Synthesis of polyheteroatomic heterocycles: relevance of microwave-assisted reactions

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Química

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Abstract

Heterocyclic structures, components of a large number of molecules, have been studied since the mid-1800s due to their wide occurrence in nature, such as in the Heme and Chlorophyll A, and the discovery of their usefulness in organic chemistry, creating an interesting new branch, which continues today. From the first applications of simple heterocycles in main fields of research, such as in medicine, pharmaceutical, agrochemical and energy materials, polyheteroatomic heterocycles have achieved a remarkable position in the development of new products for clinical use with most advantageous features that allow different interactions with the biological target, not always possible with a simple heterocyclic ring. And this is the real aim of this thesis, based on a new research project on particular polyheteroatomic heterocyclic systems, namely 1,2,5-oxadiazoles, also called furazans, five-membered rings likely to be useful for the architectural structure of new drugs. Furthermore, this work wants to propose possible innovative methods to synthesize furazans from acyclic substrates in order to obtain specific heterocycles with particular substituents on the ring. Even more importantly, our attention has focused on the possibility to exploit microwave-assisted organic synthesis (MAOS) for its ability to optimize strategies both from the point of view of the time and of the yield.

Keywords

Polyheteroatomic heterocycles, 1,2,5-oxadiazoles, furazans, aminofurazan synthesis, microwave-assisted reactions.
Resumo

As estruturas heterocíclicas, componentes de um número elevado de moléculas, são estudadas desde meados do século 19 devido à sua considerável ocorrência na natureza, de que são exemplos os grupos hemo e a clorofila A, e à sua utilidade em Química Orgânica, criando um novo e interessante ramo de investigação que continua nos nossos dias. Desde as primeiras aplicações de heterociclos simples nos principais campos de investigação, como a medicina, as ciências farmacêuticas ou agroquímicas e os materiais para energia, os heterociclos poli-heteroatómicos atingiram uma posição notável no desenvolvimento de novos produtos para uso clínico, com características muito vantajosas que permitem interacções diversas com os alvos biológicos, nem sempre possíveis com anéis heterocíclicos simples. É este o objectivo da presente tese, com base num novo projecto de Investigação sobre uma classe particular de sistemas heterocíclicos poli-heteroatómicos, designadamente os 1,2,5-oxadiazoles, também chamados furazanos, que são anéis de cinco membros potencialmente úteis para a arquitectura estrutural de novos fármacos. Além disso, este trabalho visa propor possíveis métodos inovadores para a síntese de furazanos a partir de substratos acíclicos, de modo a obter heterociclos especíﬁcos com substituintes particulares no anel. Adicionalmente, a nossa atenção focou-se na possibilidade de explorar a síntese assistida por micro-ondas (SAMO) no que toca à sua capacidade de permitir a optimização de estratégias, tanto do ponto de vista do tempo de reacção como do rendimento.

Palavras-chave

Heterociclos poli-heteroatómicos, 1,2,5-oxadiazoles, furazanos, síntese de aminofurazanos, reacções assistidas por micro-ondas.
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Abbreviation list

MAOS: Microwave-assisted organic synthesis
IUPAC: International Union of Pure and Applied Chemistry
DDT: 1,1-Bis(p-chlorophenyl)-2,2,2-trichloroethane
PGRs: Plant growth regulators
OLEDs: Organic light-emitting diodes
TADF: Thermally activated delayed fluorescence
[Ni(acac)]_2: Nickel(II) acetylacetonate
DTBP: Di-tert-butyl peroxide
TMPMgCl∙LiCl: 2,2,6,6-Tetramethylpiperidinylmagnesium chloride lithium chloride complex solution
TMSBr: Bromotrimethylsilane
PTS: Polyoxyethanyl-α-tocopheryl sebacate
DNA: Deoxyribonucleic acid
RNA: Ribonucleic acid
GABA: Gamma-aminobutyric acid
HTS: High-throughput screening
Asn: Asparagine
Tyr: Tyrosine
Ser: Serine
AIDS: Acquired Immune Deficiency Syndrome
MW: Microwave irradiation
QSAR: Quantitative Structure Activity Relationship
HIV: Human Immunodeficiency Virus
ROI: Reactive oxygen intermediates
CW/BW: Chemical and biological weapons
HEM: High performance energetic materials
FVP: Flash vacuum pyrolysis
DMAP: 4-Dimethylaminopyridine
TLC: Thin-layer chromatography
1. Polyheteroatomic Heterocycles

1.1 Overview on the heterocycles

Two hundred years ago, the chemical science was an undivided field; around 1900 a division into inorganic, organic and physical chemistry became necessary. Over the years, a progressive segmentation into subdisciplines, very often interconnected, has become necessary. Heterocycle included inside compounds have been studied since half of 1800s due to their wide occurrence in nature; however the heterocyclic chemistry was born as a branch of organic chemistry only after the Second World War.

Two main types of molecular structures could be recognized in organic chemistry: the aliphatic acyclic compounds, in which the atoms form a chain, and the cyclic (aliphatic or aromatic) compounds, in which the atoms form a ring. If only one element take part to the formation of a cyclic compound, then we refer to an isocyclic compound (e.g. if the ring consists of C-atoms only, then we speak of carbocyclic compound). Cyclic compounds with at least two different atoms in the ring are known as heterocyclic compounds. The ring itself is called a heterocycle. If the ring contains no C-atom, then we speak of an inorganic heterocycle. If at least one ring atom is a C-atom, then the molecule is an organic heterocyclic compound. In this case, all the ring atoms which are not carbon are called heteroatom (Fig. 1).

Nitrogen, oxygen and sulfur are the most common heteroatoms, but heterocyclic rings containing other heteroatoms are also widely known. In a 1983 report, the International Union of Pure and Applied Chemistry (IUPAC) recognized 15 elements coming from groups II to IV of the periodic system capable of forming cyclic structures with carbon atoms.¹

To determine the stability and reactivity of heterocyclic compounds, it is useful to compare them with their carbocyclic analogues. In principle, it is possible to derive every heterocycle from a carbocyclic compound by replacing appropriate CH₂ or CH groups by heteroatoms. If one limits oneself to monocyclic systems, one can distinguish four types of heterocycles as follows:²

![Fig. 1 Differences between heterocyclic and isocyclic compounds: (a) (4-dimethylaminophenyl)pentazole, an isocyclic compound; (b) Cyclopenta-1,3-diene, isocyclic and carbocyclic compound; (c) Borazine, an inorganic heterocyclic compound; (d) Pyridine, an organic heterocyclic aromatic compound.](image-url)
• **Saturated heterocycles (heterocycloalkanes):** in this category, there are no multiple bonds between the ring atoms. The compounds react largely like their aliphatic analogues.

• **Partially unsaturated systems (heterocycloalkenes):** if the multiple bonds are between two C-atoms of the ring compounds react essentially like alkenes or alkynes. The heteroatom can also be involved in a double bond, with reactivity close to the corresponding acyclic double bonds.

• **Systems with the greatest possible number of noncumulated double bonds (heteroannulenes):** each heteroatom can donate one electron pair to the conjugated system and its nonbonding electron pair does not contribute (as in pyridine), or else, one electron pair of the heteroatom is incorporated into the conjugated system (delocalization of the electrons, such as in furane or pyrrole).

• **Heteroaromatic systems (heteroarenes):** this includes heteroannulenes, which comply with the HÜCKEL rule, i.e. which possess \((4n + 2)\) π-electrons delocalized over the ring.

In 1887 and 1888, Hantzsch\(^3\) and Widman\(^4\) independently introduced methods for naming five- and six-membered nitrogen monocycles. The system was extended to include rings of other sizes, additional heteroatoms, and the expression of various levels of hydrogenation. In 1957, the IUPAC Commission on Nomenclature of Organic Chemistry codified this extension of the Hantzsch-Widman system as part of its rules for the nomenclature of organic chemistry.\(^5\)

Nowadays the extended Hantzsch-Widman system accomplishes several tasks. First, the identity of the different atoms is established by placing different prefixes for each type of non-carbon atom. The three mainly used prefixes are oxa-, thia-, and aza- for oxygen, sulfur, and nitrogen, respectively (the final ‘a’ is elided before a vowel). Second, the position of the heteroatoms is denoted by ring atom numbers. Numbering starts at an oxygen, sulfur or nitrogen (in decreasing order of preference) and continues in such a way that the heteroatoms are assigned the lowest possible numbers. Third, the size and degree of unsaturation of the ring is determined by the suffix at the end (Table 1); partially saturated rings are indicated by the prefixes ‘dihydro’, ‘tetrahydro’, etc.

<table>
<thead>
<tr>
<th>Ring size</th>
<th>Ring with Nitrogen</th>
<th>Ring without Nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum unsaturation</td>
<td>One double bond</td>
</tr>
<tr>
<td>3</td>
<td>-irine</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>-ete</td>
<td>-etine</td>
</tr>
<tr>
<td>5</td>
<td>-ole</td>
<td>-oline</td>
</tr>
<tr>
<td>6</td>
<td>-ine</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>-epine</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 1 Common name endings for heterocyclic compounds.

<table>
<thead>
<tr>
<th></th>
<th>-ocine</th>
<th>-</th>
<th>-ocin</th>
<th>-ocin</th>
<th>-</th>
<th>-ocane</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>-onine</td>
<td>-</td>
<td>-</td>
<td>-onin</td>
<td>-</td>
<td>-onane</td>
</tr>
<tr>
<td>10</td>
<td>-ecine</td>
<td>-</td>
<td>-</td>
<td>-ecin</td>
<td>-</td>
<td>-ecane</td>
</tr>
</tbody>
</table>

In compounds with maximum insaturation, if the double bonds can be arranged in more than one way, their positions are defined by indicating the nitrogen or carbon atoms which are not multiply bonded, and consequently carry an ‘extra’ hydrogen atom, by ‘1H-’, ‘2H-’ etc. In partially saturated compounds, the positions of the hydrogen atoms can be indicated by ‘1,2- dihydro’, etc. (together with the 1H-type notation if necessary); alternatively, the position of the double bonds can be specified; for example ‘Δ³-’ indicates that a double bond is between atoms 3 and 4. A positively charged ring is denoted by the suffix ‘-ium’.

Many heterocycles, as well as many other organic compounds, were identified early on, and received trivial names which are still preferred. Fig. 2 shows some of the most known monocyclic compounds, with the common (trivial) name in red and a systematic name based on the Hantzsch-Widman system given in black.

Fig. 2 Common monocyclic compounds with trivial and systematic name.

Among these common monocyclic compounds, there are some which belong to a well-defined type of heterocycles of the four cited before: the aromatic heterocycles. In particular, the most used in organic synthesis, and not just, are the five-membered rings, like furan, pyrrole and thiophene, and the six-membered rings, like pyridine.

When is an heterocycle aromatic? To establish the aromaticity of a heterocyclic compound, it needs to respect some criteria which must be applied to each compound that we want to call aromatic. They are the following:

- The molecule must be cyclic;
- Every atom in the ring must have an occupied p orbital, which overlaps with p orbitals on either side. In this way, the molecule is fully conjugated;
- The molecule must be planar;
The molecule must contain an even number of pairs of π electrons and it must satisfy Huckel's rule: \((4n+2)\pi\) electrons, where \(n\) is an integer starting from zero.

