A new practical and efficient one-pot synthesis of polyfunctionalized quinolines from β-nitroacrylates under heterogeneous conditions

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Abstract

The core of this thesis work was the development of an innovative and efficient protocol for synthesizing 2-carboxyquinoline derivatives since this class of compounds is largely employed as useful building blocks of biologically active molecules, as well as, they are important ligands in metal catalyzed reactions. With the aim to achieve our goal, we exploited the reactivity of β-nitroacrylates in combination with 2-aminobenzaldehydes. In this context, we organized the work in two main steps: (i) optimization of the reaction conditions doing a deep screening in terms of solvents, bases and temperature, and (ii) demonstration of the generality of our method, by extension of the best reaction conditions to a plethora of functionalized substrates.

In conclusion, polyfunctionalized quinolines were synthesized with a convenient and innovative synthetic pathway thanks to the employment of β-nitroacrylates, which have been demonstrated to be very reactive, versatile and suitable precursors of nitrogen containing heterocycle compounds.

Key words: quinolines, β-nitroacrylates, one-pot processes, solid supported reagents, heterocycles.

O núcleo deste trabalho de dissertação foi desenvolver um protocolo sintético inovador e eficiente para a preparação de derivados 2-carboquinolínicos, pois este compartimento de classe é amplamente utilizado como uma construção útil de moléculas biologicamente ativas, assim como ligandos importantes em reações metal catalisado. Para atingir nosso objetivo, exploramos a reatividade dos β-nitroacrilatos em combinação com 2-aminobenzaldeídios.

Nesse sentido, organizamos o trabalho em duas fases principais: (i) otimizando as condições de reação, realizando uma precisão triagem em termos de solventes, bases e temperatura, e (ii) demonstrando a generalidade do nosso método, estendendo as melhores condições de reação a uma ampla gama de substratos funcionalizados.

Em conclusão, os chinols polifuncionais foram preparados com uma conveniente rota sintética inovadores, graças à utilização de β-nitroacrilatos, que se revelaram particularmente precursores reativos, versáteis e úteis de compostos de nitrogênio heterogêneos.

Palavras-chave: quinolinas, β-nitroacrilatos, processos de um recipiente, reagentes de suporte sólido, heterociclos.
1. Nitrogen-containing heterocycles

Heterocyclic compounds are molecules in which one or more carbon atoms of the ring are displaced by atoms of other elements. The word “heterocycle” is composed by cyclic part (from Greek “kyklos”, that mean “circle”), meaning that the molecule is constituted at least by one ring, and by the prefix hetero- (from Greek “heteros”, meaning “other” or “different”) refers to the non-carbon atoms, or heteroatoms, in the ring. A heterocyclic ring may comprise of three or more atoms and may contain more than one similar or dissimilar heteroatoms.

A first classification of heterocyclic compounds is based on the aromatic character or not of the ring that includes the heteroatom; so we can distinguish between non-aromatic heterocyclic compounds and aromatic one.

Subsequent classification can be done to the type of heteroatoms and successively subclassifications involve the number of atoms that form the cycle, and the number of further cycles fused together.¹

Heterocyclic chemistry includes at least half of all organic chemistry research worldwide, due to their largely use in different research areas and, among them, the nitrogen-containing heterocycles are the most studied ones.² They find applications in materials science, agrochemistry,³ biochemistry⁴ and medicinal chemistry.⁵

Now I am going to treat about nitrogen-containing heterocycles because during my thesis period I worked on them. In Figure 1 some examples nitrogen-containing heterocycles are reported: among the most important there are pyrrole for the five member ring, pyridine for the six member ring, indole and quinoline for the fused heterocyclic systems.

Figure 1 Aromatic nitrogen-containing heterocycles
1.1 Pyrrole

Pyrrole is isoelectronic with the cyclopentadienyl anion, but is electrically neutral because of the higher nuclear charge on nitrogen. The other consequence of the presence of nitrogen in the ring is the loss of radial symmetry, so that pyrrole does not have five equivalent mesomeric forms (Figure 2). It has one with no charge separation, and two pairs of equivalent forms in which there is charge separation, indicating density drift away from the nitrogen.\(^6\)

Pyrrole structure is widespread in nature in fact we can find it in compounds such as the haem, present in blood, and the chlorophylls, essential for photosynthesis, that are fundamental to life.\(^7\) (Figure 3)

One other natural compound containing pirrole is Bilirubin\(^5\), shown in Figure 4, it is a yellow-brown pigment contained in the bile and it is produced by the haemoglobin catabolism. This molecule is an important indicator of the haemoglobin’s correct metabolism in the blood or of a liver abnormality.
1.2 Imidazole

Imidazole is a planar 5-membered ring. It exists in two equivalent tautomeric forms, because hydrogen can be located on either of the two nitrogen atoms. The compound is classified as aromatic due to the presence of a sextet of \(\pi\)-electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring. Some resonance structures of imidazole are shown in Figure 5.

Many natural products, especially alkaloids, contain the imidazole ring, it is in fact present in important biological building-blocks, such as histidine and the related hormone histamine reported in Figure 6.

Histidine is an \(\alpha\)-amino acid containing imidazole and it is classified as aromatic. It is used in the biosynthesis of proteins and it isn’t thought essential only for infants but for adults also as longer-term studies showed.\(^8\) Furthermore histidine is a precursor of histamine that is a hormone involved in local immune responses besides regulating physiological function in the gut and acting as a neurotransmitter.\(^9\) Histamine acting also in the inflammatory response and has a central role as a mediator of pruritus.\(^{10}\)
Even metabolites produced by marine sponges often contain imidazole moiety. Since the discovery of the first alkaloid of this family in 1971, that is Oroidin, many hundreds of such compounds have been isolated, some of these are shown in Figure 7.11

![Histidin and Histamin](image)

**Figure 6** Natural compounds containing imidazole moiety

![Oroidin and Girolline](image)

**Figure 7** Alkaloid compounds come from marine sponge

### 1.3 Pyridine

![Pyridine structure](image)

**Figure 8** Pyridine structure

The structure of pyridine (Figure 8) is completely analogous to that of benzene, because it is related by replacement of CH by N. There are obviously differences that are:

(i) the departure from perfectly regular hexagonal geometry caused by the presence of the heteroatom, in particular the shorter carbon-nitrogen bonds;

(ii) the replacement of a hydrogen in the plane of the ring with an unshared electron pair, likewise in the plane of the ring, located in an $sp^2$ hybrid orbital and not at all involved in the aromatic $\pi$ electron sextet. It is this nitrogen lone pair which is responsible for the basic properties of pyridines;

(iii) a strong permanent dipole due to the greater electronegativity of nitrogen compared with carbon.12
We can find pyridine in many natural compounds, for instance in Nicotine that is a potent parasympathomimetic alkaloid found in the nightshade family plants. It is made in the roots and accumulates in the leaves of Nicotiana rustica in amounts of 2–14%, the tobacco plant Nicotiana tabacum, Duboisia hopwoodii and Asclepias syriaca, in more it acts as stimulant drug.\textsuperscript{13}

There are other alkaloids containing pyridine (Figure 9), one of these is Trigonelline. It has been isolated from fenugreek seeds, specifically from \textit{Trigonella foenum-graecum},\textsuperscript{14} hence the name and it occurs in many other plants such as garden peas and potatoes. Trigonelline is also found in coffee, in particular higher levels of it is found in arabica coffee.\textsuperscript{15} In addition Trigonelline is a product of niacin metabolism.

\textit{Niacin}, also known as vitamin B3 or nicotinic acid, is an organic natural compound. \textit{Niacin} is primarily used in pharmaceutical field in the treatment of hypercholesterolemia and pellagra.\textsuperscript{16}

\textbf{1.4 Diaazines}

Also diazines are six-membered systems but with C\textsubscript{4}H\textsubscript{4}N\textsubscript{2} molecular formula, therefore their structure have two nitrogen atoms and accordingly two lone pairs in the ring (Figure 10).\textsuperscript{17} There are three isomers which result from the different positions of nitrogens: pyrazine (1,4-diazine), pyrimidine (1,3-diazine) and pyridazine (1,2-diazine) like we can see in Figure 11.
1.5 Indole

Indole is a bicyclic heteroaromatic compound formally composed by the fusion of a benzene ring onto the C2/C3 positions of pyrrole producing the corresponding benzopyrrole known as indole (Figure 12).

The single overall electronic structure of indole is not completely described by the structure shown in Figure 12, because this implies localization of the lone pair on the nitrogen atom, this is represented better by resonance structures shown in Figure 13 that make different contributions to the electronic structure of indole.  

In nature it is easy to found molecules with indole moiety, (Figure 14) one example is Tryptophan, an α-amino acid that is used in the biosynthesis of proteins. It contains indole in its side chain and it is classified as a non-polar, aromatic amino acid. It is essential in humans, namely the body cannot synthesize it but it must be obtained from the diet. Tryptophan is also a precursor to melatonin and serotonin.
Serotonin is a monoamine neurotransmitter, it is primarily found in the gastrointestinal tract, blood platelets, and the central nervous system of animals, including humans. It shows biochemical activity in fact it is generally thought that it contributes to feelings of well-being and happiness.

