4$/2 i-PrMgCl

Halofurans are also important derivatives that provide an opportunity for further functionalizations. In particular, iodo- and bromofurans are useful as substrates in a variety of C-C bond-forming reactions,[131] and they also serve as building blocks for combinatorial chemistry,[132] but, the direct halogenations of 2,5-unsimmetrycally substituted furans generally leads to mixtures of regioisomers.[133] Sniady *et al.* synthesized 2,5-substituted-3-halofurans **84** starting from commercially available styrene oxide or its derivatives, as presented in **Scheme 34**.[134]



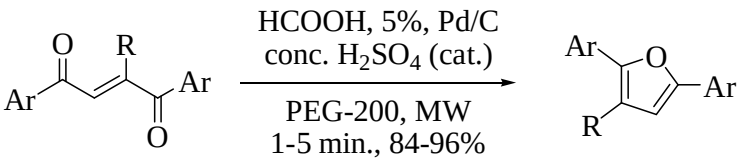
Scheme 34. Synthesis of halofurans

The latter approaches, require the preparation of rather advanced staring materials such as allenones and alkynones. However, recently Ze Tang and co-workers reported a highly efficient new procedure for the synthesis of tetra-subsituted furans **87** using propargilic alcohol **85**, 1,3-diketones **86** and a catalytic amount of $InCl_3$, eliminating the need of any kind of base, and making the reaction truly catalytic as shown in **Scheme 35**.[135]



Scheme 35. Probable mechanism for the furan formation

Finally, as reported above, being the Paal-Knorr condensation one of the most popular reaction used for the synthesis of furans, in which 1,4-dicarbonyl compounds are converted to furan derivatives via acid mediated dehydrative cyclization,[136] and having this approach a lots of disadvantages concerning, the requirement of stringent conditions, long reaction times, and lack of applicability, it has been reported in 2003, a facile, high-yielding, one-flask preparation of furan derivatives from 2-ene-1,4-diones and 2-yne-1,4-diones using formic acid in the presence of a catalytic amount of palladium on carbon (5%), and PEG as solvent, a suitable solvent for performing the microwave mediate conversion of enedione **88** to **89** (**Scheme 36**).[137]

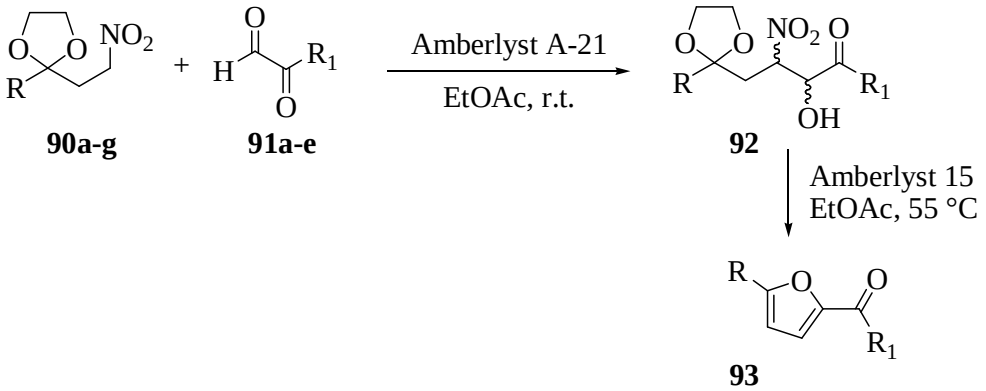


88 **89**

Scheme 36. Microwave-mediated transformations of 2-butene-1,4-diones to furan derivatives

4.6.1 Synthesis of 2,5-disubstituted furan derivatives from functionalized nitroalkanes, under heterogeneous conditions[138]

The availability of uncomplicated synthetic procedures which permit the preparation of polysubstituted furans is an important task for organic chemists. This concept, combined with our previous experience in the synthesis of heterocycles from aliphatic nitrocompounds,[139] have led us to explore a new approach for the synthesis of functionalized 2,5-substituted furans. Herein we present an innovative, mild and efficient method, for the synthesis of a series of 2,5-disubstituted furans **93** starting from functionalized nitroalkanes of type **90**.[140] As reported in **Scheme 37**, the synthetic strategy was initially planned as two independent steps, starting from the nitroaldol (Henry) reaction of **90** with the aldehyde **91**,[141] under basic conditions, followed by acid treatment of the obtained β-nitroalcohol **92**.

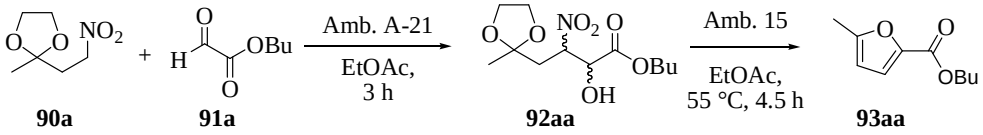


Scheme 37. General pathway to the synthesis of furan derivatives

Based on the high reactivity that nitro compounds showed recently under solid heterogeneous catalysis,[142] and with the scope to optimize the process, we investigated both the steps under different amounts of Amberlyst A21 (anionic macromolecular ion-exchange resin) and Amberlyst 15 (cationic macromolecular ion-exchange resin), respectively. We have chosen, as a model, the reaction of an equimolar ratio of **90a** (R =

Me) with **91a** (R_1 = OBu) in the minimum amount of ethyl acetate, as an eco-friendly solvent.[143] As reported in **Table 8**, the best result of the first step was obtained using 0.5 g of Amberlyst A21 per mmol of substrate at room temperature, while the best performance of the second step, needs 0.7 g of Amberlyst 15 per mmol of substrate, at 55 °C.

Table 8. Screening of different amounts of the two promoters



90a **91a** **92aa** **93aa**

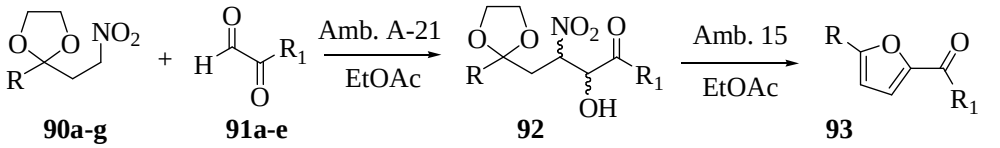
g of Amberlyst A21 per mmol of **90a**	Yield (%)a of **92aa**
0.3	73
0.5	81
0.7	80
g of Amberlyst A15 per mmol of 92aa	**Yield (%)a of 93aa starting from 92aa (temperature °C)**
0.5	traces (r.t.)
0.5	72 (55)
0.7	81 (55)
0.9	80 (55)

Because both the steps gave good results under heterogeneous conditions, we modified our initial procedure in order to combine the two reaction steps and with the aim to produce directly, the target compound **93aa**, avoiding any isolation and purification of the intermediate **92aa** and increasing the eco-sustainability of the process.[144] The new revised procedure, consists of the nitroaldol reaction of **90a** with **91a** in ethyl acetate and at room temperature, promoted by Amberlyst A21, followed by filtration of the promoter and successive addition of Amberlyst 15 to the percolate, containing the crude nitroalkanol **92aa**, and heating at 55 °C for the

appropriate length of time. Thus, the direct formation of the furans **93aa** takes place in good overall yield (78%).

In order to verify the generality of our procedure, we extended the methodology to a variety of nitroalkanes **90** and aldehydes **91**. As reported in **Table 9**, all the products were isolated in good overall yields (56–84%), independently from the nature of both (i) the alkyl or aryl groups (R) in the nitroalkanes **90** and (ii) the α-oxoaldehyde derivatives **91**.

Table 9. Preparation by two-step route of the furan derivatives **93**

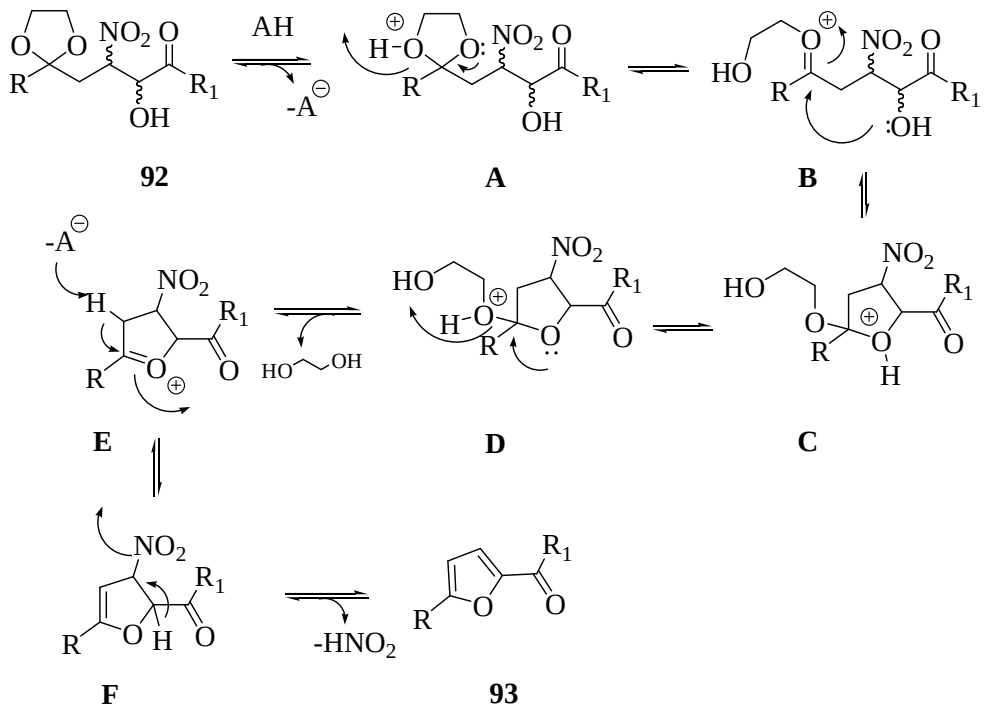


90a-g **91a-e** **92** **93**

R	**90**	R_1	**91**	Reaction time of **92**/h	Reaction time and yield of **93**/h	
Me	**a**	OBu	**a**	**aa** (3)	**aa** (4.5)	78
Me	**b**	Ph	**b**	**ab** (7)	**ab** (4.5)	65
n-C_5H_{11}	**c**	OBu	**c**	**ba** (3)	**ba** (4.5)	61
Ph	**d**	OEt	**d**	**cc** (3)	**cc** (4)	80
p-PhC_6H_4	**e**	OEt	**e**	**dc** (3)	**dc** (4.5)	60
Et	**f**	*p*-MeC_6H_4	**f**	**ed** (4)	**ed** (4.5)	56
Et	**g**	OBn	**g**	**ee** (3)	**ee** (4)	69
$Ph(CH_2)_2$	**h**	OEt	**h**	**fc** (8)	**fc** (4.5)	84
$Ph(CH_2)_2$	**i**	Ph	**i**	**fd** (7)	**fd** (4.5)	61
2-Naphthyl	**l**	Ph	**l**	**gb** (6)	**gb** (6)	68

A plausible mechanism for the one-pot conversion of the nitroalcohols **92** into the furans **93** is reported in **Scheme 38**, in which the formed nitroalkanol **92** is protonated at the oxygen with the formation of the intermediate **A**. The latter, leads to the opening of 1,3-dioxolane ring with the formation of **B**, which proceeds to the hetero-cyclization by the attack of the hydroxyl group to the oxonium cation, affording the intermediate **C**. Then, the process undergoes an acid–base equilibrium (**D**) followed by the

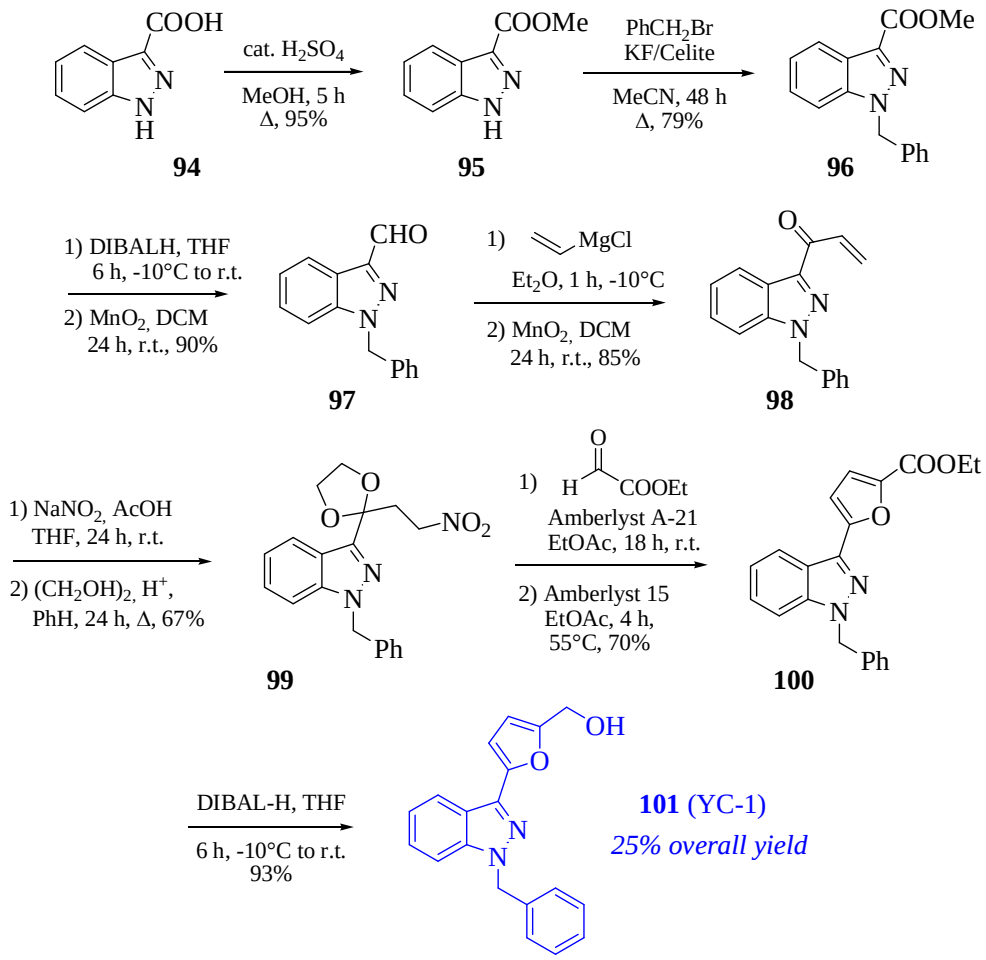
elimination of a mole of ethylene glycol, with the formation of the structure **E** which is converted, after deprotonation (**F**) and elimination of nitrous acid, into the target furan system **93**. Thus, by the appropriate choice of the nitroalkane **90** it is possible to introduce the needed alkyl (or aryl) group at 5-position of the target furan. Moreover, it is important to note the key role of the nitro functionality that firstly acts as good electron-withdrawing group, allowing the generation of a new C,C bond (**90 + 91** to **92**), then as good leaving group favoring the generation of a new C,C double bond (**F** to **93**) by elimination of nitrous acid.



Scheme 38. Proposed reaction mechanism for the formation of furan derivatives

Practical application, synthesis of YC-1

As a practical application of our procedure we report here the total synthesis of 1-benzyl-3-(5-hydroxymethyl-2-furyl)- indazole (**YC-1**) (**Scheme 39**), a very important pharmaceutical target that exhibits significant inhibitory effects against thrombin-,AA-, collagen-, and PAF-induced platelet aggregation.[145] The synthesis starts from the commercially available indazole-3-carboxylic acid **94**, which was converted into the corresponding methyl ester **95**, by methanol and in the presence of sulfuric acid.[146] Then, **95** was benzylated by CsF-Celite, with MeCN as solvent and under reflux for 48 hours, affording the derivative **96**.[147] The latter was initially reduced, by DIBAL-H, to the corresponding primary alcohol, which was then submitted to oxidation, by activated MnO_2 in DCM, affording the aldehyde **97**. The compound **97**, was then alkylated with vinylmagnesium chloride in diethyl ether at -10 °C, affording the corresponding allylic alcohol, which was directly converted into the α,β-unsaturated ketone **98**, under MnO_2 and DCM oxidation. Then, the enone **98** was nitrated using $NaNO_2$, in the presence of AcOH and in THF, and the formed crude β-nitro ketone was protected by ethylene glycol, under refluxing benzene and using the Dean Stark apparatus.[140] Finally, **99** reacted with ethyl glyoxalate following our procedure (Amberlyst A21 and Amberlyst 15) affording the furan derivative **100**, which was reduced by DIBAL-H into the target product **101** (**YC-1**) and in 25% overall yield.

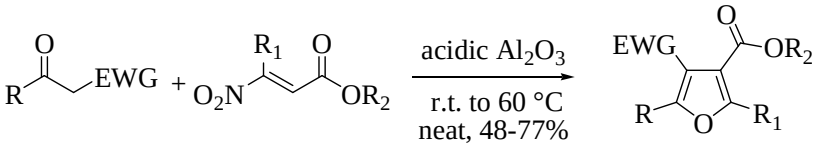


Scheme 39. Synthetic pathway of biologically active compound **101** (YC-1)

Although, the overall yield of our approach is comparable to the main already reported procedures,[148] differently to them, our approach involves for the first time, to the best of our knowledge, the formation of furan ring during the synthetic process. This peculiarity could offer an easy access to a library of analogs of the compound **100**, having similar activity to the target by the appropriate selection of the aldehyde **91**.

4.6.2 Synthesis of tetrasubstitued furans in a One-Pot process and under acidic solvent-free conditions[149]

As previously reported, furan derivatives can be prepared from a large variety of starting materials but all these approaches have some difficulties, concerning problematic solvents and the straining to a restricted class of substrates. In this context, in a development of our earlier studies to Michael addition of substrates containing active methylene groups to nitroalkenes,[150] we have investigated the reactivity of β-nitroacrylates **103** with α-functionalized carbonyl derivatives **102** in order to obtain new classes of polyfunctionalized furans **104**, under mild conditions (**Scheme 40**).



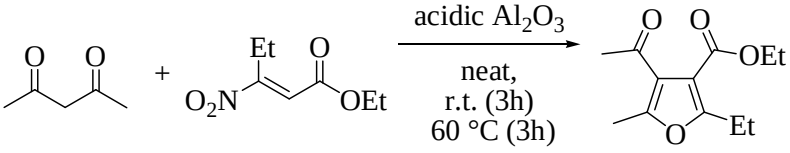
102 **103** **104**

EWG = keto, ester, nitro, cyano.

Scheme 40. General pathway to the synthesis of tetra substituted furans

Based on our experience, and due to the ready enolization of substrates **102**, began the optimization studies of the reaction under acidic conditions. Furthermore, in order to avoid the presence of any solvent, we focused our attention on solid acids. Thus, we investigated a range of solid promoters (acidic alumina, Montmorillonite K-10 and zeolite HSZ-320), under neat conditions, using the reaction of **102a** with **103a** as model, and we found acidic alumina to be the most effective. Subsequently, we tested a variety of substrate/promoter ratios (r.t. for 3 h than heating at 60 °C for 3 h) and, as shown in **Table 10**, the optimal result was obtained using an alumina/substrate ratio of 1.2 g/mmol.

Table 10. Screening of a variety of substrate/promoter ratios

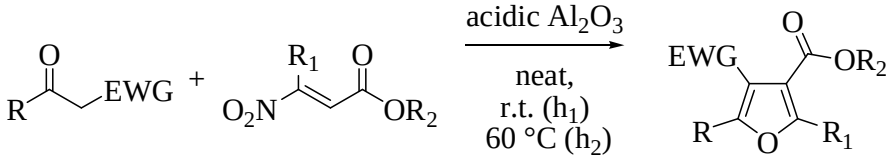


102a **103a** **104aa**

Ratio of the acidic Al_2O_3/substrate	Yield (%) of **104aa**
3.0 g/mmol	68
1.5 g/mmol	70
1.2 g/mmol	77
1.0 g/mmol	66
3.0 g/mmol	68

Encouraged by these results, and in order to assess the generality of our method, a number of different α-functionalized carbonyl derivatives **102** and β-nitroacrylates **103** was tested. As shown in **Table 11**, the reactions proceeded in satisfactory to good overall yields (48-77%).

Table 11. Generality of our method



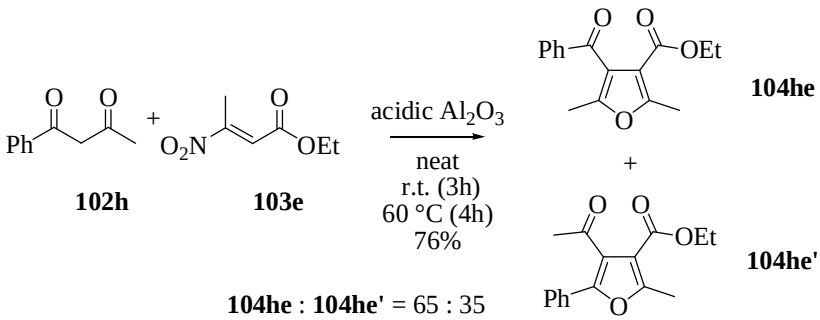
102 **103** **104**

102
- **a** R = Me; EWG = COMe
- **b** R = Me; EWG = COOEt
- **c** R = Pr; EWG = COOEt
- **d** R-EWG = -$(CH_2)_3C(O)$-
- **e** R = Et; EWG = COEt
- **f** R = Ph; EWG = NO_2
- **g** R-EWG = -$CH_2C(CH_3)_2CH_2C(O)$-
- **h** R = Ph; EWG = CN

103
- **a** R_1 = Et; R_2 = Et
- **b** R_1 = $(CH_3)_2CH(CH_2)_2$; R_2 = Et
- **c** R_1 = $CH_3(CH_2)_4$; R_2 = Et
- **d** R_1 = $PhCH_2CH_2$; R_2 = Et
- **e** R_1 = Me; R_2 = Et
- **f** R_1 = Bu; R_2 = Et
- **g** R_1 = $CH_3(CH_2)_4$; R_2 = Bu
- **h** R_1 = $MeOC(O)(CH_2)_4$; R_2 = Et

Ketone	β-Nitroacrylate	Yield (%) of **104**		Time (h_1 + h_2)
1a	**2a**	**aa**	77	3 + 3
1a	**2b**	**ab**	70	3 + 3
1a	**2c**	**ac**	72	3 + 3
1b	**2a**	**ba**	56	4 + 15
1c	**2d**	**cd**	48	4 + 24
1d	**2e**	**de**	75	3 + 3
1d	**2f**	**df**	76	3 + 3
1e	**2g**	**eg**	58	3.5 + 6
1e	**2c**	**ec**	57	3.5 + 8
1f	**2a**	**fa**	49	3 + 3
1g	**2h**	**gh**	50	3.5 + 5
1h	**2c**	**hc**	49	3 + 3

It is important to note that tetrasubstituted furans **104** obtained by this protocol possess at least two functionalities, such as keto, ester, nitro and cyano groups in the 3- and 4-positions. Such functionalities, whilst very useful for subsequent transformations, are difficult to introduce by other approaches. In addition, by the appropriate choice of the alkyl groups (R and R_1) in the starting material **102** and **103**, it is possible to introduce a variety of substituents at the 2- and 5-positions. Regarding the regioselectivity of the procedure; by using non-symmetrical ketones, we tested the reaction of **102h** with **103e** (**Scheme 41**) and, although the reaction works with good overall yield (76%), the regioselectivity is moderate and we isolated the regioisomeric products **104he** and **104he'** in 65:35 ratio.



102h **103e**

104he : **104he'** = 65 : 35

Scheme 41. The regioselectivity of our method

4.7 Conclusions

The research on new processes with a low environmental impact has become a need felt urgent for the protection of the environment and of the human health. From this perspective, the results reported in this thesis, represent interesting examples of how, through alternative reaction conditions like domino reactions, it is possible to achieve new polyfunctionalized molecules, reducing in the same time the amount of waste and the usage of hazardous materials. Thanks to the high flexibility of nitro compounds and β-nitroacrylates, we were able to synthesize different polyfunctionalyzed homo- and heterocycles, such as, bicyclo[3.3.1]nonanes, by the easy preparation, under very mild reaction conditions and in very good overall yields. Moreover, an example of preparation of a *bis*-bicyclo derivative, with the simultaneous formation of eight new C,C bonds, has been reported. Carbazoles and 2,5-disubsituted furans were also obtained in a similar way, exploiting the high reactivity of protected β-nitroketones. Every single step was carried out under heterogeneous conditions so that work-up operations are minimized to an easy filtration of the promoters and the purification steps is close to the targets. Moreover, in these conditions, thanks to the mild environment, it has been possible to achieve the total synthesis of a very important pharmaceutical target such as 1-benzyl-3-(5'-hydroxymethyl-2'-furyl)-indazole (YC-1). Finally, it has been possible, exploiting the reactivity of β-nitroacrylates, to synthesize 2H-1,4-bonzoxazine-2-one, dihydroquinoxaline and tetra substituted furan, derivatives. Thus, we have discovered new procedures for the synthesis of these compounds which permit the use of mild reaction conditions and the presence of other important functionalities, such as ether, nitrile, ketal and nitro, that can be preserved under aforesaid reaction conditions, and that can be converted if it is needed.

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[28] Crystal data for **23f**: M_r=434.44, size 0.20x0.20x0.08 mm, tetragonal, *I*41/a, *a*=24.3642(10), *c*=14.4734(12) Å, *V*=8591.6(9) Å ^{3}, Z=16, ρ=1.343 gcm^{-3}, μ=0.104 mm^{-1}, $Mo_{K\alpha}$, radiation (λ=0.71073 Å), *T*=296(2) K, 1.64<θ<25.00, 40342 collected

and 3779 independent reflections, (R_{int}=0.0276), R_1=0.0508 [I>2σ(I)], wR_2=0.1383. Crystal data for **23g**: M_r=464.46, size 0.20x0.18x0.10 mm, monoclinic, $P2_1/n$, a=11.635(5), b=13.533(6), c=13.983(6) Å, β=90.358(6), V= 2201.6(16) Å ^{3}, Z=4, ρ=1.401 g cm^{-3}, μ=0.109 mm_1, $Mo_{K\alpha}$, radiation (λ=0.71073 Å), T=296(2) K, 2.09<θ<25.00, 15017 collected and 3865 independent reflections, (R_{int}=0.1534), R_1=0.0764 [I>2 σ(I)], wR_2=0.2454. CCDC 705363 (**23f**) and 705364 (**23g**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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CHAPTER 5

PROCEDURES & SPECTROSCOPIC DATA

5.1 Synthesis of polyfunctionalized bicyclo[3.3.1]nonanes

Single-crystal X-ray diffraction studies

X-ray data collections have been performed at room temperature on a Bruker APEX II diffractometer, equipped with a CCD detector operating at 50 kV and 30 mA, using Mo/Kα radiation. An empirical correction was applied using SADABS.[1] The structures were solved by direct methods and refined by full-matrix least squares on F^2 using SHELXL97.[2] The non-hydrogen atoms were subjected to anisotropic refinement, the disordered ones were split in two positions using anisotropic displacement parameter restraints. Hydrogen atoms were added in calculated positions, which were not refined but continuously updated with respect to their carbon atoms, and were given a fixed isotropic thermal parameters.