In the case of heterocycles, this latter rule is fulfilled thanks to the lone pair on the heteroatom that is delocalized inside the π electrons system of the ring. For example, furan has got the oxygen atom which is \(sp^2\) hybridized. One lone pair is in the π system and the other in the plane of the ring (analogous to C-H bond on the other positions). The sum of π electrons is 6, so furan is aromatic. If these aromatic rings, both five- and six-membered, are fused with benzene ring, it can be possible to obtain new aromatic heterocycles with different structures, as showed in Fig. 3 below.

![Chemical structures](image)

**Fig. 3** Common benzofused aromatic heterocycles.

All these structures are planar containing 10 π-electrons including the non-bonding electron pair of heteroatom as in monocyclic heterocycles. These 10 π-electrons are delocalized over the ring. Because of the involvement of non-bonding lone pair of heteroatom in aromatization, it makes the five- and six-membered rings more prone to attack by electrophilic reagents.
1.1.1 Natural occurrence

Heterocycles are by far one of the largest and most significant classes of organic compounds, mainly because they are the basis of life. This is not an overstatement if we think that the majority of macromolecules constituting living organisms are built around heterocyclic motifs. The first natural molecules that may come to mind are, for sure, Heme and Chlorophyll, which are the oxygen carriers in animals and plants, respectively (Fig. 4). Both of them are derivatives of porphyrin, aromatic heterocyclic macrocycles composed of four modified pyrrole subunits (in the case of Heme) or three modified pyrrole subunits and one of pyrroline (in the case of Chlorophyll), interconnected at their α carbon atoms via methine bridges (=CH−).

![Fig. 4 Representation of the pigments of life: Heme and Chlorophyll a.](image)

Heterocycles are also present in most vitamins, an organic compound required by an organism as a vital nutrient in limited amounts; it cannot be synthesized in sufficient quantities by the organism and must be obtained from the diet. One of the most remarkable vitamins is Vitamin C or ascorbic acid, very important for our life because it is involved in several collagen synthesis reactions for wound-healing and for preventing bleeding from capillaries, but also it acts as an antioxidant against free radicals and the oxidative stress (Fig. 5). It has to take it by eating many fruits, vegetables and beef liver in order to prevent diseases derived by its deficiency, like the scurvy.

![Fig. 5 Vitamin C or ascorbic acid structure.](image)

Moreover, heterocycles are found in another class of organic molecules, fundamental for organisms: the amino acids, essential for the construction of several proteins. These biologically important organic compounds are composed of amine (-NH₂) and carboxylic acid (-COOH) functional groups, along with a side-chain specific to each amino acid. Precisely, this latter differentiates properties and characteristics of a single amino acid and it is also maintained after that the new protein is formed.
Recent estimates tell us that about 500 amino acids are known, 22 of these ones are present in the eukaryote organisms, available to synthetize proteins, and only 9 are essential amino acids, that means they are not produced de novo by the organism and they have to be assimilated from the diet. One of these essential amino acids contain an heterocycle and it is tryptophan (Fig. 6), which have an indole functional group and is the biochemical precursor of important compounds, like serotonin and the Vitamin B3 or nicotinic acid.

![Tryptophan structure](image)

Fig. 6 Tryptophan structure.

It is possible to continue with an almost infinite series of examples that demonstrate the spread occurrence of heterocyclic compounds in nature, which certainly is the best teacher and source of inspiration for synthetic chemists. Why does nature utilize heterocycles? The answer to this question is provided by the fact that heterocycles are able to get involved in an extraordinarily wide range of reaction types. Depending on the pH of the medium, they may behave as acids or bases, forming anions or cations. Some interact readily with electrophilic reagents, others with nucleophiles, yet others with both. Some are easily oxidized, but resist reduction, while others can be readily hydrogenated but are stable toward the action of oxidizing agents. Certain amphoteric heterocyclic systems simultaneously demonstrate all of the above-mentioned properties. The ability of many heterocycles to produce stable complexes with metal ions has great biochemical significance.
1.1.2 Applications

Heterocycles are therefore inextricably interlaced into the life processes and the vital interest of the pharmaceutical and agrochemical industries in heterocycles is often connected with their natural occurrence.

In fact, among the vast number of pharmacologically active heterocyclic compounds, many of which are in regular clinical use, some of these are natural products, for example antibiotics such as penicillin and cephalosporin, alkaloids such as vinblastine, ellipticine, morphine, and reserpine, and cardiac glycosides such as those of the Digitalis plant (Fig. 7).

Fig. 7 Examples of natural pharmacologically active heterocyclic compounds.

The large majority of drugs\(^8\) (Fig. 8) and biologically active compounds, like antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, hypnotics, and vasopressor modifiers agents, include synthetic heterocycles as central structural moiety.
It is also possible to find a great variety of heterocycles in agrochemical compounds because they serve as pesticides, insecticides, herbicides, fungicides and rodenticides. Since the discovery in the 1940s of the powerful insecticides, like 1,1-bis(p-chlorophenyl)-2,2,2-trichloroethane (DDT), research on pesticides and plant growth regulators (PGRs) became a major activity of many industrial firms and heterocycles being prominent among them. Some of these chemical compounds were synthesized early in the 1850s, but they were commercialized just after the 1950s to contrast the negative effects of DDT in humans and animals. The most sold are all derivatives of pyridine because they exhibit a variety of types of biochemical activity; For example, there are herbicides like picloram, diquat, paraquat and fluridone or insecticides like chlorpyrifos (Fig. 9).
Some pyridine agrochemicals.

However, in research of the 2000s, many derivatives of various five-membered rings have been introduced successfully as agrochemicals (Fig. 10).

![Chemical structures of picloram, chlorpyrifos, paraquat, diquat, fluridone, captan, procydmide, carbofuran, and A nematocide.]

**Fig. 9** Some pyridine agrochemicals.

**Fig. 10** Derivatives of pyrroles, furans, and thiophenes as agrochemicals.

Besides the great importance in medicinal and agrochemistry, heterocyclic chemistry is an inexhaustible resource of novel compounds. Since rings can be of any size, from three-membered upward, and since the heteroatoms can be drawn in almost any combination from a large number of elements (though nitrogen, oxygen, and sulfur are still by far the most commons), the number of possible heterocyclic systems is almost limitless, making available compounds with the most diverse physical, chemical, and biological properties. Practical applications include dyestuffs (Fig. 11), copolymers, solvents, photographic sensitizers and developers, and antioxidants and vulcanization accelerators in the rubber industry.
Fig. 11 Examples of dyestuff containing heterocyclic structures.

Furthermore, heterocycles found a large application as organic conductors, semiconductors, molecular wires, and organic light-emitting diodes (OLEDs) (Fig. 12).[^11]

Fig. 12 Examples of highly efficient organic light-emitting diodes (OLEDs) and novel electroluminescence mechanism using thermally activated delayed fluorescence (TADF).

At last, but not the least, they are valuable synthetic intermediates. Therefore, substantial attention has been paid to develop efficient and straightforward methods to synthesize heterocycles.[^12]
Therefore, an enormous number of heterocyclic compounds is known and this number continues to increase very rapidly. Over 31 million compounds are now recorded in Chemical Abstracts and a very large proportion of these are heterocyclic.
1.1.3 Strategies for the synthesis of heterocycles

Chemistry of heterocyclic compounds is so vast that it is almost impossible to summarize in a single chapter their several ways of synthesis. However, from a conceptual point of view, it is possible to divide the preparation of polyfunctionalized heterocycles using two major strategies (Scheme 1), or combination of both of these:

I. Incorporation of functional group in a pre-existing heterocycle.
II. Ring construction through cyclization of acyclic precursors.

Scheme 1 Possible strategies for the synthesis of polysubstituted heterocycles.

Nowadays, formation of cyclic core followed by incorporation of further functionalization is a frequent approach to access heterocycles. Electrophilic or nucleophilic substitution are often used, and recently organometallic C-H functionalization has been developed (Fig. 13).13

Even these type of functionalization are extremely important, however, increasing the complexity of the system, regioselectivity remains a big problem to overcome. Presence of different heteroatoms, for example, could influence greatly the electronic feature of the ring, leading to low yield of desired products.14
Fig. 13 Some selected organometallic C-H functionalization of heterocycles. (a) Pd(II) catalyzed sequential C-H functionalization of oxazole. (b) Nickel catalyzed THF functionalization. (c) Organ magnesium metallation-functionalization of pyrimidine.

Differently, cyclization reactions give well defined polysubstitution, generally with high regio- and stereochemical control. For this reason, the cyclization of acyclic precursors that contain linearly encoded functional group, is still largely used for the synthesis of heterocycles. In literature, we can come across several typology of *ex-novo* synthesis of polysubstituted heterocycles: unimolecular reaction that involved intramolecular cyclization of bifunctional molecules; but also multicomponent process such as cycloaddition, annihilation reactions, cyclocondensation and several other types (Fig. 14). In these reactions, key steps are frequently the instauration of a carbon heteroatom linkage. Most common, σ bond forming reactions such as nucleophilic displacements at saturated or unsaturated carbon, and condensation reaction have been reported. Additionally ring closure reactions involving conjugated π-systems are extremely useful in preparation of five or six membered ring heterocycles.
Fig. 14 Selected example of cyclization of acyclic reactant. (a) Prins Cyclization. (b) 1,3-dipolar Cycloaddition (c) Cycloisomerization of functionalized allenes (d) Annulation of strained cyclopropanes. (e) Hantzsch cyclocondensation.

Naturally, it is not possible to define which approach is the best or the worst, but it all depends on the type of application it is intended. Nevertheless, it is possible to state that a functionalization approach could be favorable for diversity oriented synthesis application, where starting from the same core it is possible to create several congeners. Instead, the cyclization approach could be extremely useful in target oriented synthesis, since several step of protection/deprotection, reduction/oxidation and so on, could be avoided creating the heterocyclic core de novo.
1.2 Heterocycles with more heteroatoms

In the previous section of this thesis, it was developed the general theme of the heterocycles, their main features and their importance for the formation of natural and synthetic compounds. However, this is only the beginning because the heterocyclic chemistry is open to a more complex world that looks over the simple heterocycles and their derivatives. So, now we have to consider the common case where more than one heteroatom is present in the ring.

The usual rules for stems to indicate ring size and suffixes for degree of saturation are used, as are the prefixes for the various heteroatoms. They are listed in the following order of priorities, derived from the main groups of the Periodic System, and then within each group by increasing atomic number:

Group VI (O>S>Se>Te)> Group V (N>P>As)> Group IV (Si>Ge)> Group III (B).

This listing can be simplified greatly by taking out the most commonly found heteroatoms in their order, which gives O>S>N>P. Each heteroatom is then given a number as found in the ring, with that of highest priority given position 1.
1.2.1 Importance in nature and applications

When we think about polyheteroatomic heterocycles, we obviously deal with heterocyclic compounds with similar, if not identical, characteristics, and the same will be also the pool where they can be caught: nature.