1.6 Quinoline

Quinoline, represented in Figure 15, is an heterocyclic ring system that is formally derived by fusion with benzene and pyridine rings. Being quinolines the subject of my thesis I will thoroughly deal in the next chapter.

1.7 Further nitrogen heterocycle compounds

The main nitrogen-containing heterocycles and their spread in nature have been shown until now. Nevertheless there are many other nitrogen heterocyclic compounds biosynthesized by animals and plants that are biological active and play a major role in biochemical processes.

One example are the purine (adenine and guanine) and pyrimidine (cytosine, thymine and uracil) found in RNA and DNA. (Figure 16) These heterocyclics participate in polar interactions, due to the electronegativity differences between the carbon and nitrogen. In particular they are involved in hydrogen bridge bonds that are decisive for the formation of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), which are the carrier of genetic information in all living beings.
While an example of natural compounds come from plants, in particular derived from *Papaver somniferum* plant also note as opium poppy, is represented by *Papaverine* (*Figure 17*). It is an opium alkaloid antispasmodic drug containing a isoquinoline moiety. It is used primarily in the treatment of visceral spasm, vasospasm especially those involving the heart and the brain.21

![Figure 16 Nitrogenous base of DNA](image)

There are many other natural pharmacologically active nitrogen-containing heterocycles; for instance cephalosporin and penicillin, in *Figure 18*, show antibiotic properties. In particular *Penicillin G* was discovered in 1928, derived from *Penicillium* fungi, it was among the first medications to be effective against many bacterial infections caused by staphylococci and streptococci. Penicillins antibiotics are still widely used today, though many types of bacteria have developed resistance following extensive use.22 One other nitrogen-containing heterocycles with antibiotic properties are the *Cephalosporin C*, it was first isolated in 1961 from fungi of the genus *Acremonium*. Although not a very active antibiotic itself, synthetic analogs of *Cephalosporin C*, such as *Cefalotin*, became some of the first marketed cephalosporin antibiotic drugs.23

![Figure 17 Papaverine structure](image)
For that reason many of the synthetic molecules with therapeutic activities were inspired by nitrogen-containing heterocycles scaffold.

In pharmaceuticals is known Anastrozole (Figure 19), an aromatase-inhibiting drug approved for the treatment of breast cancer after surgery and also for metastasis in both pre and postmenopausal women. The gravity of breast cancer is increased by estrogen, as sex hormones cause hyperplasia, and differentiation at estrogen receptor sites, in fact Anastrozole works by inhibiting the synthesis of estrogen.\textsuperscript{24, 25}

Another example of medicine with heterocycles containing nitrogen is Pantoprazole.\textsuperscript{26} (Figure 20) It is a particular pyridylsulfinylbenzimidazole molecule that possess gastric antisecretary and consequently anti-ulcerative activity.\textsuperscript{27}
2. The Quinoline System

2.1 Structure

As previously introduced, quinolines are heterocyclic aromatic compounds and are characterized by a double-ring structure composed of a benzene and a pyridine ring fused at two adjacent carbon atoms. The simplest member of the quinoline family is quinoline itself, a compound with molecular structure C₉H₇N represented in Figure 21. The molecule exists as a resonance hybrid with a resonance energy of 198 kJ mol⁻¹, the resonance structures are shown in Figure 22.

![Figure 21 Quinoline structure](image1)

![Figure 22 Risonance structures of Quinoline](image2)

As we can see from the π-electron density value of quinoline (Figure 23) it is easy to understand that the chemistry of that compounds is a mixture of that of benzene and pyridine. In effect electrophilic substitution is favoured by the benzene ring while nucleophilic substitutions is favoured by the pyridine ring. Like pyridine, quinoline is moderately basic in fact it has a pKₐ of 4.94 and a dipole of 2.10 D.

Quinoline appears as colourless hydroscolic liquid with a piercingly strong odor. If exposed to sunlight for a longer period of time it will turn yellow later brown, while when it is placed in organic solvents it dissolves well, but not so well in cold water.
2.2 Historical Introduction

Quinoline was discovered in coal tar distillated by Runge in 1834 and named “Leukol” (from λευκο- and oleum). The same compound was also obtained by Gerhardt in 1842 by alkaline distillation of quinine, cinchonine, or strychnine, and was named by him “Chinolein” or “Chinolin”. Not until 1882 the identity of leukol and chinolin was established and that thanks to Hoogewerff and Van Dorp which showed that the samples from coal tar and from alkaloid distillation had the same boiling point, thereby forming the same products: hydrate, platinichloride, bichromate, and argentonitrate. Both samples were also converted by oxidation into quinolinic acid and then decarboxylated to nicotinic acid. Korner was cited as the first to propose the structural formula for quinoline but already Dewar in 1871 suggested that quinoline had the same relationship to pyridine that naphthalene had to benzene. The quinoline structure was confirmed by the syntheses in which allylaniline was passed over glowing lead oxide, or from o-nitrocinnamaldehyde (1) as shown in Scheme 1.

![Figure 23 π-Electron density of Quinoline](image)

**Scheme 1 Quinoline synthesis**
2.3 Application

Quinoline derivatives represent an interesting class of compounds widely applied in several research areas.

2.3.1 Quinolines in new material development

Quinoline are used in the area of new material, for instance the quinoline 3 in Figure 24 shows potential as dichroic dyes for application in liquid crystal displays.

![Figure 24](image)

Still about photoluminescent materials field, several quinoline-based chromophores attract notable attention for their use as sensitizers for constructing luminescent complexes. One example is the molecule 4 show in Figure 25 that has been developed as an efficient electroluminescence material in organic light emitting diode (OLED) fabrication.

![Figure 25](image)

Quinolines are also used in multi-nuclear discrete coordination architectures and polymeric coordination networks. They constitute suitable organic ligands favoring structure specific self-assembly that is crucial for the construction of discrete coordination architectures.
2.3.2 Biological activities of some quinolines derivatives

Moreover quinolines have gained attention due to their broad biological activities, indeed constitute an important class of compounds for new drug development. As a result, many researchers have synthesized these compounds as target structures and evaluated their properties.\(^{34}\)

Among this type of quinolines are well known quinine, natural compounds used for the treatment of malaria until the 1930s. Since that moment quinine, and other synthetic quinolines such as Chloroquine, Amodiaquine, and Mefloquine (Figure 26) have been mainstays of malaria chemotherapy for much of the past 50 years.

![Figure 26 Quinoline antimalarials](image)

The key to the success of these important synthetic quinoline, has been the excellent clinical efficacy, limited host toxicity, ease of use and simple, cost-effective synthesis. However, the value of synthetic quinoline based antimalarials has been seriously worn in recent years, mainly as a result of the development and spread of parasite resistance.\(^ {35}\)

Nonetheless today again we are studying new molecules containing quinoline to use as antimalarials, in fact, molecule 5 in Figure 27 showed high antiproliferative activity by mixed mechanisms of action. The compound acts by forming an intercalative complex with DNA, in this way is inhibited DNA topoisomerase II and it blocks also the cell cycle in G2/M phase.\(^ {36}\)
Even so quinolines are utilized in the treatment of many other diseases; for example recent studies demonstrate that treatment with chloroquine derivatives, in particular molecule 6, shown in Figure 28, can be preventive against Alzheimer’s disease. Alzheimer’s disease is the common cause of dementia characterized by the accumulation of amyloid-β produced by breakage of amyloid-β precursor protein (APP). 37

![Figure 27](image1) 1-[4-(3H-Pyrrolo[3,2-f]quinolin-9-ylamino)-phenyl]-ethanone hydrochloride

![Figure 28](image2) N^4-(7-Chloroquinolin-4-yl)-N^1,N^1-diisopropylpentane-1,4-diamine

Quinolines find also application in the use against bacterial infections. About that small quinoline molecules have demonstrate potent dispersal activity against bacterial biofilms. These bacteria are surface-attached communities, and their infections are known for their resistance to conventional antibiotics, microbicidal agents and host immune responses. Specifically quinolines derivatives, such as molecule 7 show in Figure 29, are active for methicillin-resistant S. aureus and S. epidermidis; recognized as the most frequent cause of biofilm-associated nosocomial and indwelling medical device infections. 38

![Figure 29](image3) Bromoquinoline
2.3.3 Quinolines in organocatalysis

Enantioselective organic catalysis represents a research field in rapidly growing in modern organic chemistry. An important number of organic reactions that once required the use of metal-based, enantiopure catalysts, now are performed with equal degrees of chemical and stereochemical efficiency, exploiting substoichiometric amounts of structurally simple organic molecules often more stable and cheaper than their organometallic equivalents.\(^{39}\)

The catalytic enantioselective allylation of aldehydes provides an example of how an organometallic catalyst can be effectively replaced by a metal-free one. Herein, an enantiomerically pure quinoline-N-oxide, molecule 8 shown in Figure 30, acts as catalysts for the enantioselective allylation of aromatic aldehydes with allyl(trichloro)silane. It makes products with moderate to good chemical efficiency, up to 73% chemical yield, and satisfactory stereoselectivity, up to 50% ee.\(^{40}\)

![Figure 30 N-2-[1-(2-Amino-1-naphthyl)]naphthyl-2-quinoline-N-oxide carboxyamide](image)

One other example of quinoline used in organocatalysis is supplied by novel cinchona alkaloids that catalyse, molecule 9 an intramolecular cyclopropanation reaction via ammonium ylides that forms [4.1.0]-bicycloalkanes. This organocatalyst provides products in excellent yields, as single diastereomers and with ee values usually over 95%.\(^{41}\) (Figure 31)

![Figure 31 Cinchona alkaloid catalyst](image)
New asymmetric methods to generate the cyclopropane motif have attracted attention owing to their ubiquitous presence in a diverse range of natural products and their crucial role in the mode of action of many therapeutic agents. Moreover, the rigid structure and strain-driven reactivity make them attractive intermediates in complex molecule synthesis.\textsuperscript{42}

\textbf{2.4 Synthesis of Quinolines}

Accordingly in literature there are many various synthetic routes due to the formation of quinolines but the great majority of that have been prepared by ring formation, rather than by transformation from other quinoline derivatives and have been obtained by variants of two main approaches.