In the solid state the packing of both **23f** and **23g** compounds seem to be driven mainly by steric effects, as there are only weak intermolecular hydrogen interactions whose C-H...O distances are comprised in the range 3.155(3) - 3.181(4) Å for **23f** and 3.018(27)-3.223(9) Å for **23g**. They mostly involve the oxygen atoms of the NO_2 groups and are responsible for their observed torsion angle of about 58° with respect to the bicyclo[3.3.1]nonane framework.

[1] [G. M. Sheldrick, SADABS, 1996, University of Göttingen, Germany].

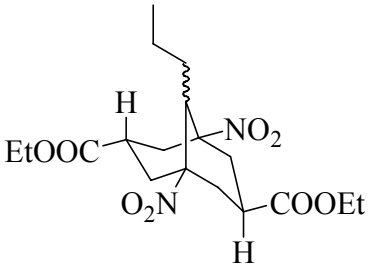
[2] [G. M. Sheldrick, SHELX97, 1997, University of Göttingen, Germany].

Crystal data and collection details for **23f** and **23g**

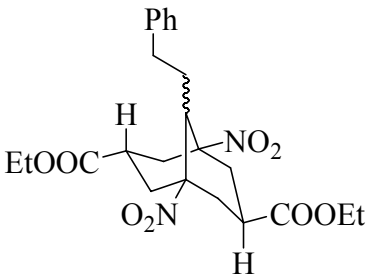
Compound	**23f**	**23g**
Formula	$C_{21}H_{26}N_2O_8$	$C_{22}H_{28}N_2O_9$
Fw	434.44	464.46
T, K	296(2)	296(2)
λ, Å	0.71073	0.71073
Crystal system	Tetragonal	Monoclinic
Space group	$I4_1/a$	$P2_1/n$
a, Å	24.3642(10)	11.635(5)
b, Å	24.3642(10)	13.533(6)
c, Å	14.4734(12)	13.983(6)
α, °	90	90
β, °	90	90.358(6)
γ, °	90	90
Cell Volume, Å^3	8591.6(9)	2201.6(16)
Z	16	4
D_c, g cm^{-3}	1.343	1.401
μ, mm^{-1}	0.104	0.109
F(000)	3680	984
Crystal size, mm	0.20 x 0.20 x 0.08	0.20 x 0.18 x 0.10
θ limits, °	1.64 to 25.00	2.09 to 25.00
Index ranges	-28<=h<=28; -28<=k<=28; -17<=l<=17	-13<=h<=13; -16<=k<=16; -16<=l<=16
Reflections collected	40342	15017
Independent reflections	3779 [R(int) = 0.0276]	3865 [R(int) = 0.1534]
Completeness to θ = 25.00°	99.9	100.0
Data / restraints / parameters	3779 / 0 / 282	3865 / 6 / 311
Goodness on fit on F^2	1.046	1.014
R_1 ($I > 2\sigma(I)$)	0.0508	0.0764
wR_2 (all data)	0.1383	0.2454
Largest diff. peak and hole, e Å^{-3}	0.425 and -0.355	0.354 and -0.403

*General procedure for the synthesis of compounds **23***:

Ethyl(2-bromomethyl)acrylate (1 mmol, 0.140 mL) was added dropwise to a stirred solution of the appropriate nitrocompound (0.5 mmol for aliphatic nitrocompounds and 0.6 mmol for aromatic nitrocomponds) and DBU (2.5 equiv, 228 mg, 0.224 mL) in CH_3CN (5 mL). After stirring for the opportune time (see **Table 1** pag. 76) at room temperature, the reaction mixture was treated with 0.5N HCl (5 mL) and the organic phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined layers were dried with anhydrous Na_2SO_4, filtered, evaporated under reduced pressure, and then purified by flash chromatography (cyclohexane/ethylacetate), yielding the pure bicycle[3.3.1]nonane derivative.

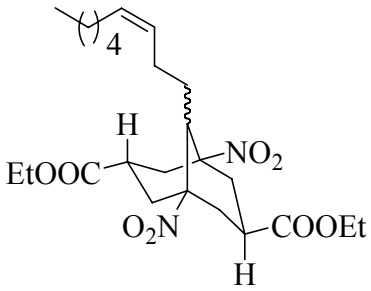


23a. White solid: m.p. = 142-144°C; IR (nujol) (NaCl disc): 2924, 1730, 1545, 1345, 1199 cm^{-1}; ^1H NMR δ ($CDCl_3$, ppm) 0.77 (t, 3H, *J* = 6.8 Hz), 1.07-1.22 (m, 4H), 1.26 (t, 3H, *J* = 7.3 Hz), 1.31 (t, 3H, *J* = 7.3 Hz), 2.34-2.44 (m, 4H), 2.50 (dt, 2H *J* = 12.4, 3.0 Hz), 2.67 (dt, 2H, *J* = 13.2, 3.0 Hz), 2.99 (s, 1H), 3.01-3.15 (m, 2H), 4.16 (q, 2H, *J* = 7.3 Hz), 4.22 (q, 2H, *J* = 7.3 Hz); ^{13}C NMR δ ($CDCl_3$, ppm) 14.3, 14.4, 14.5, 22.6, 29.2, 29.5, 37.2, 38.0, 39.3, 47.6, 62.0, 91.4, 171.7, 172.8. EI-MS (70eV) m/z: 355, 252, 233, 178(100), 159, 105, 91, 55, 29. Anal. Calcd. for $C_{18}H_{28}N_2O_8$ (400.23): C, 53.99%; H, 7.05%; N, 7.00%; Found: C, 55.11%; H, 7.20%; N, 6.91%.

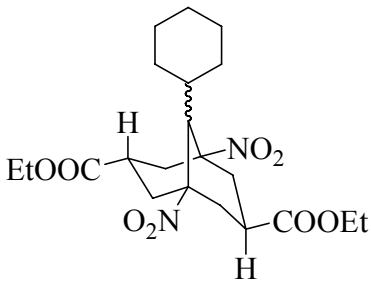


23b. Waxy; IR (nujol) (NaCl disc): 2923, 1741, 1542, 1347, 1194 cm^{-1}; ^1H NMR δ ($CDCl_3$, ppm) 1.27 (t, 3H, *J* = 6.8 Hz), 1.28 (t, 3H, *J* = 6.8 Hz), 1.35-1.47 (m, 2H), 2.38-2.52 (m, 8H), 2.69 (t, 2H, *J* = 13.2 Hz), 2.95-3.19 (m, 3H), 4.17 (q, 2H, *J* = 6.8 Hz), 4.18 (q, 2H, *J* = 6.8 Hz), 6.96-7.32 (m, 5H); ^{13}C NMR δ ($CDCl_3$, ppm) 14.4, 14.5, 29.6, 30.1, 35.9, 37.1, 38.0, 39.2, 47.4, 62.0, 62.1, 91.6,

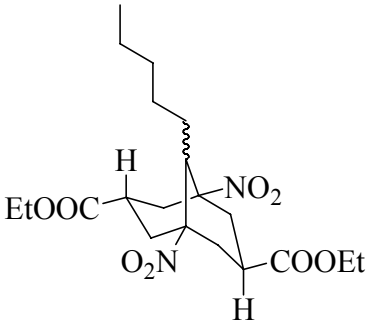
126.5, 128.6, 128.7, 141.0, 171.7, 172.5. EI-MS (70eV) m/z: 462(M^+), 383, 325, 295, 249, 221, 178, 117, 91(100), 65, 29. Anal. Calcd. for $C_{23}H_{30}N_2O_8$ (462.50): C, 59.73%; H, 6.54%; N, 6.06%; Found: C, 59.08%; H, 6.47%; N, 5.78%.



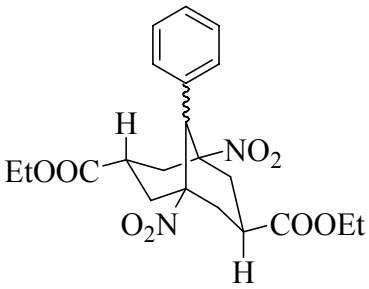
23c. Yellow oil; IR (nujol) (NaCl disc): 2930, 1732, 1547, 1348, 1192 cm^{-1}; ^1H NMR δ ($CDCl_3$, ppm) 0.88 (t, 3H, *J* = 6.8 Hz), 1.10-1.34 (m, 8H), 1.26 (t, 3H, *J* = 6.8 Hz), 1.31 (t, 3H, *J* = 7.3 Hz), 1.76-1.98 (m, 4H), 2.34-2.52 (m, 6H), 2.62-2.72 (dt, 2H, *J* = 13.2, 2.6 Hz), 2.97-3.16 (m, 3H), 4.16 (q, 2H, *J* = 6.8 Hz), 4.21 (q, 2H, *J* = 7.3 Hz), 5.08-5.16 (m, 1H), 5.29-5.38 (m, 1H); ^{13}C NMR δ ($CDCl_3$, ppm) 14.3, 14.4, 14.5, 22.8, 27.0, 27.2, 27.3, 29.6, 31.7, 37.2, 38.0, 39.3, 47.3, 62.0, 62.2, 91.5, 127.4, 132.0, 171.8, 172.7. EI-MS (70eV) m/z: 482(M^+), 343, 315, 269, 241, 205, 178, 131, 105(100), 55, 29. Anal. Calcd. for $C_{24}H_{38}N_2O_8$ (482.57): C, 59.74%; H, 7.94%; N, 5.81%; Found: C, 59.60%; H, 8.18%; N, 5.71%.



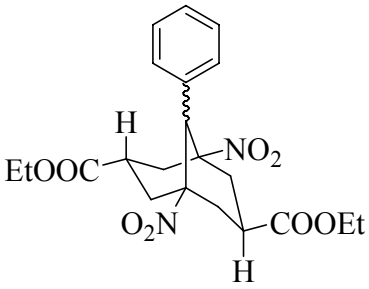
23d. Waxy; IR (nujol) (NaCl disc): 2923, 1743, 1728, 1542, 1376, 1205 cm^{-1}; ^1H NMR δ ($CDCl_3$, ppm) 0.94-1.16 (m, 6H), 1.25 (t, 3H, *J* = 6.8 Hz), 1.31 (t, 3H, *J* = 7.3 Hz), 1.53 (d, 1H, *J* = 11.5 Hz), 1.60-1.76 (m, 4H), 2.28-2.36 (dd, 2H, *J* = 13.6, 5.5 Hz), 2.40-2.48 (dd, 2H, *J* = 15.3, 7.3 Hz), 2.55-2.69 (m, 4H), 3.03 (s, 1H), 3.00-3.15 (m, 2H), 4.14 (q, 2H, *J* = 6.8 Hz), 4.22 (q, 2H, *J* = 7.3 Hz); ^{13}C NMR δ ($CDCl_3$, ppm) 14.3, 14.4, 25.7, 27.5, 30.2, 32.7, 37.5, 38.0, 39.9, 41.8, 51.9, 62.0, 92.1, 171.7, 173.0. EI-MS (70eV) m/z: 393, 336, 271, 253, 207, 178, 131, 105(100), 55, 29. Anal. Calcd. for $C_{21}H_{32}N_2O_8$ (440.49): C, 57.26%; H, 7.32%; N, 6.36%; Found: C, 56.64%; H, 7.45%; N, 6.20%.



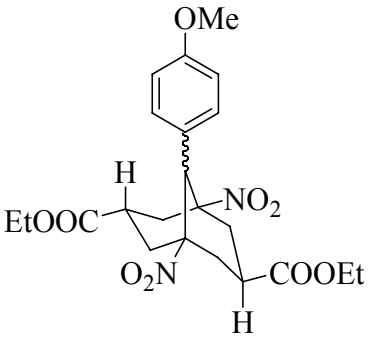
23e. Yellow oil; IR (neat) (NaCl disc): 2957, 1732, 1548, 1368, 1193 cm^{-1}; ^1H NMR δ ($CDCl_3$, ppm) 0.81 (t, 3H, *J* = 6.8 Hz), 1.05-1.22 (m, 8H), 1.26 (t, 3H, *J* = 7.3 Hz), 1.31 (t, 3H, *J* = 7.3 Hz), 2.34-2.43 (m, 4H), 2.48 (dt, 2H *J* = 12.8, 2.6 Hz), 2.66 (dt, 2H, *J* = 13.2, 2.6 Hz), 2.97 (s, 1H), 2.95-3.15 (m, 2H), 4.16 (q, 2H, *J* = 7.3 Hz), 4.21 (q, 2H, *J* = 7.3 Hz); ^{13}C NMR δ ($CDCl_3$, ppm) 14.1, 14.3, 14.4, 22.3, 27.1, 29.0, 29.5, 32.0, 37.2, 38.0, 39.3, 47.8, 62.0, 91.5, 171.8, 172.8. EI-MS (70eV) m/z: 383, 351, 335, 261, 178, 131, 105(100), 91, 55, 29. Anal. Calcd. for $C_{20}H_{32}N_2O_8$ (428.48): C, 56.06%; H, 7.53%; N, 6.54%; Found: C, 55.94%; H, 7.81%; N, 6.52%.



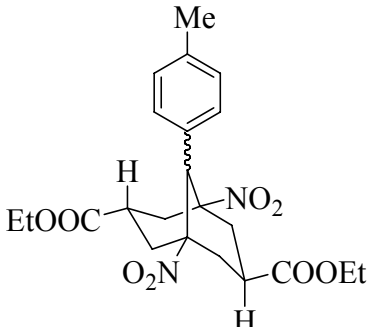
(*exo*-3,*endo*-7-**23f).** White solid: m.p. = 150-153°C; IR (nujol) (NaCl disc): 2924, 2360, 1742, 1557, 1376, 1191 cm^{-1}; ^1H NMR δ ($CDCl_3$, ppm) 1.29 (t, 3H, *J* = 7.3 Hz), 1.34 (t, 3H, *J* = 7.3 Hz), 2.16-2.35 (m, 4H), 2.76-2.96 (m, 5H), 3.23-3.56 (m, 1H), 4.21 (q, 2H, *J* = 7.3 Hz), 4.28 (q, 2H, *J* = 7.3 Hz), 4.29 (s, 1H), 7.22-7.32 (m, 5H); ^{13}C NMR δ ($CDCl_3$, ppm) 14.4, 14.5, 31.6, 35.0, 36.0, 37.6, 52.1, 62.0, 62.1, 89.1, 129.1, 129.5, 131.0, 131.4, 172.6, 172.9. EI-MS (70eV) m/z: 434(M^+), 341, 267, 252, 193, 178, 105(100), 91, 29. Anal. Calcd. for $C_{21}H_{26}N_2O_8$ (434.44): C, 58.06%; H, 6.03%; N, 6.45%; Found: C, 58.14%; H, 6.01%; N, 6.34%.



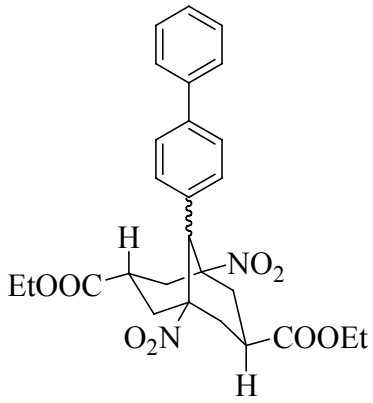
23f. Diastereomeric mixture (*exo*-3,*endo*-7/*exo*-3,*exo*-7 = 3/2); white solid: m.p. = 149-156°C; IR (nujol) (NaCl disc): 2924, 2360, 1742, 1557, 1376, 1191 cm^{-1}; ^1H NMR δ ($CDCl_3$, ppm) 1.29-1.37 (m, 6H), 2.17-2.35 (m, 2.4H), 2.46-2.53 (m, 1.6H), 2.78-2.97 (m, 4H), 3.04 (dt, 1H, *J* = 13.3, 3.0 Hz), 3.21-3.34 (m, 0.6H), 3.46-3.58 (m, 0.4H), 4.17-4.26 (m, 2H), 4.27-4.34 (m, 3H), 7.23-7.25 (m, 5H); ^{13}C NMR δ ($CDCl_3$, ppm) 14.3, 14.4, 29.6, 31.6, 35.0, 36.1, 37.6, 38.1, 40.9, 52.1, 55.2, 62.1, 62.2, 62.3, 89.1, 91.2, 129.0, 129.1, 129.2, 129.5, 130.9, 131.1, 131.3, 131.6, 171.7, 172.6, 172.9, 173.2. EI-MS (70eV) m/z: 434(M^+), 341, 267, 252, 193, 178, 105(100), 91, 29. Anal. Calcd. for $C_{21}H_{26}N_2O_8$ (434.44): C, 58.06%; H, 6.03%; N, 6.45%; Found: C, 58.14%; H, 6.01%; N, 6.34%.



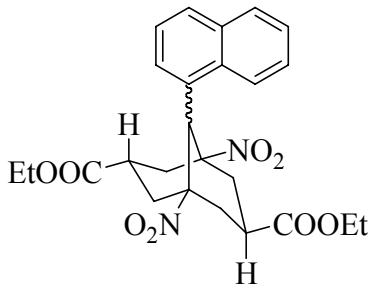
23g. Diastereomeric mixture (*exo*-3,*endo*-7/*exo*-3,*exo*-7 = 65/35); white solid: m.p. = 146-149°C; IR (nujol) (NaCl disc): 2954, 2359, 1729, 1541, 1376, 1206 cm^{-1}; ^1H NMR δ ($CDCl_3$, ppm) 1.30 (t, 3H, *J* = 7.3 Hz), 1.35 (t, 3H, *J* = 7.3 Hz), 2.15-2.32 (m, 3H), 2.41-2.51 (m, 1H), 2.80-2.94 (m, 3H), 3.01 (dt, 1H, *J* = 12.4, 3.0 Hz), 3.18-3.32 (m, 0.3H), 3.45-3.56 (m, 0.7H), 3.73 (s, 3H), 4.21 (q, 2H, *J* = 7.3 Hz), 4.25 (s, 1H), 4.29 (q, 2H, *J* = 7.3 Hz), 6.75-7.25 (m, 5H); ^{13}C NMR δ ($CDCl_3$, ppm) 14.3, 14.4, 29.6, 31.6, 34.9, 36.1, 37.5, 37.6, 40.8, 51.4, 54.5, 55.4, 62.0, 62.1, 62.2, 89.0, 91.2, 114.4, 114.5, 122.5, 132.3, 132.5, 160.0, 160.3, 171.7, 172.7, 173.0, 173.3. EI-MS (70eV) m/z: 464(M^+), 371, 297, 252, 223, 178, 135(100), 105, 29. Anal. Calcd. for $C_{22}H_{28}N_2O_9$ (464.47): C, 56.89%; H, 6.08%; N, 6.03%; Found: C, 56.86%; H, 6.14%; N, 5.93%.



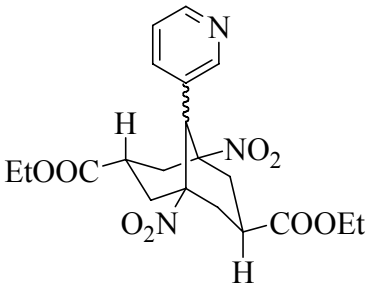
23h. White solid: m.p. = 182-185°C; IR (nujol) (NaCl disc): 2923, 1733, 1547, 1376, 1190 cm^{-1}; ^1H NMR δ ($CDCl_3$, ppm) 1.29 (t, 3H, *J* = 6.8 Hz), 1.36 (t, 3H, *J* = 7.3 Hz), 2.26 (s, 3H), 2.43-2.52 (m, 4H), 2.80-2.90 (dt, 2H, *J* = 13.6, 3.0 Hz), 2.98-3.09 (dt, 2H, *J* = 15.3, 3.0 Hz), 3.19-3.32 (m, 2H), 4.18 (s, 1H), 4.20 (q, 2H, *J* = 6.8 Hz), 4.30 (q, 2H, *J* = 7.3 Hz), 7.03-7.23 (m, 4H); ^{13}C NMR δ ($CDCl_3$, ppm) 14.3, 14.4, 21.2, 29.6, 37.6, 38.1, 40.8, 54.8, 62.1, 62.2, 91.2, 128.4, 129.7, 130.9, 139.1, 171.7, 173.2. EI-MS (70eV) m/z: 448(M^+), 355, 281, 252, 207, 178, 119(100), 105, 29. Anal. Calcd. for $C_{22}H_{28}N_2O_8$ (448.50): C, 58.92%; H, 6.29%; N, 6.25%; Found: C, 58.74%; H, 6.42%; N, 6.13%.



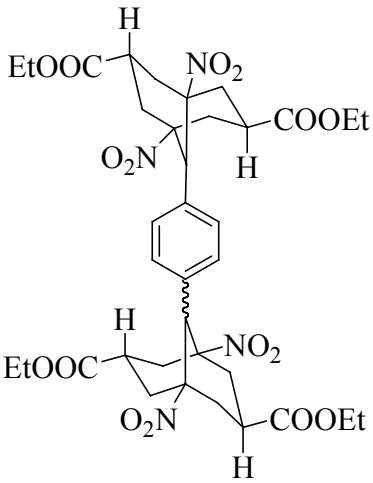
23i. White solid; m.p. = 180-184°C; IR (nujol) (NaCl disc): 2924, 1735, 1544, 1376, 1200 cm^{-1}; ^1H NMR δ ($CDCl_3$, ppm) 1.30 (t, 3H, *J* = 7.3 Hz), 1.38 (t, 3H, *J* = 7.3 Hz), 2.48-2.57 (m, 4H), 2.82-2.92 (dt, 2H, *J* = 13.6, 3.0 Hz), 3.03-3.13 (dt, 2H, *J* = 15.3, 3.0 Hz), 3.22-3.36 (m, 2H), 4.21 (q, 2H, *J* = 7.3 Hz), 4.29 (s, 1H), 4.32 (q, 2H, *J* = 7.3 Hz), 7.30-7.54 (m, 9H); ^{13}C NMR δ ($CDCl_3$, ppm) 14.4, 14.5, 30.0, 37.7, 38.1, 41.0, 54.9, 62.2, 62.3, 91.3, 127.3, 127.7, 127.8, 129.0, 130.5, 131.5, 140.1, 141.8, 171.7, 173.3. EI-MS (70eV) m/z: 510(M^+), 417, 343, 269, 252, 178(100), 105, 29. Anal. Calcd. for $C_{27}H_{30}N_2O_8$ (510.54): C, 63.52%; H, 5.92%; N, 5.49%; Found: C, 63.61%; H, 6.01%; N, 5.38%.



23j. White solid: m.p. = 164-167°C; IR (nujol) (NaCl disc): 2924, 2361, 1730, 1545, 1376, 1195 cm^{-1}; ^1H NMR δ ($CDCl_3$, ppm) 1.27 (t, 3H, *J* = 6.8 Hz), 1.37 (t, 3H, *J* = 7.3 Hz), 2.47-2.56 (m, 4H), 2.81-2.90 (dt, 2H, *J* = 10.6, 3.0 Hz), 3.09-3.20 (dt, 2H, *J* = 11.9, 3.0 Hz), 3.21-3.38 (m, 2H), 4.19 (q, 2H, *J* = 6.8 Hz), 4.32 (q, 2H, *J* = 7.3 Hz), 4.40 (s, 1H), 7.36-7.90 (m, 7H); ^{13}C NMR δ ($CDCl_3$, ppm) 14.4, 14.5, 27.1, 29.7, 37.7, 38.1, 41.0, 55.0, 62.1, 62.3, 91.3, 126.6, 127.6, 128.6, 128.7, 128.9, 129.3, 130.5, 133.0, 133.2, 171.7, 173.4. EI-MS (70eV) m/z: 484(M^+), 391, 317, 243, 215, 178(100), 156, 141, 105, 29. Anal. Calcd. for $C_{25}H_{28}N_2O_8$ (484.50): C, 61.98%; H, 5.82%; N, 5.78%; Found: C, 61.20%; H, 5.92%; N, 5.40%.

