EXERCISES IN ORGANIC SYNTHESIS BASED ON SYNTHETIC DRUGS

Marcus Vinícius Nora de Souza

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Exercises in Organic Synthesis Based on Synthetic Drugs

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CONTENTS

PREFACE

Chemistry is a science based on compositions, properties, reactions and transformations of substances. In 1777, it was divided into two main fields by the Swedish chemist Torbern Olof Bergman: organic and inorganic chemistry. However, due to the vast amount of information obtained over the centuries, modern chemistry has been divided into five main branches: organic, inorganic, analytical and physical chemistry, and biochemistry. Nowadays, despite this division, these main branches are subdivided into several sub-branches demonstrating the tremendous scientific and technological development of chemistry. In the case of organic chemistry, it presented a large number of sub-branches, such as organic synthesis, medicinal chemistry, asymmetric synthesis, natural products, green chemistry, organometallic chemistry, physical organic chemistry, polymer chemistry, forensic chemistry, among others. Due to the importance of chemistry as the physical sciences in our world, many researchers considered it as a central science closely linked with applied and life sciences.

Chemistry plays a critical role in drug discovery against the most different types of diseases. The development of a new drug is an extremely complex process involving different areas and, types of knowledge. Considering that, two sub-branches of organic chemistry are fundamental at the beginning of this process: organic synthesis and medicinal chemistry. Organic synthesis is the preparation in the laboratory of simple or complex substances using chemical reactions in a rational and planned way, starting with simpler atoms or elements. Medicinal chemistry is a discipline that is at the interface of several areas, such as, chemistry, medical, biological, and pharmaceutical sciences. Its objective is the design, discovery, identification, and preparation of bioactive compounds as well as the study of other aspects such as their mechanisms of action, metabolism, and a structure-activity relationship.

Due to the crucial importance of organic synthesis and medicinal chemistry in the development of new drugs, the objective of this book is to present different exercises aiming at the search for biologically active compounds against the most diverse types of diseases in both humans and animals. The development of a new drug begins with the search, planning, design, and evaluation being necessary for its preparation in the laboratory. This initial step is a long and complicated process for a biologically active compound to become a drug. For this to happen, organic synthesis is of fundamental importance since, through it, we can obtain the most varied types of simple or complex substances for biological evaluation. Thus, the present book will address different techniques and strategies for the synthesis of biologically active compounds and drugs. Through the exercises presented, the reader will be able to propose, obtain, and evaluate in a logical way compounds to be studied. Considering that, this book is useful for students of graduation and post-graduation in **chemistry**.

It is worth mentioning that the present book has a wide range of bibliographical references, extracted from different scientific journals and books. The exercises presented are based on this material. In case the reader wants to delve into specific content, drug, or illness, it is advisable to consult such references. This book will be studied only for the drugs and biologically active compounds developed in the laboratory.

CONSENT FOR PUBLICATION

Not applicable

CONFLICT OF INTEREST

The author confirms that there is no conflict of interest.

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CHAPTER 1

How to Build a Drug: Exercises Based on the Concept of Retrosynthetic Analysis

Abstract: Concepts involving retrosynthesis were and are essential to the development of organic synthesis as science and art. Therefore, the first four exercises are based on this concept. These exercises were subdivided into themes and degrees of increasing difficulty so that the reader could gradually progress and become familiar with their concepts. Thus, the first exercise begins with the retrosynthetic analysis of drugs based on the identification of only two synthons and their respective synthetic equivalents (reagents and substances) necessary for their synthesis. Exercises **2**, **3**, and **4** are thematic and based on the identification of epoxides, piperazines, and aldehydes, used in the synthesis of drugs and bioactive substances as well as other synthons and their respective synthetic equivalents present in the exercises.

Keywords: Aldehydes, Drugs, Epoxides, Exercises, Medicinal chemistry, Organic synthesis, Piperazines, Reagentes, Retrosynthetic analysis, Substances, Synthons.

INTRODUCTION

For a new drug to reach the pharmacy shelf, a long and complicated process is necessary also involving large sums of money. This process requires multiple steps with a large number of specificities and areas such as chemists, physicians, pharmacologists, biochemists, economists, lawyers, among others. In this context, one of the first steps in this process is to obtain biologically active compounds in laboratories for evaluation, and for this, the use of organic synthesis is critical.