\textit{Approach 1.} The first major class of synthesis is that in which a monosubstituted benzene or cyclohexane is cyclized by a reaction involving a substituent on the side chain; it includes Skraup, Doebner-von Miller, Knorr, Conrad-Limpach synthesis.

\textit{Approach 2.} The second major class of synthesis is that in which an o-disubstituted benzene, or a substituted cyclohexane, undergoes intramolecular condensation or reacts with a second, two-carbon, fragment in an intermolecular condensation; it includes the Friedlander and Pfitzinger synthesis.\textsuperscript{43}

\textbf{2.4.1 Approach 1}

These types of chemical synthesis generally have the same alkylaniline or Schiff base intermediate that is rarely isolated.

\textbf{2.4.1.1 Skraup and Doebner-von Miller Synthesis}

In 1880 Skraup noticed that alizarin blue had to be a quinoline derivative, and that alizarin blue was obtained from nitroalizarin and glycerol; therefore also reaction between nitrobenzene and glycerol should give quinoline. In fact from nitrobenzene, glycerol, and concentrated sulphuric acid a modest yield of quinoline was obtained, while a yield of 10\% of quinoline was obtained starting from aniline, glycerol, and sulphuric acid. The best results have been obtained from the now
known classical reaction mixture of Skraup composed of aniline, nitrobenzene, glycerol, and concentrated sulfuric acid.\textsuperscript{44}

The reaction mechanism is represented by the following *Scheme 2* in which we can see that sulfuric acid catalyzes the dehydration of glycerol (10) to acrolein (11) and nitrobenzene acts as oxidizing agent.\textsuperscript{45}

\begin{center}
\textbf{Scheme 2} Skraup reaction mechanism
\end{center}

Shortly after, in 1881, Doebner and von Miller successfully modified and generalized Skraup’s method; they utilized ethylene glycol in place of glycerol and obtained a 2-methylquinoline. Successively they deduced that to improve the yield of 2-methylquinoline they should use a better intermediate so they utilized crotonaldehyde that with aniline, nitrobenzene, paraldehyde, and sulphuric acid gave rise to the synthesis that bears their names.\textsuperscript{46}

The Doebner–Miller reaction is traditionally described in process in which the first stage is probably a crotonic condensation of two molecules of an aldehyde or ketone, resulting in the formation of an $\alpha,\beta$-unsaturated compound. The latter reacts with the aniline (13a), giving a Schiff base (14) and, intermediately, after cyclocondensation 4-amino-1,2,3,4-tetrahydroquinoline (15). Then dihydroquinoline (16) is formed, and further oxidation leads to the quinaldine (17) derivative (*Scheme 3*).\textsuperscript{47} Zinc chloride both with and without hydrochloric acid can be used as condensing agent.
2.4.1.2 Conrad-Limpach Synthesis

The original Conrad and Limpach synthesis, with one major modification, has been more widely used compared to any other route to 4-quinolones. Limpach at first used paraffin oil as the cyclization medium, but then boiling diphenyl ether or a mixture of diphenyl ether with diphenyl, Dowtherm, has been reported as superior. In this reaction a minimum time at high temperature, such as 260-280 °C is required. Furthermore the common practice has been to add a solution of the amino-acrylate to preheated cyclization medium, preferably maintaining high dilution, after that cyclization is completed in a few minutes. Older procedures using acid catalysts or heating without solvents gave much poorer yields. \(^{48}\)

The synthesis of 4-quinolones is here reported because often it isomerizes to 4-hydroxyquinolines. This happened through the thermal condensation of primary aromatic amines (13a) with the carbonyl group of β-ketoesters (18), afterwards it is followed by the cyclization of Schiff base intermediates. During the condensation of primary aromatic amines with β-ketoesters, the amino group might also react at the ester group of β-ketoesters to form β-ketoacetamide intermediates, that cyclize to 2-hydroxyquinolines (19) (Scheme 4). \(^{49}\)
2.4.1.3 The Knorr Synthesis

This reaction, discovered by Knorr in 1886, provides 2-hydroxyquinoline ring by the treatment of β-ketoester with aryl amine above 100°C.

The mechanism, represented in Scheme 5, involves first the reaction between the amino group (13a) with β-ketoester (20) that furnishes anilide (21) and successively the cyclization of the latter in presence of acid by the loss of water molecule to afford quinoline derivative (22).

Scheme 4 Conrad-Limpach reaction mechanism

Scheme 5 Knorr reaction mechanism
2.4.2 Approach 2

2.4.2.1 Friedländer Synthesis

Friedländer synthesis using 2-aminobenzaldehyde and acetaldehyde; in particular the starting materials are o-aminoaryl aldehydes or ketones and a ketone possessing an α-methylene group.

Two possible reaction mechanisms exist for this reaction and are represented in *Scheme 6*. In the first mechanism 2-amino substituted carbonyl (23) and carbonyl (24) react in a rate-limiting step giving aldol adduct (25). Subsequently this intermediate loses water in an elimination reaction to unsaturated carbonyl (26) and then loses water again in imine formation to quinoline (29). In the second mechanism the first step is Schiff base formation (26) followed by Aldol reaction (28) and finally after elimination is obtained quinoline derivative (29).

![Scheme 6 Friedlander reaction mechanism](image)

2.4.2.2 Pfitzinger Synthesis

This is a chemical reaction first discovered at the end of the nineteenth century by Pfitzinger in which isatin with base and a carbonyl compound yield substituted quinoline-4-carboxylic acids even called cinchoninic acid.

Pfitzinger Synthesis is the most widely used modification of the Friedlander reaction and it is characterized by simplicity of the procedure, and the high yields of product.
The reaction mechanism of this reaction, shown in Scheme 7, involves the conversion of isatin (30) by the action of a strong nucleophiles, such as sodium hydroxide or potassium hydroxide, into the salt of isatoic acid (31), which condenses with ketones with the release of water, forming another salt (32). The latter undergoes cyclization through the -CO and -CH₂ groups and is converted into the salt of 4-quinolinecarboxylic acid (33), the treatment of which with acids, usually acetic, gives the required final compounds (34).

2.5 2-Carboxyquinolines

2-Carboxyquinolines are a particular class of quinolines that possesses a carboxylic group in position 2 like we can see in Figure 32.

Compounds containing 2-carboxyquinoline framework are widespread in nature. An example is the Thiostrepton (Figure 33), the most complex and best characterized member of the thiopeptide antibiotics. Isolated in 1955 it is produced by Streptomyces azureus ATCC 14921, S. hawaiiensis ATCC 12236, and S. laurentii ATCC 31255, and it is used as a topical antibiotic in veterinary medicine. This molecule has many biological activities; it is widely used in recombinant DNA research, it is active against gram-positive bacteria and exhibits antimalarial activity against Plasmodium falciparum. In addition it exerts its biological action by binding
to the 23S region of ribosomal RNA and ribosomal protein L11, thereby blocking the GTPase-dependent activities of the 50S ribosomal subunit.

![Thiostrepton structure](image)

**Figure 33** Thiostrepton structure

2-Carboxyquinolines, due to their unique chemical and biological properties, have attracted wide interest from pharmaceutical and synthetic materials. Some interesting examples are reported in *Figure 34*, such as the *Kynurenic acid* that has proved to be a useful agent for the potential control of neurodegenerative disorders. There are also active compounds, like molecule 35, that acts as potent 5-hydroxytryptamine antagonist, while molecule 36 can be used as a potent lead compound for inhibiting the binding of Insulin-like Growth Factor (IGF) to IGF-binding proteins. In addition, quinoline-2-carboxylates are key intermediates for the preparation of quinox ligands which have been widely applied in asymmetric catalysis; for example 2-quinolinecarboxylic acid has been shown to be a promising ligand for the ruthenium-catalyzed dehydrative alkylation of alcohols.⁵³
2.5.1 Synthesis

Due to their dramatic importance, significant efforts continue to be given concerning the development of new 2-carboxyquinoline structures and new methods for their construction.