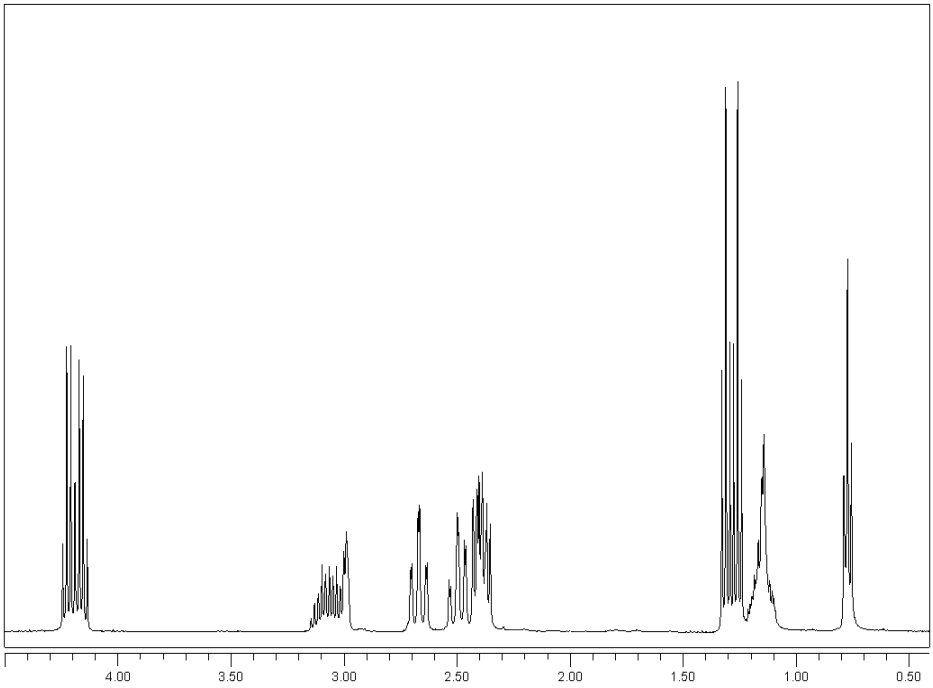


23k. Diastereomeric mixture (*exo*-3,*endo*-7/*exo*-3,*exo*-7 = 85/15); **3k'- 3k"**; White solid: m.p. = 149-155°C; IR (nujol) (NaCl disc): 2922, 1732, 1547, 1376, 1188 cm^{-1}; ^{1}H NMR δ ($CDCl_3$, ppm) 1.28 (t, 3H, *J* = 6.8 Hz), 1.36 (t, 3H, *J* = 7.3 Hz), 2.22-2.43 (m, 1H), 2.50-2.61 (m, 3H), 2.74-2.96 (m, 4H), 3.21-3.67 (m, 1.7H), 3.43-3.57 (m, 0.3H), 4.20 (q, 2H, *J* = 6.8 Hz), 4.27 (s, 1H), 4.30 (q, 2H, *J* = 7.3 Hz), 7.10-8.65 (m, 4H); ^{13}C NMR δ ($CDCl_3$, ppm) 14.4, 14.5, 29.7, 31.6, 35.1, 35.9, 37.5, 37.6, 38.1, 40.7, 49.9, 52.7, 62.3, 62.5, 88.8, 90.9, 123.7, 128.0, 138.1, 138.3, 150.2, 150.6, 152.3, 171.4, 173.0. EI-MS (70eV) m/z: 435(M^+), 389, 358, 352, 286, 268, 252, 194, 178(100), 106, 29. Anal. Calcd. for $C_{20}H_{25}N_3O_8$ (435.43): C, 55.17%; H, 5.79%; N, 9.65%; Found: C, 55.36%; H, 5.94%; N, 9.11%.

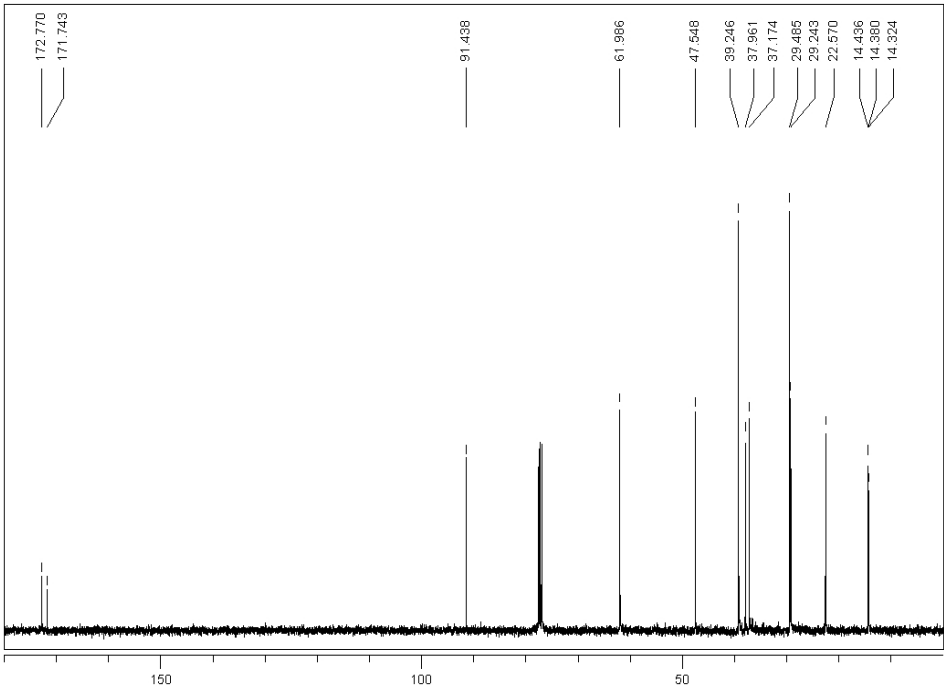


25. Yellow solid: M.P. > 300°C; IR (nujol) (NaCl disc): 2923, 1731, 1547, 1461, 1376, 1241 cm^{-1}; ^{1}H NMR δ ($CDCl_3$, ppm) 1.18 (t, 6H, *J* = 7.3 Hz), 1.27 (t, 6H, *J* = 7.3 Hz), 2.43-2.74 (m, 14H), 3.32 (s, 5H), 3.37-3.52 (m, 3H), 4.02-4.13 (m, 5H), 4.22 (q, 3H, *J* = 7.3 Hz), 7.14 (s, 4H); ^{13}C NMR δ ($CDCl_3$, ppm) 14.7, 28.9, 36.4, 37.0, 54.5, 61.5, 61.9, 92.2, 131.2, 133.5, 172.6, 173.9; ESI-MS: ($M+Na^+$) 813; Anal. Calcd. for $C_{36}H_{46}N_4O_{16}$ (790.77): C, 54.68%; H, 5.86%; N, 7.09%; Found: C, 54.45%; H, 6.07%; N, 6.70%.

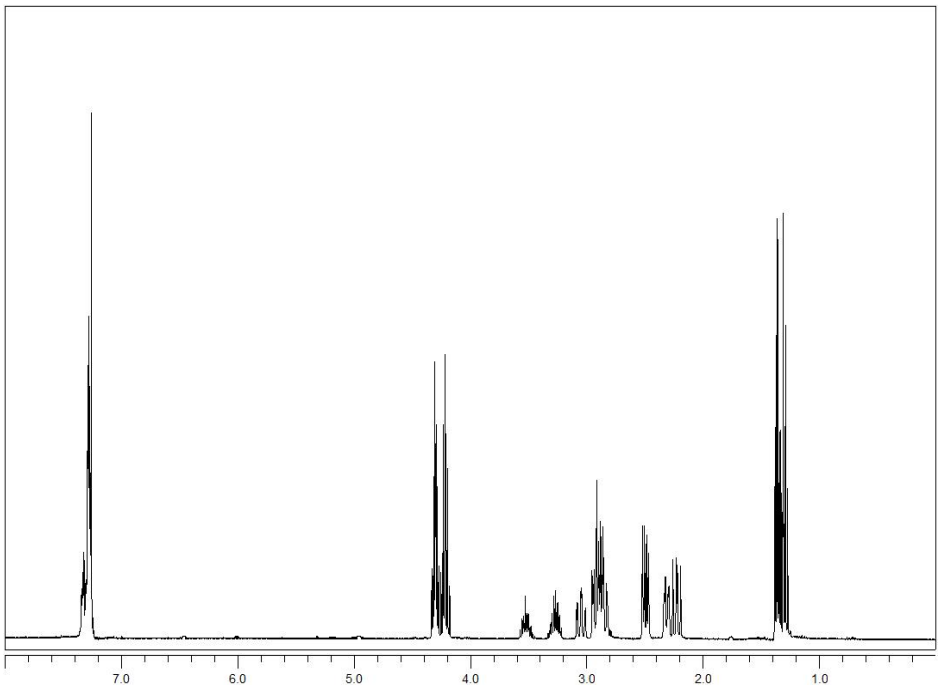
^{1}H-NMR 400MHz of Compound **23a**



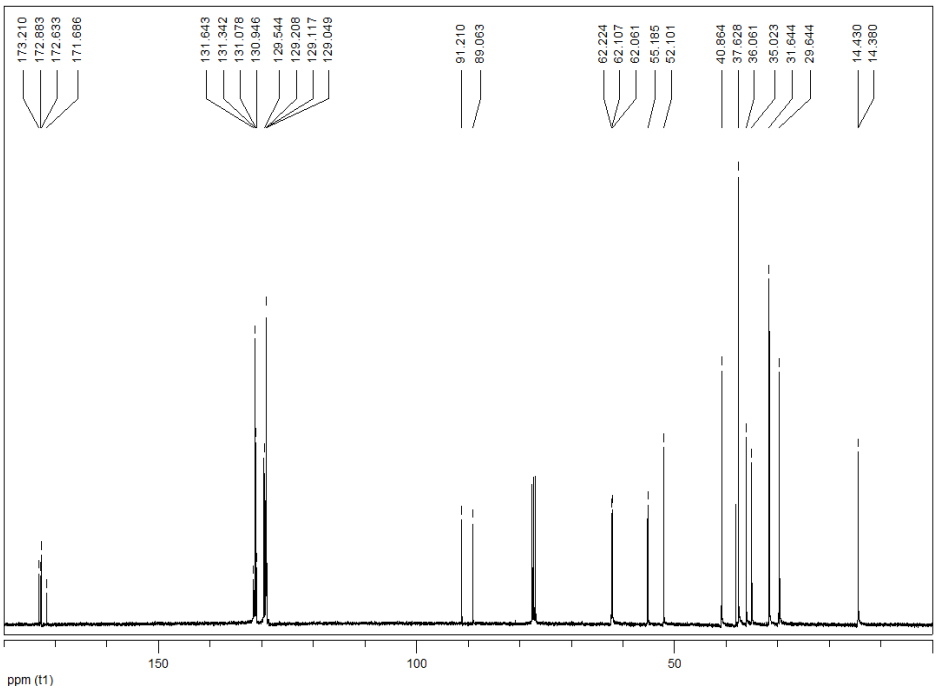
^{13}C-NMR 100MHz of Compound **23a**



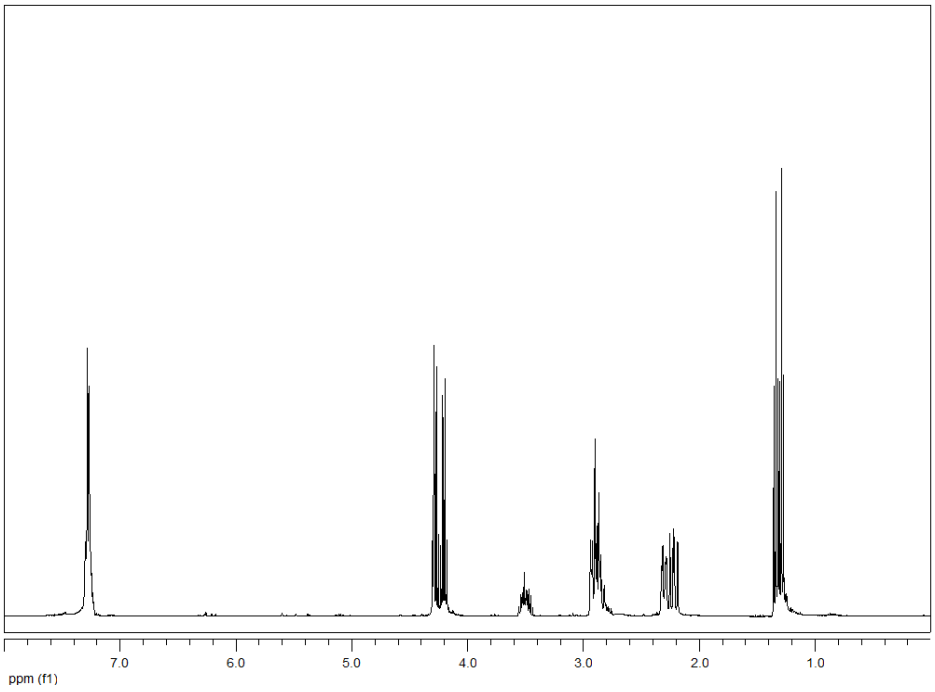
^{1}H-NMR 400MHz of Compound **23f** (diastereomeric mixture)



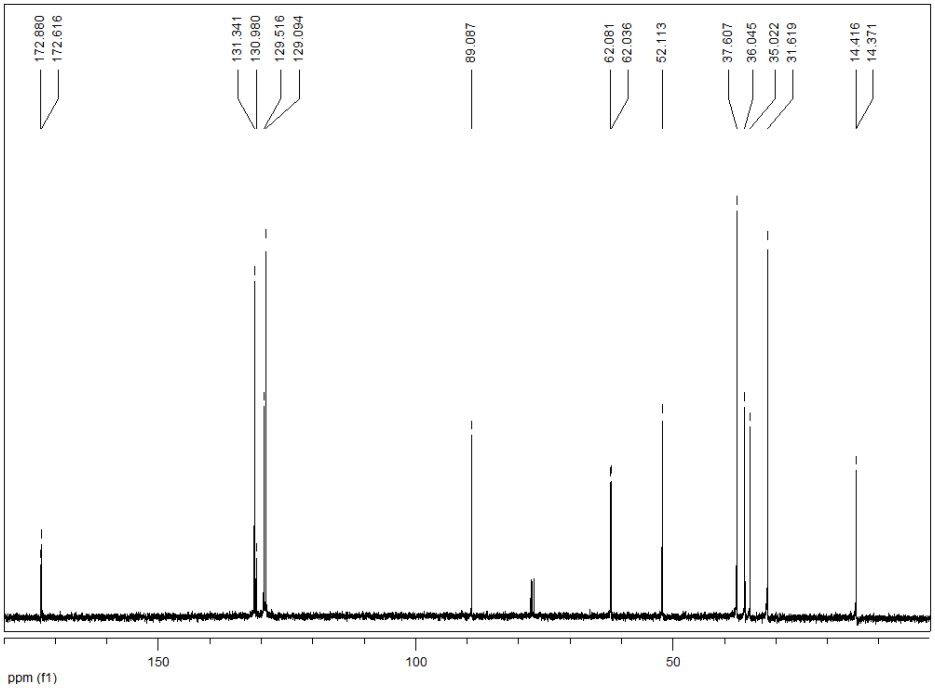
^{13}C-NMR 100MHz of Compound **23f** (diastereomeric mixture)



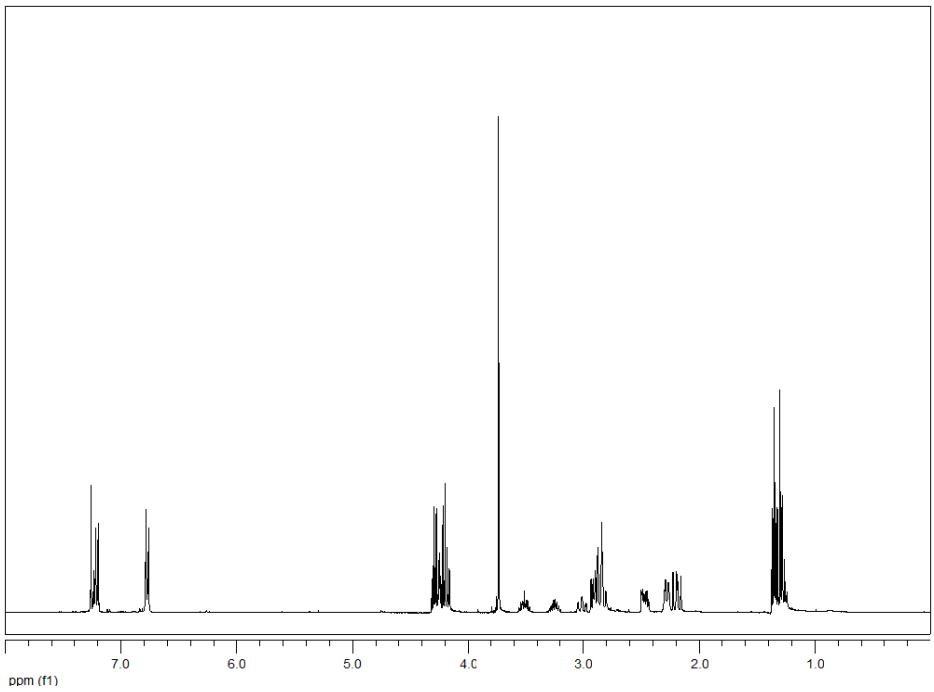
^{1}H NMR 400 MHz of Compound *exo*-3,*endo*-7 **23f**



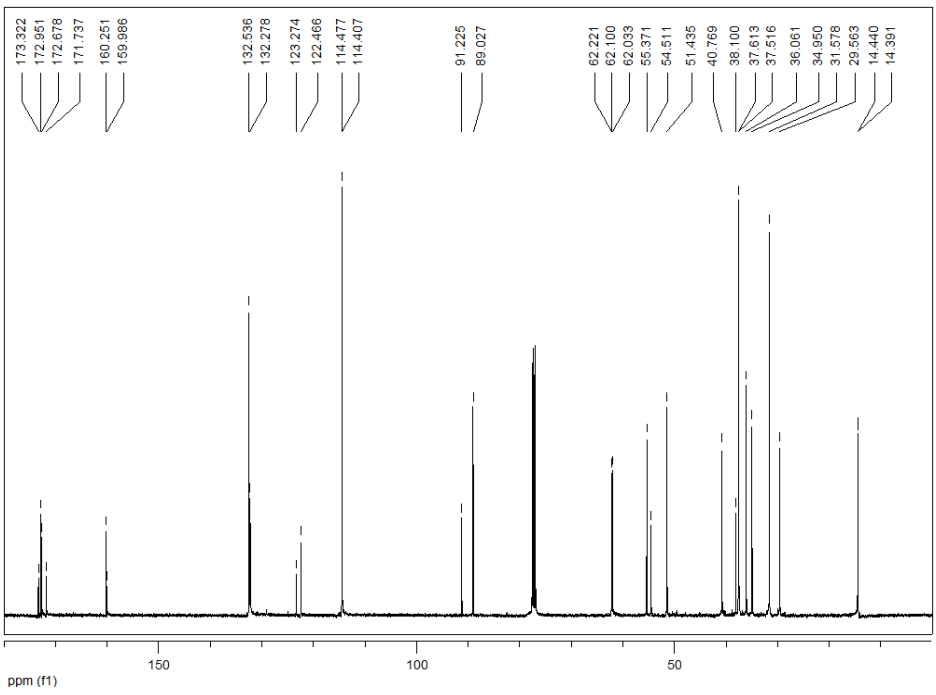
^{13}C-NMR 100MHz of Compound *exo*-3,*endo*-7 **23f**



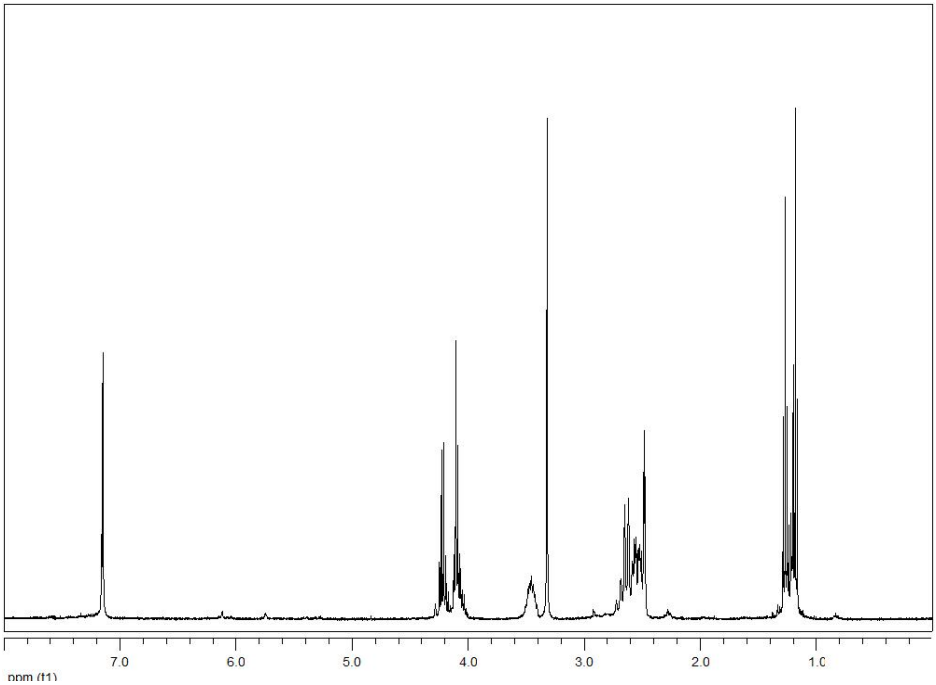
^{1}H NMR 400 MHz of Compound **23g** (diastereomeric mixture)



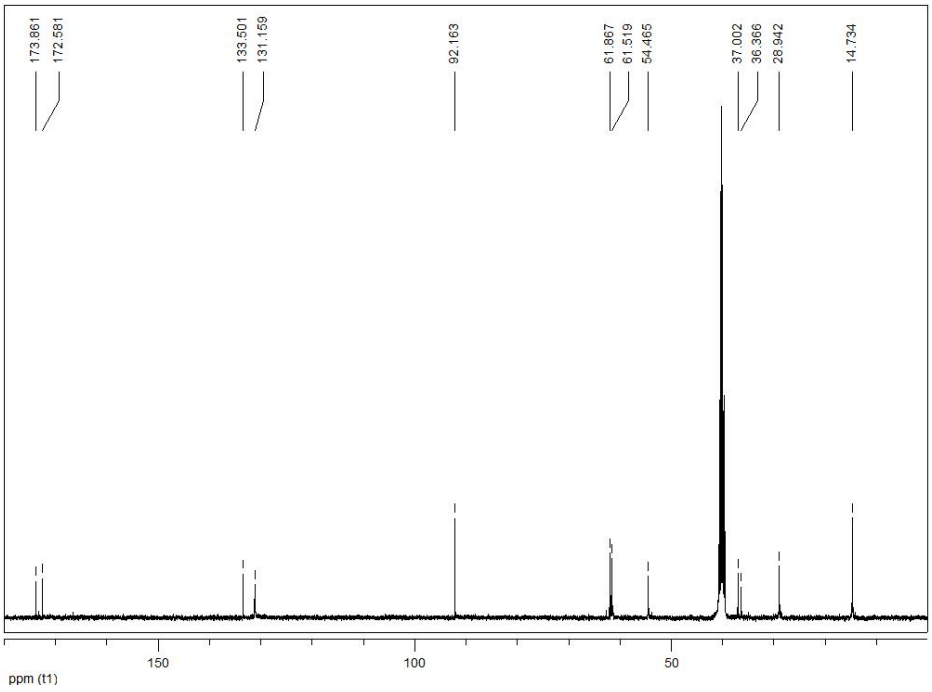
^{13}C-NMR 100MHz of Compound **23g** (diastereomeric mixture)



^{1}H-NMR 400MHz of Compound **25**



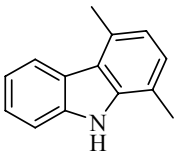
^{13}C-NMR 100MHz of Compound **25**



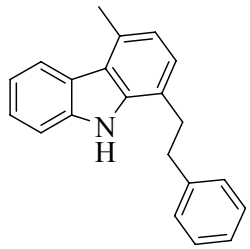
5.2 Synthesis of unsymmetrical 1,4-disubstituted carbazoles from sulfonylindoles

*General Procedure for the Preparation of Carbazoles **42***:

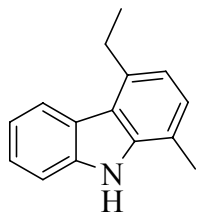
To a stirred solution of sulfonylindole **37** (1.0 mmol) and nitroalkane **40** (1.0 mmol) in dichloromethane (4 mL), potassium fluoride on basic alumina (2.0 g) was added at room temperature. After stirring for the appropriate time (see Table 1), the mixture was filtered over a short pad of celite and washed with EtOAc (15 mL). Removal of the solvent at reduced pressure, gave crude nitroalkyl indole **41** that was dissolved in *i*-PrOH (4 mL) and heated at reflux. To the boiling mixture Amberlyst 15 (1 g), was then added and heating was continued for the appropriate time (see **Table 2** pag. 87). After cooling, the solid promoter was filtered off and washed with EtOAc (3-8 mL). The crude product obtained after removal of the solvent at reduced pressure was purified by flash chromatography (hexanes/toluene 90:10).



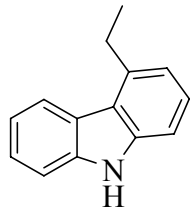
42a. White solid, m.p. 101–103°C; (Bedford, R.B., Betham, M., *J. Org. Chem.*, **2006**, *71*, 9403): 90–92°C. IR (cm^{-1}, nujol) ν: 1216, 1590, 1615, 3054, 3408. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.55 (s, 3H), 2.88 (s, 3H), 6.97 (d, 1H, *J* = 7.7 Hz), 7.16 (d, 1H, *J* = 7.3 Hz), 7.25–7.31 (m, 1H), 7.41–7.51 (m, 2H), 8.06 (bs, 1H), 8.21 (d, 1H, *J* = 7.7 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 16.8, 20.7, 110.7, 117.2, 119.6, 121.0, 121.5, 122.8, 124.6, 125.2, 126.3, 131.0, 138.9, 139.5. GC-MS (70eV): *m/z*: 195([M^+], 100), 194(97), 180(98), 167(25), 152(20), 97(17). Anal. Calcd. for $C_{14}H_{13}N$ (195.26): C, 86.12; H, 6.71; N, 7.17. Found: C, 86.21; H, 6.93; N, 7.16.



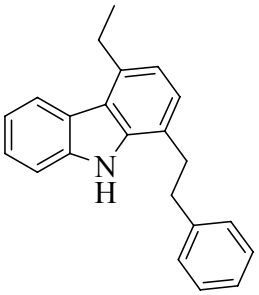
42b. Yellow solid, m.p. 116–119°C. IR (cm^{-1}, nujol) ν: 1250, 1588, 3030, 3420. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.88 (s, 3H), 3.08 (t, 2H, *J* = 6.8 Hz), 3.21 (t, 2H, *J* = 6.8 Hz), 6.98 (d, 1H, *J* = 7.3 Hz), 7.16 (d, 1H, *J* = 7.3 Hz), 7.20–7.34 (m, 6H), 7.38-7.41 (m, 2H), 7.83 (bs, 1H), 8.18(d, 1H, *J* = 7.7 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 20.7, 33.6, 36.4, 110.6, 119.3, 121.0, 121.3, 122.6, 124.4, 125.1, 125.4, 126.3, 126.6, 127.7, 128.7, 131.3, 138.6, 139.7, 142.1. GC-MS (70eV): *m/z*: 285([M^+], 40), 195(26), 194(100), 167(6), 91(8), 65(3). Anal. Calcd. for $C_{21}H_{19}N$ (285.38): C, 88.38; H, 6.71; N, 4.91. Found: C, 88.50; H, 6.78; N, 4.98.