The most immediate example that we can bring is undoubtedly DNA, the molecule that encodes the genetic instructions used in the development and the functioning of all known living organisms. Nucleotides, the building blocks of our nucleic acid, are composed of a five-carbon sugar (ribose or deoxyribose), at least one phosphate group and a nitrogenous base. The latter exists in 4 different types and all four are derivatives of pyrimidine and purine ring structures. In fact, there are adenine and guanine for the purine bases and then, thymine and cytosine for the pyrimidine bases (Fig. 15).

![DNA structure and its nitrogenous bases.](image)

Fig. 15 DNA structure and its nitrogenous bases.

Four of the nitrogenous bases (also uracil in RNA instead of thymine) possess carbonyl groups. In early studies, the oxygen was written in the tautomeric hydroxyl form, and this confused the structural assignment of their bonding to the pentose. The tautomerism is expressed in Fig. 16 for cytosine as an example, where the enol form can be viewed as a hydroxypyrimidine.
In the solid state, only the keto form is observed, but in an aqueous solution, a small amount of the enol form is present in the tautomeric equilibrium. Recognition of the keto form as dominant played a significant role in the unraveling of the structure of the nucleic acids and led J. D. Watson and F. Crick to propose the famous double helix held together by H-bonds to the carbonyl oxygens. Another class of natural organic compounds that must be taken into account are vitamins. We have already mentioned some examples of these important molecules because they are vital for our organism and are specific co-factors behaving as the "helper molecules" that assist enzyme's biological activity in biochemical transformations. A particular attention goes to vitamins belonging to the B family, which are all water-soluble and contain an heterocyclic motif with more than one heteroatom.

The final group to consider is the amino acid family from which all proteins are constructed we have already discussed previously. One of the essential amino acids with an heterocyclic side chain is histidine, containing an imidazole functional group. Histidine on biological decarboxylation is the precursor of the notorious histamine.
which in the human body plays a crucial role in the immune response, including allergic reactions and it is useful in the creation of a vast family of pharmaceuticals called antihistamines (Fig. 18).

![Histidine and Histamine structures](image)

**Fig. 18** Structures of histidine and histamine.

Aromatic and non-aromatic polyheteroatomic heterocyclic rings are a predominant architectural constant of pharmaceuticals and allow for variable interactions with the biological target which are not possible using simpler carbocyclic motifs.

Perhaps some of the most common drugs used nowadays and, probably everyday, are based on 7-membered rings and they are the benzodiazepines. Benzodiazepines are a psychoactive drug, whose core chemical structure is the fusion of a benzene ring and a diazepine ring. Different ones are used for the treatment of seizures, insomnia, depression, or anxiety. Examples of benzodiazepines include alprazolam (XANAX®, Pfizer, Inc.) and diazepam (VALIUM®, Roche Laboratories) (Fig. 19).

![Examples of benzodiazepines](image)

**Fig. 19** Examples of benzodiazepines.

Benzodiazepines work by increasing the efficiency of a natural brain chemical, neurotransmitter gamma-aminobutyric acid (GABA), to decrease the excitability of neurons. This reduces the communication between neurons and, therefore, has a calming effect on many of the functions of the brain. The fastest compound, related to the speed of onset, is precisely diazepam that is rapidly absorbed by the organism, but it has a long half-life of around 40-250 hours. For this reason, diazepam and benzodiazepines with analogous features are called long-acting compounds, which have the advantage of a reduced severity of rebound effects and withdrawal, but at the same time they have a risk of accumulation in the elderly and in individuals with severely impaired liver function.
1.2.2 Five-membered heterocycles

Now, it is time to focused the attention on five-membered heterocyclic compounds (Table 2), because they are particularly important due to their remarkable variety of applications. Their chemistry, synthesis and transformations have, therefore, received considerable attention and importance.

<table>
<thead>
<tr>
<th>HETEROATOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
</tr>
<tr>
<td>pyrazole</td>
</tr>
<tr>
<td>imidazole</td>
</tr>
<tr>
<td>triazoles</td>
</tr>
<tr>
<td>tetrazole</td>
</tr>
</tbody>
</table>

Table 2 Main five-membered polyheteroatomic heterocycles.

Five-membered heterocycles with more than one heteroatom are ubiquitous in nature and their significance is hinted, as seen above, by their presence in an enormous number of natural products, such as adenine, histidine, caffeine, uric acid and so on. Due to this common presence, they are known to interact with the receptor sites on enzymes, and hence their synthesis opens new horizons in enzyme receptor interactions for curing physiological disorders. To confirm this, in Fig. 20 is shown the abundance of five-membered heterocycles in general within top 200 drugs: the relevance of these rings in biologically active compounds is highlighted by the fact that in 59 drugs is present a five-membered heterocycle.
As presented in the initial overview on the heterocycles, the aromatic cycles can be fused with benzene ring to give rise to various possible structures. This is also valid to the aromatic polyheteroatomic heterocycles, as showed in Fig. 21. In fact, it may be useful to synthesize them because they are compounds better to employ in some organic synthetic ways compared to the monocyclic ones, taking advantage of their major stability.

![Diagram of heterocycles](image)

**Fig. 20** The abundance of five-membered heterocycles within top 200 drugs.

The number of substituents, their chemical structures and their positions on the heterocyclic ring are of crucial importance in determining the characteristic of a whole molecule. Versatile methodologies exist for attaching a wide variety of functional groups and a large numbers of analogs of a certain scaffold type could be synthesized using multiparallel synthesis. This approach is especially used in pharmaceutical industry during the high-throughput screening (HTS), wherein large libraries of chemicals are tested for their ability to interact with a specific target. A direct route to broad coverage aims at the development of a novel heterocyclic scaffold, which in turns is derivatized with standard reactions in order to create a thematic library. The novel scaffold
material may be prepared in bulk and then appropriately portioned for multiple derivatizations in parallel. The latter may involve common reactions, but the resulting products are novel.\textsuperscript{18}

One of the best examples on importance of substituents in aromatic heterocycles containing drugs is observed in timolol (Fig. 22), a β-adrenergic receptor blocker indicated for treating glaucoma, heart attacks and hypertension. In its ophthalmic form (brand name: Timoptol in Italy) is used to lower intraocular pressure by reduction of aqueous humour production.\textsuperscript{19}

![Timolol chemical structure.](image)

In a recent report,\textsuperscript{20} an X-ray co-crystal structure of timolol within the β\textsubscript{2}-adrenergic receptor (Fig. 23) disclosed its better biological activity compared with the analogous β-blockers which have a carbazole system as core.

![X-ray co-crystal structures of timolol in the β-adrenergic receptor.](image)

In fact, this data nicely exemplifies the stronger binding of timolol, as its morpholine group is involved in an extra hydrogen-bonding network with nearby amino acids (Asn, Tyr, Ser) and the thiadiazole motif itself protrudes deeper into the actual binding pocket which results in stronger interactions. As every type of heterocycles, also five-membered ring was soon transfer from nature to medicinal and clinical fields with the development of new drugs. The first synthetic heterocyclic pharmaceutical
seems to be antipyrine (Scheme 2). Antipyrine is a pyrazole analgesic and an antipyretic, like aspirin. Ludwig Knorr used Emil Fischer’s discovery of phenylhydrazine to synthesize antipyrine, and in 1883, Knorr was granted a patent on the synthesis.\textsuperscript{21} In 1899, four years after market introduction, sales had grown to almost 800 metric tons.\textsuperscript{22} More recently, antipyrine has been used in a solution with benzocaine to relieve ear pain and swelling caused by middle ear infections.

![Scheme 2 Knorr’s synthesis of antipyrine.](image)

Furthermore, the progress of more and more synthetic drugs brought to the involvement of these family of heterocycles also in pharmaceutical products of particular relevance, as the synthesis of anabolic steroids, the derivatives of natural steroids, like testosterone or cholesterol. Anabolic steroids are drugs that are structurally related to the natural cyclic steroid ring system and have similar effects to testosterone in the body. They increase protein within cells, especially in skeletal muscles. They also have androgenic and virilizing properties, including the development and maintenance of masculine characteristics such as the growth of the vocal cords, testicles and body hair. Anabolic steroids were first made in the 1930s and are now used therapeutically in medicine to stimulate bone growth and appetite, induce male puberty and treat chronic wasting conditions, such as cancer and AIDS. However, equally to all the medicines, health risks can be produced by long-term use or excessive doses; exactly some sportive athletes can get into these risks when they assume this substances to improve their performances. For these reasons, anabolic steroids are classified as doping agents.

One signifiable example of these cited compounds, where a polyheteroatomic heterocycle is present, is furazabol (17β-hydroxy-17α-methyl-5α-androstano[2,3-c]furazan) that is an anabolic steroid doping agent and its chemical structure is the same as that of stanozolol except for a furazan ring fused to the steroidal skeleton in place of the pyrazole (Fig. 24). It is used clinically as an hypolipidaemic and anabolic agent. This latter because it was demonstrates that it possess a very good myotrophic/androgenic ratio, that is the relationship between the increasing of muscle weight and the androgenic activity, which emphasis or develop male characteristics in a person. In general, steroids containing more heteroatoms inside the five-membered ring are of great interest since they have been found to be highly potent anabolic steroids with low androgenic activity.\textsuperscript{23}
This last example of pharmaceutical compound introduces the real aim of this thesis, that deals with polyheteroatomic heterocycles, but more in particular with 1,2,5-oxadiazole, or even called furazans, and their related synthesis because it is possible get an improvement or an innovation on the synthetic pathways of these molecules, of which we already know surprising features and advantages towards clinical and medicinal uses. But it is still not enough!
2. Microwaves-assisted organic synthesis

Since the first published reports in 1986, the use of Microwaves heating to “accelerate” organic chemical transformations has gained a considerable attention. The application of Microwave Irradiation (MW) has already established its valuable potential in organic and medicinal chemistry worldwide. In particular, in the pharmaceutical industries MW-assisted synthesis is used extensively as frontline methodology in most discovery programs. Although at the beginning, a slow uptake of the technology was necessary for the lack of controllability and reproducibility, more than 2000 article have been published since now in the area of microwave-assisted organic synthesis (MAOS). The attention on Microwave Heating is due essentially to its ability to increase reaction rate, along with the capability to reduce side reaction, increase yield and improve reproducibility.

Microwaves are a form of electromagnetic energy that falls at the lower frequency end of the electromagnetic spectrum and is defined in a measurement of frequency as 30 to 3000 Gigahertz, corresponding to wavelengths of 1 cm to 0.1 mm (Fig. 25).

The ability of this type of electromagnetic wave to enhance reaction potential is based on the efficient heating of material by “microwave dielectric heating” effect. This effect depends on the ability of a specific material to absorb microwave energy and convert it into heat. There are two major mechanisms for the conversion of electromagnetic energy into heat. The first one is the dipole rotation (Fig. 26), that is an interaction in which polar molecules try to align themselves with rapidly changing electric field of the microwave. The benefits obtained through this mechanism are related to the polarity of the molecules and their ability to align with the electric field.