It is known that Friedländer synthesis of quinolines from o-aminobenzaldehydes is usually carried out via a two-step procedure, in which reduction of an nitro-substrate (37) is followed by condensation with an enolizable carbonyl compound (38) in the presence of a Brønsted or Lewis acid catalyst (Scheme 8). A complicating factor in the reaction is the instability of the intermediate o-amino aldehyde, which can readily undergo self-condensation reactions. This is why modifications are made to this reaction; therefore o-nitrobenzaldehyde is converted to a primary amine to reduction of the nitro group. The reaction changes are helpful in reducing problems due to o-aminobenzaldehyde instability but also increase the number of synthetic operations that must be performed. 54
The reaction shown in Scheme 9 is a copper-catalyzed [5+1] annulation of 2-ethynylanilines (40) with an N,O-acetal (41), which functioned as a C1 part, leading to the preparation of quinoline derivatives with an ester substituent on the 2-position.

![Scheme 9](image)

To promote the cyclization reaction is used a copper-catalyst in dichloromethane solvent, the best one is CuBr$_2$ by which they have had the best yields with lower reaction times.$^{55}$

The next reaction, represented in Scheme 10, is an iron-catalyzed oxidative tandem synthesis of quinolines from anilines (13), aldehydes (40), and various olefins (41). The reaction was optimized with the presence of FeCl$_3$ as a Lewis acid catalyst at 60 °C in dichloromethane, in addition it uses TEMPO oxoammonium salt T$^{+}$BF$_4$− in catalytic amounts thanks to its efficiency.$^{56}$

![Scheme 10](image)

The following reaction represents a copper-catalyzed method for the synthesis of quinoline-2-carboxylate derivatives. The reaction occurs through sequential intermolecular addition of alkynes (42) onto imines (43) and subsequent intramolecular ring closure by arylation (Scheme 11).$^{57}$

![Scheme 11](image)
In this other reaction on considering the mechanism (Scheme 12), the first generally proposed step is the formation of propargylic amines (44) that is produced via an intermediate that was formed by successive complexation of substrates to the metal center. The subsequent step involves a cyclization that may occur directly through a Friedel-Crafts-type addition giving the desired products. Alternatively, could be obtained oxidation products under the specific reaction conditions.

![Scheme 12](image_url)

The numerous advantages of copper catalysts make them highly attractive for chemical synthesis from environmental and economic points of view, moreover the efficiency of this system allowed the reactions to be carried out at room temperature.53

Owing to the importance 2-carboxyquinolines, and limited literature concerning their synthesis, during my thesis period I focused my attention on implementing a new synthetic methodology for synthesizing 2-carboxyquinoline derivatives in a one-pot way. In this context, as will be seen later, I investigated the reactivity β-nitroacrilate.
3. β-Nitroacrylates

3.1 Introduction

Over the past ten years, the research group in which I spent my thesis period has paid particular attention to the chemistry of β-nitroacrylates. These compounds are an emerging class of versatile nitroolefins widely employed as building blocks in the synthesis of polyfunctionalized systems.\textsuperscript{58}

β-Nitroacrylates are nitro alkenes conjugated with an ester group in β position respect to the nitro in Figure 35. The synthetic utility of these compounds is due to the simultaneous presence of two different electron-withdrawing groups, the ester and the nitro, which give an appreciable reactivity compared to simple nitro alkenes (46) or α,β-unsaturated esters (47).\textsuperscript{59}

![Figure 35](image)

The principal resonance structures of a generic β-nitroacrylate, as shown in Scheme 13, highlights how the double bond is particularly electron-poor in α position, due to the power of attraction of the nitro group (a).

![Scheme 13](image)

β-Nitroacrylates can be synthesized through different approaches, and the most useful one involves nitroalkenes and glyoxalates.\textsuperscript{60} In particular, this approach is based on (i) the formation of a new carbon-carbon bond, by an Henry reaction to
give the nitroalcohol 48, and (ii) its dehydration to provide the target nitroalkene 45.\(^6\) (Scheme 14)

\[
\begin{align*}
\text{R}^1\text{NO}_2 + \text{HCO}_2\text{OR}_2 & \xrightarrow{\text{Henry reaction}} \text{R}^1\text{NO}_2\text{O}_2\text{C}_2\text{OR}_2 \\
\text{Dehydration} & \xrightarrow{} \text{R}^1\text{NO}_2\text{C}_2\text{OR}_2
\end{align*}
\]

**Scheme 14** Synthesis of β-nitro acrylate

3.2 Synthetic Applications in nitrogen-containing heterocycles

β-Nitroacrylates are considered as a strategic starting materials for the preparation of a variety of molecular structure.\(^6\)

Among the different compounds synthesized I'm going to deal with heterocyclic derivatives containing nitrogen which can be subdivide into 5-membered and 6-membered ring.

3.2.1 Synthesis of 5-membered nitrogen heterocycles derivatives

Below are reported two different examples of the synthesis of 5-membered nitrogen heterocycles starting from β-nitroacrylates (Figure 36).

**Figure 36**

**Synthesis of imidazole derivatives**

In recent years, Meshram and colleagues\(^6\) developed a new synthetic protocol with the use of ionic liquids. A mild and novel approach is described for the synthesis of functionalized fused imidazole analogues in solvent-free and catalyst-free condition, between analine (13a) and β-nitroacrylates (45) in ionic liquid. The short reaction time, good isolated yields, generality and environmentally benign reaction media are the significant features of this protocol.
The plausible mechanism for the formation of desired product is here reported. Initially, the Michael addition of 2-aminopyridine (52) occurs on to β-nitroacrylate (45) to form Michael adduct (53). Then the adduct (53) tautomerizes into the reactive species (54) (nitro tautomer), which is promptly attacked by the nitrogen atom of the pyridine ring, with the formation of the five membered ring (55). Finally, elimination of water and nitroxyl molecules, lead to the formation of the target imidazo[1,2]pyridine (49) (Scheme 15).

**Synthesis of pyrroles**

Herein, is presented a new, efficient, one-pot synthesis of pyrrole-2-carboxylate, reported by Ballini research group in 2015. These compounds derivatives starting from ketal-functionalized β-nitroacrylates in combination with primary amines under acidic heterogeneous conditions.
This approach consists in a one-pot process which involves (i) at least a Michael addition of the primary ammine (57) to β-nitroacrylate (56), then the formation of the intermediate (58), (ii) the in situ acidic treatment of the latter molecule giving the opening of 1,3-dioxolane ring (59), with successively cyclization-aromatization of the former β-nitroacrylate moiety (60) and formation of pyrrole (50) (Scheme 18).

**Scheme 18** Plausible mechanism of one-pot synthesis of pyrrole-2-carboxylate

**Synthesis of indoles**

In 2014 Ballini and their colleagues developed a synthetic strategy in which exploits the high reactivity of β-nitroacrylates (45) in combination with o-bromoanilines (61) to provide alkyl indole-2-carboxylates (51).

This novel and simple one-pot synthesis involves 2 steps: at first β-nitroacrylate (45) and o-bromoaniline (61) take place to an *aza*-Michael reaction that allows the
formation of α-enamino esters (62) that then are directly transformed into alkyl indole-2-carboxylates (51) by palladium-catalyzed Heck reaction (Scheme 20).

By the proper selection of β-nitroacrylate and o-bromoaniline precursors, it is possible to introduce different substituents into the benzene ring, to modify the ester moiety, and to introduce several functionalities onto the C-3 alkyl chain. Furthermore, this reaction represents a convenient and alternative strategic approach thanks also to the simple conditions used to prepare intermediates such as 62, in fact the whole process involves just one aqueous workup and a single chromatographic purification.

3.2.2 Synthesis of 6-membered nitrogen heterocycles derivatives

Below in Figure 37 are reported three examples of synthesis to perform different kind of 6-membered nitrogen heterocycles compounds.

![Scheme 20 Plausible mechanism of indole-2-carboxylates](image-url)
**Synthesis of dihydroxyquinoxalines**

The dihydroxyquinoxalines are a class of heterocyclic compounds, which have a certain importance in the pharmacological industry, especially for their structural relationship with benzodiazepines and their biological activity.\(^{66}\) In this context, a recent one-pot synthesis developed by Ballini and colleagues in 2009 acquired great importance. The reaction of o-phenilenediamine (66) with β-nitroacrylates (45) allows the *in situ* preparation of dihydroquinoxalines (63), *via* anti-Michael reaction, under uncatalysed reaction conditions (Scheme 21).\(^{67}\)

![Scheme 21 One-pot synthesis of dihydroquinoxalines](image)

From the mechanistic point of view, the cyclization follows the first Michael addition 67, and derives from the attack by the second nucleophilic amino group to the carboxyl functionality, forming a stable six-cycle terms. The reaction takes place with good yields at room temperature, using ethyl acetate as solvent and in the presence of an excess of 66. It should be noted that, in this way, it is possible to introduce other functionalities (ethers, nitriles, ketones...) by means the substituent group on the 45, and still obtain good yields. Moreover, the nitro group of the product can be converted into other functionalities or it can be exploited for the formation of new carbon-carbon bond thanks to the possibility of creating a stabilized carbanion.