It is no exaggeration to mention that at present modern organic synthesis can synthesize in logic and planned manner any substance of natural or synthetic origin thanks to the contribution of several scientists in various periods of human history. In modern organic chemistry, professor Robert Bruns Woodward (1917-1979) (Nobel Prize in 1965) is considered by many as the father of modern organic synthesis for his outstanding contributions in the synthesis of natural products with extremely complex chemical structures (Fig. **1**). Another important scientist is professor Elias James Corey (1928-) (Nobel Prize in 1990), who introduced and successfully applied in the synthesis of natural products the

Marcus Vinícius Nora de Souza

concept of retrosynthetic analysis. This concept can efficiently and rationally simplify the synthesis of the target molecule with simple or complex chemical structures by retroactive analysis of the substance in question up to the starting materials. The target molecule is logically disconnected in parts until it reaches the starting materials and these disconnections, named by Corey as synthons, which are fragments with nucleophilic and electrophilic centers being synthetic equivalents (reagents or building blocks). In 1989, the book, *The Logic of Chemical Synthesis* brilliantly demonstrated the application of his concepts (Fig. **2**).

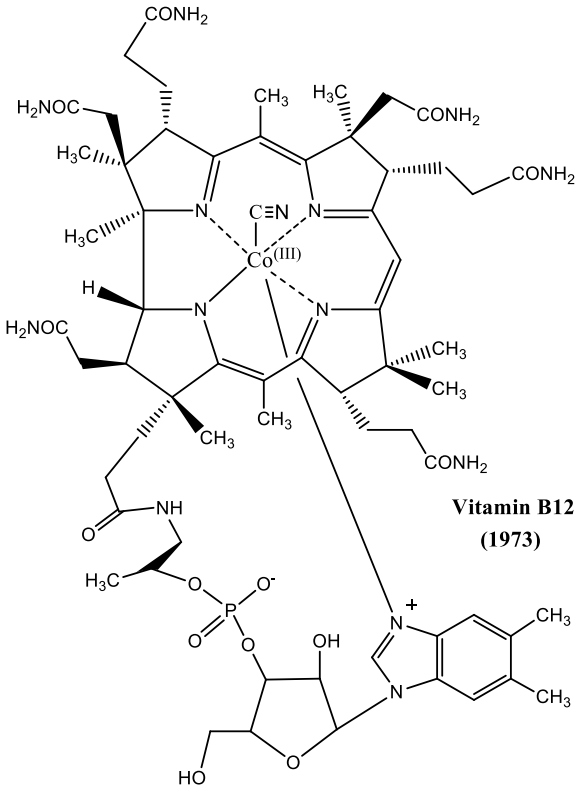


Fig. (1). Professor Robert Burns Woodward (1917-1979) and the chemical structure of vitamin B12, which to date has been the first and only synthesis to be performed in the laboratory of this complex natural product. This synthesis, which has more than one hundred steps, was carried out in collaboration with the Swiss Albert Eschenmoser (1925-) in the early 1960s with a team of approximately one hundred people and was published in 1973.
Source of the picture: The Nobel prize website.
https://www.nobelprize.org/prizes/chemistry/1965/woodward/facts/

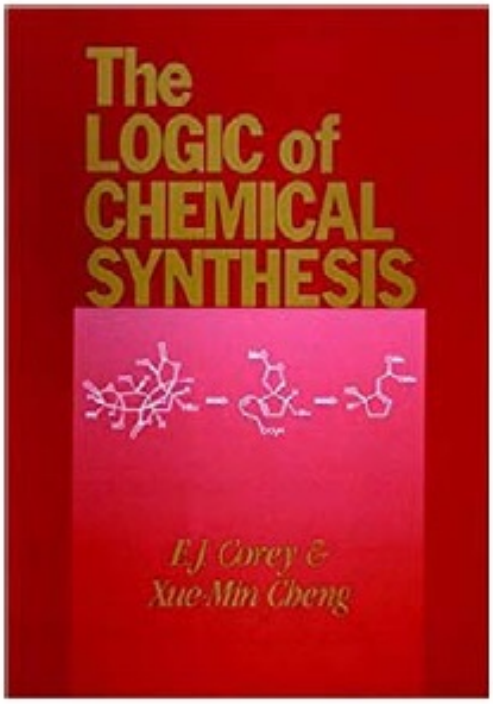


Fig. (2). Professor Elias James Corey (1928-) and his famous book.
Source of the picture: The Nobel prize website.
https://www.nobelprize.org/prizes/chemistry/1990/corey/biographical/