Fig. 25 Electromagnetic spectrum.
The second way to transfer energy is ionic conduction (Fig. 27), which occurs if there are free ions or ionic species present in the substance being heated. The electric field generates ionic motion as the molecules try to orient themselves to the rapidly changing field.

The loss tangent (δ) is used to compare the abilities of different solvents to generate heat from microwaves. This parameter is expressed as the ratio between the dielectric constant $\varepsilon'$ and the loss factor $\varepsilon''$ (the capacity to convert the absorbed energy into heat). Usually, solvents with high Loss tangent value are generally used in order to obtain high heating rates. Loss tangent values for common solvents are shown in Table 3.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Loss Tangent (δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylene glycol</td>
<td>1.350</td>
</tr>
<tr>
<td>Ethanol</td>
<td>0.941</td>
</tr>
<tr>
<td>DMSO</td>
<td>0.825</td>
</tr>
<tr>
<td>Acetic Acid</td>
<td>0.174</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Loss Tangent (δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>0.123</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>0.062</td>
</tr>
<tr>
<td>THF</td>
<td>0.047</td>
</tr>
<tr>
<td>Hexane</td>
<td>0.020</td>
</tr>
</tbody>
</table>

**Table 3** Loss Tangent (δ) for common solvents.

Ultimately, the ability of Microwave Heating to promote reactions in a more efficient way than thermal condition is due to its spectacular capability to produce heat directly from the intern of the reaction vessel. This avoids the heat dissipation typical of traditional thermal reactions, and allows a quicker rising of reaction temperature (Fig. 28). In addition, microwave irradiation allows the so-called “superheating effect”, or rather the ability to rapidly heat the reactions much above the boiling point of the solvent.
These features ensure to decrease the time of chemical transformation and consequently the thermal
stress of the system, enabling to reduce catalyst/promoters loading, by-product formation or reactant
decomposition, increase yields and sometimes the possibility to carry on sluggish transformation.
Actually, there is also a debate centered around the question whether the observed effect of
microwave irradiation can in all cases be rationalized by the purely thermal/kinetic phenomena
described above, or whether some effect are also connected to the so-called non-thermal microwave
effect. This effect should derive from the fact that electromagnetic field could induce molecule to
undergo chemical reaction, facilitating bond cleavage/formation.\textsuperscript{31} Unfortunately, the definition of what
constitutes a non-thermal microwave effect is somewhat vague and different scientific communities
may have different theories.
The various possibilities offered by the microwave technology are particularly attractive for heterocyclic
ring formations.\textsuperscript{32} For all these reasons during the period of my thesis, developing new methodologies
for the synthesis of polyheteroatomic heterocyclic systems, a special attention has been given to the
microwave technology. Fortunately, good results were obtained on yields and reaction time in
synthesis of substituted 1,2,5-oxadiazoles (chapters 3).
3. Synthesis of 1,2,5-oxadiazoles and derivatives

During the period spent in Marcantoni’s research group, we embraced a new and innovative project of a notorious pharmaceutical company, Dompè S.p.a in L’Aquila, for synthesizing new biologically active drugs for clinical uses. The idea of this project is based on the development of a good and suitable synthetic strategy to form specific heterocycles which have more than one heteroatom inside because these particular compounds have a biological activity bigger than the analogue heterocycles with only one heteroatom. Among the great variety of polyheteroatomic heterocycles, there is a family of heterocyclic compounds that seems to be the most advantageous to our intention: oxadiazoles and their derivatives. In the specific case, 1,2,5-oxadiazoles, or also called furazans, are selected to be the main cores of the final medicinal products on the basis of quantitative structure-activity relationship (QSAR) studies, that are mathematical correlations that express quantitatively the biological activity of a drug as a function of certain physical-chemical or structural characteristics of the molecule. In fact, this types of oxadiazoles would be more stable and more soluble compared to the 1,2,5-thiadiazoles, already synthetized by the cited company. For all these reasons, this work wants to suggest some different alternatives that are proved by the research group to synthetize 1,2,5-oxadiazole, starting exclusively from acyclic precursors until to form the cyclic compound because we consider this strategy easier and more economic. Therefore, in the following paragraphs, it is shown an overview on oxadiazoles in general, furazans and some derivatives up to now produced, and then each synthetic procedures, including the innovative use of the microwaves technology, are described.
3.1 General aspects

Organic compounds containing heterocyclic ring systems are of great importance both medicinally and industrially. As an example, five-membered ring heterocycles containing two carbon atoms, two nitrogen atoms, and one oxygen atom, known as oxadiazoles, are of considerable interest in different areas of medicinal and pesticide chemistry and also polymer and material science. Oxadiazole rings can exist in different regioisomeric forms: two 1,2,4-isomers (if asymmetrically substituted), a 1,3,4-isomer, a 1,2,5-isomer and two 1,2,3-isomers (if asymmetrically substituted), but the latter is unstable and reverts to the diazoketone tautomer \(^{34}\) (Fig. 29a). The 1,2,5-regioisomer is significantly less common and orients the side chains \(R^1\) and \(R^2\) in different positions relative to the other three isomers. The two 1,2,4- and the 1,3,4-regioisomeric oxadiazoles all present the \(R^1\) and \(R^2\) side chains with essentially the same exit vector arrangement, thus placing the side chains in very similar positions. The consequence is that matched pairs will show the same overall molecular shapes and are thus expected to bind in a similar fashion. Moreover, oxadiazoles display interesting hydrogen bond acceptor properties, and it will be shown that the regioisomers exhibit significantly different hydrogen bonding potentials.

The level of interest is clearly shown, as over the past ten years the number of patent applications containing oxadiazole rings has increased considerably (Fig. 29b).
Fig. 29 (a) Two 1,2,4-oxadiazoles (if asymmetrically substituted), 1,3,4-oxadiazole, one 1,2,5-oxadiazole and two 1,2,3-oxadiazoles (if asymmetrically substituted). (b) The number of patent applications containing oxadiazoles has increased significantly between 2000 and 2008.\textsuperscript{35}

Within drug discovery and development, a number of compounds containing an oxadiazoles moiety are in late stage clinical trials, including zibotentan (a), as an anticancer agent, and ataluren (b) for the treatment of cystic fibrosis. So far, one oxadiazole containing compound, raltegravir (c), an antiretroviral drug for the treatment of HIV infection, has been launched onto the marketplace (Fig. 30). It is clear that oxadiazoles are having a large impact on multiple drug discovery programs across a variety of disease areas, including diabetes, obesity, inflammation, cancer and infection.

Fig. 30 Examples of oxadiazoles in drugs: zibotentan (a), ataluren (b) and raltegravir (c).

Oxadiazole rings have been introduced into drug discovery programs for several different purposes. In some cases, they have been used as an essential part of the pharmacophore, favorably contributing to ligand binding.\textsuperscript{36} In other cases, oxadiazole moieties have been shown to act as a flat, aromatic linker.
to place substituents in the appropriate orientation,\textsuperscript{37} as well as modulating molecular properties by positioning them in the periphery of the molecule.\textsuperscript{38}

As seen above in the graphic of published patents and in the examples of commercially available drugs reported, the less common oxadiazole used to synthetize new and efficient pharmaceutical products are the 1,2,5-oxadiazoles, both for problems that may be encountered during their synthesis and for choosing appropriate substituents to make more and more active this compounds. On these basis, our research begins with the wish to know and discover as soon as possible a great variety of synthetic methods and to promote also this not well known class of oxadiazoles in the medicinal and clinical fields.

Initially, we have to say that in literature there is not an abundant number of articles, papers or patents which describe exhaustively the employment of furazans for the formation of biological and agrochemical products. So, we have got few examples to start our work with necessary knowledge on the chemical and physical characteristics and the different methods to synthetize simple furazans or their derivatives.

The first detailed description of the 1,2,5-oxadiazoles that we can find in literature is a publication made by the chemical laboratories of Harvard University, thanks to the scientists R. A. Olofson and J. S. Michelman.\textsuperscript{39} They report some properties of furazan itself and record the preparation and some reactions of it.

As reported in Table 4 below, furazan is a stable liquid with a melting point of -28 °C and a boiling point of 98 °C at 760 mmHg. An accurate determination of the structure of furazan has been completed by Wilson and Saegebarth\textsuperscript{40} at Harvard and they divulged the significance of these results. The molecule is planar and the bond angles and bond lengths are of particular interest because the N-O-N angle of furazan has an abnormal size and the H-C-N angle is much smaller than the H-C-C angle.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. p. (760 mmHg), °C</td>
<td>98</td>
</tr>
<tr>
<td>M. p., °C</td>
<td>-28</td>
</tr>
<tr>
<td>( \rho_{20} ), g/ml</td>
<td>1.168</td>
</tr>
<tr>
<td>( n^D )</td>
<td>1.4077</td>
</tr>
<tr>
<td>( \lambda_{\text{H}_{2}O}, \mu (\varepsilon) )</td>
<td>Only end absorption</td>
</tr>
<tr>
<td>NMR, ( \tau )</td>
<td>1.34</td>
</tr>
<tr>
<td>Neat</td>
<td>1.34</td>
</tr>
<tr>
<td>CCl(_4) (infinite dilution)</td>
<td>1.81</td>
</tr>
<tr>
<td>( J^{13}_C-H_i ), Hz</td>
<td>199</td>
</tr>
<tr>
<td>Microwave spectrum, Å</td>
<td></td>
</tr>
<tr>
<td>O-N length</td>
<td>1.380</td>
</tr>
<tr>
<td>N-C length</td>
<td>1.300</td>
</tr>
<tr>
<td>C-C length</td>
<td>1.421</td>
</tr>
<tr>
<td>C-H length</td>
<td>1.076</td>
</tr>
</tbody>
</table>
As would be expected, furazan exhibits a single peak at very low field in its NMR spectrum, a peak which moves from $\tau$ equal to 1.34 in the neat liquid to 1.81 at infinite dilution in carbon tetrachloride; the peak is relatively broad (2.2 Hz at one-half peak height) which implies a spin interaction of the proton with the nitrogen atom. The $^{13}$C-H coupling constant is a remarkably high 199 Hz.

The mass spectra of furazan and dideuterofurazan (Fig. 31) are in agreement with the respective molecular weights and indicate at least two general modes of fragmentation (Fig. 32) under ionizing radiation. The weakness of the N-O bond in furazan, suggested by an analysis of its mass spectrum, is the most important factor in the chemistry of this ring system.