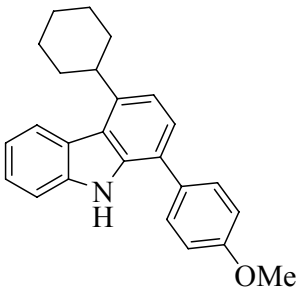
42c. Yield: 64% (from pure **41c**), 61% (from crude **41c**). White solid, m.p. 61–63°C. IR (cm^{-1}, nujol) ν: 1214, 1588, 1614, 3055, 3403. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.48 (t, 3H, *J* = 7.7 Hz), 2.56 (s, 3H), 3.27 (q, 2H, *J* = 7.7 Hz), 7.00 (d, 1H, *J* = 7.3 Hz), 7.19 (d, 1H, *J* = 7.3 Hz), 7.25-7.31 (m, 1H), 7.41–7.46 (m, 1H), 7.50 (dt, 1H, *J* = 0.9, 8.1 Hz), 8.04 (bs, 1H), 8.17 (d, 1H, *J* = 8.1 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 14.5, 16.8, 27.3, 110.7, 117.3, 119.2, 119.6, 120.7, 122.9, 123.9, 125.2, 126.5, 137.5, 139.1, 139.6. GC-MS (70eV): *m/z*: 209([M^+], 90), 194(100), 180(9), 167(14), 152(8). Anal. Calcd. for $C_{15}H_{15}N$ (209.29): C, 86.08; H, 7.22; N, 6.69. Found: C, 86.12; H, 7.38; N, 6.70.



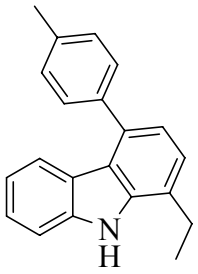
42d. Yield: 68% (from pure **41d**), 62% (from crude **41d**). White solid, m.p. 69–71°C. IR (cm^{-1}, nujol) ν: 1216, 1580, 1620, 3055, 3401. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.50 (t, 3H, *J* = 7.7 Hz), 3.30 (q, 2H, *J* = 7.7 Hz), 7.09 (d, 1H, *J* = 7.7 Hz), 7.25–7.32 (m, 2H), 7.36–7.48 (m, 3H), 8.03 (bs, 1H), 8.18 (d, 1H, *J* = 8.1 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 14.3, 27.5, 108.4, 110.9, 119.2, 119.6, 121.3, 122.9, 123.4, 125.3, 126.0, 139.7, 139.9. GC-MS (70eV): *m/z*: 195([M^+], 97), 194(24), 181(32), 180(100), 178(16), 167(22), 152(25), 90(16), 77(13). Anal. Calcd. for $C_{14}H_{13}N$ (195.26): C, 86.12; H, 6.71; N, 7.17. Found: C, 86.12; H, 6.91; N, 7.17.



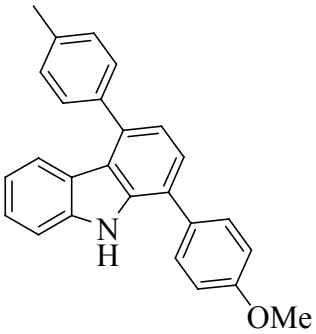
42e. White waxy solid. IR (cm^{-1}, nujol) ν: 1213, 1519, 1587, 1607, 3054, 3430. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.50 (t, 3H, *J* = 7.7 Hz), 3.09–3.15 (m, 2H), 3.18-3.24 (m, 2H), 3.29 (q, 2H, *J* = 7.3, 15.0 Hz), 7.04 (d, 1H, *J* = 7.7 Hz), 7.20-7.45 (m, 9H), 7.71 (bs, 1H), 8.17 (d, 1H, *J* = 7.7 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 14.4, 27.3, 33.7, 36.4, 110.7, 119.2, 119.6, 121.1, 121.3, 122.8, 123.8, 125.2, 125.6, 126.4, 128.7, 128.8, 137.8, 138.8, 140.0, 142.2. GC-MS (70eV): *m/z*: 299([M^+], 41), 268(3), 208(100), 196(36), 91(10), 65(3). Anal. Calcd. for $C_{22}H_{21}N$ (299.41): C, 88.25; H, 7.07; N, 4.68. Found: C, 88.08; H, 7.15; N, 4.68.



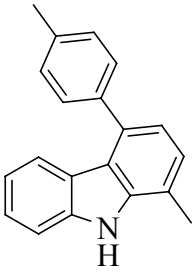
42f. Yield: 65% (from pure **41f**), 62% (from crude **41f**). White solid, m.p. 71–73°C. IR (cm^{-1}, nujol) ν: 1228, 1580, 1619, 3055, 3409. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.34–1.47 (m, 1H), 1.42 (t, 3H, *J* = 7.7 Hz), 1.54–1.72 (m, 4H), 1.84–1.93 (m, 1H), 1.95–2.03 (m, 2H), 2.16–2.26 (m, 2H), 2.92 (q, 2H, *J* = 7.7 Hz), 3.46–3.56 (m, 1H), 7.10 (d, 1H, *J* = 7.7 Hz), 7.23–7.30 (m, 2H), 7.39–7.45 (m, 1H), 7.49 (dt, 1H, *J* = 0.9, 8.1 Hz), 8.06 (bs, 1H), 8.13 (d, 1H, *J* = 7.7 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 13.9, 24.1, 26.8, 27.5, 33.4, 41.0, 110.7, 116.0, 119.6, 120.6, 123.0, 123.3, 123.8, 124.6, 125.1, 138.4, 139.6, 141.5. GC-MS (70eV): *m/z*: 277([M^+], 100), 262(11), 248(10), 234(14), 208(30), 206(24), 205(28), 204(31), 191(23), 180(36). Anal. Calcd. for $C_{20}H_{23}N$ (277.40): C, 86.59; H, 8.36; N, 5.05. Found: C, 86.21; H, 8.45; N, 5.02.



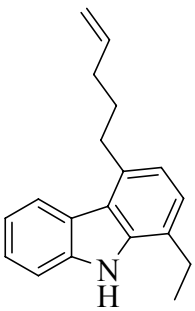
42g. Yield: 56% (from pure **41g**), 53% (from crude **41g**). Yellow sticky solid. IR (cm^{-1}, nujol) ν: 1216, 1503, 1583, 1615, 3022, 3429. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.47 (t, 3H, *J* = 7.7 Hz), 2.50 (s, 3H), 2.98 (q, 2H, *J* = 7.7, 15.4 Hz), 7.00 (t, 1H, *J* = 7.3 Hz), 7.08 (d, 1H, *J* = 8.1 Hz), 7.29–7.39 (m, 4H), 7.46 (d, 1H, *J* = 8.1 Hz), 7.52–7.59 (m, 3H), 8.11 (bs, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 14.0, 21.6, 24.3, 110.7, 119.2, 120.6, 121.5, 122.7, 123.8, 124.4, 124.8, 125.7, 129.3, 129.4, 135.7, 137.2, 138.6, 138.7, 139.8. GC-MS (70eV): *m/z*: 286(22), 285([M^+], 86), 270(100), 254(27), 226(3), 127(13). Anal. Calcd. for $C_{21}H_{19}N$ (285.38): C, 88.38; H, 6.71; N, 4.91. Found: C, 88.21; H, 6.68; N, 4.83.



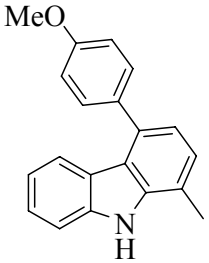
42h. Yellow solid, m.p. 160–163°C. IR (cm^{-1}, nujol) ν: 1177, 1527, 1605, 2924, 3381. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.49 (s, 3H), 3.90 (s, 3H), 6.98 (m, 1H), 7.09 (d, 2H, *J* = 8.5 Hz), 7.16 (m, 1H), 7.29–7.43 (m, 5H), 7.57 (d, 3H, *J* = 7.7 Hz), 7.65 (d, 2H, *J* = 8.6 Hz), 8.66 (bs, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 21.5, 55.5, 110.7, 114.8, 119.1, 121.1, 121.6, 122.6, 123.4, 123.7, 125.5, 125.7, 129.2, 129.7, 131.4, 136.6, 137.2, 137.8, 138.3, 140.0, 159.2. GC-MS (70eV): *m/z*: 363([M^+], 100), 348(29), 318(11), 304(11), 181(7), 152(8). Anal. Calcd. for $C_{26}H_{21}NO$ (363.45): C, 85.92; H, 5.82; N, 3.85. Found: C, 86.09; H, 5.53; N, 3.94.



42i. Yield: 58% (from pure **10i**), 55% (from crude **10i**). Brown sticky solid. IR (cm^{-1}, nujol) ν: 1214, 1504, 1587, 1614, 3052, 3418. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.51 (s, 3H), 2.61 (s, 3H), 7.02 (t, 1H, *J* = 7.7 Hz), 7.06 (d, 1H, *J* = 7.7 Hz), 7.29 (d, 1H, *J* = 7.3 Hz), 7.33–7.39 (m, 3H), 7.47 (d, 1H, *J* = 7.7 Hz), 7.55 (d, 2H, *J* = 7.3 Hz), 7.60 (d, 1H, *J* = 7.7 Hz), 8.09 (bs, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 17.1, 21.6, 110.7, 118.6, 119.3, 120.5, 121.4, 122.8, 123.8, 125.7, 126.4, 129.3, 129.4, 135.8, 137.2, 138.6, 139.3, 139.8. GC-MS (70eV): *m/z*: 271([M^+], 100), 270(33), 254(23), 180(7), 127(14), 121(10). Anal. Calcd. for $C_{20}H_{17}N$ (271.36): C, 88.52; H, 6.31; N, 5.16. Found: C, 88.72; H, 6.44; N, 5.04.

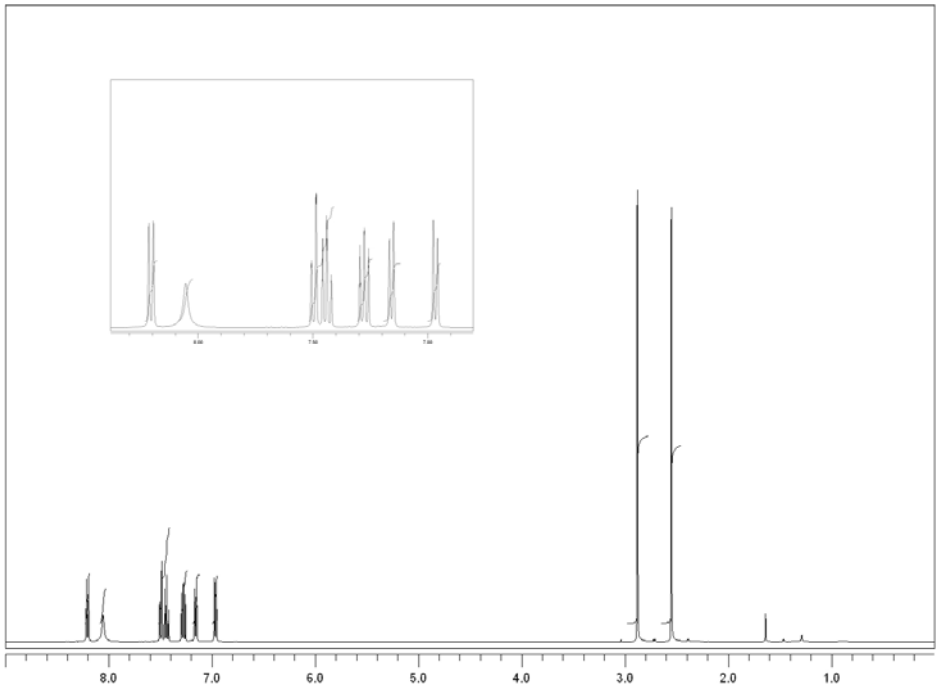


42j. White waxy solid. IR (cm^{-1}, nujol) ν: 1216, 1518, 1608, 3053, 3417. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.44 (t, 3H, *J* = 7.7 Hz), 1.94–2.03 (m, 2H), 2.31 (q, 2H, *J* = 7.3, 14.5 Hz), 2.93 (q, 2H, *J* = 7.3, 15.4 Hz), 3.24–3.29 (m, 2H), 5.06 (dd, 1H, *J* = 1.3, 10.3 Hz), 5.14 (dd, 1H, *J* = 1.3, 17.1 Hz), 5.91–6.02 (m, 1H), 7.03 (d, 1H, *J* = 7.7 Hz), 7.20–7.32 (m, 2H), 7.43–7.52 (m, 2H), 8.06 (bs, 1H), 8.15 (d, 1H, *J* = 7.7 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 14.1, 24.2, 29.3, 33.8, 34.1, 110.8, 115.2, 119.7, 120.5, 121.1, 122.8,123.6, 124.0, 124.4, 125.3, 135.7, 133.6, 139.0, 139.6. GC-MS (70eV): *m/z*: 263([M^+], 53), 248(3), 234(6), 209(67), 208(100), 193(52), 180(59), 167(7). Anal. Calcd. for $C_{19}H_{21}N$ (263.38): C, 86.65; H, 8.04; N, 5.32. Found: C, 86.28; H, 8.21; N, 5.32.

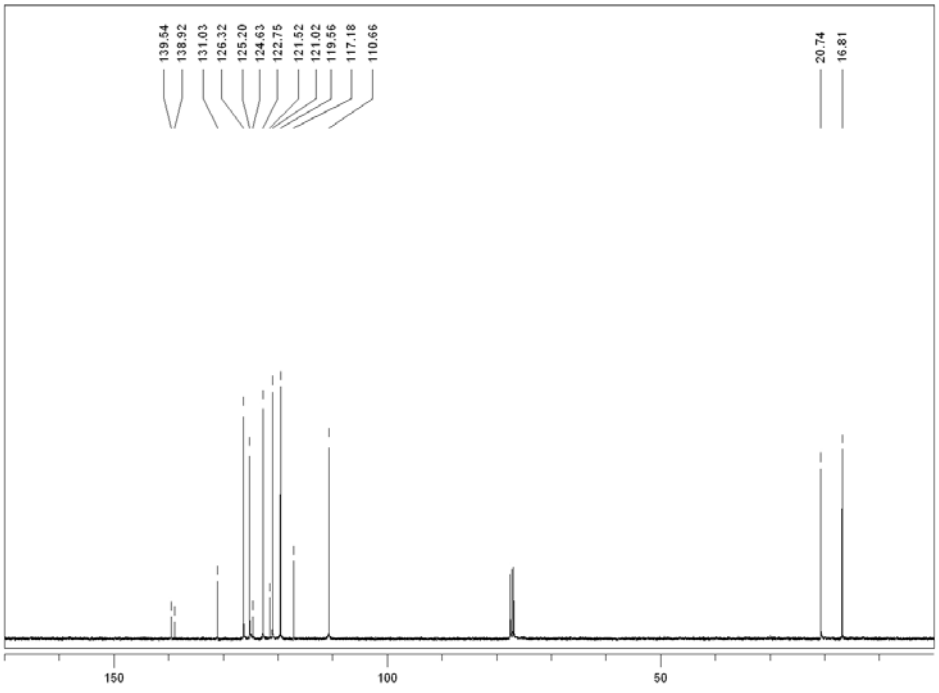


42k. White sticky solid. IR (cm^{-1}, nujol) ν: 1227, 1525, 1607, 3046, 3380. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.61 (s, 3H), 3.93 (s, 3H), 6.95–7.10 (m, 4H), 7.26 (d, 1H, *J* = 7.7 Hz), 7.32–7.37 (m, 1H), 7.46 (d, 1H, *J* = 8.1 Hz), 7.52–7.58 (m, 3H), 8.12 (bs, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 17.0, 55.6, 110.7, 113.9, 118.5, 119.2, 120.6, 121.3, 122.7, 123.8, 125.6, 126.4, 130.6, 133.9, 135.4, 139.2, 139.8, 159.2. GC-MS (70eV): *m/z*: 287([M^+], 100), 272(34), 242(25), 228(38), 120(18), 108(17). Anal. Calcd. for $C_{20}H_{17}NO$ (287.36): C, 83.59; H, 5.96; N, 4.87. Found: C, 83.56; H, 6.12; N, 4.90.

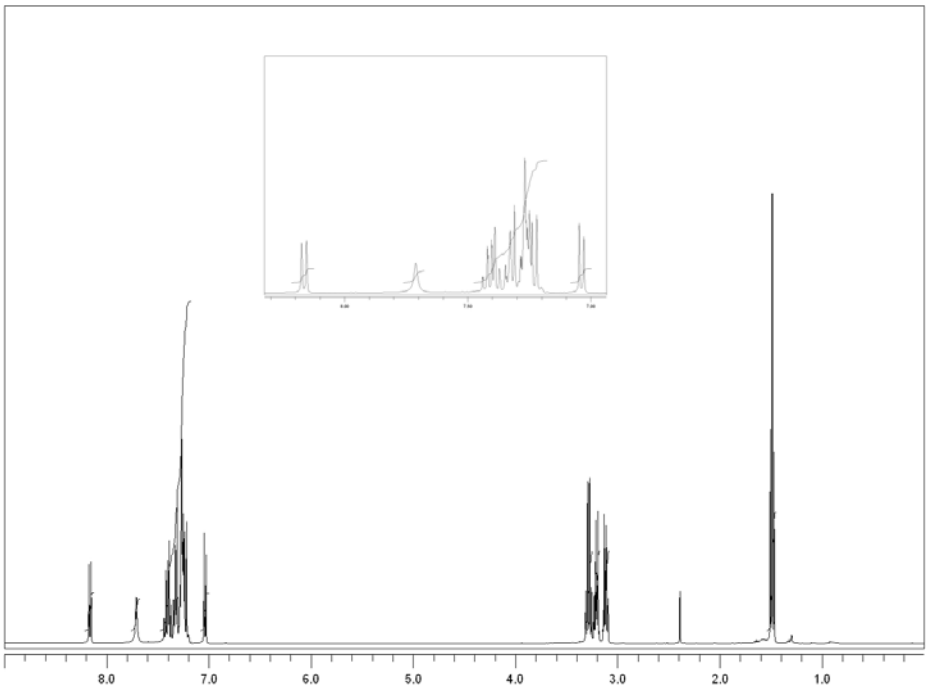
^{1}H NMR (400MHz. $CHCl_3$), **42a**



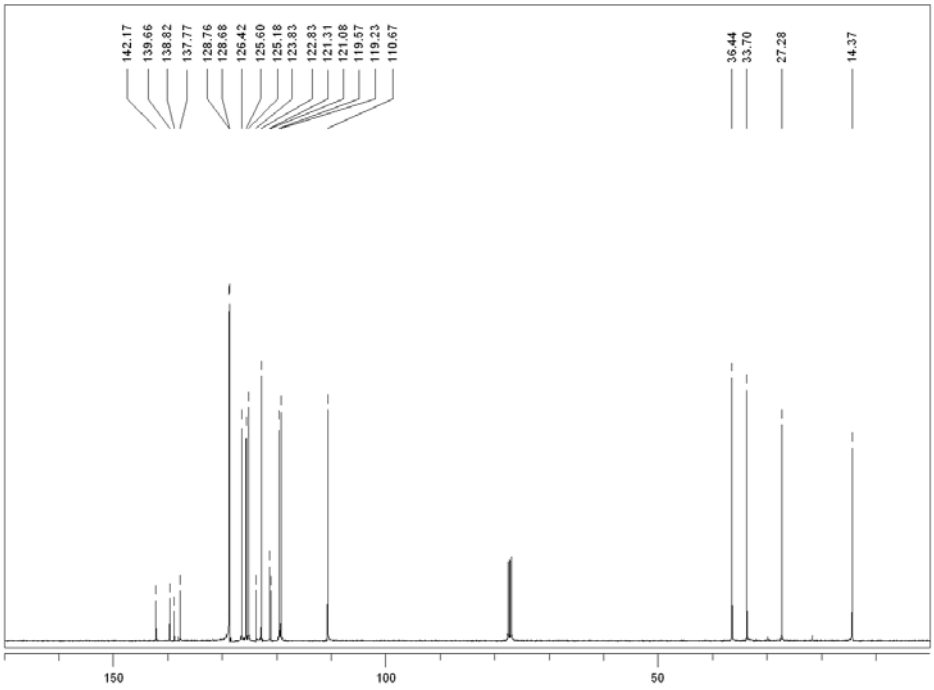
^{13}C NMR (100MHz. $CHCl_3$), **42a**



[1] HNMR (400MHz. $CHCl_3$), **42e**



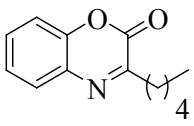
^{13}C NMR (100MHz. $CHCl_3$), **42e**



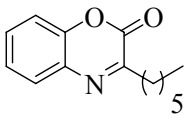
5.3 Synthesis of 2H-1,4-benzoxazin-2-one derivatives under heterogeneous conditions

*Typical Procedure for the Synthesis of 2H-1,4-Benzoxazin-2-ones **57***:

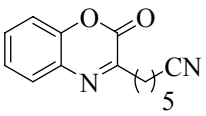
To a stirred solution of the β-nitroacrylate **52** (1 mmol) in EtOAc (2 mL), the appropriate aminophenol **53** (1 mmol) and the carbonate on polymer (1 mmol, 286 mg) were added. The resulting reaction mixture was heated at 558C and stirred for the required time (the reaction progress was monitored by withdrawing aliquots, which were analyzed by TLC, (see **Table 5** pag. 96), then the catalyst was filtered off, washed with EtOAc, the filtrate was concentrate under vacuum to give the crude products **57a–m**, which were purified by flash chromatography column (hexane-ethyl acetate).



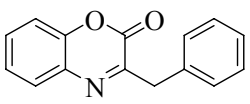
57a. Yellow waxy solid. IR (nujol) n: 756, 1065, 1614, 1748 cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ: 0.91 (t, 3H, *J* = 7.3 Hz), 1.32-1.47 (m, 4H), 1.73-1.83 (m, 2H), 2.85-2.91 (m, 2H), 7.27 (d, 1H, *J* = 8.5 Hz), 7.34 (t, 1H, *J* = 7.7 Hz), 7.46 (t, 1H, *J* = 7.7 Hz), 7.72 (d, 1H, *J* = 8.1 Hz). ^{13}C NMR ($CDCl_3$, 100MHz) δ: 14.2, 22.6, 26.3, 31.7, 34.4, 116.5, 125.6, 129.0, 130.6, 131.4, 146.6, 153.2, 158.4. GC-MS (70eV) *m/z*: 217 [M+], 161, 146, 133 (100), 104, 77, 63, 51, 39, 29. Anal. Calcd. For $C_{13}H_{15}NO_2$ (217.26): C, 71.87; H, 6.96; N, 6.45. Found: C, 63.75; H, 7.11; N, 6.33.



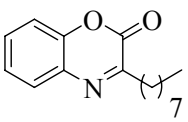
57b. Yellow waxy solid. IR (nujol) ν: 754, 1063, 1615, 1747 cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ: 0.89 (t, 3H, *J* = 7.3 Hz), 1.27-1.49 (m, 6H), 1.72-1.82 (m, 2H), 2.84-2.91 (m, 2H), 7.26 (dd, 1H, *J* = 1.3, 8.1 Hz), 7.33 (dt, 1H, *J* = 1.3, 7.7 Hz), 7.42-7.48 (m, 1H), 7.72 (dd, 1H, *J* = 1.7, 8.1 Hz). ^{13}C NMR ($CDCl_3$, 100MHz) δ: 14.3, 22.7, 26.5, 29.2, 31.8, 34.4, 116.5, 125.6, 129.0, 130.6, 131.4, 146.6, 153.2, 158.4. GC-MS (70eV) *m/z*: 231 [M+], 203, 188, 161 (100), 146, 133. Anal. Calcd. For $C_{14}H_{17}NO_2$ (231.29): C, 72.70; H, 7.41; N, 6.06. Found: C, 72.88; H, 7.59; N, 5.94.



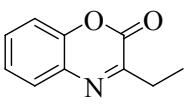
57c. Yellow waxy solid. IR (nujol) ν: 754, 1061, 1619, 1747, 2251 cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ: 1.55-1.66 (m, 2H), 1.70-1.79 (m, 2H), 1.80-1.89 (m, 2H), 2.38 (t, 2H, *J* = 6.8 Hz), 2.88-2.93 (m, 2H), 7.28 (dd, 1H, *J* = 1.3, 8.1 Hz), 7.35 (dt, 1H, *J* = 1.3, 7.7 Hz), 7.44-7.50 (m, 1H), 7.7 (dd, 1H, *J* = 1.3, 8.1 Hz). ^{13}C NMR ($CDCl_3$, 100MHz) δ: 17.3, 25.4, 25.5, 28.4, 33.8, 116.6, 119.9, 125.7, 129.1, 130.9, 131.3, 146.6, 153.2, 157.5. GC-MS (70eV) *m/z*: 242 [M+], 174, 161 (100), 146, 133, 104, 77, 63. Anal. Calcd. for $C_{14}H_{14}N_2O_2$ (242.27): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.60; H, 5.93; N, 11.39.



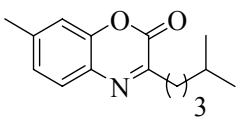
57d. Yellow solid, m.p. 75-77 °C. IR (nujol) ν: 701, 754, 1023, 1079, 1610, 1732 cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ: 2.10-2.21 (m, 2H), 2.78 (t, 2H, *J* = 7.7 Hz), 2.94 (t, 2H, *J* = 7.7 Hz), 7.07-7.39 (m, 7H), 7.42-7.50 (m, 1H), 7.73 (dd, 1H, *J* = 1.3, 8.1 Hz). ^{13}C NMR ($CDCl_3$, 100MHz) δ: 28.0, 33.9, 35.7, 116.6, 125.6, 126.2, 128.6, 128.8, 129.0, 130.7, 131.4, 141.9, 146.6, 153.2, 157.9. GC-MS (70eV) *m/z*: 265 [M+], 161 (100), 133, 91, 77, 65. Anal. Calcd. For $C_{17}H_{15}NO_2$ (265.31): C, 76.96; H, 5.70; N, 5.28. Found: C, 77.15; H, 5.85; N, 5.11.