As an example of the application of the concepts developed by Professor Corey, we will propose the synthesis of the drug nevirapine (Fig. **3**). This drug is an anti-HIV drug approved in 1996 by the FDA (Food and Drug Administration), being a non-nucleoside reverse transcriptase inhibitor (NNRTI). At first glance, analyzing its chemical structure seems to be a very complicated task to propose its synthesis. However, when we use the retrosynthetic analysis, disconnecting our target molecule (nevirapine), we created logically nucleophilic and electrophilic centers (synthons). As we know, amines are nucleophilic and carbonyl groups reacting with nucleophiles due to their electrophilic character indicating which reagents will be used in this synthesis. It is essential to highlight how the retrosynthetic analysis was able to simplify the synthesis of the anti-HIV nevirapine. This concept is highly recommended in future synthetic analyzes.

CHAPTER 2

Organizing Synthetic Routes and Identifying Reagents

Abstract: In this chapter, the exercises below are based on two themes. First, exercises based on the synthesis of several drugs and bioactive compounds used to treat various diseases. Therefore, several reaction conditions are presented. However, these conditions are disordered, and it is up to the reader to order them. The other theme is to identify reagents used for the preparation of a specific target molecule. This type of training is essential because it allows the reader to contact different types of reagents and chemical transformations and use them in a sequentially correct way.

Keywords: Bioactive compounds, Chemical transformations, Drugs, Exercises, Medicinal chemistry, Molecules, Reaction conditions, Reagents, Synthesis.

EXERCISES 5 TO 8

INTRODUCTION

After the exercises on retrosynthetic analysis, the reader is now invited to practice other essential aspects of a particular synthetic route. It is worth mentioning that the retrosynthetic analysis has to be allied to solid chemical knowledge. In this context, the identification of reactions, reagents, intermediates, and chemical transformations are essential. Considering that, different exercises in this book are intended to make the reader familiar with these themes.

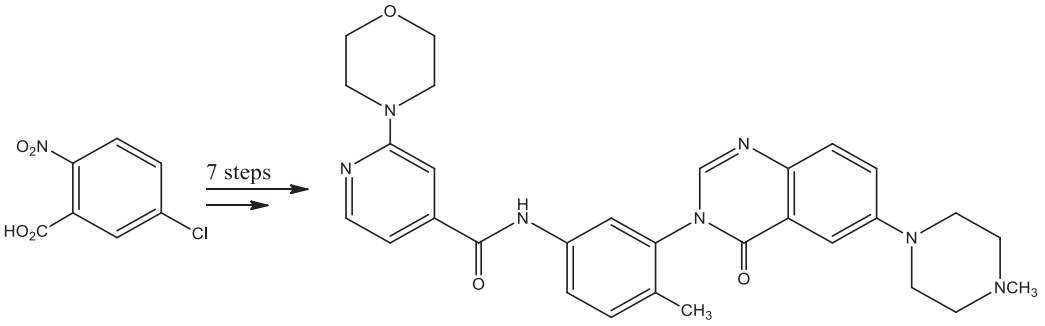
Exercises **5** to **8** present some of these objectives, Exercise **5**, for example, proposes different syntheses with the reagents arranged incorrectly, and it is up to the reader to order them. Exercise **6** aims at identifying the reagents used and their correct order of use in the preparation of a given drug (target molecule). Exercise **7** has the objective of identifying the structure of the drugs, having information of the starting materials and reagents used. Exercise **8** presents a series of gaps in the synthesis of different drugs, and it is up to the reader to complete them. It is worth mentioning that it is highly recommended that the reader continues using the concept of retrosynthesis in the resolution of the exercises.

Marcus Vinícius Nora de Souza

EXERCISE 5 - ORGANIZING SYNTHETIC ROUTES

In the exercises below, different synthetic bioactive substances are presented, including some drugs used to treat various diseases. However, the reactional conditions for obtaining them are disordered, and it is up to the reader to order them.