![Fig. 31 Mass spectra of furazan and dideuterofurazan.](image-url)
The first synthesis appeared was made with phenylfurazan, a 1,2,5-oxadiazole derivative, and the author is A. Russanow\textsuperscript{41} by steam distillation of phenylglyoxime (1) and Ponzio\textsuperscript{42} later accomplished the dehydration in sulfuric acid but the yield by both methods was poor. Russanow reported that, when phenylglyoxime is heated with acetic anhydride, the product is not phenylfurazan (2), as might be expected, but O-acetyl-α-oximinophenylacetonitrile (3). In fact, when phenylglyoxime is heated with one equivalent of acetic anhydride, the product in 87\% yield is phenylfurazan. However, when phenylglyoxime is heated with four equivalents of acetic anhydride, the product mixture contains 27\% phenylfurazan and 58\% of the oxime acetate (3). Though phenylfurazan does decompose to compound 3 under the reaction conditions, this reaction is too slow to allow one to postulate phenylfurazan as an intermediate in Russanow's procedure. In the presence of excess acetic anhydride the dioxime diacetate is undoubtedly formed before the monoacetate can undergo cyclization. This species then eliminates acetic acid to yield compound 3 (Scheme 3).

Starting from this point, the scientific research has developed more and more works on the furazan's world, trying to understand if these organic compounds were applicable enough for the production of drugs or other chemicals, such as herbicides,\textsuperscript{43} pesticides\textsuperscript{44} and energetic materials.\textsuperscript{45} Soon, researchers focused their attention on the formation of new potential and efficient pharmaceutical products against serious illnesses hard to cure, like cancers and autoimmune diseases.
In fact, already at the end of 1960s, after the published synthetic procedure by Russanow, there was the employment of furazan derivatives for the preparation of prospective antileukemic and immunosuppressive drugs.\textsuperscript{46} In particular, the studied molecules were benzo-2,1,3-oxadiazoles (benzofurazans) and their N-oxides (benzofuroxans) with various substituents on the benzene ring, because both of them showed an optimal drug activity as a powerful inhibitors of nucleic acid and protein biosynthesis in many types of animal cells, but with an especially toxic effect upon the metabolism of leukocytes \textit{in vitro}, like in sheep lymphocytes. The benzofuroxans were generally less potent \textit{in vitro} than the corresponding benzofurazans (e.g. 4-nitro compound); however, benzofuroxans with appropriate substituents in the right positions were more potent drugs \textit{in vivo} than the corresponding benzofurazans (e.g. 5-nitro compound). That's why benzofuroxans (4) were usually converted to benzofurazans (6) either by deoxygenation with triethylphosphite\textsuperscript{47} or reduction with alkaline hydroxylamine to quinone dioxime (5), which readily dehydrated on boiling with alkali (Scheme 4).\textsuperscript{48}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\textbf{(4)}};
\node at (2.5,0) {\textbf{(5)}};
\node at (5,0) {\textbf{(6)}};
\draw[->] (0.5,0) -- (2,0);
\draw[->] (2.5,0) -- (4,0);
\node at (1.25,-0.5) {\textbf{NH}_2\textbf{OH}};
\node at (3.75,-0.5) {-\textbf{H}_2\textbf{O}};
\node at (2,-1) {\textbf{P}\textbf{(OC}_2\textbf{H}_5)_3}};
\end{tikzpicture}
\end{center}

\begin{center}
\textbf{Scheme 4 Conversions of benzofuroxans in benzofurazans.}
\end{center}

Thus, as seen above, also furoxans and their derivatives, present effective biological activities. Indeed, furoxans (1,2,5-oxadiazole-2-oxides) and benzofuroxans represent an important class of NO donors.\textsuperscript{49} Endogenous NO is a potent antimicrobial agent. Together with reactive oxygen intermediates (ROI), NO is one of the toxic mediators released by activated macrophages against pathogens. NO-mediated cellular toxicity is due to the generation of reactive species and/or inhibition of essential enzymes. Moreover, exogenous NO also displays cytotoxic and cytostatic effects against viruses and microbial agents including protozoa, for example \textit{Plasmodium falciparum}, the aetiological agent of the most deadly form of human malaria.\textsuperscript{50} In addition to a variety of NO-related bioactivities, furoxans also show cytotoxicity,\textsuperscript{51} mutagenicity, immunosuppression, central muscle relaxant properties, anticonvulsive effects, monoamino oxidase inhibition, and direct vasodilator and blood pressure lowering activities. Instead, benzofuroxans are potent antileukemic and immunosuppressive drugs and can be used as \textit{in vitro} inhibitors of RNA synthesis in sheep lymphocytes, as well described previously. Finally, furoxans are widely used in organic chemistry as intermediates for the synthesis of many heterocycles.\textsuperscript{52}

As for every general heterocycle, 1,2,5-oxadiazole-2-oxides can be synthesized easily by ring closure or cycloaddition reactions. In particular, monocyclic furoxans are normally prepared by oxidative
cyclization of 1,2-dioximes and many different oxidizing agents can be used for this purpose: hypohalite, ferricyanide, ceric ions, nitric acid and nitrogen oxides, manganese dioxide, lead tetraacetate, N-iodosuccinimide, phenyliodine(III) bistrifluoroacetate and copper(II) complexes.\textsuperscript{53} Furthermore, furazans represent a unique type of heterocyclic compounds and have been studied vigorously in the last decade also in other applications aside from the medicinal one. The most remarkable is surely the field of high density energetic materials. Energetic materials can be considered compounds or mixtures of compounds that constitute a source of massive controllable energy. Interest in the design of new materials with higher energy content, better performance, lower cost, less sensitivity to impact and with less danger to synthesize and process has allowed this research area to remain active. Moreover, continued concerns related to the potential use of chemical and biological weapons (CW/BW) has necessitated the development of new mechanisms of defense.\textsuperscript{54} The energetic material, after an initiation process, undergoes very rapid self-propagating decomposition, producing gases at tremendous pressure and with the evolution of a lot of heat. Temperatures ideally can reach up to 6000 K and the pressure up to 40 GPa. The performance of an energetic material is mainly evaluated on the basis of the type of products that are formed, the energy that is released, the pressure and speed of detonation, and the thermal and chemical stability of the material. The synthesis of new high energy materials has been focused on the use of heterocyclic compounds, like furazans, because composed exclusively of carbon, hydrogen, nitrogen and oxygen atoms and due to the relatively positive heat of formation ($\Delta H_f^\circ$) of these compounds. 1,2,5-Oxadiazoles have been included in several publications as great building blocks for the generation of insensitive High Performance Energetic Materials (HEM),\textsuperscript{55} as the aromaticity present in the ring increases the thermal stability, while the planarity increases the density. Precisely, aminofurazans derivatives has been used as the core of these energetic materials, incorporating fluorine into the system (Fig. 33) because gives rise to compounds of higher density and the high fluorine content along with the presence of hydrogen leads to the formation of hydrogen fluoride (HF) upon detonation, generating a large amount of energy. This combination is possible using SF\textsubscript{5} groups.\textsuperscript{56}
In addition, it is also very important to analyze the studies made on the thermal decomposition of aminofurazan derivatives at different temperatures because they have shown that the major products are CO, CO₂, H₂O, HCN, N₂ (when the azo or hydrazine moieties are present) and NO₂ (when present as a nitro group in the molecule). Minor products include HCNO, NH₃, HNO₃ and N₂O. Indeed, a factor not to be overlooked is to analyze accurately the different stabilities of 1,2,5-oxadiazoles, both in the reaction conditions and as thermal decomposition. In general, furazans are not very stable compounds because they give ring opening rapidly and easily, so they become difficult products to prepare and isolate.

Furazans are most often prepared by heating the corresponding glyoximes in water, aqueous ammonia, or aqueous sodium hydroxide, but no product from the reaction of glyoxime itself in aqueous neutral or basic solutions has been reported. And then, the simplest way to synthesis these oxadiazoles is to do an easy dehydration of the readily available glyoxime, choosing the proper dehydration conditions. This is because a dehydration of a glyoxime in alkaline media would be doomed to failure, since it is known that monosubstituted furazans undergo immediate ring opening in basic solution. But also dehydration in strongly acidic media does not look promising since salt formation with the weakly basic heterocycle would complicate isolation procedures. After careful consideration of all these factors, one would expect the most practical synthesis of furazan should involve a dehydration of glyoxime in a mildly acidic medium under conditions in which furazan is removed from the reaction mixture as it is generated, exploiting high temperatures both to induce more spontaneous cyclization and to avoid the keeping of stereochemical integrity of glyoxime, usually maintained at room temperature. However, in this case too, a problem arises: an high-temperature dehydration may introduce the possibility of thermal decomposition of any heterocycle formed.
The earliest reports concerning the thermolytic cleavage of a furazan ring date from 1888 when it was noted that heating diphenylfurazan (7) at temperatures higher than 200 °C afforded benzonitrile together with some phenyl isocyanate (10). Similar formation of phenyl isocyanate from the thermolysis of diphenylfuroxan (8) suggested a common pathway with the known benzonitrile oxide (9) as intermediate (Scheme 5).

![Scheme 5](image_url)

Scheme 5 Thermal fragmentation of furazans and furoxans.

Later, Boulton and Mathur observed that fusion of the oxadiazole to a five-membered ring lowers the temperature required for ring opening; similarly, Tsuge et al. found that more complex fused furazans, undergo cleavage to nitrile and nitrile oxide fragments under mild conditions. All these results demonstrate that, as was found for furoxans, the thermolytic ring cleavage does not require special structural features such as ring strain, but is a general reaction for furazans, although it requires more forcing conditions.

Finally, thanks to a conventional flash vacuum pyrolysis (FVP) apparatus and technique, it was possible to isolate and identify the nitrile oxide fragments. The major pathway involves ring cleavage at O(1)–N(2) and C(3)–C(4), rather than O(1)–N(5) and C(3)–C(4) and it is noted that fragmentation favors the more 'stable' nitrile oxide. For example, acetonitrile oxide have a much shorter lifetime than benzonitrile oxide and 4-methoxybenzonitrile oxide is longer lived that benzonitrile oxide, an effect attributed to the electron-donating methoxy substituent.

Hence, from the overview just made on the 1,2,5-oxadiazoles, or furazans, it is possible to understand that these compounds are really innovative for the research and they have great utility for a lot of applications. So, now it is time to go into the real core of the thesis, that deal with different furazans and their derivatives synthesis, the problems experienced and the good results obtained with innovative synthetic pathways.
3.2 Results and discussion

3.2.1 Synthesis of aminofurazans from aroyl cyanides

At the beginning of the thesis period, the first method that we tested was focused on the synthesis of aminofurazans, a well-defined category of polyheteroatomic heterocycles at the center of our project. Probably, the reason of this choice is because aminofurazans are well known to be essential constituents in a diverse range of non-natural products of potential chemotherapeutic and agrochemical interest. The ring family, for example, includes the H$_2$-receptor histamine antagonist, the M$_1$ selective muscarinic agonist, and pesticides.

Due to the small amount of publications about our target molecules, we started to synthesize aminofurazans from a one-step synthesis studied by Indian researchers Lakhan and Singh, who made a screening of reactions between aromatic α-ketonitriles with a bifunctional nucleophile hydroxylamine. The exact method involves the reaction between an aroyl cyanide (11) and hydroxylamine hydrochloride in 1:2 molar ratio in the presence of anhydrous sodium acetate, as base for promoting the cyclization, in absolute ethanol and it proceeds to give 3-amino-4-aryl-1,2,5-oxadiazoles (13) as the unique products with yields from 40% to 85% (Scheme 6). The ring system is formed simply by heating the reagents under gentle reflux for 1-2 hours on a steam-bath and the ethanol distilled off.