**Synthesis of indoles**

The reaction of β-nitroacrylates (45a) with pyrroles (68), under solvent and promoter-free conditions, allows the formation of Friedel–Crafts adducts (69) which, after *in situ* treatment with Amberlyst-15 in isopropyl alcohol under reflux, provide polysubstituted indoles (64), *via* a benzannulation reaction, in a one-pot process (Scheme 22).\(^{68}\)
In this context, the assembling of the indole core starting from benzene derivatives represents the prevalent procedure, where are some drawbacks, such as the need for hard reaction conditions (very low or high temperature), very strong bases or there are the problems of regioselectivity. Based on these experiences, this synthesis result a mild and efficient method for the one-pot synthesis of polysubstituted indoles. The reaction between starting compounds 45a and 68 quickly react, under solvent and catalyst-free conditions, giving the intermediate (69) via a Friedel–Crafts reaction. Then, in situ acidic treatment of the formed adduct 69, under heterogeneous conditions (Amberlyst-15) in refluxing 2-propanol, favors the aromatization of the former β-nitroacrylate moieties, allowing the one-pot synthesis of indoles 64 in consistent overall yields (50–74%). Moreover, thanks to the mild reaction conditions a variety of important functionalities, such as ester, cyano and chlorine, can be preserved.

**Synthesis of piperazines**
As useful example of preparation of alkyl 3-substituted 5-oxopiperazine-2-carboxylates (65) using β-nitroacrylates as key starting materials has been reported by Ballini and colleagues in 2013. This approach involves, firstly, conjugate addition of glycine methyl ester hydrochlorides (70) to β-nitroacrylates (45) followed by successive conversion of the nitro group into the amine functionality, affording target compounds by a domino reduction/cyclization process (Scheme 23).
The reaction addition is promoted by Amberlyst-A21, while the Raney-Ni was used as a catalyst in the reduction of the nitro to amine, in such a way the synthesis is conducted under fully heterogeneous conditions.
4. One-pot reactions

4.1 Introduction

One of the fundamental objectives of organic synthesis is the construction of complex molecules from simpler ones and this should be made in efficiency and environmental sustainability way. The sustainability of chemical processes is nowadays a central aspects that must be considered, and also the implementation of new green methodologies is of dramatic importance.\textsuperscript{63} The increase in molecular complexity generally accompanies a decline in the reaction synthetic efficiency. As a goal, the creation of many bonds, rings or stereocenters in a single transformation is a required condition for high synthetic efficiency. The ideal situation would constitute single-step synthesis. More realistically, in order to obtain general synthetic methods, the combination of multiple reactions in single operations is a powerful means to increase molecular complexity and enhance synthetic efficiency. The modern syntheses, such as one-pot process, must conform with the needs of our environment which includes the preservation of resources and the avoidance of toxic reagents as well as toxic solvents.\textsuperscript{71}

A one-pot process has been defined as the strategy to improve the efficiency of a chemical reaction, whereby a reactant is subjected to successive chemical reactions in just one reactor,\textsuperscript{72} in which during the reaction, it is possible modify the reaction conditions.

This feature is much desired by chemists because it avoids the work-up and purification of the intermediates, thus saving time and resources. Such approach also possesses economic benefits due to the reduction of process time and the minimization of the waste generation.

By the other hand there are several restrictions to carrying out a one-pot synthesis. One of these is constituted by the fact that each reaction has to proceed in excellent yield, in which the generation of by-products is minimized as much as possible. This because as the number of reactions increases, by-products accumulate affecting mainly the following reactions with a resulting in diminishing yields.

It must also take account of the solvent in fact if the solvent employed in the previous reaction has a high boiling point, this may be unsuitable or suboptimal for the next reaction. In this case it is difficult to remove the solvent completely in
vacuum and moreover the higher evaporation temperature may harm the structural integrity of the product via thermal decomposition.

Another relevant factor is the amount of reagents utilized during the reaction. In fact if the reagent used in the previous reaction is in excess and it cannot be removed under reduced pressure, the next reaction has to be carried out in the presence of this reagent and the following reaction conditions need to be compatible to it. It is thus desirable to use reagents with a low boiling point and in stoichiometric amounts relative to the reactant; alternatively, the remaining reagents can be deactivated before the next reaction step.

A confirmation of the applicability and usefulness of the one-pot reactions is given by the synthesis of (−)-Oseltamivir, a neuraminidase inhibitor, between the most effective drugs for the treatment of influenza.\textsuperscript{73}

Thanks to Yujiro Hayashi\textsuperscript{74} and colleagues today it is possible to synthesize (−)-Oseltamivir (71) in a one-pot sequence in 36% yield by changing conditions only 6 times over nine reaction steps. The reaction steps including in the order are: a diphenylprolinol silyl ether mediated (74), asymmetric Michael reaction (72 and 73 → 75), a domino Michael reaction, a Horner–Wadsworth–Emmons reaction (75 → 76) combined with a retro-aldol Horner–Wadsworth–Emmons elimination (77 → 76), a retro-Michael reaction (78 → 76), a base-catalyzed isomerization, a thiol-Michael reaction (76 → 79), a reduction of the nitro group to an amine (79 → 80), and finally a retro-Michael reaction of the thiol (80 → 71).

The present synthesis is of considerable importance because it is the first example of a stereochemically complex drug being synthesized in a single reactor, in significant yield, without the need to evaporate or swap solvents.
4.2 Domino and Tandem processes

It should be noted that there are different types of one-pot processes but there is not a precise definition for them indeed this has created confusion in the last period. For this reason there are several terminologies to describe multi-step reactions that take place in one pot, these include: “domino reaction” and “tandem reaction”. Nicolaou in 2006 pointed out that these descriptions are comparatively interchangeable. Instead Tietze suggested the usage of “domino reaction” rather than “tandem reaction”, and defines this process as “a transformation of two or more bond-forming reactions under identical reaction conditions, in which the latter transformations take place at the functionalities obtained in the former bond forming reactions”. During the process there is a structural change of the molecule that accompanies the initial reaction and creates an intermediate to
perform the second transformation. As a requisite for all domino reactions, the used substrates must have more than two functionalities of comparable reactivity. They can be situated in one or two molecules or, as in the case of multicomponent domino reactions, in at least three different molecules. For a major clarification, individual transformations of independent functionalities in one molecule, also forming several bonds under the same reaction conditions, are not classified as domino reactions.77

Denmark proposed to keep the overarching definition of “tandem reactions” as reactions that occur one after the other, and to use the modifiers cascade or domino, to consecutive, and sequential reaction to specify how the two or more reactions follow.78 In general a tandem reaction defines a particular process when there are two transformations with two different functionalities of the same molecule at the same time. However, if three or even more bonds are formed in one sequence, the term “tandem” cannot be used at all. The terms domino and tandem are often confused when describing a type of reaction. An excellent illustration being the domino stones, where one stone tips over the next, which tips the next and so on. In literature, the word “tandem” is frequently used to describe this type of process (therefore the misunderstanding of the terminology). Instead, it’s less appropriate as the encyclopaedia defines tandem as “locally, two after each other”, as in a tandem bicycle. Finally, the “tandem reactions” terminology expresses a strategy for rapid construction of complex structure that involves the functionalities of only one molecule at the same time.70

An example known in literature in which is found tandem process is the synthesis of Morphine79(81), studied due to its analgesics properties. In this synthesis the enone (82), obtained by Grignard methodology, was reduced under Luche conditions, then the resulting allylic alcohol was involved into an Eschenmoser-Claisen rearrangement. This rapidly assembled the key quaternary center in 83 for the synthesis of Morphine. Oxidative cleavage of the monosubstituted double bond, followed by treatment with N-methylhydroxylamine provide the nitrone (84), which cyclized in spontaneous way to give the isoxazolidine 85. Hydrogenation of 85 resulted in cleavage of the N-O bond and the benzyl group to give an amino diol. The HCl salt of the amino diol cyclized in vacuo to give a cyclic amide. This amide treated with nitrophenylselenyl cyanide and tributylphosphine gave an intermediate selenide which was oxidized in situ to give the enone (86). A carbene mediated cyclization followed by reduction gave the final product 81 (Scheme 25).
The latter approach can be considered a further subgroup of domino reactions: the multicomponent reaction (MCR). The term was created by Prof. Ivar Ugi. MCRs usually refer to reactions where more than two starting materials react to form a product; the atoms of each of these starting materials can be found in the product, irrespective of the mechanism. These types of methods significantly reduce the number of synthetic operations, required to prepare a particular target molecule for this reason the development of new MCR-based methodologies contribute to the green chemistry methodologies.

A useful example for better understanding this mechanism of synthesis is well defined by the Tropinone reaction, as reported by Mikami (Scheme 26).