Example

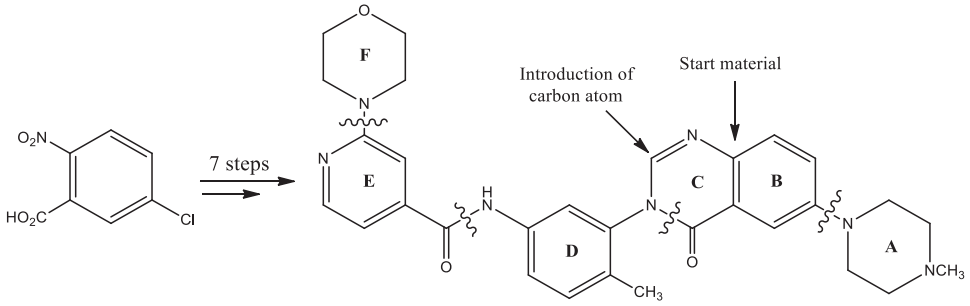


Anti-inflammatory
Bioorg. Med. Chem. Lett.
2012, *22*, 3879

(**a**) 4-chloro-2-chloropyridine acid chloride, (**b**) $(OEt)_3CH$, AcOH, EtOH, 70ºC, 98%; NEt_3, CH_2Cl_2, rt, 91%; (**c**) morpholine, 100ºC, 57%; (**d**) $(COCl)_2$, DMF, CH_2Cl_2, 0ºC to rt; (**e**) 2-methyl-5-nitroaniline, NEt_3, CH_2Cl_2, rt (99% 2 steps); (**f**) H_2, 10% Pd/C, MeOH, rt, 80%; (**g**) *N*-methylpiperazine, 100ºC, 83%.

Answer

However, it is worth emphasizing the importance of first doing a retrosynthetic analysis, because it will undoubtedly provide relevant information for solving the problem. In this context, the first question to ask is where the starting material in the target molecule is? It looks like that the fused nuclei **C** and **B** are derived from this raw material. The next step is to identify which transformations occur. We can highlight the following: a) conversion of the carboxylic acid into amide *via* formation of an acid chloride; b) coupling with the core **D**; c) synthesis of the nucleus **C** using a carbon atom and d) introduction of the *N*-methylpiperazine (nucleus **A**). The disconnections and coupling in the **D**-**F** rings are easy to see in conjunction with the reaction conditions shown. Thus, the ordered reaction sequence is as described below.

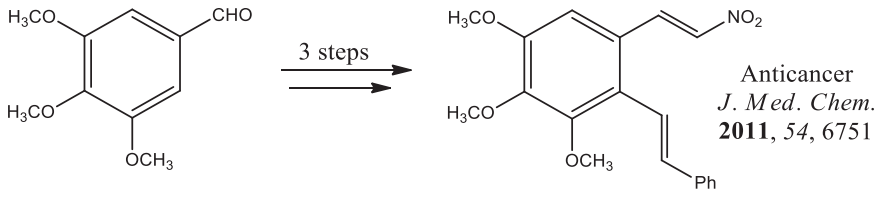


Bioorg. Med. Chem. Lett. **2012**, *22*, 3879

(a) $(COCl)_2$, DMF, CH_2Cl_2, 0°C at rt; (**b**) 2-methyl-5-nitroaniline, NEt_3, CH_2Cl_2, rt (99%; 2 steps); (**c**) *N*-methylpiperazine, 100°C, 83%; (**d**) H_2, 10% Pd/C, MeOH, rt, 80%; (**e**) $(OEt)_3CH$, AcOH, EtOH, 70°C, 98%; (**f**) 2-chloropyridine-4-carbonyl chloride, NEt_3, CH_2Cl_2, rt, 91%; (**g**) morpholine, 100°C, 57%.

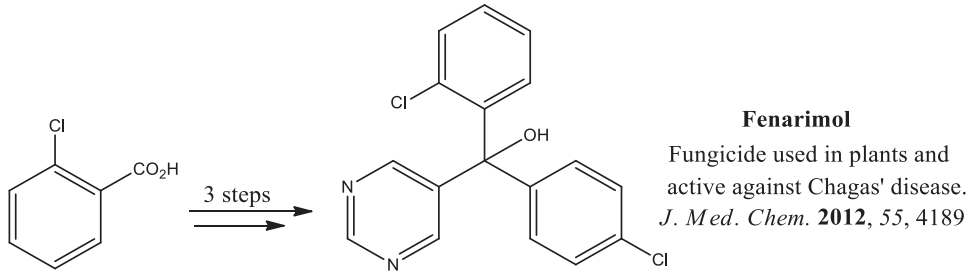
EXERCISES

1)



(**a**) nitromethane and base (NH_4OAc), 100ºC, 3h.; (**b**) Heck reaction with styrene; (**c**) Br_2, AcOH, rt.