![Scheme 6 Reaction scheme of one-step synthesis of 3-amino-4-aryl-1,2,5-oxadiazoles.](image)

A second synthetic pathway is also feasible, separating the previous scheme in two distinct steps (Scheme 7). Undoubtedly, it involves the formation of α-amino-α'arylglyoxime (12) as the key intermediate, actually isolated as the end product of the first step, when the dehydrating agent anhydrous sodium acetate was not used.
Reaction scheme of two-step synthesis of 3-amino-4-aryl-1,2,5-oxadiazoles.

**Scheme 7** Reaction scheme of two-step synthesis of 3-amino-4-aryl-1,2,5-oxadiazoles.

A plausible reaction mechanism for one-step synthesis has been suggested as shown in Scheme 8. Hydroxylamine may react here by two different ways giving the same intermediate 12. Nucleophilic addition of hydroxylamine to the cyano group of 11, yielding an amidoxime, is followed by reaction with the second molecule of hydroxylamine at the carbonyl group forming 12 as the product (Route A). Alternatively, reaction of hydroxylamine at the carbonyl group is followed by its addition to the cyano group leading to the formation of 12 as the intermediate (Route B). Then, in the presence of anhydrous sodium acetate, the intermediate α-amino-α'-arylglyoxime (12) undergoes cyclization with dehydration readily to yield 3-amino-4-aryl-1,2,5-oxadiazoles (13) as the final product.

**Scheme 8** Reaction mechanism of one-step synthesis of 3-amino-4-aryl-1,2,5-oxadiazoles.

For the first time, we attempted the same procedure written in the article, following every minimal particular and molar ratio, using the commercially available and economic benzoyl cyanide, as starting material. Moreover, we also added CeCl$_3$·7H$_2$O/CuI system (molar ratio 1:1) in the reaction to promote
the nucleophile addition of hydroxylamine on the carbonyl group, as cerium(III) coordinates very easily with the oxygen, making the carbonyl more electrophilic\cite{65} (Scheme 9). With this change, we also try to accelerate the reaction rate, perhaps obtaining the final product at room temperature, instead to use reflux, which might carry to a thermal fragmentation of the heterocycle formed, as we already know from literature. Attempts are also made without catalyst system in different refluxing solvents, like CH$_3$CN, benzene and DMF, which help us to avoid eventual nucleophilic side reactions by the great amount of the solvent that could act when the mixture is under reflux (Table 5).

Scheme 9 Synthesis of 3-amino-4-phenyl-1,2,5-oxadiazoles (15).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst system (eq.)</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yields (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>----</td>
<td>EtOH abs.</td>
<td>78, reflux</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>CeCl$_3$·7H$_2$O/CuI</td>
<td>EtOH abs.</td>
<td>78, reflux</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>CeCl$_3$·7H$_2$O/CuI</td>
<td>CH$_3$CN</td>
<td>82, reflux</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>----</td>
<td>Benzene (Dean-Stark apparatus)</td>
<td>80, reflux</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>----</td>
<td>DMF</td>
<td>153, reflux</td>
<td>24</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$: the yields correspond to gas chromatography and mass spectrometry analysis.

Table 5 Reaction conditions of synthesis of 15 with CeCl$_3$·7H$_2$O/CuI system.

Unfortunately, all the tests with catalyst system failed and there is not formation of our expected product, but there are present a series of by-products probably coming from thermal decomposition of the furazan eventually formed and, above all, from the nucleophilic addition of the solvent on the carbonyl group, thanks to its big quantity in the reaction mixture compared with that of hydroxylamine and to the aptitude of the cyano group to exit to the system of benzoyl cyanide, as it is a good leaving group. In fact, in the case of the synthesis with absolute ethanol as solvent, the main by-product obtained with 80% of yield is ethyl benzoate, whose formation is also confirmed by a mass spectrometry analysis, with the same percentages. The same problem is observed for the synthesis with CH$_3$CN, but now with the formation of benzamide for about 85% of yields. The remaining part of by-products is all derivatives of thermal degradation. The explanation of these results may be the too
much strong coordination of the Ce(III) with the carbonyl oxygen that favors the nucleophilic addition on the carbonyl group by the solvent used, instead by hydroxylamine, with consequent leaving of the cyano group.

However, the other two attempts made with aprotic solvents, such as benzene and dimethylformamide (DMF) failed at the same way. The benzene test was performed with a Dean-Stark apparatus, so as to remove the water content formed from the cyclodehydration of the corresponding glyoxime intermediate in order to prevent some water side reactions. However, in these cases, even if the nucleophilic addition by solvents on the carbonyl group is not occurred, the final furazan is not produced and we have all by-products from thermal fragmentation. This is because solvents used are both high-boiling (80 °C for benzene; 153 °C for DMF) and reflux starts after more time, so reaction times are longer and thermal fragmentations are favored. The main by-product is isocyanate (10), coming from the rearrangement of nitrile oxide fragment, as already demonstrated in literature (Fig. 34).^59

Fig. 34 Thermal fragmentation of a general phenylfurazan and formation of isocyanate (10) by rearrangement.

In the original method, the hydroxylamine was put in the reaction mixture just as it is, as hydrochloride salt because it is a more stable form of the simple hydroxylamine to be stored. Sometimes, hydroxylamine in this form is less reactive with some organic substrates and maybe this is one of that situations. So, we attempted to unlock hydroxylamine from hydrochloride to make it more reactive towards carbonyl group, but also more rapid in the nucleophilic addition rather than solvent used. There are a lot of publications about the unlocking and we chose that with NaOMe in MeOH. But also this procedure is unsuccessful another time in favor of the almost complete formation of ethyl benzoate, in the first entry, with a 80% of yield again; so, the nucleophilic attack of solvent is once more preferred and the activation of hydroxylamine is unnecessary for the purposes of obtaining furazans.

Not yet satisfied of these unproductive outcomes, finally we changed route switching to the other pathway proposed by Lakhan and Singh in the same article: the synthesis of 3-amino-4-phenyl-1,2,5-oxadiazoles (15) in two separated steps, isolating the corresponding glyoxime intermediate. Indeed, we began with the first step using benzoyl cyanide (14) as starting material, which reacts with two equivalents of hydroxylamine hydrochloride in absolute EtOH or t-BuOH under reflux conditions in order to synthesize α-amino-α'-phenylglyoxime (16), as final product (Scheme 10). The choice of t-BuOH is just for the steric hindrance that this solvent can make, limiting the nucleophilic attack on the carbonyl group.
Scheme 10 Synthesis of α-amino-α'-phenylglyoxime (16).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH abs.</td>
<td>78, reflux</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>t-BuOH</td>
<td>82, reflux</td>
<td>24</td>
<td>0</td>
</tr>
</tbody>
</table>

a: the yields correspond to gas chromatography and mass spectrometry analysis after 24 hours.

Table 6 Reaction conditions of synthesis of 16.

Although the synthesis of α-amino-α'-phenylglyoxime (16) does not occur in these circumstances (Table 6), we can note a curious result. The employment of t-BuOH, as reaction solvent, reduces the formation of by-product coming from its nucleophilic attack on the carbonyl group, as we expected, in favor of the addition of one equivalent of hydroxylamine on the same carbonyl group to obtain phenylglyoxylic nitrile oxime (17) (Fig. 35), reaching 40% of it, checked with mass spectrometry analysis.

Fig. 35 Phenylglyoxylic nitrile oxime structure.

From this little result, it might be predicted that a great excess of hydroxylamine (from 2.5 to 5 eq.) can reach the end of the synthesis with the formation of 16, going through the intermediate 17 and subsequently attacking on the cyano group, but it is not real because the effective tests made certify that the result does not change anyway.

Therefore, after all these failed experiments, we decided to give up this synthetic procedure and explore other ways to obtain aminofurazans, because each approach that can be used in this work proposed by Indian researchers lead to a unique final: the nucleophilic attack by the solvent on the carbonyl group, totally erroneous for our purpose.
3.2.2 Synthesis of aminofurazans from alkyl β-aryl-β-oxopropionates

Before proceeding with our exploration, we initially tested the Russian method proposed by Sheremetev and his research group, to check if it is reasonable for the synthesis of 3-amino-4-arylfurazans (13). The procedure is very interesting, since it is a one-pot process without isolation step of intermediates and leads straightforward to the final product through a multi-step mechanism. The one-pot synthesis involves hydrolysis of the corresponding ester of a β-aryl-β-oxo acid (18), nitrosation at the activated methylene group, and treatment of the resulting intermediate (20) with an alkaline solution of hydroxylamine in the presence of urea afforded the target aminofurazan (13). The suggested mechanism is shown in Scheme 11. Earlier, Sheremetev himself obtained 3-alkyl-4-aminofurazans from ethyl β-alkyl-β-oxopropionates with the same synthetic pathway.

![Scheme 11](image_url)

Scheme 11 One-pot synthesis of 3-amino-4-arylfurazans (13).

The starting esters of β-aryl-β-oxo acids are commercially accessible or easily prepared, so we used our available ethyl 3-oxo-3-phenylpropanoate or ethyl benzoylacetae, as starting material. The various steps to proceed are a lot and, from one to the other, elapses quite a long time, making reaction times very long and risking the formation of some by-products. In fact, four days are estimated to perform all the steps and to reach the final furazan. Moreover, the experimental part suggested by Russians guides primarily to the furazan ring intermediate (24), but thanks to all the chemical reagents in excess, 24 undergoes ring opening with basic conditions of the system and then, aryglyoxylic nitrile oxime (25) is formed until to get 3-amino-4-arylfurazans (13).

Fortunately, our two preliminary tests with this synthesis are satisfactory because we obtained the target molecule, 3-amino-4-phenylfurazan (15), starting from ethyl benzoylacetae (27) (Scheme 12), in very small amounts, which correspond to yields of 5% for the first attempt and 8% for the second one, with the same condition (Table 7). Probably, the second time we were more careful in each step. Finally, the pure product 15 is obtained by recrystallization from CHCl₃-light petroleum (1:1).
Scheme 12 One-pot synthesis of 3-amino-4-phenylfurazans (15).

Table 7 Reaction conditions for one-pot synthesis of 15.

<table>
<thead>
<tr>
<th>Entry</th>
<th>NaOH aq. (eq.)</th>
<th>HClO₄/NaNO₂ (eq.)</th>
<th>NH₂OH-HCl (eq.)</th>
<th>Urea (eq.)</th>
<th>Reflux temp. (°C)</th>
<th>Time (h)</th>
<th>Yields (%)³</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>2.5:1.2</td>
<td>4</td>
<td>1.0</td>
<td>110</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>2.5:1.2</td>
<td>4</td>
<td>1.0</td>
<td>110</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

a: Yields are referred to isolated compounds.