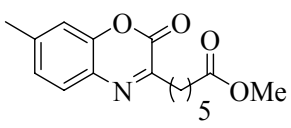
57e. Yellow waxy solid. IR (nujol) ν: 754, 1062, 1617, 1748 cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ: 0.87 (t, 3H, J = 6.8 Hz), 1.19-1.49 (m, 10H), 1.72-1.83 (m, 2H), 2.84-2.91 (m, 2H), 7.27 (dd, 1H, *J* = 1.3, 8.1 Hz), 7.34 (dt, 1H, *J* = 1.3, 7.7 Hz), 7.42-7.49 (m, 1H), 7.72 (dd, 1H, *J* = 1.3, 7.7 Hz). ^{13}C NMR ($CDCl_3$, 100MHz) δ: 14.3, 22.8, 26.6, 29.3, 29.5, 29.6, 32.0, 34.4, 116.5, 125.5, 128.9, 130.6, 131.4, 146.6, 153.2, 158.4. GC-MS (70eV) *m/z*: 259 [M+], 188, 175, 161 (100), 146, 133, 41. Anal. Calcd. for $C_{16}H_{21}NO_2$ (259.34): C, 74.10; H, 8.16; N, 5.40. Found: C, 74.31; H, 8.29; N, 5.26.



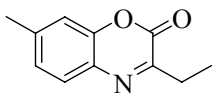
57f. Yellow waxy solid. IR (nujol) ν: 703, 747, 771, 915, 979, 1091, 1610, 1751 cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ: 1.32 (t, 3H, *J* = 7.3 Hz), 2.91 (q, 2H, *J* = 7.3 Hz), 7.26 (dd, 1H, *J* = 1.3, 8.1 Hz), 7.33 (dt, 1H, *J* = 1.3, 8.1 Hz), 7.41-7.47 (m, 1H), 7.72 (dd, 1H, *J* = 1.3, 8.1 Hz). ^{13}C NMR ($CDCl_3$, 100MHz) δ: 10.5, 27.7, 116.5, 125.6, 129.0, 130.6, 131.4, 146.6, 153.2, 159.0. GC-MS (70eV) *m/z*: 175 [M+], 146 (100), 132, 91, 63. Anal. Calcd. for $C_{10}H_9NO_2$ (175.18): C, 68.56; H, 5.18; N, 8.00. Found: C, 68.78; H, 5.36; N, 7.87.



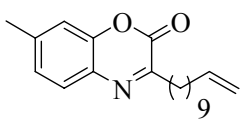
57g. White solid, m.p. 57-59°C. IR (nujol) ν: 705, 764, 819, 886, 951, 962, 1043, 1149, 1622, 1747 cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ: 0.89 (d, 6H, *J* = 6.8 Hz), 1.26-1.35 (m, 2H), 1.53-1.66 (m, 1H), 1.71-1.81 (m, 2H), 2.44 (s, 3H), 2.79-2.86 (m, 2H), 7.04-7.07 (m, 1H), 7.12-7.16 (m, 1H), 7.58 (d, 1H, *J* = 8.1 Hz). ^{13}C NMR ($CDCl_3$, 100MHz) δ: 21.8, 22.8, 24.6, 28.0, 34.6, 38.8, 116.6, 126.6, 128.5, 129.4, 141.8, 146.5, 153.4, 157.1. GC-MS (70eV) *m/z*: 245 [M+], 202, 175 (100), 160, 147, 78, 41. Anal. Calcd. for $C_{15}H_{19}NO_2$ (245.32): C, 73.44; H, 7.81; N, 5.71. Found: C, 73.64; H,7.96; N, 5.59.



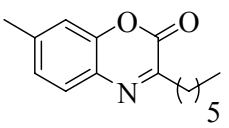
57h. Yellow solid, m.p. 90-92°C. IR (nujol) ν: 705, 778, 822, 1109, 1150, 1622, 1725, 1747 cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ: 1.39-1.50 (m, 2H), 1.64-1.83 (m, 4H), 2.32 (t, 2H, *J* = 7.7 Hz), 2.43 (s, 3H), 2.81-2.88 (m, 2H), 3.65 (s, 3H), 7.05 (s, 1H), 7.13 (dd, 1H, *J* = 1.7, 8.1 Hz), 7.57 (d, 1H, *J* = 8.1 Hz). ^{13}C NMR ($CDCl_3$, 100MHz) δ: 21.8, 24.8, 26.1, 29.0, 34.0, 34.1, 51.7, 116.6, 126.6, 128.5, 129.4, 141.9, 146.4, 153.4, 156.7, 174.3. GCMS (70eV) *m/z*: 289 [M+], 257, 230, 201, 188, 175, 160 (100), 147, 78. Anal. Calcd. for $C_{16}H_{19}NO_4$ (289.33): C, 66.42; H, 6.62; N, 4.84. Found: C, 66.60; H, 6.73; N, 4.71.



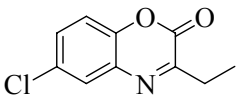
57i. White solid, m.p. 102-104°C. IR (nujol) ν: 711, 828, 884, 959, 1093, 1622, 1748 cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ: 1.32 (t, 3H, *J* = 7.3 Hz), 2.44 (s, 3H), 2.89 (q, 2H, *J* = 7.3 Hz), 7.05-7.07 (m, 1H), 7.14 (dd, 1H, *J* = 2.1, 8.1 Hz), 7.59 (d, 1H, *J* = 8.1 Hz). ^{13}C NMR ($CDCl_3$, 100MHz) δ: 10.6, 21.8, 27.6, 116.6, 126.7, 128.6, 129.5, 141.8, 146.5, 153.5, 157.7. GC-MS (70eV) *m/z*: 189 [M+], 160 (100), 146, 78, 51. Anal. Calcd. for $C_{11}H_{11}NO_2$ (189.21): C, 69.83; H, 5.86; N, 7.40. Found: C, 69.99; H, 5.98; N, 7.29.



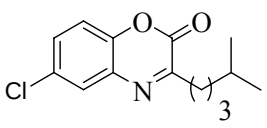
57j. Yellow solid, m.p. 71-73°C. IR (nujol) ν: 706, 723, 890, 907, 1620, 1641, 1740 cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ: 1.22-1.47 (m, 12H), 1.70-1.81 (m, 2H), 1.98-2.08 (m, 2H), 2.44 (t, 3H), 2.81-2.88 (m, 2H), 4.88-5.03 (m, 2H), 5.73-5.87 (m, 1H), 7.06 (s, 1H), 7.14 (dd, 1H, *J* = 1.7, 8.1 Hz), 7.58 (d, 1H, *J* = 8.1 Hz). ^{13}C NMR ($CDCl_3$, 100MHz) δ: 21.8, 26.6, 29.1, 29.3, 29.5, 29.6, 34.0, 34.3, 114.3, 116.6, 126.6, 128.5, 129.4, 139.4, 141.7, 146.5, 153.4, 157.1. GCMS (70eV) *m/z*: 313 [M+], 202, 189, 175 (100), 160, 147, 78, 55, 41. Anal. Calcd. for $C_{20}H_{27}NO_2$ (313.43): C, 76.64; H, 8.68; N, 4.47. Found: C, 76.80; H, 8.81; N, 4.36.



57k. White solid, m.p. 78-82°C. IR (nujol) ν: 705, 725, 823, 887, 959, 1086, 1622, 1731 cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ: 0.88 (t, 3H, *J* = 7.3 Hz), 1.25-1.47 (m, 6H), 1.70-1.81 (m, 2H), 2.44 (s, 3H), 2.81-2.88 (m, 2H), 7.06 (s, 1H), 7.11-7.17 (m, 1H), 7.58 (d, 1H, *J* = 8.1 Hz). ^{13}C NMR ($CDCl_3$, 100MHz) δ: 14.2, 21.8, 22.7, 26.6, 29.2, 31.8, 34.3, 116.6, 126.6, 128.5, 129.4, 141.8, 146.5, 153.4, 157.1. GC-MS (70eV) *m/z*: 245 [M+], 202, 188, 175 (100), 160, 147, 78, 41. Anal. Calcd. for $C_{15}H_{19}NO_2$ (245.32): C, 73.44; H, 7.81; N, 5.71. Found: C, 73.58; H, 7.96; N, 5.59.



57l. Yellow solid, m.p. 84-87°C. IR (nujol) ν: 826, 885, 927, 976, 1093, 1618, 1737 cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ: 1.29 (t, 3H, *J* = 7.3 Hz), 2.90 (q, 2H, *J* = 7.3 Hz), 7.19 (d, 1H, *J* = 8.9 Hz), 7.38 (dd, 1H, *J* = 2.5, 8.9 Hz), 7.70 (d, 1H, *J* = 2.1 Hz). ^{13}C NMR ($CDCl_3$, 100MHz) δ: 10.3, 27.8, 117.7, 128.6, 130.5, 130.6, 131.9, 145.2, 152.6, 160.3. GC-MS (70eV) *m/z*: 211 [M+2+], 209 [M+], 183, 182, 181, 180 (100), 166, 63. Anal. Calcd. for $C_{10}H_8ClNO_2$ (209.63): C, 57.30; H, 3.85; N, 6.68. Found: C, 57.44; H, 3.93; N, 6.54.

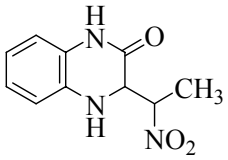


57m. Yellow waxy solid. IR (nujol) ν: 816, 883, 929, 1067, 1541, 1610, 1753 cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz) δ: 0.90 (d, 6H, *J* = 6.4 Hz), 1.25-1.35 (m, 2H), 1.54-1.68 (m, 1H), 1.71-1.82 (m, 2H), 2.83-2.89 (m, 2H), 7.21 (d, 1H, *J* = 8.9 Hz), 7.41 (dd, 1H, *J* = 2.5, 8.9 Hz), 7.72 (d, 1H, *J* = 2.5 Hz). ^{13}C NMR ($CDCl_3$, 100MHz) δ: 22.7, 24.3, 28.0, 34.6, 38.7, 117.7, 128.6, 130.5, 130.6, 131.9, 145.1, 152.6, 159.7. GC-MS (70eV) *m/z*: 265 [M+], 222, 195 (100), 180, 167, 102, 63, 41. Anal. Calcd. for $C_{14}H_{16}ClNO_2$ (265.74): C, 63.28; H, 6.07; N, 5.27. Found: C, 63.41; H, 5.99; N, 5.16.

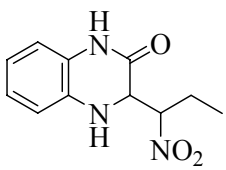
5.4 Synthesis of dihydroquinoxalinone derivatives, via an *anti*-Michael reaction

Typical procedure for the conjugate addition of o-phenylendiamine to β-nitroacrylates:

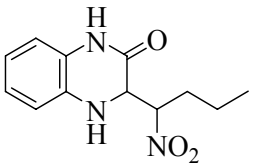
β-Nitroacrylate **69** (1 mmol) and *o*-phenylenediamine **68** (1.25 mmol) were dissolved in EtOAc (2 mL) and mixed at room temperature, with magnetic stirring, for 2 hours. Then, acetone (2 mL, in order to increase the solubility of **71**) and 0.8 g of silica gel (Silica Gel 60, 0,040-0,063 mm, 230-400 mesh ASTM, Merck), were added and the mixture was stirred for 5 min. Finally, the solvent was removed under vacuum and the crude product (adsorbed on silica) was charged onto a chromatography column (cyclohexane/EtOAc) allowing the pure products **71** (see **Table 7** pag. 103).



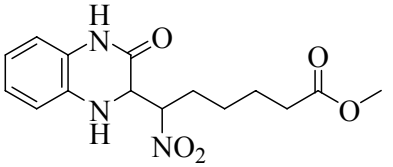
71a. (diastereomeric mixture). Yellow solid. IR (KBr) ν: 1363, 1547, 1689, 3051, 3416 cm^{-1}. ^1H NMR (400MHz, Acetone) δ: 1.58 (d, 2.04H, *J* = 6.8 Hz), 1.62 (d, 0.96H, *J* = 6.8 Hz), 4.46-4.49 (m, 0.32H), 4.81 (t, 0,68H, *J* = 3.4Hz), 4.99-5.01 (m, 0.32H), 5.12-5.20 (m, 0.68H), 5.61 (bs, 0.68H), 5.80 (bs, 0.32H), 6.64-6.71 (m, 1H), 6.75-6.89 (m, 3H), 9.65 (bs, 1H). ^{13}C NMR (100 MHz, Acetone) δ: 13.7, 15.5, 59.5, 60.5, 83.3, 84.8, 114.8, 115.2, 115.9, 116.0, 119.6, 119.7, 124.3, 124.5, 206.2. API-ES (m/z): 244.2 ($M + Na^+$). Anal. Calcd. for $C_{10}H_{11}N_3O_3$ (221.21): C, 54.29; H, 5.01; N, 19.00. Found: C, 54.44; H, 4.71; N, 18.86.



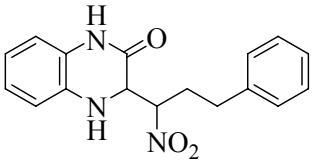
71b. (diastereomeric mixture). Yellow solid, IR (KBr) ν: 1362, 1546, 1686, 3049, 3414 cm^{-1}. ^1H NMR (400MHz, Acetone) δ: 0.95 (t, 3H, *J* = 7.3 Hz), 1.88-2.02 (m, 1H), 2.07-2.25 (m, 1H), 4.39 (dd, 0.27H, *J* = 3.4, 6.8 Hz), 4.62 (dd, 0.73H, *J* = 2.6, 4.3 Hz), 4.76-4.84 (m, 0.27H), 4.88-4.97 (m, 0.73H), 5.68 (bs, 0.73H), 5.81 (bs, 0.27H), 6.66-6.76 (m, 1H), 6.79-6.92 (m, 3H), 9.65 (bs, 1H). ^{13}C NMR (100 MHz, Acetone) δ: 10.6, 10.8, 23.1, 24.1, 59.4, 59.8, 90.3, 91.5, 114.9, 115.6, 116.0, 116.1, 119.8, 119.9, 124.4, 124.5, 126.0, 126.3, 132.7, 133.4, 163.6, 164.2. API-ES (m/z): 258.2 ($M + Na^+$). Anal. Calcd. for $C_{11}H_{13}N_3O_3$ (235.24): C, 56.16; H, 5.57; N, 17.86. Found: C, 56.44; H, 5.71; N, 17.65.



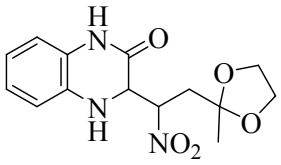
71c. (diastereomeric mixture). Yellow solid, IR (KBr) ν: 1360, 1545, 1684, 3052, 3415 cm^{-1}. ^{1}H NMR (400 MHz, Acetone) δ: 0.90 (t, 2.22H, *J* = 7.3 Hz), 0.91 (t, 0.88H, *J* = 7.3 Hz), 1.27-1.41 (m, 2H), 1.80-1.94 (m, 1H), 2.10-2.24 (m, 1H), 4.39 (dd, 0.26H, *J* = 3.4, 6.8 Hz), 4.61-4.64 (m, 0.74H), 4.84-4.90 (m, 0.26H), 5.00-5.10 (m, 0.74H), 5.66 (bs, 0.74H), 5.82 (bs, 0.26H), 6.67-6.73 (m, 1H), 6.80-6.90 (m, 3H), 9.66 (bs, 1H). ^{13}C NMR (100 MHz, Acetone) δ: 14.0, 14.1, 20.2, 20.3, 32.0, 33.0, 59.8, 60.2, 89.0, 90.0, 90.1, 115.2, 115.3, 115.8, 115.9, 116.2, 116.3, 116.4, 120.1, 120.2, 124.7, 124.8, 206.6. API-ES (m/z): 272.3 ($M + Na^{+}$). Anal. Calcd. for $C_{12}H_{15}N_3O_3$ (249.27): C, 57.82; H, 6.07; N, 16.86. Found: C, 58.03; H, 5.97; N, 16.61.



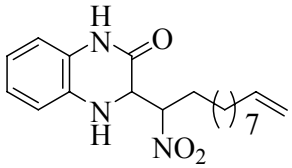
71d. (diastereomeric mixture). Yellow solid, IR (KBr) ν: 1363, 1544, 1677, 1735, 3067, 3397 cm^{-1}. ^{1}H NMR (400 MHz, Acetone) δ: 1.26-1.48 (m, 2H), 1.51-1.70 (m, 2H), 1.86-2.02 (m, 1H), 2.07-2.25 (m, 1H), 2.26-2.35 (m, 2H), 3.58 (s, 1.5H), 3.59 (s, 1.5H), 4.41 (dd, 0.5H, *J* = 3.0, 6.8 Hz), 4.64 (dd, 0.5H, *J* = 2.6, 4.3 Hz), 4.85-4.93 (m, 0.5H), 4.99-5.06 (m, 0.5H), 5.67 (bs, 0.5H), 5.82 (bs, 0.5H), 6.67-6.74 (m, 1H), 6.78-6.91 (m, 3H), 9.64 (bs, 1H). ^{13}C NMR (100 MHz, Acetone) δ: 24.9, 25.0, 26.0, 26.1, 29.4, 30.3, 33.8, 33.9, 51.6, 59.4, 59.9, 88.7, 89.7, 114.9, 115.5, 116.0, 116.1, 119.8, 119.9, 124.3, 124.4, 126.0, 126.2, 132.6, 133.4, 163.7, 164.1, 173.8, 173.9. API-ES (m/z): 344.4 ($M + Na^{+}$). Anal. Calcd. for $C_{15}H_{19}N_3O_5$ (321.33): C, 56.07; H, 5.96; N, 13.08. Found: C, 56.38; H, 6.18; N, 12.81.



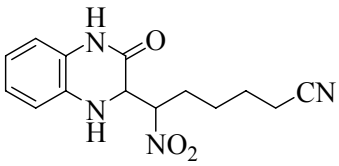
71e. (diastereomeric mixture). Yellow solid, IR (KBr) ν: 1361, 1544, 1679, 3059, 3397 cm^{-1}. ^{1}H NMR (400 MHz, Acetone) δ: 2.18-2.32 (m, 1H), 2.40-2.55 (m, 1H), 2.59-2.74 (m, 2H), 4.49 (dd, 0.35H, *J* = 3.0, 6.8 Hz), 4.66 (dd, 0.65H, *J* = 2.6, 4.3 Hz), 4.91-4.98 (m, 0.35H), 4.99-5.05 (m, 0.65H), 5.74 (bs, 0.65H), 5.86 (bs, 0.35H), 6.65-6.73 (m, 1H), 6.78-6.90 (m, 3H), 7.11-7.32 (m, 5H), 9.67 (bs, 1H). ^{13}C NMR (100 MHz, Acetone) δ: 31.6, 32.5, 32.6, 32.7, 59.6, 60.0, 88.1, 89.5, 114.9, 115.4, 116.0, 116.1, 119.8, 119.9, 124.4, 124.5, 125.9, 126.1, 127.1, 129.2, 129.3, 129.4, 129.5, 132.6, 133.2, 141.1, 141.3, 163.7, 164.0. API-ES (m/z): 334.4 ($M + Na^{+}$). Anal. Calcd. for $C_{17}H_{17}N_3O_3$ (311.34): C, 65.58; H, 5.50; N, 13.50. Found: C, 65.84; H, 5.73; N, 13.23.



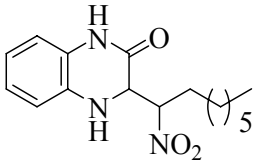
71f. (diastereomeric mixture). Yellow solid, IR (KBr) ν: 1040, 1376, 1553, 1683, 3051, 3389 cm^{-1}. ^{1}H NMR (400 MHz, Acetone) δ: 1.21-1.26 (m, 3H), 2.21 (dd, 0.75H, *J* = 1.7, 15.4 Hz), 2.38 (dd, 0.25H, *J* = 2.6, 15.4 Hz), 2.64-2.79 (m, 1H), 3.71-3.96 (m, 4H), 4.33 (dd, 0.25H, *J* = 3.0, 7.3 Hz), 4.50 (dd, 0.75H, *J* = 2.6, 4.3 Hz), 4.89-4.96 (m, 0.25H), 5.06-5.13 (m, 0.75H), 5.66 (bs, 0.75H), 5.82 (bs, 0.25H), 6.67-6.76 (m, 1H), 6.79-6.91 (m, 3H), 9.67 (bs, 1H). ^{13}C NMR (100 MHz, Acetone) δ: 24.3, 24.4, 38.4, 39.0, 60.1, 60.3, 65.4, 65.5, 84.1, 85.7, 108.5, 114.9, 115.7, 115.9, 116.0, 116.1, 119.8, 119.9, 124.4, 124.5, 125.9, 126.0, 132.4, 132.9, 163.4, 163.5. API-ES (m/z): 330.4 ($M + Na^{+}$). Anal. Calcd. for $C_{14}H_{17}N_3O_5$ (307.30): C, 54.72; H, 5.58; N, 13.67. Found: C, 54.36; H, 5.31; N, 13.83.



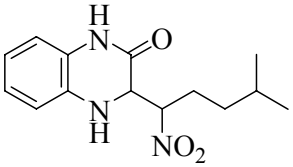
71g. (diastereomeric mixture). Yellow solid, IR (KBr) ν: 1361, 1543, 1602, 1683, 3050, 3412 cm^{-1}. ^{1}H NMR (400 MHz, Acetone) δ: 1.15-1.45 (m, 14H), 1.81-1.98 (m, 1H), 2.10-2.24 (m, 1H), 4.38 (dd, 0.38H, *J* = 3.0, 6.8 Hz), 4.59-4.62 (m, 0.62H), 4.82-5.02 (m, 3H), 5.72-5.95 (m, 2H), 6.65-6.75 (m, 1H), 6.78-6.90 (m, 3H), 9.91 (bs, 1H). ^{13}C NMR (100 MHz, Acetone) δ: 26.5, 34.5, 59.5, 60.0, 88.9, 90.0, 114.7, 114.9, 115.5, 116.0, 116.1, 119.7, 119.8, 124.3, 124.4, 139.9, 206.3. API-ES (m/z): 368.4 ($M + Na^{+}$). Anal. Calcd. for $C_{19}H_{27}N_3O_3$ (345.44): C, 66.06; H, 7.88; N, 12.16. Found: C, 66.38; H, 7.66; N, 12.54.



71h. (diastereomeric mixture). Yellow solid, IR (KBr) ν: 1339, 1542, 1689, 2218, 3052, 3416 cm^{-1}. ^{1}H NMR (400 MHz, Acetone) δ: 1.43-1.59 (m, 2H), 1.60-1.76 (m, 2H), 1.86-2.02 (m, 1H), 2.16-2.30 (m, 1H), 2.41-2.55 (m, 2H), 4.43 (dd, 0.17H, *J* = 3.0, 6.8 Hz), 4.61-4.68 (m, 0.83H), 4.88-4.96 (m, 0.17H), 5.02-5.10 (m, 0.83H), 5.66 (bs, 0.87), 5.83 (bs, 0.17), 6.62-6.75 (m, 1H), 6.76-6.91 (m, 3H), 9.66 (bs, 1H). ^{13}C NMR (100 MHz, Acetone) δ: 13.7, 16.2, 16.3, 25.0, 25.1, 25.2, 25.3, 58.5, 58.7, 87.7, 88.7, 88.8, 114.3, 114.7, 115.3, 115.4, 119.1, 119.2, 123.7, 205.5. API-ES (m/z): 311.3 ($M + Na^{+}$). Anal. Calcd. for $C_{14}H_{16}N_4O_3$ (288.30): C, 58.32; H, 5.59; N, 19.43. Found: C, 58.58; H, 6.18; N, 18.81.



71i. (diastereomeric mixture). Yellow solid, IR (KBr) ν: 1346, 1552, 1687, 3053, 3414 cm^{-1}. ^{1}H NMR (400 MHz, Acetone) δ: 0.83-0.88 (m, 3H), 1.20-1.38 (m, 10H), 1.85-1.98 (m, 1H), 2.09-2.26 (m, 1H), 4.40 (dd, 0.33H, *J* = 3.4, 7.3 Hz), 4.61-4.64 (m, 0.67H), 4.83-4.90 (m, 0.33H), 4.99-5.05 (m, 0.67H), 5.69 (bs, 0.67H), 5.83 (bs, 0.33H), 6.67-6.76 (m, 1H), 6.78-6.92 (m, 3H), 9.66 (bs, 1H). ^{13}C NMR (100 MHz, Acetone) δ: 14.7, 23.7, 26.9, 27.0, 32.8, 59.8, 60.3, 89.3, 90.3, 115.3, 115.9, 116.4, 116.5, 120.2, 120.3, 124.8, 126.4, 133.0, 133.8, 206.6. API-ES (m/z): 328.4 ($M + Na^+$). Anal. Calcd. for $C_{16}H_{23}N_3O_3$ (305.37): C, 62.93; H, 7.59; N, 13.76. Found: C, 63.03; H, 7.18; N, 13.41.

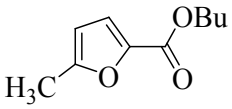


71j. (diastereomeric mixture). Yellow solid, IR (KBr) ν: 1347, 1557, 1685, 3051, 3420 cm^{-1}. ^{1}H NMR (400 MHz, Acetone) δ: 0.83-0.88 (m, 6H), 1.08-1.32 (m, 2H), 1.49-1.60 (m, 1H), 1.88-2.00 (m, 1H), 2.08-2.25 (m, 1H), 4.41 (dd, 0.40H, *J* = 3.0, 7.3 Hz), 4.61-4.64 (m, 0.60H), 4.81-4.87 (m, 0.40H), 4.95-5.01 (m, 0.60H), 5.70 (bs, 0.60H), 5.83 (bs, 0.40H), 6.65-6.75 (m, 1H), 6.78-6.91 (m, 3H), 9.68 (bs, 1H). ^{13}C NMR (100 MHz, Acetone) δ: 21.7, 22.1, 27.0, 27.6, 27.7, 27.9, 34.8, 34.9, 58.8, 59.3, 88.4, 88.5, 114.2, 114.8, 115.3, 115.4, 119.1, 119.2, 123.7, 123.8, 125.3, 125.5, 132.0, 132.7, 163.0, 163.5, 205.6. API-ES (m/z): 280.3 ($M + Na^+$). Anal. Calcd. for $C_{14}H_{19}N_3O_3$ (277.32): C, 60.63; H, 6.91; N, 15.15. Found: C, 59.98; H, 7.18; N, 15.73.

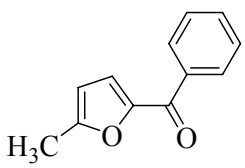
5.5 Synthesis of 2,5-disubstituted furan derivatives from functionalized nitroalkanes

*General procedure for the synthesis of compounds **93***:

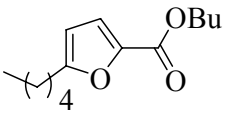
To a stirred solution of the nitro compound **90** (1 mmol) and aldehyde **91** (1 mmol) in EtOAc (1mL), 500 mg of Amberlyst A21 were added. The resulting heterogeneous mixture was stirred for the appropriate time (see **Table 9** pag. 114) at room temperature, then the catalyst was filtered off by washing with EtOAc. The solution was concentrated until arrive at a volume of 6 mL, then Amberlyst A15 was added and the mixture was stirred at 55°C. After completion of the reaction (see Table 3), the catalyst was removed by filtration, washing with EtOAc and, after evaporation of the solvent, the crude product **93** was purified by flash chromatography column.