This is a one-pot synthesis of Tropinone by domino ene-type reactions between siloxyallylsilane (87) and dimetoxy pirrolidine (90), without acidification and decarboxylation. In this reaction there are three starting materials that are placed in the same reaction vessel, so it can be considered as a multicomponent reaction. In the first part of the mechanism, the primary amine (89) reacts with the diketone
(88) to perform a pirrolidine derivative (90), obtained via prototropic ene-type reaction. Compound 90, in presence of 87 and catalytic amount of TMSOTf, conducts a domino reaction to obtain the Tropinone (Scheme 27).

The catalyst only reacts with one methoxy group at a time, resulting in the formation of the iminium ion, firstly with the intermediate 91 and after with 92. These intermediates are formed in a sequence so as to promote the closure of the ring which leads to the final product.
5. Thesis work

The main target of my thesis was the development of a new method for the synthesis of 2-carboxyquinoline, through an alternative and efficient synthetic procedure. After many years of study, by the research group where I did my thesis work about the chemistry of nitro compounds and solid supported reagents (SSR), I contributed to the development and optimization of one-pot synthesis between β-nitroacrylates and 2-aminobenzaldehyde in two steps.

We considered to start from an aza-Michael reaction to the amine (nucleophile) (92) and β-nitroacrylate (45), since β-nitroacrylates are very good Michael acceptors in α position like previously explained in chapter 3. Right after to this first reaction we have the formation of the 6 member ring (93), that concludes the first step. After that the idea for the second step consisted in the elimination of nitrous acid and successively elimination of water similarly to give, as reported in literature for analogous intermediate (94), the aromatized compounds 95 (Scheme 28).

Scheme 28 Hypothesized synthetic pathway
5.1 Optimization

The first approach for the development of the new synthetic methodology is defining the optimal reaction conditions to obtain the synthetic target as efficiently as possible. This step is usually called “optimization of reactions conditions”, in such a way as to define the solvent, stoichiometry and temperature.

Although our scope was to realize a one-pot process, in order to optimize both transformations, we initially studied the synthesis as two distinct steps.

5.1.1 First step: aza-Michael addition

Following our project, the first step studied is the aza-Michael reaction between 2-aminobenzaldehyde and β-nitroacrylate. In this part of the work we went to study what were the best conditions for this reaction so we made a screening taking into consideration the use of promoters, the temperature, the use of solvent, the reaction time and the quantity of stoichiometric reagents (Table 1).

For this purpose we chose, as sample reaction, the synthesis between the 2-aminobenzaldehyde (92a) and the β-nitroacrylate (45b) reported in Scheme 29.

![Scheme 29 Aza-Michael reaction](image)
Table 1 Optimization study of first step

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents Equiv.</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Promoter</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>92a 45b</td>
<td>/</td>
<td>60</td>
<td>18</td>
<td>/</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>1 1</td>
<td>CH₃CN</td>
<td>60</td>
<td>18</td>
<td>DBU</td>
<td>/</td>
</tr>
<tr>
<td>3</td>
<td>1 1</td>
<td>CH₃CN</td>
<td>60</td>
<td>18</td>
<td>CrCl₃·7H₂O·NaI /</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 1</td>
<td>CH₂Cl₂</td>
<td>80</td>
<td>18</td>
<td>BF₃·Et₂O /</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1 1,1</td>
<td>/</td>
<td>70</td>
<td>18</td>
<td>/</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>1,1 1</td>
<td>/</td>
<td>100</td>
<td>24</td>
<td>/</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td>1 1,1</td>
<td>/</td>
<td>50</td>
<td>24</td>
<td>/</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>1 1,1</td>
<td>/</td>
<td>40</td>
<td>18</td>
<td>/</td>
<td>35</td>
</tr>
<tr>
<td>9</td>
<td>1 1,2</td>
<td>/</td>
<td>70</td>
<td>18</td>
<td>/</td>
<td>55</td>
</tr>
<tr>
<td>10</td>
<td>1,2 1</td>
<td>/</td>
<td>70</td>
<td>18</td>
<td>/</td>
<td>64</td>
</tr>
</tbody>
</table>

The first test was made in solvent and promoter-free conditions in which we got a quite good yield. Then we tested the reaction in the presence of promoters of both acidic character (CrCl₃·7H₂O·NaI, BF₃·Et₂O) and in basic one (DBU) using different solvents (CH₃CN, CH₂Cl₂), but in this way we didn’t obtained product. As expected we saw once again how the β-nitroacrylates involved in the reaction of aza-Michael are reactive solvent-free and promoter-free.

A particular precaution must be taken when agitating the reaction mixture. In fact, precisely because the absence of solvent, it should have a good shake, in such a way as to have the right contact of reagents for the formation of the intermediate. This is explained as the lack of stirred has led to the failure of some tests. At this point we made other tests by changing temperature, stoichiometry of reagents and reaction time. At the end of the various tests we concluded that the optimum conditions for the first step were those shown in the entry 5 of Table 1.

In summary the best yield (66%) was obtained under the following conditions:

- 2-Aminobenzaldehyde: 1 mmol;
- β-Nitroacrylate: 1,1 mmol;
- Solvent-free and promoter-free;
- Temperature: 70°C;
- Reaction time: 18h.
Once obtained this excellent result, we focused our attention to optimize the II step.

5.1.2 Second step: aromatization

At this point, we proceeded analyzing the elimination of the nitrous acid and water from tetrahydroquinoline 93a (Scheme 30).

This reaction can be performed with a base promoter, thus we combined various basic systems (and their stoichiometry) with different temperatures in order to have a large screening of conditions.

Following are listed all bases that we used, they are grouped in homogeneous and heterogeneous one.

Homogeneous bases

- 1,1,3,3-Tetramethylguanidine (TMG);
- 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD);
- 1,8-Diazabicycloundec-7-ene (DBU).

Heterogeneous bases

- 1,5,7-triazabicyclo[4.4.0]dec-5-ene on polymer (TBD on polymer);
- 2-Tert-butyllimino-2-diethylamino-1,3-dimethylpherhydro-1,3,2-diazaphosphorine on polymer (BEMP on polymer);
- Carbonate on polymer.

In Table 2 are reported all the combinations studied on the conversion of substrate 93a into 95a; these reactions were performed at 50°C for 24 hours in acetonitrile (10 mL/mmol).
Table 2 Optimization of second step

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Equiv.</th>
<th>T (°C)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMG</td>
<td>1,5</td>
<td>70</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>TMG</td>
<td>2</td>
<td>70</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>TBD on polymer sup.</td>
<td>1,5</td>
<td>50</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>TBD on polymer sup.</td>
<td>2</td>
<td>50</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>TBD on polymer sup.</td>
<td>1,2</td>
<td>50</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>BEMP on polymer sup.</td>
<td>0,6</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td>7</td>
<td>BEMP on polymer sup.</td>
<td>1</td>
<td>50</td>
<td>79</td>
</tr>
<tr>
<td>8</td>
<td>BEMP on polymer sup.</td>
<td>1,25</td>
<td>50</td>
<td>86</td>
</tr>
<tr>
<td>9</td>
<td>BEMP on polymer sup.</td>
<td>1,5</td>
<td>50</td>
<td>82</td>
</tr>
<tr>
<td>10</td>
<td>DBU</td>
<td>1,25</td>
<td>50</td>
<td>36</td>
</tr>
<tr>
<td>11</td>
<td>Carbonate on polymer</td>
<td>1,25</td>
<td>50</td>
<td>57</td>
</tr>
</tbody>
</table>

As reported in Table 2 when this reaction is carried out with DBU it provides only a 36% yield. While using TMG and carbonate on polymer the reaction shows a similar yield respectively of 59 and 57%. The reaction performed with TBD gives different yield depending of the amount of base used, the best result was for 1,5 equivalent with a 80% of yield.

Finally, after a deep screening, we found that BEMP on polymer (1.25 eq.) supply the best result with a 86% yield. In fact, increasing or decreasing the quantity of BEMP on polymer, the reaction worsens in terms of yield. Moreover we already saw that TBD provides a comparable yield to BEMP but was utilized 1.5 eq of TBD against 1.25 of BEMP, so the use of BEMP is considered advantageous since it involves less wastage.

After that, we tested the reaction even with two acid promoters (Al$_2$O$_3$ acid, Zeolite HSZ-320), in both cases product was obtained only in trace amounts.

In conclusion, the optimal reaction conditions for the second step involve the use of BEMP on polymer (1.25 eq.) at 50°C for 24 hours in acetonitrile (10 mL/mmol).
5.2 Application of the one-pot process

At this point we are ready to carry out the reaction in a one-pot process (*Scheme 31*).