Now, our new approach is to search where the problem is inside the procedure and understand why such little yields are obtained. Surely, the first reason is the very high reflux temperature in the last step that can compromise the final yield of the product 15. In fact, by gas chromatographic analysis, it is demonstrated the presence of many unidentified by-products after reflux time (about 3 hours), due to thermal decomposition. In addition, the second reason could be the presence of some problems arising from incorrect reagents quantities and their molar ratio or unsuitable reaction conditions, such as pH of the aqueous mixture. Therefore, the strategy advanced by us was to divide each single step and control if all the reaction parameters are acceptable. Soon, in the first step, we noticed that the necessary quantity of base NaOH to hydrolyze completely the starting ethyl benzoylacetate (27) was three times higher than that described in the article; so, already from the first step, the yield of benzoylacetate sodium salt decreased of about 30%, whereas with our approach only 10%, but we never had the whole hydrolysis. After that, the addition of HClO₄ in the mixture is essential to neutralize the base in excess and make an acidic medium for nitrosation at the methylene group and decarboxylation to give compound 21. If the pH is not acid, around to 2 or 3, this step does not occur and thus, we have a net decrease of formation of 21; for this reason, we had to checked every time if we had acid pH. At this point, the reflux step starts and the temperature begin to be higher and higher, promoting thermal fragmentation of products. Indeed, it occurred a remarkable reduction of furazan 15 yields with a significant increase of several by products. Verifying always the same major problems with high temperature and long reaction times, like in the Indian procedure (see chapter 3.2.1), we decide to stop our synthesis to 2-oxo-2-arylacetaldehyde.
oxime (21), due to its easy preparation\textsuperscript{70,71} and its very high yields, and move to possible innovative processes for furazans synthesis, using compound 21 as starting substrate.
3.2.3 Synthesis of phenylfurazans through protected oximes

Once prepared our new starting material, 2-oxo-2-phenylacetaldehyde oxime (28), we could plan the innovative procedure to synthesis, not more aminofurazans, which are very difficult to obtain, also for the unavoidable presence of an amino group on the heterocycle, but a general 1,2,5-oxadiazole, without any lien on the nature of the two substituents bound to the polyheteroatomic heterocyclic system. Starting from compound 28, particularly easy to achieve and quite stable, we will mostly synthesize phenylfurazan (2), which is the related product of the cyclization of the corresponding glyoxime intermediate (1) (Fig. 36).

![Fig. 36](image)

Now, our novel strategy is built up to form furazans avoiding high-temperature reflux conditions and prolonged reaction times, that favor inevitably formation of a great variety of by-products because of thermal decomposition. Therefore, the first idea we thought, shown in the Scheme 13, is to create a protection on the OH group of the initial α-aldo oxime (28), so that a subsequent addition of hydroxylamine hydrochloride in the mixture leads exclusively to a nucleophilic attack on the carbonyl group, producing the corresponding protected glyoxime. At this point, we can suppose that the final cycloaddition to form the phenylfurazan product (2) undergoes more spontaneously, thanks to the protecting group, which acts as a very suitable leaving group, also at room temperature or with very mild warming temperatures.

![Scheme 13](image)

In literature, there are a lot of publications that explain how to protect a general oxime, almost all with the same reagents and media, but with a substantial difference: every starting oxime is α-keto oxime, so it never has a hydrogen in the α position to the carbonyl group, but there is always a substituent, both alkyl and aryl one. Our compound 28 is α-aldo oxime and presents this unique chemical property
to have α-H atom, and it can be represent a notable problem for the protection step. In fact, all the procedures indicate an alkaline reaction environment, with use of 4-dimethylaminopyridine (DMAP)\textsuperscript{73} or triethylamine (Et\textsubscript{3}N),\textsuperscript{74} as bases, and a general sulfonyl chloride,\textsuperscript{75} as protecting group and good leaving group. Maybe, these basic reaction conditions can cause deprotonation of α-H atom and not occur the sulfonylation expected. However, this doubt is soon dissolved, analyzing pK\textsubscript{a}s of the related compounds. Protonated Et\textsubscript{3}N has a pK\textsubscript{a} value around 11 and protonated DMAP has smaller pK\textsubscript{a} value at about 9, whereas the pK\textsubscript{a} of α-H atom of oxime 28 is, indeed, around 13; these results show us that a deprotonation to α position does not happen.

Thus, we proceeded with our method beginning with the first step, the protection. We have to say that our synthetic mechanism involves a mix of reagents and media among all those cited above. In fact, we tested two different sulfonyl groups, p-tosyl one (Scheme 14) and mesyl one (Scheme 15), using chloride derivatives as reagents; in either cases, the base chosen was DMAP in 1:1 molar ratio with the starting oxime 28, and Et\textsubscript{3}N dry was added in small amounts, as co-solvent of CH\textsubscript{2}Cl\textsubscript{2}. The whole reaction was processed at room temperature, as we wanted.\textsuperscript{76}

![Scheme 14](image1)

Scheme 14 The protection step of 28 by p-toluenesulfonyl chloride (p-TsCl).

![Scheme 15](image2)

Scheme 15 The protection step of 28 by methanesulfonyl chloride (MsCl).

Unfortunately, in either attempts, the protection does not occur and the reaction, monitored by TLC, gas chromatography and mass spectrometry screening, highlights no variations during also long time (24-48 hours), keeping substantially unchanged reactant oxime (28) and p-TsCl, transformed into acid (p-TsOH), but displaying an increasing formation of by-products, which were not identified. This probably means that the protection of an oxime is more suitable when we have α-keto oximes as starting compounds, maybe because of some effects of the substituent in α position that promote the sulfonylation; while if we have α-aldo oximes, the most reached outcomes are only by-products without ever noticed the presence of protected oximes, or even completely no reaction at all.
3.2.4 Synthesis of phenylfurazans with ultrasound and microwave-assisted reactions

Considering the previous failed end results, we decided to change completely route by simplistic pathways to synthetize phenylfurazans (2) and we chose to get help by other chemical techniques and instrumentation that can facilitate the formation of our target heterocycles with acceptable yields, preventing the rise of a great amount of by-products unwanted by us.

For the first time, our approach is focused on an easy chemical equipment and technique, which has increasingly been used in organic synthesis in recent years: chemical applications of ultrasound threw doors open to an exciting new field of research. A large number of organic reactions can be carried out in higher yield, shorter reaction time and milder conditions under ultrasonic irradiation. Also oximes can be synthetize with this method and the oximation is a very efficient method for reaching more rapidly our intent to obtain furazans.

Previously, condensation of primary amine with carbonyl compound was first reported by Schiff in 1864 and since then a great number of these reactions were performed and reviewed. When hydroxylamine is employed, the condensation gives oximes, along with water as a by-product, which might represent a possible problem for secondary side reactions. The experimental conditions mostly depend on the nature of the starting materials and basicity of the reaction medium; usually, reactions proceed smoothly at pH close to neutral. In organic chemistry, it is generally believed that reactions of a carbonyl compound and hydroxylamine at pH close to neutral occurred through nucleophilic attack of the nitrogen electron pair to the electrophilically activated C=O carbon. Usually, the preparation of oximes via condensation of the carbonyl compounds and hydroxylamine hydrochloride needs longer reaction time, as just tested.

Thus, we took advantage by this innovative chemical application of ultrasound to be employed either on α-aldo oxime synthetized before, that is 2-oxo-2-phenylacetaldehyde oxime (28), or on the phenylglyoxal (33), which is the parent material into compound 28 synthesis. In both cases, there are the presence of at least one carbonyl group, where the sonochemical technique can act in appropriate way and the formation of phenylglyoxime (1) as end product. Herein, we wish to check an effortless sonochemical synthesis of oximes in EtOH, in the presence of Na$_2$SO$_4$ or not, with mild temperature (25-35 °C) (Scheme 16).

\[
\begin{align*}
\text{O} & \quad \text{N-OH} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
(28) & \quad \text{or} \\
\text{O} & \quad \text{C} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
(33) & \\
\text{NH}_2\text{OH-HCl} & \quad \text{Na}_2\text{SO}_4 \\
& \quad \text{EtOH} \\
& \quad \text{H}_2\text{O} \\
& \quad 25-35 \, ^\circ\text{C} \\
& \rightarrow \\
\text{N-OH} & \quad \text{N-OH} \\
(1) &
\end{align*}
\]

Scheme 16 Synthesis of phenylglyoxime (1) by sonochemical application.
The outcome of these new approaches are surprising. Either we start from compound (28) or from compound (33), the results do not change because we have always the formation of phenylglyoxime (1). Yields are low due to the presence of two important unexpected compounds which arise after the determined reaction time. The first, and maybe the most significant, is phenylfurazan (2), while the second is phenylglyoxylic nitrile oxime (17) (Scheme 17). In Table 8, there are all the other conditions of this synthetic process.

Scheme 17 Unexpected results with sonochemical synthesis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting substrate</th>
<th>NH$_2$OH-HCl (eq.)</th>
<th>Na$_2$SO$_4$ (eq.)</th>
<th>Time (h)</th>
<th>Yields (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1)</td>
</tr>
<tr>
<td>1</td>
<td>(28)</td>
<td>1.25</td>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>(33)</td>
<td>2.50</td>
<td>1</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>(28)</td>
<td>5.00</td>
<td>----</td>
<td>24</td>
<td>7</td>
</tr>
</tbody>
</table>

$^a$: the yields correspond to gas chromatography and mass spectrometry analysis.

Table 8 Reaction conditions of synthesis of 1 by sonochemical application and the other two determined compounds: 2 and 17.
The big problem that we met is to recognize which was compound 2 and which was compound 17 due to their same molecular weights, that is 146 g/mol. In fact, to mass spectrometry analysis, there were two peaks with identical m/z, but also fragmentations were similar and plausible for both molecules. With other accurate analysis, such as $^1$H-NMR and $^{13}$C-NMR, we could understand the right compounds related to the right peaks. After this misunderstanding, we could continue our tests, also with the help of gas chromatography analysis, since we obtained all the information to identify all the reaction compounds (Fig. 37).

These two unpredictable compounds 2 and 17 are not thermal by-products because reaction temperatures are near to the room ones, so it is improbably that they derive from there. For the former, we can suggest that, besides to form the expected glyoxime (1), ultrasound promotes also an overreaction that leads to the cycloaddition obtaining the desired phenylfurazan (2). For the latter, instead, it is harder the explanation because nitrile oxime (17) can be derived by two distinct fates. At first, it could be formed by ring cleavage of phenylfurazan previously obtained, so it is considered a degradation by-product for too long reaction time; this case is already observed in the Russian procedure, described in chapter 3.2.2, where, in general manner, arylfurazans ring opened to give the corresponding nitrile oxime, which provide at the end the final aminofurazan. Whereas, in second instance, it could be formed after nucleophilic attack of hydroxylamine on the carbonyl group and subsequent dehydration of the already present oxime in $\alpha$ position to the carbonyl group, so it is believed to be an intermediate of the reaction that will drive towards the final product. Also this occurrence is already seen above, in chapter 3.2.1, when it was proposed Indian method and there,
the nitrile oxime act as intermediate to give the corresponding glyoxime, which, for dehydration, provides aminofurazan. Therefore, after these interesting results, we tried to process the same synthesis by improving yields of phenylfurazan (2), attempting to overcome the formation of phenylglyoxylic nitrile oxime (17) by use of the microwave instrumentation (Scheme 18).