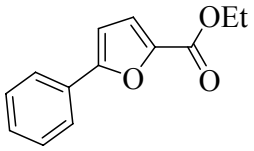
93aa. Clear oil. IR (cm^{-1}, neat) ν: 1726, 1599, 1534, 1299, 1209, 1139, 1021, 799, 760. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 0.94 (t, 3H, *J* = 7.3 Hz), 1.36-1.47 (m, 2H), 1.65-1.75 (m, 2H), 2.36 (s, 3H), 4.26 (t, 2H, *J* = 6.8 Hz), 6.08 (dd, 1H, *J* = 0.9, 3.4 Hz), 7.05 (d, 1H, *J* = 3.4 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 13.9, 14.2, 19.4, 31.0, 64.7, 108.5, 119.3, 143.5, 157.3, 159.2. GC-MS (70 eV): *m/z*: 182([M+], 15), 126(100), 109(89), 81(42), 53(49), 41(11), 29(11). Anal. Calcd. for $C_{10}H_{14}O_3$ (182.22): C, 65.91; H, 7.74. Found: C, 65.99; H, 7.80.



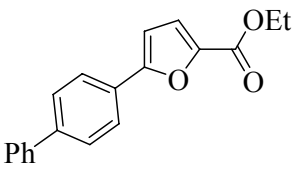
93ab. Clear oil. IR (cm^{-1}, neat) ν: 3061, 1641, 1599, 1509, 1320, 1211, 1172, 1024, 880, 803, 725, 697, 651. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 2.44 (s, 3H), 6.20 (dd, 1H, *J* = 0.9, 3.4 Hz), 7.10 (d, 1H, *J* = 3.4 Hz), 7.43-7.50 (m, 2H), 7.53-7.59 (m, 1H), 7.88-7.92 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 14.4, 109.3, 123.2, 128.6, 129.3, 132.4, 137.9, 151.1, 159.0, 182.5. GC-MS (70 eV): *m/z*: 186([M+], 100), 171(37), 157(15), 109(97), 105(51), 77(61), 53(21), 51(29). Anal. Calcd. for $C_{12}H_{10}O_2$ (186.21): C, 77.40; H, 5.41. Found: C, 77.45; H, 5.45.



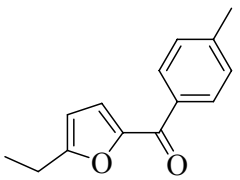
93ba. Yellow oil. IR (cm^{-1}, neat) ν: 1727, 1595, 1530, 1466, 1299, 1204, 1139, 1016, 799, 761. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 0.86-0.91 (m, 3H), 0.95 (t, 3H, *J* = 7.3 Hz), 1.28-1.36 (m, 4H), 1.37-1.48 (m, 2H), 1.62-1.75 (m, 4H), 2.67 (t, 2H, *J* = 7.7 Hz), 4.27 (t, 2H, *J* = 6.8 Hz), 6.10 (d, 1H, *J* = 3.4 Hz), 7.06 (d, 1H, *J* = 3.4 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 14.0, 14.2, 19.4, 22.6, 27.6, 28.5, 31.0, 31.5, 64.7, 107.6, 119.1, 143.3, 159.3, 161.8. GC-MS (70 eV): *m/z*: 238([M+], 22), 182(48), 181(31), 165(47), 126(44), 109(100), 81(39), 52(15), 41(22), 29(19). Anal. Calcd. for $C_{14}H_{22}O_3$ (238.32): C, 70.56; H, 9.30. Found: C, 70.65; H, 9.37.



93cc. Clear oil. IR (cm^{-1}, neat) ν: 1714, 1573, 1531, 1481, 1302, 1272, 1140, 1019, 959, 922, 804, 763, 691, 671. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 1.40 (t, 3H, *J* = 7.3 Hz), 4.38 (q, 2H, *J* = 7.3 Hz), 6.73 (d, 1H, *J* = 3.8 Hz), 7.24 (d, 1H, *J* = 3.8 Hz), 7.31-7.37 (m, 1H), 7.38-7.45 (m, 2H), 7.76-7.81 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 14.6, 61.1, 107.0, 120.0, 125.1, 129.0, 129.1, 129.8, 144.1, 157.7, 159.1. GC-MS (70 eV): *m/z*: 216([M+], 73), 188(56), 171(40), 144(61), 131(16), 115(100), 89(21), 63(16). Anal. Calcd. For $C_{13}H_{12}O_3$ (216.23): C, 72.21; H, 5.59. Found: C, 72.24; H, 5.64.

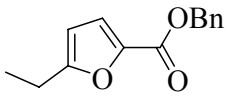


93dc. White solid, m.p. 99-101°C. IR (cm^{-1}, nujol) ν: 1721, 1377, 1304, 1157, 1021, 840, 800, 762, 720. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 1.41 (t, 3H, *J* = 7.3 Hz), 4.40 (q, 2H, *J* = 7.3 Hz), 6.77 (d, 1H, *J* = 3.4 Hz), 7.26 (d, 1H, *J* = 3.4 Hz), 7.34-7.40 (m, 1H), 7.43-7.49 (m, 2H), 7.60-7.68 (m, 4H), 7.86 (d, 2H, *J* = 8.5 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 14.7, 61.2, 107.2, 120.1, 125.5, 127.2, 127.7, 127.9, 128.7, 129.1, 140.5, 141.8, 144.2, 157.5, 159.1. GC-MS (70 eV): *m/z*: 292([M+], 100), 264(49), 220(38), 191(61), 190(44), 165(17), 95(16). Anal. Calcd. for $C_{19}H_{16}O_3$ (292.33): C, 78.06; H, 5.52. Found: C, 77.99; H, 5.49.

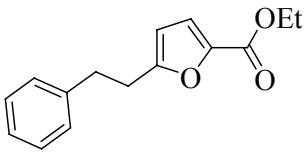


93ed. Yellow waxy solid. IR (cm^{-1}, nujol) ν: 1634, 1607, 1513, 1316, 1210, 1170, 1111, 1036, 977, 943, 883, 831, 811, 790, 754. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 1.31 (t, 3H, *J* = 7.7 Hz), 2.42 (s, 3H), 2.78 (q, 2H, *J* = 7.7 Hz), 6.20 (dt, 1H, *J* = 0.9, 3.4 Hz), 7.11 (d, 1H, *J* = 3.4 Hz), 7.27 (d, 2H, *J* = 8.1 Hz), 7.83 (d, 2H, *J* = 8.1 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 12.0, 21.8,

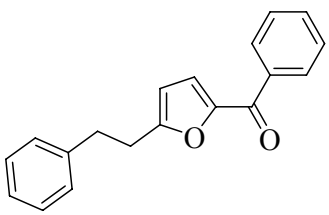
22.0, 107.5, 122.4, 129.2, 129.5, 135.2, 143.1, 151.1, 164.0, 182.2. GC-MS (70 eV): *m/z*: 214([M+], 74), 199(45), 185(42), 171(40), 123(31), 119(100), 91(60), 65(31), 39(14). Anal. Calcd. for $C_{14}H_{14}O_2$ (214.26): C, 78.48; H, 6.59. Found: C, 78.53; H, 6.64.



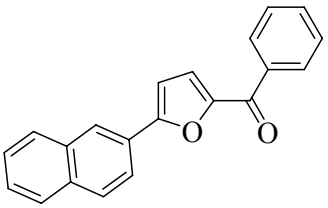
93ee. Clear oil. IR (cm^{-1}, neat) ν: 3065, 3033, 1719, 1594, 1529, 1379, 1297, 1212, 1132, 1019, 968, 783, 758, 698. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 1.27 (t, 3H, *J* = 7.7 Hz), 2.72 (q, 2H, *J* = 7.7 Hz), 5.32 (s, 2H), 6.12 (d, 1H , *J* = 3.4 Hz), 7.13 (d, 1H, *J* = 3.4 Hz), 7.33-7.46 (m, 5H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 12.0, 21.9, 66.4, 107.0, 119.7, 128.5, 128.5, 128.7, 136.1, 142.9, 158.9, 163.2. GC-MS (70 eV): *m/z*: 230([M+], 36), 123(90), 107(15), 96(29), 91(100), 65(24), 39(13). Anal. Calcd. for $C_{14}H_{14}O_3$ (230.26): C, 73.03; H, 6.13. Found: C, 72.97; H, 6.07.



93fc. Clear oil. IR (cm^{-1}, neat) ν: 3063, 3028, 1720, 1595, 1530, 1454, 1368, 1301, 1204, 1127, 1019, 955, 864, 801, 760, 698. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 1.37 (t, 3H, *J* = 7.3 Hz), 3.00 (s, 4H), 4.35 (q, 2H, *J* = 7.3 Hz), 6.07 (d, 1H, *J* = 3.4 Hz), 7.07 (d, 1H, *J* = 3.4 Hz), 7.15-7.23 (m, 3H), 7.25-7.31 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 14.6, 30.3, 34.1, 60.9, 108.3, 119.1, 126.4, 128.5, 128.6, 140.7, 143.5, 159.1, 160.3. GC-MS (70 eV): *m/z*: 244([M+], 29), 171(22), 153(100), 125(46), 91(72), 79(16), 65(15), 52(13). Anal. Calcd. for $C_{15}H_{16}O_3$ (244.29): C, 73.75; H, 6.60. Found: C, 73.80; H, 6.63.



93fd. Clear oil. IR (cm^{-1}, neat) ν: 3061, 3027, 1639, 1599, 1508, 1320, 1302, 1212, 1171, 1023, 978, 962, 930, 880, 804, 789, 750, 722, 697, 676. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 3.01-3.14 (m, 4H), 6.19 (d, 1H, *J* = 3.4 Hz), 7.11 (d, 1H, *J* = 3.4 Hz), 7.17-7.25 (m, 3H), 7.27-7.33(m, 2H), 7.45-7.51(m, 2H), 7.54-7.60 (m, 1H), 7.88-7.92 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 30.4, 34.1, 109.0, 122.8, 126.5, 128.5, 128.5, 128.7, 129.3, 132.4, 137.8, 140.5, 151.1, 161.8, 182.5. GC-MS (70 eV): *m/z*: 276([M+], 26), 185(100), 171(17), 157(28), 105(87), 91(50), 77(51), 65(13), 51(15). Anal. Calcd. for $C_{19}H_{16}O_2$ (276.33): C, 82.58; H, 5.84. Found: C, 82.63; H, 5.79.

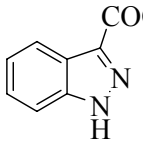


93gb. White solid, m.p. 112-114°C. IR (cm^{-1}, nujol) ν: 3052, 1666, 1631, 1598, 1516, 1377, 1323, 1268, 1177, 1026, 989, 958, 881, 864, 801, 786, 747, 723, 697, 677. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 6.94 (d, 1H, *J* = 3.8 Hz), 7.32 (d, 1H, *J* = 3.8 Hz), 7.47-7.55 (m, 4H), 7.57-7.63 (m, 1H), 7.79-7.92 (m, 4H), 7.98-8.03 (m, 2H), 8.33 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 108.1, 122.7, 123.4, 124.6, 126.7, 127.0, 127.1, 128.0, 128.6, 128.7, 128.9, 129.4, 132.6, 133.4, 133.7, 137.8, 151.6, 158.7, 182.4. GC-MS (70 eV): *m/z*: 298([M+], 100), 270(10), 241(8), 221(20), 165(48), 105(19), 77(25). Anal. Calcd. for $C_{21}H_{14}O_2$ (298.33): C, 84.54; H, 4.73. Found: C, 84.58; H,4.69.

5.5.1 Practical application, synthesis of YC-1

*Synthetic procedure of ester **95***:

To a stirred solution of **94** (6 mmol) in MeOH (20 mL), conc. H_2SO_4 (2 mL) was added and the resulting mixture was refluxed for 2 hours. Then, water (40 mL) was added to the reaction mixture and methanol was evaporated under vacuum. The resulting aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL), the combined organic layer was dried over dry Na_2SO_4 and, after filtration and evaporation of the solvent, the crude product **95** was isolated. The resulted ester **95** was pure enough to be, directly, involved in the following reaction without any further purification. The compound **95** was characterized by m.p. and ^{1}H NMR, compared to those reported in literature (Liu, Z., Shi, F., Martinez, P.D.G., Raminelli, C., Larock, R., *J. Org. Chem.,* **2008**, *73*, 219).



Yield: 95%. White solid, m.p. 160-162 °C. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 4.00 (s, 3H), 7.22-7.27 (m, 1H), 7.34-7.39 (m, 1H), 7.57 (dt, 1H, J = 0.9, 8.5 Hz), 8.16 (dt, 1H, J = 0.9, 8.1 Hz), 12.91 (bs, 1H).

*Synthetic procedure of ester **96***:

To a stirred heterogeneous mixture of compounds **95** (3 mmol) and CsF-Celite system (4.5 mmol), in 70 mL of acetonitrile, the benzylbromide (6 mmol) was added and the mixture was refluxed 48 hours. Then, the solvent was evaporated and the residue was dissolved in ethyl acetate (40 mL). The promoter was filtered off by a short pad of celite and, the filtrate was evaporated under reduced pressure affording the crude **96**, which was purified by flash chromatography column.

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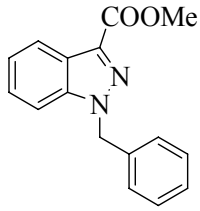
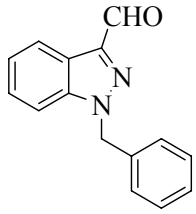


Yield: 79%. White solid, m.p. 80-82°C. IR (cm^{-1}, nujol) ν: 751, 788, 1068, 1183, 1608, 1681. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 4.05 (s, 3H), 5.71 (s, 2H), 7.18-7.39 (m, 8H), 8.24 (dt, 1H, *J* = 1.3, 8.1 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 52.3, 54.3, 116.3, 122.4, 123.5, 124.3, 127.3, 127.4, 128.3, 129.0, 135.1, 135.8, 140.7, 163.3. GC-MS (70 eV): *m/z*: 266([M+], 57), 235(11), 207(56), 205(20), 102(11), 91(100), 65(30). Anal. Calcd. for $C_{16}H_{14}N_2O_2$ (266.29): C, 72.16; H, 5.30; N, 10.52. Found: C, 72.04; H, 5.33; N, 10.48.

*Synthetic procedure of aldehyde **97***:

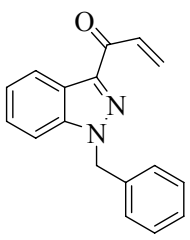
To a stirred solution of ester **96** (3 mmol), in dry THF (25 mL) and under inert atmosphere at -10 °C, a 1 M hexanes solution of DIBAL-H (9 mmol) was added dropwise. The resulting mixture was stirred at the same temperature for 1 hour, after that additional 9 mmol of the DIBAL-H solution were added. Finally the reaction was stirred at room temperature for 6 hours (the reaction was monitored by TLC), then it was quenched initially, by slowly addition of water (10 mL), and successively by 1M aq. HCl (20 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (3 x 20 mL), then the combined organic layer was dried over dry Na_2SO_4 and the solvent was evaporated under vacuum affording the crude intermediate alcohol, which was solubilized in CH_2Cl_2 (50 mL) and activated MnO_2 (21 mmol) was added. The resulting heterogeneous mixture was stirred at room temperature 24 hours, after that, MnO_2 was filtered off by short pad of celite, and the filtrate was evaporated under reduced pressure affording the crude **97**, which was purified by flash chromatography column.



Yield: 90%. White solid, m.p. 68-70°C. IR (cm^{-1}, nujol) ν: 699, 751, 789, 1670. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 5.69 (s, 2H), 7.22-7.27 (m, 2H), 7.29-7.37 (m, 4H), 7.40-7.44 (m, 2H), 8.32 (dt, 1H, *J* = 1.3, 8.1 Hz), 10.27 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 54.3, 110.1, 122.5, 124.3, 127.5, 127.8, 128.5, 129.2, 135.5, 141.1, 143.4, 187.2. GC-MS (70 eV): *m/z*: 236([M+], 78), 207(44), 159(9), 91(100), 65(20). Anal. Calcd. for $C_{15}H_{12}N_2O$ (236.27): C, 76.25; H, 5.12; N, 11.86. Found: C, 76.15; H, 5.14; N, 11.93.

*Synthetic procedure of unsaturated ketone **98***:

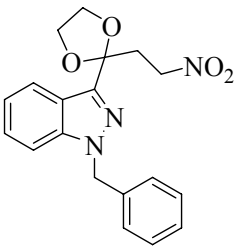
To a stirred solution of aldehyde **97** (3 mmol), in dry Et_2O (30 mL) and under inert atmosphere at -10 °C, a 1.6 M solution in THF of vinylmagnesium chloride (3.6 mmol) was slowly added. The resulting mixture was stirred at the same temperature for l.5 hours, then it was initially quenched by slowly addition of water (10 mL) and, successively, by 1M aq. HCl (20 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (3 x 20 mL), then the organic layer was dried over dry Na_2SO_4 and the solvent was evaporated under vacuum, affording the crude allylic alcohol. The latter, was solubilized in CH_2Cl_2 (50 mL), following by addition of activated MnO_2 (21 mmol). The resulting heterogeneous mixture was stirred at room temperature 24 hours, after that, MnO_2 was filtered off by short pad of celite, and the filtrate was evaporated under reduced pressure affording the crude **98**, which was purified by flash chromatography column.



Yield: 85%. White solid, m.p. 69-71°C. IR (cm^{-1}, nujol) ν: 712, 744, 954, 1065, 1147, 1377, 1604, 1658. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 5.68 (s, 2H), 5.88 (dd, 1H, *J* = 2.1, 10.3 Hz), 6.63 (dd, 1H, *J* = 2.1, 17.5 Hz), 7.20-7.41 (m, 8H), 7.69 (dd, 1H, *J* = 10.3, 17.5 Hz), 8.45 (dt, 1H, *J* = 1.3, 8.1 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 54.2, 110.0, 123.4, 124.0, 127.4, 128.3, 128.4, 129.1, 132.9, 135.9, 141.0, 142.7, 185.3. GC-MS (70 eV): *m/z*: 262([M+], 75), 235(11), 207(22), 171(15), 145(13), 91(100), 65(18), 55(10). Anal. Calcd. for $C_{17}H_{14}N_2O$ (262.31): C, 77.84; H, 5.38; N, 10.68. Found: C, 77.94; H, 5.43; N, 10.59.

*Synthetic procedure of nitro compound **99***:

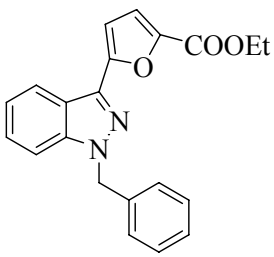
To a stirred solution of unsaturated ketone **98** (3 mmol), in THF (2 mL), $NaNO_2$ (6 mmol) and AcOH (6 mmol) were added and the resulting mixture was stirred at room temperature for 24 hours. After completion of the reaction (monitored by TLC), the system was diluted with water (10 mL) and extracted with ethyl acetate (3 x 20 mL). Then, the organic layer was dried over dry Na_2SO_4 and the solvent was evaporated under vacuum affording the crude β-nitro ketone. The so obtained β-nitro ketone was placed in a dried nitrogen flushed flask, equipped with a Dean-Stark apparatus and condenser, after that, benzene (7 mL), ethylene glycol (18 mmol) and *p*-toluensulfonic acid (0.15 mmol) were added and the solution was refluxed for 24 hours. The mixture was cooled and $NaHCO_3$ saturated aqueous solution (10 mL) was added. The organic layer was separated and the aqueous phase was extracted with $CHCl_3$ (3 x 20 mL). The organic layer was dried over dry Na_2SO_4 and the solvent was evaporated under vacuum affording the crude product **99**, which was purified by flash chromatography column.



Yield: 67%. Yellow solid, m.p. 85-87°C. IR (cm^{-1}, nujol) ν: 728, 914, 1027, 1378, 1551, 1615. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 2.94 (t, 2H, *J* = 6.8 Hz), 3.95-4.05 (m, 2H), 4.10-4.20 (m, 2H), 4.63 (t, 2H, *J* = 6.8 Hz), 5.60 (s, 2H), 7.13-7.21 (m, 3H), 7.23-7.37 (m, 5H), 7.90 (d, 1H, *J* = 8.1 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 36.0, 53.4, 65.5, 70.9, 106.8, 109.8, 121.5, 121.7, 121.8, 126.9, 127.3, 128.0, 128.9, 136.7, 140.8, 143.8. GC-MS (70 eV): *m/z*: 353([M+], 3), 180 (22), 279(100), 235(16), 91(58), 65(6). Anal. Calcd. for $C_{19}H_{19}N_3O_4$ (353.37): C, 64.58; H, 5.42; N, 11.89. Found: C, 64.63; H, 5.45; N, 11.70.

*Synthetic procedure of furan **100***:

To a stirred solution of the nitro compound **99** (3 mmol) and ethyl glyoxalate **91a** (3 mmol) in EtOAc (3mL), Amberlyst A21 (1.5 g) was added. The resulting heterogeneous mixture was stirred for 18 hours at room temperature, then the catalyst was filtrated off by washing with EtOAc (20 mL). The solution was concentrated until arrive at a volume of 18 mL, then Amberlyst A15 (2.1 g) was added and the mixture was stirred at 55°C for 4 hours. Then, the catalyst was removed by filtration, washing with EtOAc (10 mL), and, after evaporation of the solvent, the crude product **100** was purified by flash chromatography column.

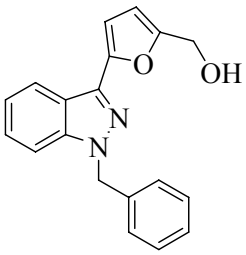


Yield: 70%. White solid, m.p. 88-90°C. IR (cm^{-1}, nujol) ν: 728, 746, 1139, 1376, 1594, 1617, 1720. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 1.43 (t, 3H, *J* = 7.3 Hz), 4.42 (q, 2H, *J* = 7.3 Hz), 5.65 (s, 2H), 7.01 (d, 1H, *J* = 3.4 Hz), 1.19-7.40 (m, 9H), 8.27 (d, 1H, *J* = 8.1 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 14.6, 53.6, 61.1, 108.2, 109.8, 119.8, 121.9, 122.2, 122.3, 127.26, 127.28, 128.1, 129.0, 135.6, 136.5, 140.7, 144.1, 153.0, 159.0. GC-MS (70 eV): *m/z*: 346([M+], 89), 126(16), 91(100), 65(9). Anal. Calcd. for $C_{21}H_{18}N_2O_3$ (346.38): C, 72.82; H, 5.24; N, 8.09. Found: C, 72.86; H, 5.29; N, 8.04.

*Synthetic procedure of furan **101***:

To a stirred solution of ester **100** (3 mmol), in dry THF (25 mL) and under inert atmosphere at -10 °C, a 1 M hexanes solution of DIBAL-H (9 mmol) was added dropwise. The resulting mixture was stirred at the same temperature for 1 hour, after that additional 9 mmol of DIBAL-H solution were added. Finally the reaction was stirred at room temperature for 6 hours (the reaction was monitored by TLC), then it was initially quenched by slowly addition of water (10 mL), and successively by 1M aq. HCl (20 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The resulting organic layer was dried over dry Na_2SO_4,

and the solvent was evaporated under vacuum, affording the crude product **101** which was purified by flash chromatography column.

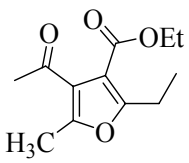


Yield: 93%. White solid, m.p. 110-112°C. IR (cm^{-1}, nujol) ν: 727, 742, 769, 1015, 1030, 1377, 1495, 1615, 3310. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 2.28 (bs, 1H), 4.74 (s, 2H), 5.65 (s, 2H), 6.47 (d, 1H, *J* = 3.4 Hz), 6.87 (d, 1H, *J* = 3.4 Hz), 7.17-7.38 (m, 8H), 8.05 (d, 1H, *J* = 8.1 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 53.4, 57.8, 108.1, 109.8, 109.9, 121.5, 121.6, 121.7, 127.1, 127.2, 128.0, 128.9, 136.4, 136.8, 140.7, 148.8, 154.1. GC-MS (70 eV): *m/z*: 304([M+], 100), 287(40), 213(10), 128(20), 91(76), 65(11). Anal. Calcd. for $C_{19}H_{16}N_2O_2$ (304.34): C, 74.98; H, 5.30; N, 9.20. Found: C, 75.01; H, 5.33; N, 9.16.

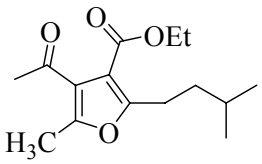
5.6 Synthesis of tetrasubstitued furans in a One-Pot process and under acidic solvent-free conditions

*Typical Procedure for the synthesis of compounds **104***:

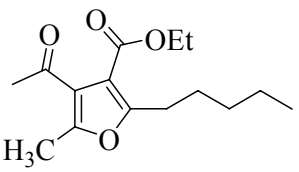
To a stirred mixture of the active methylene derivative **102** (1 mmol) and β-nitroacrylate **103** (1 mmol), acid alumina (1.2 g) was added. The resulting heterogeneous mixture was initially stirred at room temperature, then heated at 60°C and stirred for the appropriate time (see **Table 11** pag. 119; reaction progress was monitored by TLC). After completion of the reaction the cooled heterogeneous system was directly charged onto a silica gel column (eluting with hexanes-EtOAc) to give the pure product **104**.



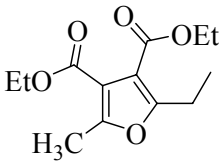
104aa. Clear oil. IR (cm^{-1}, neat) ν: 1050, 1189, 1301, 1577, 1684, 1716. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 1.21 (t, 3H, *J* = 7.7 Hz), 1.32 (t, 3H, *J* = 7.3 Hz), 2.35 (s, 3H), 2.40 (s, 3H), 2.86 (q, 2H, *J* = 7.7 Hz), 4.29 (q, 2H, *J* = 7.3 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 12.6, 13.2, 14.4, 21.2, 31.2, 60.9, 112.1, 123.0, 153.7, 161.8, 163.8, 197.3. GC-MS (EI, 70 eV): *m/z*: 224[M+], 181, 178(100), 163, 135, 122, 108, 57, 43, 29. Anal. Calcd. for $C_{12}H_{16}O_4$ (224.25): C, 64.27; H, 7.19. Found: C, 64.34; H, 7.23.