![Scheme 31 One-pot process](image)

In order to test the effectiveness of the process we extended this procedure to a wide range of substrates for introducing new functionalities by combing different β-nitroacrylates with different 2-aminobenzaldehydes. Products reported in *Figure 38* were thus obtained, they all are 2-carboxyquinoline (95a-i) with the exception of molecule 94a in which only the elimination of nitrous acid and no water took place.
5.3 Starting materials

5.3.1 2-Aminobenzaldehyde

As regards the amino benzaldehydes, shown in Figure 39, all have been synthesized in laboratory starting from different substrates.
2-Aminobenzaldehyde (92a) was synthesized from 2-aminobenzylalcohol as reported in the Scheme 32.

\[
\begin{align*}
\text{NH}_2 & \quad \text{MnO}_2 \\
\text{CH}_2\text{Cl}_2 \text{ dry} & \quad \text{NH}_2
\end{align*}
\]

Scheme 32

The remaining three 2-aminobenzaldehyde (92b-d) were synthesized from the corresponding nitrobenzaldehydes (97). In all cases the reduction was performed in the presence of iron and acetic acid as shown in the Scheme 33.

\[
\begin{align*}
\text{NO}_2 & \quad \text{Fe, reflux} \\
\text{EtOAc, AcOH, H}_2\text{O} & \quad \text{NH}_2
\end{align*}
\]

Scheme 33

5.3.2 β-Nitroacrylates

All β-nitroacrylates shown in Figure 40 were synthesized according to the Ballini’s procedure already presented in Chapter 3.
6. Conclusion

In conclusion, the work done in laboratory was aimed at implementing an innovative and efficient one-pot process to synthesize an important class of polyfunctionalized quinolines, specifically 2-carboxyquinolines. The title compounds were prepared in good overall yields starting from 2-aminobenzaldehydes and β-nitroacrylates, thus demonstrating once again their versatility as precursors of heterocycles.

Moreover the use of solid supported base (BEMP) minimized the work up process to an easy filtration thus minimizing solvent and materials with evident advantages in terms of sustainability.

By the different selection of the starting materials it was possible to introduce in 2-carboxyquinoline a variety of functional groups in positions 2, 3, 6 and 7.

We isolated each intermediate and final product for the characterization with $^1$H, $^{13}$C NMR spectroscopy, gas chromatography–mass spectrometry (GC-MS), FT-IR spectroscopy techniques and elemental analysis.
7. Experimental Section

7.1 General Remarks

\(^1\)H-NMR were recorded at 400 MHz on a VarianMercury Plus 400. \(^{13}\)C-NMR were recorded at 100 MHz. IR spectra were recorded with a PerkineElmer Paragon 500 FT-IR. Mass spectra were performed on a GC/MS system by means of the EI technique (70 eV). Microanalyses were performed with a CHNS-O analyzer Model EA 1108 from Fisons Instruments.

7.2 Synthetic methodology

*General Procedure for the preparation of compound 92a*\(^{82}\)

2-Aminobenzyl alcohol (96) (1 mmol) was dissolved in CH\(_2\)Cl\(_2\) dry (6,25 ml) and successively was added MnO\(_2\) (5 mmol) in three times under inert atmosphere. The reaction mixture was stirred at room temperature for 24 hours. Terminate the reaction (monitored by TLC), it was filtered and washed with EtOAc, after the evaporation of the solvent under vacuum, the crude product 92a was purified by flash chromatography column (hexane - EtOAc 8:2).

*General procedure for compounds 92b, 92c, 92d*

2-Nitrobenzaldehyde 97 (1 mmol) and iron powder (7 mmol) were placed inside a round bottom flask equipped with a condenser together with 2,3 ml ethanol, 2,3 ml acetic acid and 1,2 ml water. The solution was stirred for 5 minutes at reflux and then stirred for 15 minutes without heating until it cooled down to room temperature. The mixture was filtered with silica gel, and the residue washed with ethyl acetate. Then 16 ml of water were added to the obtained solution and extracted with ethyl acetate. The combined organic layers were washed neutral with saturated NaHCO\(_3\) solution, dried over Na\(_2\)SO\(_4\), filtered and the solvent removed under reduced pressure. Finally the crude product 92b (or 92c, 92d) was purified by flash chromatography column (hexane - EtOAc 85:15).

*General procedure for the preparation of compounds 95*

A mixture of aminobenzaldehyde 92 (1 mmol) and β-nitroacrylate 45 (1 mmol) was stirred under solvent-free conditions, at 70°C, for 18 hours. Then, acetonitrile (10 ml) and BEMP (1.25 mmol, 170 mg) were added and the solution was heated at 50°C and stirred for further 24 hours. Terminate the reaction (monitored by TLC), the promoter was filtered off and washed with EtOAc. Finally, after the evaporation
of the solvent under vacuum, the crude product 95 was purified by flash chromatography column (hexane - EtOAc 9:1).

### 7.3 Compound characterization

**Spectroscopic data of compounds 95**

**Compound 95a.** Yield 58 %.

Yellow oil. IR (cm⁻¹, neat): 1063, 1160, 1458, 1619, 1727, 2959. ¹H-NMR (CDCl₃, 400MHz) δ: 1.34 (t, 3H, J = 7.7 Hz), 1.46 (t, 3H, J = 7.3 Hz), 3.01 (q, 2H, J = 7.7 Hz), 4.53 (q, 2H, J = 7.3 Hz), 7.53-7.60 (m, 1H), 7.65-7.72 (m, 1H), 7.78 (d, 1H, J = 8.1 Hz), 8.04 (s, 1H), 8.16 (d, 1H, J = 8.5 Hz). ¹³C-NMR (CDCl₃, 100MHz) δ: 14.5, 15.4, 25.9, 62.2, 127.2, 128.2, 129.1, 129.5, 130.0, 135.6, 136.4, 146.0, 150.7, 167.1. GC-MS (70 eV): m/z: 229 ([M⁺], 29), 200 (83), 182 (14), 157 (39), 156 (99), 155 (63), 154 (100), 128 (34). Anal. Calcd. for C₁₄H₁₅NO₂ (229.28): C, 73.34; H, 6.59; N, 6.11. Found: C, 73.39; H, 6.62; N, 6.08.

![Chemical structure of 95a]

**Compound 95b.** Yield 57 %.

Yellow oil. IR (cm⁻¹, neat): 1073, 1171, 1459, 1610, 1728, 2952. ¹H-NMR (CDCl₃, 400MHz) δ: 0.9 (t, 3H, J = 7.3 Hz), 1.34-1.41 (m, 4H), 1.47 (t, 3H, J = 7.3 Hz), 1.65-1.74 (m, 2H), 2.9-2.99 (m, 2H), 4.53 (q, 2H, J = Hz 7.3), 7.55-7.60 (m, 1H), 7.67-7.72 (m, 1H), 7.79 (d, 1H, J = 8.12 Hz), 8.04 (s, 1H), 8.175 (d, 1H J = 8.55). ¹³C-NMR (CDCl₃, 100MHz) δ: 14.1, 14.4, 22.6, 30.1, 31.8, 32.7, 62.1, 127.1, 128.1, 129.0, 129.4, 130, 134.3, 137.1, 146.0, 151.0, 167.1. GC-MS (70 eV): m/z: 271 ([M⁺], 25), 245 (68), 228 (72), 224 (44), 199 (14), 198 (96), 196 (26), 182 (35), 168 (38), 166 (29), 156 (22), 155 (20), 154 (100), 143 (72), 142 (43), 141 (15), 140 (19), 132 (14), 115 (38). Anal. Calcd. for C₁₇H₂₁NO₂ (271.36): C, 75.25; H, 7.80; N, 5.16. Found: C, 75.29; H, 7.77; N, 5.13.
Compound 95c. Yield 48%.

Yellow oil. IR (cm⁻¹, neat): 1027, 1236, 1458, 1659, 1716, 2245, 2933. ¹H-NMR (CDCl₃, 400MHz) δ: 1.47 (t, 3H, J = 7.3 Hz), 1.71-1.93 (m, 4H), 1.47 (t, 3H, J = 7.3 Hz), 2.40 (t, 2H, J = 6.8 Hz), 3.03 (t, 2H, J = 7.7 Hz), 4.53 (q, 2H, J = 7.3Hz), 7.59 (t, 1H, J = 6.8Hz), 7.71 (t, 1H, J = 7.3 Hz ), 7.79 (d, 1H, J = 8.12 Hz), 8.04 (s, 1H), 8.17 (d, 1H J = 8.12). ¹³C-NMR (CDCl₃, 100MHz) δ: 14.5, 17.3, 25.4, 30.4, 32.1, 62.4, 119.7, 127.2, 128.5, 129.0, 129.9, 130.0, 133.3, 137.5, 146.2, 150.0, 166.9. GC-MS (70 eV): m/z: 282 ([M⁺], 9), 253 (29), 228 (34), 209 (38), 209 (38), 182 (19), 170 (23), 168 (48), 154 (73), 143 (100), 142 (18), 140 (18), 115 (33), 91 (15). Anal. Calcd. for C₁₇H₁₈N₂O₂ (282.14): C, 72.32; H, 6.43; N, 9.92. Found: C, 73.36; H, 6.47; N, 9.89.

Compound 95d. Yield 45%.