![Scheme 18 Microwave-assisted reaction of phenylfurazan (2).](image)

The microwave-assisted reactions allow us to use temperatures higher than boiling point of a specific solvent and favor some interactions among molecules of the system that do not occur in the reflux conditions, but at the same time they drastically reduce reaction times, avoiding a lot of side reactions and thermal degradation. And these are the expected outcomes from our synthetic pathway.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting substrate</th>
<th>NH₂OH·HCl (eq.)</th>
<th>Na₂SO₄ (eq.)</th>
<th>Solvent</th>
<th>Temp. (°C)ᵃ</th>
<th>Time (h)</th>
<th>Yields (%)ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2) (17)</td>
</tr>
<tr>
<td>1</td>
<td>(28)</td>
<td>1.25</td>
<td>1</td>
<td>EtOH/H₂O Multistep (40-165)</td>
<td>1.5</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>(33)</td>
<td>2.50</td>
<td>1</td>
<td>EtOH/H₂O</td>
<td>100</td>
<td>2</td>
<td>43 41</td>
</tr>
<tr>
<td>3</td>
<td>(33)</td>
<td>5.00</td>
<td>----</td>
<td>EtOH/H₂O</td>
<td>170</td>
<td>1</td>
<td>40 40</td>
</tr>
<tr>
<td>4</td>
<td>(33)</td>
<td>5.00 (without HCl)</td>
<td>----</td>
<td>EtOH</td>
<td>140</td>
<td>0.5</td>
<td>28 61</td>
</tr>
<tr>
<td>5</td>
<td>(28)</td>
<td>1.25</td>
<td>----</td>
<td>EtOH</td>
<td>145</td>
<td>1</td>
<td>45 40</td>
</tr>
<tr>
<td>6</td>
<td>(33)</td>
<td>2.50</td>
<td>----</td>
<td>THF</td>
<td>140</td>
<td>1</td>
<td>0 80</td>
</tr>
<tr>
<td>7</td>
<td>(33)</td>
<td>2.50</td>
<td>----</td>
<td>CH₃CN</td>
<td>140</td>
<td>0.5</td>
<td>---- ----</td>
</tr>
<tr>
<td>8</td>
<td>(33)</td>
<td>2.50</td>
<td>----</td>
<td>CH₂Cl₂</td>
<td>140</td>
<td>0.5</td>
<td>---- ----</td>
</tr>
<tr>
<td>9</td>
<td>(33)</td>
<td>2.50</td>
<td>----</td>
<td>DMF</td>
<td>200</td>
<td>0.5</td>
<td>0 85</td>
</tr>
</tbody>
</table>

ᵃ: All reactions were carried out by irradiation in a PowerMax cooling microwave oven with a reached power between 70 and 150 W, depending on the solvent used.
The yields correspond to gas chromatography and mass spectrometry analysis.

**Table 9** Reaction conditions of microwave-assisted synthesis of 2. There are also present compound 1 and 17.

In fact, as shown in Table 9, reaction time decreases extremely, giving the same yields of products in minor period. This procedure is also possible to do with several different solvents, also those that solubilize a little the reagents, since in the microwave instrument, elevated temperatures let hard solubilities too, but some of these solvents give any effective products and only by-products. Anyway, it remains the problem to obtain only furazan (2) rather than compound (17); unfortunately, still this innovative procedure is at the beginning and needs to be improved to get directly the desired furazan.
4. Experimental section

4.1 Instrumentation

All the reactions were monitored by thin layer chromatography silica gel Merk Kieselgel 60 F254 and by gas chromatography. The instrument employed is a gas chromatograph 6850 Agilent Technologies, with a capillary column (0.32 mm x 30 m) and stationary phase HP-1 Agilent of 0.40-0.45 μm thickness.

Separation and purification of compounds were realized by column flash chromatography on silica gel Merk (0.040-0.063 mm).

Characterization of the products was carried out by mass spectra and nuclear magnetic resonance spectra (NMR) of $^1$H and $^{13}$C.

Mass spectra were obtained through the serial work of a gas chromatograph and a mass spectrometer: Hewlett-Packard GC/MS 6890N. The mass spectrometer uses the EI ionization mode with an electronic beam of 70 eV.

$^1$H-NMR spectra were acquired by using a magnetic resonance spectrometer Varian Mercury Plus 400, operating at 400 MHz. Chemical shifts are expressed in δ (ppm) compared to signal of the residual solvent.
4.2 Synthetic procedures and characterization of the products

4.2.1 Synthesis of 3-amino-4-phenylfurazans from ethyl benzoylaceta
e

![Chemical structure of ethyl benzoylacetae and furazan](image)

Ethyl benzoylacetae (27) (500 mg, 2.6 mmol) was added at 0 °C to a solution of NaOH (114 mg, 2.9 mmol) in water (2 ml) and the resulting mixture was stirred for 16 h. Sodium nitrite (215 mg, 3.1 mmol) was added and then 20% HClO₄ (0.36 ml, 6 mmol) was slowly added dropwise at T <10 °C. After the acid was added completely, the reaction mixture was warmed to room temperature and left for ~24 h. Then, a solution of NH₂OH-HCl (718 mg, 10.4 mmol) in water (2 ml) was added dropwise with vigorous stirring. After half the solution of hydroxylamine was added, a solution of NaOH (468 mg, 11.7 mmol) in water (2 ml) was simultaneously added dropwise from a second dropping funnel at a temperature no higher than 30 °C. Then a mixture was heated to 95 °C over 3 h and urea (156 mg, 2.6 mmol) was added in one portion. The resulting mixture was refluxed for 6 h and cooled. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from CHCl₃-light petroleum (1:1). The product 15 was obtained as white solid with a yield of 8%.

Characterization of product 15:

![Chemical structure of product 15](image)

3-amino-4-phenyl-1,2,5-oxadiazole
C₈H₇N₃O
M.W. 161 g/mol

GC analysis: 13.46 min.

IR (neat): 3408, 3377, 3324, 3245, 1630, 1526, 1477, 1456, 1411, 1318, 981, 775 cm⁻¹.

MS (El, 70eV) m/z: 161 [M⁺], 131, 104, 91, 77, 58, 51, 39.

¹H-NMR (400 MHz, CDCl₃): δ= 4.30 (br s, 2H), 7.51-7.56 (m, 3H), 7.71-7.74 (m, 2H) ppm.

¹³C-NMR (100 MHz, CDCl₃): δ= 125.82, 127.84, 129.68, 130.82, 147.11, 154.40 ppm.
4.2.2 Synthesis of phenylfurazans with ultrasound and microwave-assisted reactions

**Ultrasounds-assisted procedure**

Phenylglyoxal (33) (160 mg, 1.2 mmol) or 2-oxo-2-arylacetaldehyde oxime (28) (180 mg, 1.2 mmol) was dissolved in ethanol (6 ml). A solution of hydroxylamine hydrochloride (207 mg, 3 mmol; H₂O, 1.5 ml), anhydrous sodium sulfate (1 mmol or 0 mmol) were added. The reaction mixture was irradiation in the water bath of the ultrasonic cleaner at 25-35 °C for an appropriate period (5 h for 28; 24 h for 33). The mixture was filtered (if without NaSO₄, no filtration.) and the solvent was evaporated under reduced pressure. The residue was dissolved in CH₂Cl₂, washed with water, and extracted with CH₂Cl₂. The combined organic layers were dried over anhydrous MgSO₄, filtered, and evaporated to dryness under reduced pressure. Purification was accomplished by recrystallization or by column chromatography on silica gel (200–300 mesh), eluted with petroleum ether or a mixture of petroleum ether and diethyl ether. The product 2 was obtained as white solid with a yield of 45%, while the product 17 was obtained as white solid with a yield of 40%.

**Microwave-assisted procedure**

Phenylglyoxal (33) (200 mg, 1.5 mmol) was dissolved in ethanol (7.5 mL). A solution of hydroxylamine hydrochloride (257 mg, 3.7 mmol; H₂O, 1.5 ml) was added. The reaction mixture was subjected to microwave irradiation for 30 min at 140 °C. The reaction was monitored by TLC until disappearance of starting material. Once the reaction was completed, the solvent was evaporated under reduced pressure. The residue was dissolved in CH₂Cl₂, washed with water, and extracted with CH₂Cl₂. The combined organic layers were dried over anhydrous MgSO₄, filtered, and evaporated to dryness under reduced pressure. Purification was accomplished by recrystallization or by column chromatography on silica gel (200–300 mesh), eluted with petroleum ether or a mixture of petroleum ether and diethyl ether.
ether. The product 2 was obtained as white solid with a yield of 40%, while the product 17 was obtained as white solid with a yield of 40%.

Characterization of product 2:

3-phenyl-1,2,5-oxadiazole  
C_{8}H_{6}N_{2}O  
M. W. 146 g/mol

GC analysis: 10.02 min.  
MS (El, 70eV) m/z: 146 [M⁺], 119, 103, 91, 89, 76, 63, 51, 39.  
\(^1\)H-NMR (400 MHz, CDCl₃): δ = 7.52-7.54 (m, 3H), 7.84-7.88 (m, 2H), 8.56 (s, 1H) ppm.  
\(^{13}\)C-NMR (100 MHz, CDCl₃): δ = 125.60, 127.68, 129.65, 131.34, 139.73, 154.65 ppm.

Characterization of product 17:

phenylglyoxylic nitrile oxime  
C_{8}H_{6}N_{2}O  
M. W. 146 g/mol

GC analysis: 12.69 min.  
MS (El, 70eV) m/z: 146 [M⁺], 129, 116, 103, 89, 77, 63, 51, 39.  
\(^1\)H-NMR (400 MHz, CDCl₃): δ = 7.44-7.49 (m, 3H), 7.79-7.81 (m, 2H), 9.69 (br s, 1H) ppm.  
\(^{13}\)C-NMR (100 MHz, CDCl₃): δ = 109.52, 126.45, 129.24, 130.21, 131.45, 148.88 ppm.
Conclusions

During the thesis period, we focused our attention on particularly efficient methods found in literature to synthesis 3-amino-4-phenylfurazans (15) and the simpler phenylfurazans (2), trying to bring some changes to processes that could improve the yields of our target products. Thanks to Russian procedure and the innovative one of microwave-assisted organic synthesis (MAOS), we reached our goal to obtain compounds (15) and (2), respectively, unfortunately with not excellent yields. However, the microwave technique give the best outcomes because it remarkably increases the formation of phenylfurazan (2) with yields of around 40% in very short reaction times and in different reaction conditions, such as using a great variety of solvents. The continuous problem that remains as a constant in this procedure is the formation of phenylglyoxylic nitrile oxime (17), which can be considered as an reaction intermediate or as a degradation by-product due to reaction conditions. So, future research perspectives should investigate and understand what it is the role of compound (17) in the microwave-assisted process and, consequently, act in direction of synthesis of single furazan, increasing yields and reducing formation of other by-products.
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