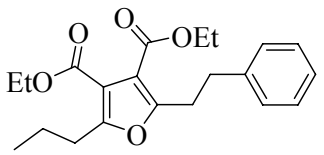
104ab. Clear oil. IR (cm^{-1}, neat) ν: 1047, 1190, 1303, 1576, 1685, 1721. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 0.92 (d, 6H, *J* = 6.0 Hz), 1.33 (t, 3H, *J* = 6.8 Hz), 1.45-1.59 (m, 3H), 2.35 (s, 3H), 2.40 (s, 3H), 2.82-2.87 (m, 2H), 4.30 (q, 2H, *J* = 6.8 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 13.2, 14.4, 22.5, 25.7, 28.0, 31.1, 37.3, 60.9, 112.5, 123.1, 153.7, 161.1, 163.8, 197.3.. GC-MS (EI, 70 eV): *m/z*: 266[M+], 220, 177(100), 164, 151, 135, 43, 29. Anal. Calcd. for $C_{15}H_{22}O_4$ (266.33): C, 67.64; H, 8.33. Found: C, 67.71; H, 8.40.



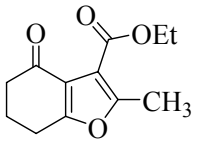
104ac. Clear oil. IR (cm^{-1}, neat) ν: 1058, 1192, 1301, 1578, 1685, 1718. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 0.88 (t, 3H, *J* = 7.3 Hz), 1.27-1.36 (m, 7H), 1.57-1.66 (m, 2H), 2.35 (s, 3H), 2.40 (s, 3H), 2.80-2.85 (m, 2H), 4.29 (q, 2H, *J* = 7.3 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 13.2, 14.1, 14.3, 22.5, 27.6, 28.0, 31.1, 31.5, 60.8, 112.6, 123.0, 153.7, 161.0, 163.9, 197.3. GC-MS (EI, 70 eV): *m/z*: 266[M+], 223, 221, 220(100), 177, 163, 135, 43. Anal. Calcd. for $C_{15}H_{22}O_4$ (266.33): C, 67.64; H, 8.33. Found: C, 67.71; H, 8.40.



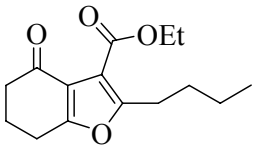
104ba. Clear oil. IR (cm^{-1}, neat) ν: 1097, 1210, 1589, 1719. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 1.21 (t, 3H, *J* = 7.7 Hz), 1.31 (t, 6H, *J* = 7.3 Hz), 2.43 (s, 3H), 2.80 (q, 2H, *J* = 7.7 Hz), 4.27 (q, 4H, *J* = 7.3 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 12.6, 13.3, 14.3, 14.4, 20.8, 60.7, 60.8, 113.1, 113.8, 155.7, 160.2, 163.9. GC-MS (EI, 70 eV): *m/z*: 254[M+], 208(100), 180, 152, 108, 43. Anal. Calcd. for $C_{13}H_{18}O_4$ (254.28): C, 61.40; H, 7.14. Found: C, 61.51; H, 7.19.



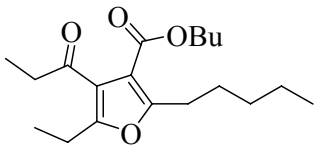
104cd. Clear oil. IR (cm^{-1}, neat) ν: 1114, 1493, 1583, 1602, 1721, 3060. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 0.92 (t, 3H, *J* = 7.3 Hz), 1.31 (q, 6H, *J* = 7.3 Hz), 1.59-1.70 (m, 2H), 2.77 (t, 2H, *J* = 7.3 Hz), 2.94 (t, 2H, *J* = 7.3 Hz), 3.09-3.15 (m, 2H), 4.21-4.31 (m, 4H), 7.13-7.22 (m, 3H), 7.24-7.29 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 13.9, 14.3, 14.4, 21.7, 29.2, 29.5, 34.6, 60.8, 113.8, 113.9, 126.4, 128.6, 128.7, 140.8, 158.2, 159.5, 163.7, 163.9. GC-MS (EI, 70 eV): *m/z*: 358[M+], 312, 267, 221(100), 193, 175, 147, 91, 65. Anal. Calcd. for $C_{21}H_{26}O_5$ (358.43): C, 70.37; H, 7.31. Found: C, 70.43; H, 7.45.



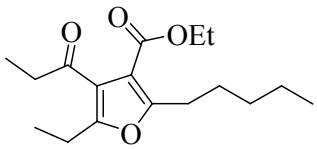
104de. Clear oil. IR (cm^{-1}, neat) ν: 1046, 1190, 1582, 1687, 1735. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 1.36 (t, 3H, *J* = 7.3 Hz), 2.08-2.17 (m, 2H), 2.46-2.51 (m, 2H), 2.48 (s, 3H), 2.82 (t, 2H, *J* = 6.4 Hz), 4.32 (q, 2H, *J* = 7.3 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 13.5, 14.4, 22.4, 23.6, 38.8, 60.9, 111.9, 119.6, 158.5, 163.6, 165.8, 192.2. GC-MS (EI, 70 eV): *m/z*: 222[M+], 194, 176(100), 166, 138, 78, 43. Anal. Calcd. for $C_{12}H_{14}O_4$ (222.24): C, 64.85; H, 6.35. Found: C, 64.94; H, 6.41.



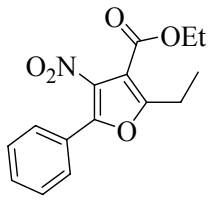
104df. Clear oil. IR (cm^{-1}, neat) ν: 1105, 1433, 1583, 1687, 1735, 3051. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 0.90 (t, 3H, *J* = 7.3 Hz), 1.27-1.40 (m, 5H), 1.56-1.67 (m, 2H), 2.09-2.17 (m, 2H), 2.49 (t, 2H, *J* = 6.8 Hz), 2.79-2.88 (m, 4H), 4.32 (q, 2H, *J* = 7.3 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 14.0, 14.3, 22.3, 22.4, 23.6, 27.1, 30.3, 38.8, 61.0, 111.5, 119.5, 162.1, 163.6, 165.8, 192.4. GC-MS (EI, 70 eV): *m/z*: 264[M+], 218, 189(100), 176, 149, 138, 121, 55. Anal. Calcd. for $C_{15}H_{20}O_4$ (264.32): C, 68.16; H, 7.63. Found: C, 68.44; H, 7.71.



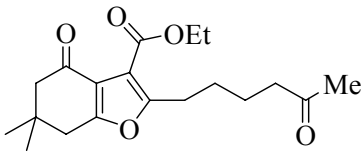
104eg. Clear oil. IR (cm^{-1}, neat) ν: 1060, 1303, 1583, 1672, 1736. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 0.88 (t, 3H, *J* = 6.8 Hz), 0.94 (t, 3H, *J* = 7.3 Hz), 1.11 (t, 3H, *J* = 7.3 Hz), 1.19 (t, 3H, *J* = 7.7 Hz), 1.26-1.45 (m, 6H), 1.59-1.70 (m, 4H), 2.65 (q, 2H, *J* = 7.7 Hz), 2.72 (q, 2H, *J* = 7.3 Hz) 2.83-2.89 (m, 2H), 4.21 (t, 2H, *J* = 6.8Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 8.5, 12.9, 13.9, 14.2, 19.4, 20.6, 22.5, 27.7, 28.0, 30.8, 31.6, 37.0, 64.7, 112.4, 113.0, 156.7, 161.1, 164.0, 201.4. GC-MS (EI, 70 eV): *m/z*: 322[M+], 293, 248(100), 237, 205, 191, 163, 57, 29. Anal. Calcd. for $C_{19}H_{30}O_4$ (322.44): C, 70.77; H, 9.38. Found: C, 70.81; H, 9.49.



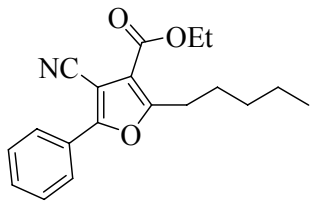
104ec. Clear oil. IR (cm^{-1}, neat) ν: 1051, 1193, 1330, 1575, 1683, 1741. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 0.83 (t, 3H, *J* = 6.8 Hz), 1.06 (t, 3H, *J* = 7.7 Hz), 1.13 (t, 3H, *J* = 7.7 Hz), 1.23-1.28 (m, 7H), 1.54-1.63 (m, 2H), 2.60 (q, 2H, *J* = 7.7 Hz), 2.66 (q, 2H, *J* = 7.3 Hz) 2.78-2.83 (m, 2H), 4.21 (q, 2H, *J* = 6.8Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 8.4, 12.8, 14.0, 14.2, 20.4, 22.4, 27.5, 27.8, 31.4, 36.8, 60.6, 112.2, 121.8, 156.7, 161.0, 163.7, 201.2. GC-MS (EI, 70 eV): *m/z*: 294[M+], 265, 248(100), 237, 205, 191, 177, 163, 57, 29. Anal. Calcd. for $C_{17}H_{26}O_4$ (294.39): C, 69.36; H, 8.90. Found: C, 69.51; H, 9.01.



104fa. Clear oil. IR (cm^{-1}, neat) ν: 1058, 1435, 1536, 1686, 1736. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 1.01 (t, 3H, *J* = 7.3 Hz), 1.39 (t, 3H, *J* = 7.3 Hz), 3.19 (q, 2H, *J* = 7.3Hz), 4.10 (q, 2H, *J* = 7.3Hz), 7.44-7.56 (m, 2H), 7.60-7.69 (m, 1H), 7.82-7.93 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 11.7, 13.8, 20.9, 61.3, 108.5, 129.0, 130.0, 130.8, 134.7, 136.0, 160.7, 160.8, 180.0, 187.3. GC-MS (EI, 70 eV): *m/z*: 289[M+], 228, 172, 105(100), 77, 51, 29. Anal. Calcd. for $C_{15}H_{15}NO_5$ (289.28): C, 62.28; H, 5.23; N, 4.84. Found: C, 62.33; H, 5.35; N, 4.76.



104gh. Clear oil. IR (cm^{-1}, neat) ν: 1223, 1583, 1689, 1736. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 1.11 (s, 6H), 1.35 (t, 3H, *J* = 7.3 Hz), 1.60-1.74 (m, 4H), 2.32 (t, 2H, *J* = 6.8 Hz), 2.38 (s, 2H), 2.69 (s, 2H), 2.89 (t, 2H, *J* = 6.8 Hz), 3.64 (s, 3H), 4.31 (q, 2H, *J* = 7.3 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 14.3, 24.5, 27.1, 27.6, 28.6, 33.8, 35.1, 37.5, 53.3, 61.0, 111.7, 118.4, 162.1, 163.5, 165.0, 174.0, 191.9. GC-MS (EI, 70 eV): *m/z*: 350[M+], 319, 304, 272, 244, 231, 217(100), 55, 29. Anal. Calcd. for $C_{19}H_{26}O_6$ (350.41): C, 65.13; H, 7.48. Found: C, 65.22; H, 7.56.

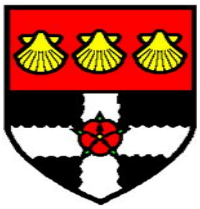


104hc. Clear oil. IR (cm^{-1}, neat) ν: 1112, 1492, 1586, 1603, 1721, 2232, 3062. ^{1}H-NMR ($CDCl_3$, 400MHz) δ: 0.90 (t, 3H, *J* = 6.8 Hz), 1.31-1.39 (m, 4H), 1.41 (t, 3H, *J* = 6.8 Hz), 1.68-1.79 (m, 2H), 3.05 (t, 2H, *J* = 7.7 Hz), 4.38 (q, 2H, *J* = 7.3 Hz), 7.40-7.50 (m, 3H), 7.98 (d, 2H, *J* = 7.3 Hz). ^{13}C-NMR ($CDCl_3$, 100MHz) δ: 14.1, 14.2, 22.4, 27.6, 27.7, 31.4, 61.3, 92.1, 114.2, 114.5, 125.7, 127.7, 129.2, 130.5, 158.7, 161.8, 163.3. GC-MS (EI, 70 eV): *m/z*: 311[M+], 282, 254, 226(100), 105, 77, 29. Anal. Calcd. for $C_{19}H_{21}NO_3$ (311.37): C, 73.29; H, 6.80; N, 4.50. Found: C, 73.33; H, 6.85; N, 4.46.

CHAPTER 6

UNIVERSITY OF READING

United kingdom



UNIVERSITY OF CAMERINO

Italy

STUDIES ON AZOMETHINE YLIDS

Supervisors

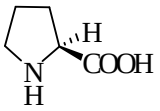
Prof. Laurence M. Harwood and Prof. Roberto Ballini

6.1 Introduction

This project was involved in investigating the application of a chiral synthetic methodology, that combines nitroolefins with chiral azomethine ylids, derived originally from amino acids in 1,3-dipolar cycloaddition reactions in order to estimate the potential of the technique in the syinthesis of proline derivatives, a range of compounds whose physiological activity is of great interest.

6.2 The natural occurrence and utility of proline derivatives

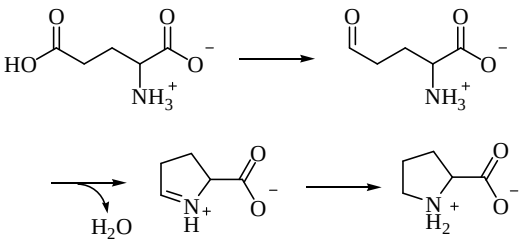
(S)-proline **1** is of essential importance in biological systems and a vital constituent of many proteins and enzymes (**Figure 1**).



1

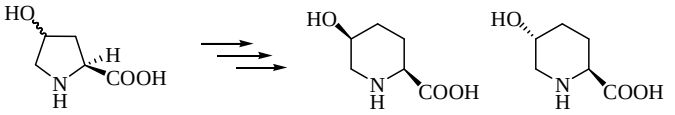
Figure 1. Proline structure

Proline is formally not an amino acid, but an **imino acid**. Nonetheless, it is called an amino acid. The primary amine on the α carbon of glutamate semialdehyde forms a Schiff base with the aldehyde which is then reduced, yielding proline (**Scheme 1**).



Scheme 1. Classical synthesis of proline

When proline is in a peptide bond, it does not have a hydrogen on the α amino group, so it cannot donate a hydrogen bond to stabilize an α-helix or a β-sheet. It is often said, inaccurately, that proline cannot exist in an α-helix. When proline is found in an α-helix, the helix will have a slight bend due to the lack of the hydrogen bond. Proline is often found at the end of α helix or in turns or loops. Unlike other amino acids which exist almost exclusively in the *trans*- form in polypeptides, proline can exist in the *cis*-configuration in peptides. The *cis* and *trans* forms are nearly isoenergetic. For this reason, there is much interest in substituting proline residues in known peptides with 4-alkyl prolines since the increased steric demand has been found to influence the secondary structure of proteins.[1] It is already known that (S)-proline, 4-hydroxyproline and 3-hydroxyproline are the more important building blocks of the connective tissue, collagen (which constituents a third of total protein content of the body) and several secondary metabolites including etamycin[2] and telomycine.[3] Another most important application of L-proline is due to the discovery of L-proline-catalysed reactions, this unique amino acid as been extensively studied as an organocatalyst. In order to enlarge the scope of proline-catalysed reactions, an extensive research program to explore derivatives has been followed, namely in the evolvement of proline-based bioactive compounds, ligands, and organocatalysts. Great importance is attributed to hydroxyproline derivatives **2**, Jung and Avery developed a diastereoselective synthesis of (2*S*,4*S*)- **3** and (2*S*,4*R*)-5-hydroxypipecolic acid **4** through a regioisomeric ring expansion reaction and stereoselective reduction. These fragments can be used in the synthesis of novel cysteine protease inhibitors (**Scheme 2**).[4]

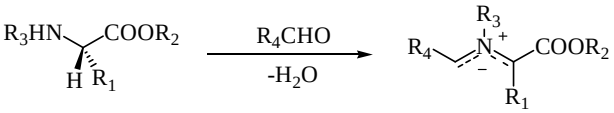


2 3 4

Scheme 2. Diastereoselective synthesis of (2*S*,4*S*)- **3** and (2*S*,4*R*)-5-hydroxypipecolic acid **4**

6.3 Enantiocontrol in 1,3-dipolar cycloadditions

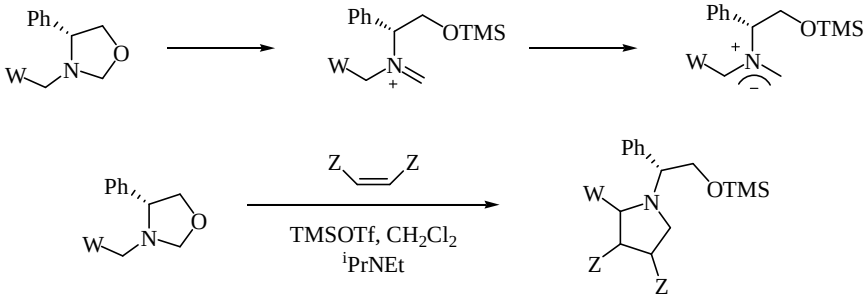
Due to resonance, a simple 1,3-dipole is achiral, and so, although azomethine ylids may be readily derived from amino acids, chirality at the α-position is necessarily lost on ylid generation (**Scheme 3**).



Scheme 3. Ylid generation

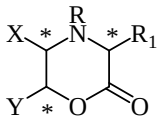
The employment of ***chiral azomethine ylids*** results in one of the most efficient ways to construct the proline skeleton. In fact, the most challenging method to achieve asymmetric induction is the use of chiral dipole as translation of chiral information from the resonating species is necessary.

In 1989 Rouden, Royer and Husson[5] developed a chiral azomethine ylid that underwent a cycloaddition reaction with activated olefins but it shown only poor diastereoselectivity (**Scheme 4**).



Scheme 4. Chiral azomethine ylid that underwent a cycloaddition reaction

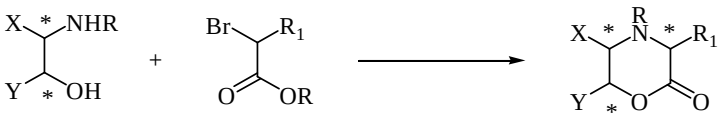
A considerable amount of success has been achieved in work carried out within *N*-phenyl maleimide as a dipolarophile using chiral oxazine-2-ones **5** as effective glycine equivalents for the asymmetric synthesis of amino acids (**Figure 2**).[6]



5

Figure 2. Chiral oxazine-2-ones **5**

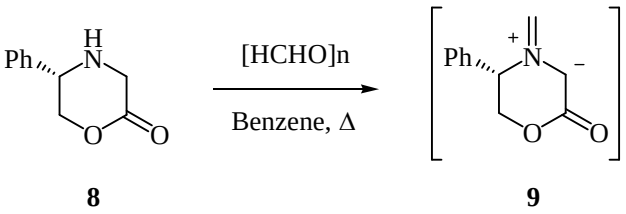
Dellaria[7] has described the facile generation of oxazine-2-ones (**Scheme 5**) by reacting an α-bromoester **6** with readily available optically active β-aminoalcohols **7**.



7 **6**

Scheme 5. Facile generation of oxazine-2-ones

Previous work within the Harwood research group has confirmed that (*S*)-5-phenyl-morpholine-2-one **8** is an excellent precursor for the synthesis of chiral azomethine ylids (**Scheme 6**).



8 **9**

Scheme 6. Synthesis of chiral azomethine ylids

The template **8** reacts with paraformaldehyde to generate the azomethine ylid **9**, which undergoes highly diastereoselective cycloaddition by subsequent trapping of **9** with several dipolarophiles. In this project we proposed to use nitroethylene and other related nitroethylene derivatives, as the electron deficient species.

6.4 Cycloaddition reactions

Cycloaddition reactions are usually rationalized using **FMO** theory[8] in which the HOMO of one adduct must interact with the LUMO of the other. In this particular case, 1,3-dipolar cycloaddition, examining the frontiers orbitals, we can see that interaction can be achieved in both of the following ways: (**Figure 3**)

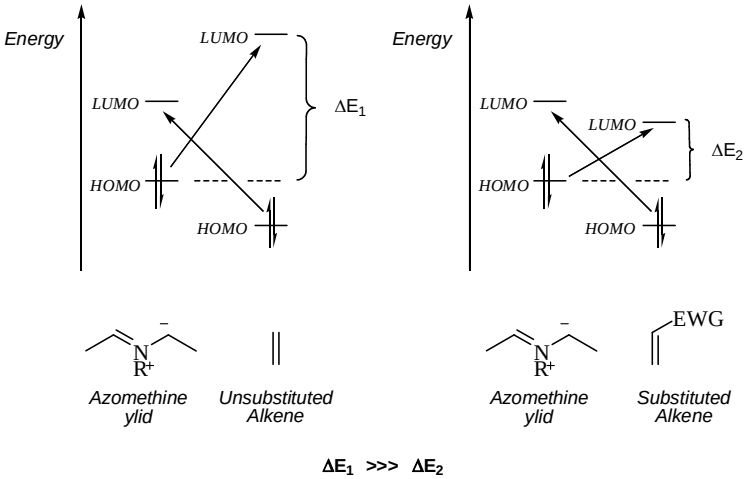
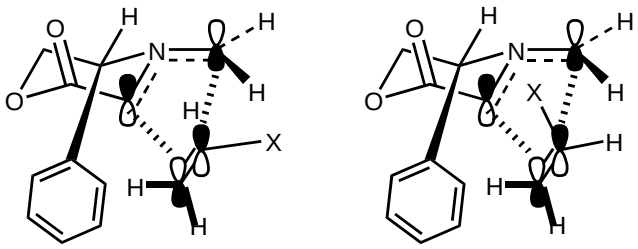


Figure 3. The frontiers orbitals relative to 1,3-cycloaddition reactions

It can be seen, that an alkene with an electron withdrawing group (EWG) will have decreased LUMO energy and this facilitates the cycloaddition by decreasing the difference in energy between the HOMO of the dipole and the LUMO of the dipolarophile. In general the direction of polarization can be described as in (**Figure 4**), depending of the largest numerical value for the orbital coefficient of the centre and can lead to predictable regiocontrol.



Exo-Transition State (**15**) ***Endo***-Transition State (**16**)

Figure 4. The direction of polarization

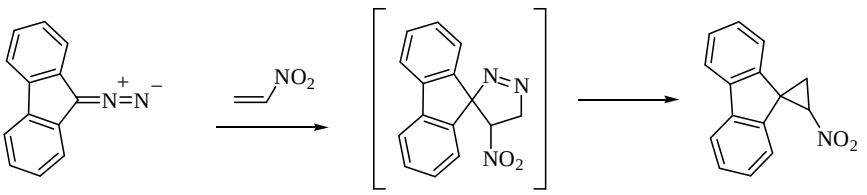
This reaction, is very similar to the Diels-Alder reaction because both involve suprafacial axial approach to maximize the frontier orbital interactions. As with the D. A. reaction this approach can be either *exo* or *endo*. The *exo*-TS **15** is in general favoured with respect to the *endo*-transition state **16**. Therefore, we predict a certain degree of stereo and regio selectivity as a result of the presence of the nitrogroup. Thus we surveyed the standard cycloaddition reaction as reported but changing nitroethylene equivalent, solvent, amount of starting materials in different bases.

6.5 Project aim and objectives

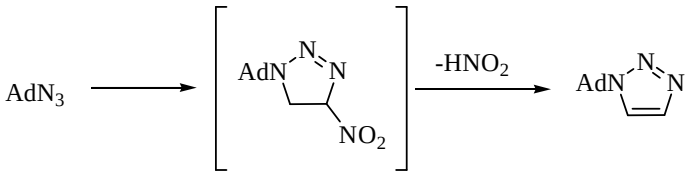
Nitroethylene as a dipolarophile and nitroethylene derivatives, as in situ precursor of nitroethylene.

The aim of this work was to develop a method to synthetize (S)-proline by reacting of morpholin-2-one **8** with nitroethylene and activated nitrolefins as a dipolarophiles. Nitroethylene[9], is the most simple nitrolefins used in organic synthesis but it has found limited application due to its behavior because it can polymerize readily in the presence of any trace of water and it is able to react violently with base. It has been applied as a very electron deficient and very reactive dienophile in Diels-Alder reactions with several types of dienes[10] and as a functional acceptor for nucleophilic radicals.[11] Moreover, Michael reactions have been carried out using it as an electron poor olefin, with a large variety of nucleophiles.