Yellow oil. IR (cm⁻¹, neat): 1074, 1179, 1436, 1615, 1730, 2949. ¹H-NMR (CDCl₃, 400MHz) δ: 1.46 (t, 3H, J = 7.3 Hz), 1.70-1.76 (m, 4H), 2.31-2.39 (m, 2H), 3.9-3.02 (t, 2H), 3.65 (s, 3H ), 4.50 (q, 2H, J = 7.3 Hz), 7.68 (t, 1H, J = 7.3 Hz), 7.77 (d, 1H, J = 8.12 Hz ), 8.02 (s, 1H), 8.15 (d, J = 8.54). ¹³C-NMR (CDCl₃, 100MHz) δ: 14.5, 24.9, 30.8, 32.6, 34.0, 51.8, 62.3, 127.2, 128.3, 129.0, 130.0, 133.8, 137.4, 146.0, 150.5, 167.0, 174.1. GC-MS (70 eV): m/z: 315([M⁺], 30), 286 (68), 284 (29), 270 (18), 242 (28), 236 (21), 228 (81), 182 (61), 180 (29), 170 (14), 168 (42), 167 (44), 156 (14), 155(22), 154 (100), 143 (52), 142 (22), 127 (14), 115 (27). Anal. Calcd. for C₁₈H₂₁NO₄ (315.37): C, 68.55; H, 6.71; N, 4.44. Found: C, 68.59; H, 6.68; N, 4.47.

Compound 95e. Yield 39%.

Brown oil. IR (cm⁻¹, neat): 1057, 1126, 1435, 1633, 1730, 2978. ¹H-NMR (CDCl₃, 400MHz) δ: 1.36 (t, 3H, J = 7.3 Hz), 1.47 (t, 3H, J = 7.3 Hz), 3.04 (q, 2H, J = 7.3 Hz), 4.54 (q, 2H, J = 7.3 Hz), 7.74 (d,1H, J = 8.9), 7.92 (d, 1H, J = 8.9), 8.11 (s, 1H), 8.49 (s, 1H). ¹³C-NMR (CDCl₃, 100MHz) δ: 14.4, 15.0, 25.8, 29.8, 32.9, 62.3, 121.3, 123.6, 123.7, 126.7, 127.8, 127.9, 128.0, 128.1, 128.4, 130.4, 131.0, 131.7, 136.0, 137.7, 144.9, 152.3, 166.6. GC-MS (70 eV): m/z: 227 ([M⁺], 21), 268 (82), 225 (36), 224
(100), 223 (66), 222 (96), 197 (21), 196 (14), 154 (31). Anal. Calcd. for C_{15}H_{14}F_{3}NO_{2} (297.28): C, 60.61; H, 4.75; N, 4.71. Found: C, 60.57; H, 4.78; N, 4.68.

**Compound 95f.** Yield 36 %.
Yellow oil. IR (cm\(^{-1}\), neat): 1072, 1173, 1481, 1615, 1722, 2977. \(^1\)H-NMR (CDCl\(_3\), 400MHz) \(\delta\): 1.46 (t, 3H, \(J = 7.3 \text{ Hz}\)), 2.64 (s, 3H), 4.52 (q, 2H, \(J = 7.3 \text{ Hz}\)), 7.60 (dd, 1H, \(J = 9.4, 2.6 \text{ Hz}\)), 7.2 (d, 1H, \(J = 2.6 \text{ Hz}\) ), 7.91 (s, 1H), 8.09 (d, 1H, \(J = 8.6 \text{ Hz}\)). \(^{13}\)C-NMR (CDCl\(_3\), 100MHz) \(\delta\): 14.5, 20.0, 62.3, 125.6, 129.6, 130.6, 131.3, 131.7, 134.2, 137.1, 144.4, 150.4, 166.6. GC-MS (70 eV): \(m/z\): 249 ([M\textsuperscript{+}], 9), 220 (18), 179 (31), 178 (15), 177 (100), 176 (18), 175 (18), 141 (24), 140 (40). Anal. Calcd. for C\(_{13}\)H\(_{12}\)ClNO\(_2\) (249.69): C, 62.53; H, 4.84; N, 5.61. Found: C, 62.50; H, 4.81; N, 5.58.

**Compound 95g.** Yield 46 %.
Yellow oil. IR (cm\(^{-1}\), neat): 1070, 1177, 1479, 1616, 1723, 2975. \(^1\)H-NMR (CDCl\(_3\), 400MHz) \(\delta\): 1.31 (t, 3H, \(J = 7.3 \text{ Hz}\)), 1.45 (t, 3H, \(J = 7.3 \text{ Hz}\)), 2.99 (q, 2H, \(J = 7.3 \text{ Hz}\)), 5.51 (q, 2H, \(J = 7.3 \text{ Hz}\)), 7.57-7.63 (m, 1H), 7.65-7.72 (m, 1H), 7.47-7.76 (m, 1H), 7.93 (s, 1H), 8.08 (d, 1H, \(J = 9.0 \text{ Hz}\)). \(^{13}\)C-NMR (CDCl\(_3\), 100MHz) \(\delta\): 14.5, 15.2, 25.9, 62.4, 125.9, 129.7, 130.6, 131.6, 134.0, 135.5, 136.7, 144.3, 150.9, 166.8. GC-MS (70 eV): \(m/z\): 263 ([M\textsuperscript{+}], 26), 236 (25), 234 (71), 218 (15), 216 (16), 192 (30), 191 (54), 190 (100), 189 (59), 188 (57), 163 (19), 154 (52), 153 (14), 128 (14), 126 (18). Anal. Calcd. for C\(_{14}\)H\(_{14}\)ClNO\(_2\) (263.72): C, 63.76; H, 5.35; N, 5.31. Found: C, 63.80; H, 5.38; N, 5.27.

**Compound 95h.** Yield 57 %.
Pale yellow oil. IR (cm\(^{-1}\), neat): 1072, 1162, 1460, 1617, 1720, 2958. \(^1\)H-NMR (CDCl\(_3\), 400MHz) \(\delta\): 1.01 (t, 6H, \(J = 7.3 \text{ Hz}\)), 1.46 (d, 3H, \(J = 6.4 \text{ Hz}\)), 1.66-1.79 (m, 3H), 1.80-1.93 (m, 3H), 2.93 (dt, 2H, \(J = 7.7, 2.1 \text{ Hz}\)), 5.19-5.31 (m, 1H), 7.58 (t, 1H, \(J = 8.1 \text{ Hz}\)), 7.71 (t, 1H, \(J = 8.1 \text{ Hz}\)), 7.79 (d, 1H, \(J = 8.1 \text{ Hz}\)), 8.05 (s, 1H), 8.24 (d, 1H, \(J = 8.1 \text{ Hz}\)). \(^{13}\)C-NMR (CDCl\(_3\), 100MHz) \(\delta\): 10.2, 14.3, 19.8, 24.8, 29.1, 35.0, 74.8, 127.5, 128.2, 129.0, 129.8, 130.3, 133.6, 137.8, 146.0,151.6, 167.1. GC-MS (70 eV): \(m/z\): 271 ([M\textsuperscript{+}], 8), 215(20), 214 (100), 200 (20), 198 (17), 182 (14), 170 (59), 168 (63), 154
Compound 95i. Yield 55 %.
Pale yellow oil. IR (cm⁻¹, neat): 1069, 1167, 1455, 1615, 1722, 2955. ¹H-NMR (CDCl₃, 400MHz) δ: 0.84-0.92 (m, 3H), 1.23-1.44 (m, 6H), 1.59-1.73 (m, 4H), 1.74-1.86 (m, 2H), 1.89-2.11 (m, 4H), 2.88-2.94 (m, 2H), 5.51-5.58 (m, 1H), 7.53-7.58(m, 1H), 7.71-7.75(m,1H), 7.77 (d, 1H , J = 8.1 Hz ), 8.02 (s, 1H), 8.17 (d, 1H, J = 8.5 Hz ). ¹³C-NMR (CDCl₃, 100MHz) δ: 14.3, 22.8, 24.1, 29.5, 31.4, 31.9, 32.8, 32.9, 79.4, 127.2, 128.1, 128.9, 129.6, 129.8, 133.7, 137.2, 145.8, 151.5,167.2. GC-MS (70 eV): m/z: 325 ([M⁺], 4), 257(14), 256 (73), 238 (14), 213 (18), 212 (100), 200 (20), 182 (17), 168 (19), 157 (16), 155 (26), 143 (55), 142 (61), 115(20). Anal. Calcd. for C₂₁H₂₇NO₂ (325.45): C, 77.50; H, 8.36; N, 4.30. Found: C, 77.55; H, 8.39; N, 4.27.

Spectroscopic data of compounds 94

Compound 94a. Yield 83 %.
Pale yellow oil. ¹H-NMR (CDCl₃, 400MHz) δ: 1.22 (t, 3H, J = 7.3 Hz), 2.15-2.33 (m, 4H), 2.98 (s, 6H), 4.06-4.27 (m, 2H), 4.93-5.06 (m, 2H), 5.47 (s, 1H), 5.70-5.82 (m, 1H), 6.11-6.17 (m, 1H), 6.70 (t, 1H, J = 7.3 Hz), 7.23-7.32 (m, 1H), 9.49-9.58 (m, 2H). Anal. Calcd. for C₁₈H₂₄N₂O₃ (316.40): C, 68.33; H, 7.65; N, 8.85. Found: C, 68.37; H, 7.63; N, 8.82.
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