Nitroethylene has shown good versatility towards 1,3-cycloaddition reactions, but only a few examples have been published to date; reaction with 9-diazafluorene takes one to a nitrocyclipropane derivative,[12] (**Scheme 7**) whilst the reaction with 1-azidoadamantene gave a 1*H*-1,2,3-triazole[13] by the additional reaction of the novel cycloadduct in both cases.(**Scheme 8**)



Scheme 7. Synthesis of nitrocyclipropane derivative

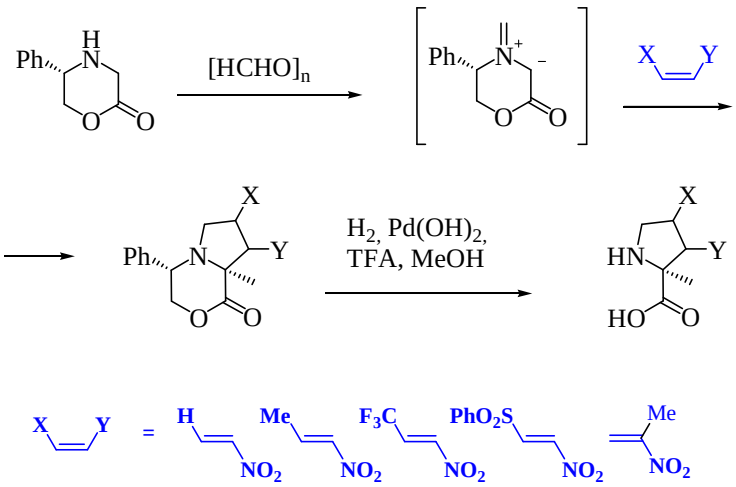


Scheme 8. Synthesis of 1*H*-1,2,3-triazole

Nevertheless, there is no reports of cycloaddition of azomethine ylids on nitroethylene, presumibly because of its highly instability. In order to escape the difficulty in handling and storing of nitroethylene as such, we considered the possibility of using some other derivatives as, nitroethylene precursors. Several reports on the thermal *in situ* generation and reaction of nitroethylene are known using precursor such as 2-nitroethyl phenyl sulfoxide,[14] 2-benzyloxy-[15] or 2-acetoxy-nitro ethane[16] and from 2-nitroethanol in the presence of dehydrating agent.[17] We intended to investigate this azomethine ylid trappy reaction, with the above nitroethylene precursor, as well as 1-nitro-1-propene, 3,3,3-trifluoro-1-nitro-1-propene and 1(2-nitrovinyl sulfonyl) benzene, because previous work within the Harwood research group has shown a better selectivity of 1,3-dipolar cycloaddition on diactivated dipolarophiles. As already reported, the plan of this project was to synthesize (S)-proline derivatives using nitroethylene equivalents and derivatives in the following manner:

- The first step is the cycloaddition between chiral azomethine ylid, formed by reaction of our template (*S*)-5-phenylmorpholin-2-one **8** and paraformaldehyde with thermal conditions, and nitroethylene equivalents, 2-acetoxy-nitroethane and 2-benzoyloxy-nitroethane, or diactivated dipolarophiles, to form two new C-C bonds;
- The second step will be the hydrogenation of bicyclic compound obtained to achieve the (S)-proline derivative;

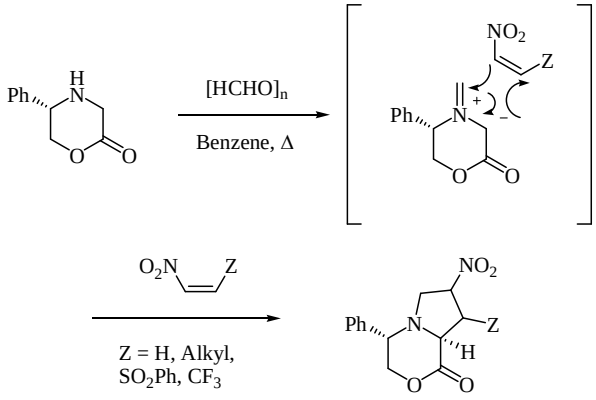
- The third step will involve the Nef reaction to convert the nitro group, present into the molecule, into a carbonyl group, or convert directly the nitro-group into an amino-group to obtain amino;
- The fourth step, and final step, will be the reduction of the carbonyl function to a hydroxyl group to achieve our final goal. (**Scheme 9**)



Scheme 9. Planned synthesis of (S)-proline derivative

6.6 Synthetic methodology

The principal reaction of this project is the 1,3-dipolar cycloaddition of α-amino acid derived azomethine ylids to electron-poor olefins. As reported, for enantiocontrol in 1,3-dipolar cycloadditions, the chiral information of the α-amino acid precursor must be kept, for this reason we incorporated the azomethine ylid in a chiral template, (*S*)-5-phenylmorpholin-2-one **8**, which was prepared from phenyl glycinol and phenyl bromoacetate[7]. Following this, a one pot procedure of ylid generation[18] with concomitant 1,3-dipolar cycloaddition has been carried out using nitroethylene as a monoactivated dipolarophile and 1-nitropropylene as a diactivated dipolarophile. (**Scheme 10**)

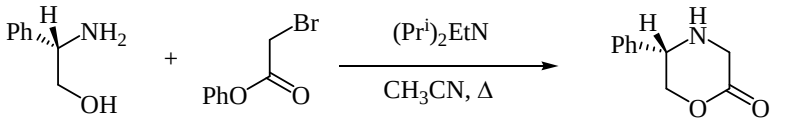


Scheme 10. 1,3-dipolar cycloaddition using nitroethylene precursors

The goal of this project was to optimize the reaction of the chiral glycine derivative, an azomethine ylid, with monoactivated and diactivated dipolarophile as nitroethylene and derivatives, and to examine the stereo- and regiocontrol of this type of reaction.

6.6.1 Preparation of the Oxazin-2-one template

The (*S*)-5-phenylmorpholin-2-one is a known compound and was made by the literature procedure (**Scheme 11**).[7]



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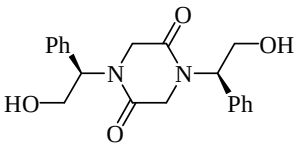
Scheme 11. Direct synthesis of (*S*)-5-phenylmorpholin-2-one

2-Phenylglycinol is commercially available in both (*R*-) and (*S*-) forms, being obtained by the reduction of phenylglycine with $LiAlH_4$. The phenyl bromoacetate is also commercially available.

The phenylglycinol was dissolved in dry acetonitrile, and stirred in the presence of diisopropylethylamine for 15 minutes. A solution of phenyl bromoacatate in acetnitrile dry was added dropwise over a period of 30 minutes, and then the mixture was stirred for 1 hours at reflux and was permitted to cool at room temperature over two days. Column chromatography, (eluting 8:2 n-Hexane-EtOAc and then EtOAc) furnished the product in a typical yield of 53%.

The product has been reported to be unstable and to have a tendency to dimerise at room temperature giving **10** and was therefore stored at -5°C. (**Figure 5**)



10

Figure 5. Dimer of (*S*)-5-phenylmorpholin-2-one

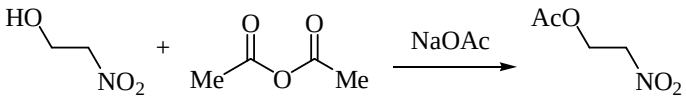
The stability of the (*S*)-5-phenylmorpholin-2-one, was tested by heating it at reflux initially in deuterated chloroform followed by analysis of the resulting spectroscopic data. No alteration of the starting material was observed and consequently the material obtained was concluded to be stable at high temperature.

6.6.2 Preparation of nitroethylene equivalents and nitroethylene derivatives as diactivated dipolarophiles

Several works discuss the importance of nitroethylene, but there are few reports of reactions with this compound because generally, the high temperatures employed leads to some decomposition of the nitroolefin.[19]
It was supposed that difficulties in handling this compound could be overcome to a large extent if it was generated *in situ*.
Therefore, we decided to study the reaction with two nitroethylene equivalents:

- 2-acetoxynitroethane
- 2-benzoyloxynitroethane

The reactions were carried out under basic conditions to assist the β-elimination to afford the nitroethylene *in situ*. Firstly, we synthesized 2-acetoxynitroethane[9] **11** using the procedure of Flaugh *et al*. (Scheme 12).[20]

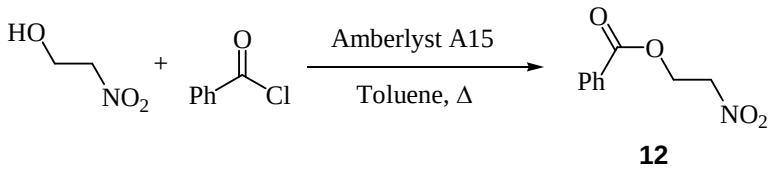


11

Scheme 12. Synthesis of 2-acetoxynitroethane[9]

A solution of NaOAc in AcO_2 was mantained at a temperature of 35°C using a cooling bath, and the requisite quantity of nitroethanol was added over a period of 30 minutes. When the reaction temperature no longer tended to

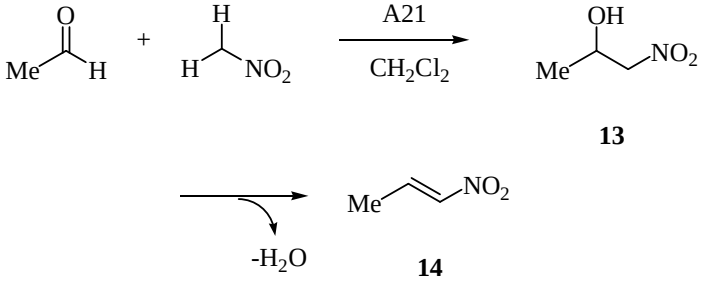
rise, the cooling bath was removed and the mixture was allowed to stir overnight. The mixture was distilled under reduced pressure to remove the excess of Ac_2O and obtain 2-nitroethylacetate in 79% yield. Secondly, we synthesized the 2-benzoyloxynitroethane[21] **12** as an alternative precursor to nitroethylene. (**Scheme 13**)



12

Scheme 13. Synthesis of 2-benzoyloxynitroethane[21]

This compound was prepared according to the established procedure with slight modifications: to a stirred solution of nitroethanol in dry toluene, was added benzoyl chloride and Amberlyst A15. The crude product was triturated with petroleum ether afford **12** as colorless crystals in 84% yield. Furthermore, we tried to prepare 1-nitropropylene **14** according to the procedure of Ballini *et al*. procedure[22], via the nitroaldol (Henry) reaction catalyzed by Amberlyst A21 as a heterogeneus catalyst. (Scheme 14)



13 **14**

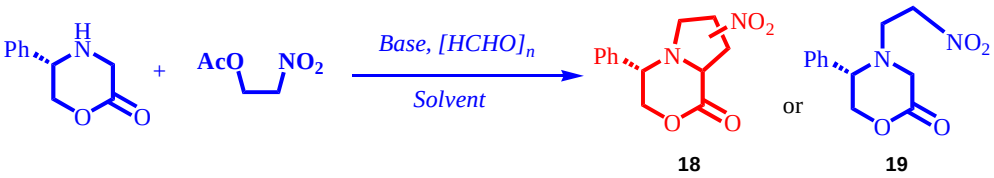
Scheme 14. Nitroolefines synthesis following Ballini *et al*. procedure[22]

To a solution of nitromethane and acetaldehyde in CH_2Cl_2 was added Amberlyst A21 as a heterogeneous base and the mixture was stirred at room temperature for 6h. After removed resin by filtration, the crude nitroalcohol was purified by chromatography to achieve the product **13** in

51% yield. After this a dehydratation was carried out, following the standard procedure[23] with the modification of treating a cold solution of β-nitroalcohol (0°C) in dry toluene, with TFAA and Et_3N added dropwise. The mixture was stirred at 0°C and under nitrogen atmosphere overnight and the distillation attempted but the product **14** could not be obtained.

After that, we focused our attention on the key reaction, the synthesis of proline derivative. We reported here our results: the reaction was carried out dropping a solution of (*S*)-5-phenylmorpholin-2-one and 2-acetoxy-nitroethane or 2-benzoyloxy-nitroethane in a selected solvent, to a solution of the same solvent, base and formaldehyde at reflux in a round bottom flask equipped with Soxhlet apparatus containing dried 3 Å molecular sieves to remove water from the solution and the mixture was stirred for the right time , **Table 1** and **Table 2**. T.L.C. analysis was used to check the reaction. The excess of formaldehyde was removed by filtration of the mixture through a pad of Celite®. At the end of each reaction the mixture was concentrated *in vacuo* and different techniques of purification were tried including normal SiO_2 chromatography, SiO_2/Et_3N to produce less acidic silica, Al_2O_3, and crystallization. We encountered so many problems in purifying the mixtures and actually we isolated a new product (Rf= 0.2 in 7:3 n-hexane/EtOAc) that is stable on silica. However, it was shown to be undesired product **19** resulting by a simple Michael addition of morpholinone in the presence of nitroethylene, without any interaction with formaldehyde.

Table 1. Synthesis using 2-acetoxynitroethane



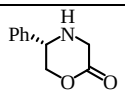
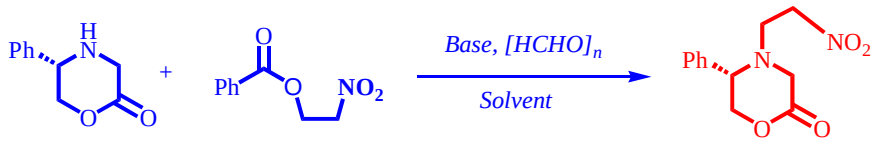
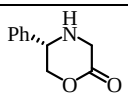
		*HCHO*	*BASE*	*Solvent*	*Yield(%)*
0.5 mmol	**0.5 mmol**	1.5 mmol	0 mg	50 mL dry Toluene	0 %
0.5mmol	**1.5mmol**	2 mmol	0 mg	50mL dry Toluene	0 %
0.6 mmol	**1.8 mmol**	2.4 mmol	0 mg	50 mL dry Toluene	0 %
0.5 mmol	**0.5 mmol**	1.5 mmol	**700 mg**	50 mL dry Toluene	0 %
0.5 mmol	**0.5 mmol**	1.5 mmol	**700 mg**	50 mL dry Toluene	10% of **19**
0.565 mmol	**1.13 mmol**	1.7 mmol	**2.4 mmol**	50 mL dry Toluene	14 % of **19**
0.565 mmol	**1.13 mmol**	1.7 mmol	**2.4 mmol**	40 mL dry **CH_3CN**	0 %
0.565 mmol	**1.13 mmol**	1.7 mmol	**500 mg**	50 mL dry Toluene	0 %
0.565 mmol	**1.7 mmol**	2.26 mmol	**1 g**	50 mL dry Toluene	18 % of **19**

Table 2. Synthesis using 2-benzoyloxynitroethane



19

		*HCHO*	*BASE*	*Solvent*	*Yield (%)* ***19***
0.565 mmol	**1.13 mmol**	1.70 mmol	**1.7 mmol**	50 mL dry Toluene	0 %
0.565 mmol	**1.7 mmol**	2.,26 mmol	**1 g**	40 mL dry Toluene	20 %
0.565 mmol	**1.7 mmol**	2.26 mmol	**1 g**	50 mL dry **THF**	30 %
0.565 mmol	**1.7 mmol**	2.26 mmol	**2 g**	50 mL dry **THF**	30 %
0.565 mmol	**1.7 mmol**	2.26 mmol	**1 g**	50 mL dry **THF**	0 %
0.565 mmol	**1.7 mmol**	**2.87 mmol**	**1 g**	**50 mL dry THF**	**58 %**

6.7 Conclusions

The data acquired from nmr analysis did not correspond to that expected for the desired cycloadduct **18**. We could clearly observe a double triplet at δ_H=2.61-2.66 ppm, shows the quadrupole effect of nitrogen, deriving from **19**, and the most important signal, that permit us to understand we're not in the presence of a cyclic derivative **18**, the multiplet at δ_H=4.23-4.34 ppm, which shows two protons at 7 position, at the α position with respect to the nitro group. It means that, unfortunately the only reaction occurred is the hetero-Michael reaction between the morpholinone and the notroethylene *in situ* generated, instead of the 1,3-dipolar cycloaddition expected. By the way, the work needs more attention, that's why it is still in progress, and the next step will be try to change reaction conditions, and starting materials, using, as model the direct dehydration of nitroethanol to get nitroethylene, with the purpose to synthesize L-proline derivatives as planned, specially for their importance as biologically active compounds. Further, we would like to extend this work using our product **19**, as asymmetric moiety in order to induce stereoselectivity.

Equipment

Nuclear magnetic resonance spectra were obtained using a Bruker AMX 400 MHz and DPX 250 MHz spectrometers.

Infra-red spectra were obtained using a Perkin Elmer 1720-X IR-Fourier Transform SpectrometerThe Lambda 900.

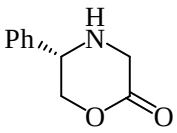
X-Ray data were obtained from an Oxford Instruments X-Calibur CCD Diffractometer equipped with both copper and molybdenum X-ray tubes.

Specific rotation measurements were obtained using a Perkin-Elmer 241 Polarimeter. Values of the specific rotation are quoted as $[\alpha]_D^t$ (c).

Melting points were obtained using an Electrothermal melting point apparatus.

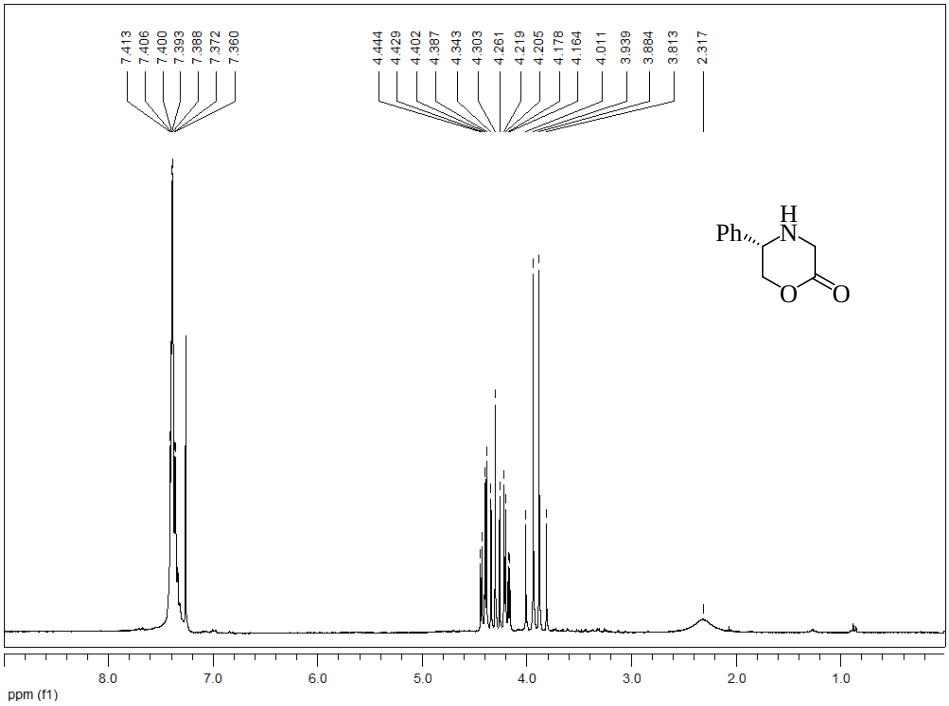
Experimental Procedures (methods)

Preparation of (S)-5-phenylmorpholin-2-one ***8***[7]

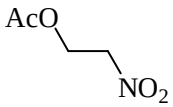


8

To a stirred solution of (*S*)-(+)-2-phenylglycinol (589 mg, 4.3 mmol) in diisopropylethylamine (1.52 g, 11.75 mmol) in dry acetonitrile (20 mL) at reflux, was added phenyl-α-bromoacetate (1.01 g, 4.7 mmol) in dry acetonitrile (20 mL) dropwise over a period of 1 hour. After that time the reaction was stirred at reflux for 2 hours and then was allowed to cool at room temperature and stirred for a further two days. The solvent was removed *in vacuo* to give a yellow oil. The oil was then purified by chromatography using a mixture of n-hexane/EtOAc 8:2 and then pure EtOAc, as eluent, to obtain the pure product as a colourless oil (405 mg, 53 %). Further purification was obtained by crystallization with Petrol to obtain our product as a white crystals, m.p. 53-55°C; *δH (250 MHz, $CDCl_3$)*, 7.37 (m, 5H, **Ph**), 4.29 (t, 1H, **2Hα**, *J* = 10.0 Hz), 4.29 (dd, 2H, **3Hα 3Hβ**, *J* = 7.5 Hz *J* = 2.5 Hz), 3.86 (dd, 2H, **6Hα 6Hβ**, *J* = 17.5 Hz *J* = 12.5 Hz), 2.31 (bs, 1H, **NH**) υ_{max} *(KBr disc)*, 3451 (b, NH), 1745 (C=O), 1220 (C-O) cm^{-1}; $[\alpha]_D^{20}$= -96.4 (c=1.0, $CHCl_3$).



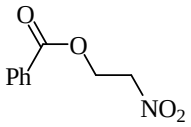
*Preparation of 2-Nitroethyl-acetate **11***[19]



11

A solution of NaOAc (2.5 g) in Ac_2O (1.8 mL, 1.97 g, 19.3 mmol) was manteined at a room temperature of 35°C using a cooling bath, and 2-nitroethanol (1.2 mL, 1,5 g, 16.7 mmol) was added over a period of 30 minutes. The mixture was stirred overnight. The solution was then poured in a large amount of cold water and extracted with three portions of CH_2Cl_2. The organic layer was dried on Na_2SO_4. The solvent was then removed *in vacuo* followed by distillation under reduced pressure to obtain 2-nitroethylacetate (1.76 g, 79 %): *δH (250 MHz. $CDCl_3$)*, 4.61 (m, 4H, AcO**C**$\mathbf{H_2}$**C**$\mathbf{H_2}$$NO_2$), 2.09 (s, 3H, **C**$\mathbf{H_3}$CO----); *δC (250 MHz. $CDCl_3$)*, 170. 7, 74.0, 60.0, 20.9.

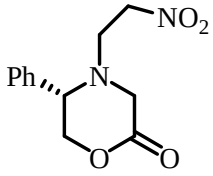
*Preparation of 2-Benzoyloxy-nitroethane **12***[20]



12

To a stirred solution of nitroethanol (3.95 mL, 55 mmol) in dry toluene (50 mL) was added benzoyl chloride (6.39 mL, 55 mmol) and Amberlyst A15 (200 mg). The solution was heated at reflux for 24 hours and then filtered to remove the amberlyst and then concentrated *in vacuo*. The crude product was dissolved in EtOAc with warming and re-crystallized from n-hexane by cooling the mixture in a freezer overnight, to afford of the product (9.0 g, 84 %). δH (250 MHz. $CDCl_3$), 7.99-8.04 (m, 2H, **Ph**), 7.56-7.63 (m, 1H, **Ph**), 7.42-7.48 (m, 2H, **Ph**), 4.84-4.88 (m, 2H, **CH_2**), 4.73-4.77 (m, 2H, **CH_2**). *δC (250 MHz, $CDCl_3$)* 165.9, 133.7, 129.8, 129.9, 128.6, 73.8, 60.0;υ_{max} (KBr disc), 1720 (C=O), 1547 (NO_2), 1370 (NO_2), 1120 (C-O) cm^{-1}.

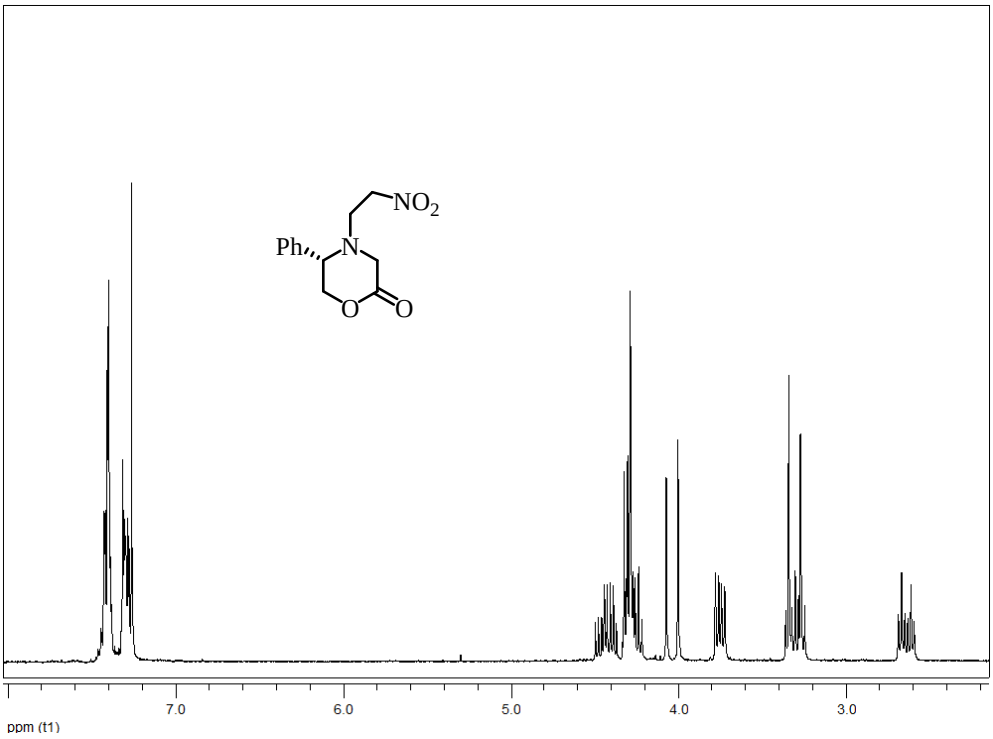
*Preparation of (S)-4-(2-nitroethyl)-5-phenylmorpholin-2-one **19***



19

A solution of (*S*)-5-phenylmorpholin-2-one (0.565mmol, 100 mg) 2-benzoyloxy-nitroethane (1.7mmol, 332 mg) in dry THF (50 mL), was added dropwise to Amberlite IRA 400 (1 g) and formaldehyde (86 mg) in dry THF (50 mL) at reflux in a round bottom flask equipped with a Soxhlet apparatus containing 3Å molecular sieves to remove water from the solution, over a period of 30 minutes, and then the mixture was stirred at reflux. T.L.C.

analysis shown that after 2 hours at reflux the reaction was finished. The excess of formaldehyde was removed by filtration of the mixture through a pad of Celite®. The mixture was concentrated *in vacuo* and purified by chromatography on silica (7:3 n-hexane/EtOAc) to furnish 86 mg of the product (58% yield). **19** was then crystallized by dissolving the solid compound in a very small amount of CH_2Cl_2 adding petrol and n-hexane to obtain a colorless needles; m.p. 99-101°C; *δH (400 MHz, $CDCl_3$)*, 7.39-7.44 (m, 3H, **Ph**), 7.26-7.31 (m, 2H, **Ph**), 4.41-4.47 (m, 1H, **8Hα** or **8Hβ**), 4.23-4.34 (m, 3H, **8Hα** or **8Hβ**, **3Hα** and **3Hβ**) 4.04 (d, 1H, **6Hα** or **6Hβ**, *J* = 16.0 Hz), 3.75 (dd, 1H, **2Hα**, *J* = 5.2 Hz *J* = 4.3 Hz), 3.31 (d, 1H, **6Hα** or **6Hβ**, *J* = 17.4 Hz), 3.26-3.33 (m, 1H, **7Hα** or **7Hβ**) 2.61-2.66 (dt, 1H, **7Hα** or **7Hβ**, *J* = 4.0 Hz); *δC (400 MHz, $CDCl_3$)*, 166.8, 135.0, 129.4, 129.3, 128.2, 72.7, 63.0, 53.7, 51.5; υ_{max} (KBr disc), 1751 (C=O), 1553 (NO_2), 1375 (NO_2), 1231 (C-O) cm^{-1}; $[\alpha]_D^{20}$= +37.4 (c=0.4, $CHCl_3$).



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