2)



(**a**) 5-bromopyrimidine, *n*-BuLi, THF, -78°C; (**b**) thionyl chloride; (**c**) $AlCl_3$, PhCl.

CHAPTER 3

Identifying Drug Structure and Completing the Gaps

Abstract: In this chapter, the exercises below are also based on two themes. The first has an objective of the identification of the structure of the drugs having information of the starting materials and reagents used. This activity also enables the reader to become familiar with different classical chemical transformations used in medicinal chemistry and with varying types of reagents, reaction conditions, and necessary intermediates. In the second theme, the exercises are based on a series of gaps in the synthesis of different drugs. Therefore, it is up to the reader to complete them. This type of exercise is a combination of the themes previously presented. It is necessary to identify the reagents' use, the reaction conditions employed, and the intermediates formed, besides the use of the concept of retrosynthesis.

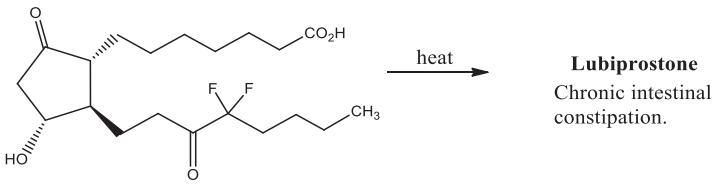
Keywords: Bioactive compounds, Chemical transformations, Drugs, Exercises, Medicinal chemistry, Molecules, Reaction conditions, Reagents, Retrosynthetic analysis, Substances, Synthesis, Synthons.

EXERCISE 7 - IDENTIFYING DRUG STRUCTURE

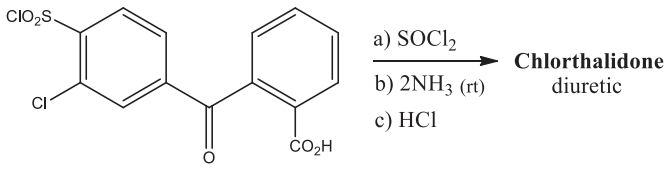
The exercises below have an objective of the identification of the structure of the drugs having information of the starting materials and reagents used.

Examples

a) What is the structure of the drug lubiprostone after heating the intermediate below?

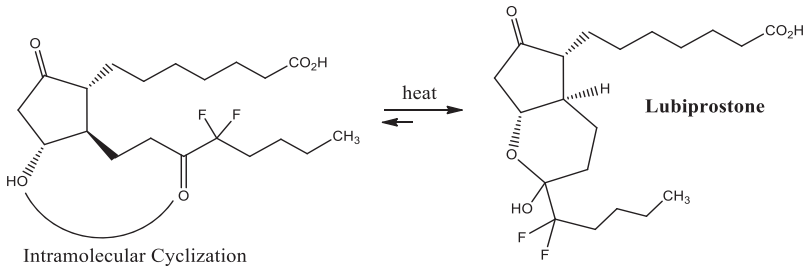


b) What is the structure of the drug below? Can step number two be performed with heating and excess ammonia? Justify.

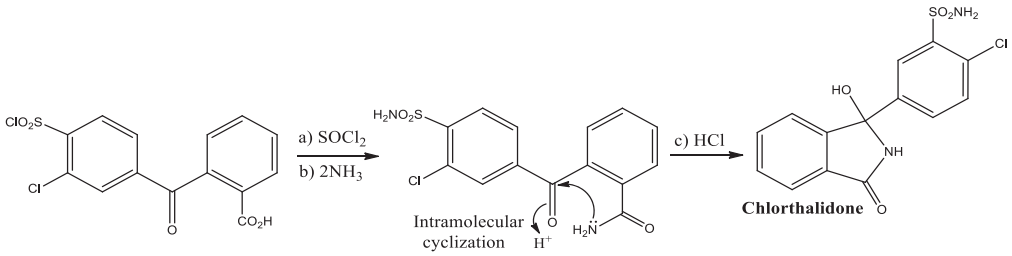


Answers

a) We can observe that an intramolecular cyclization occurs between the hydroxyl and the carbonyl, with the formation of a six-membered ring (hemiacetal - tautomerism chain-ring).



b) The first two steps are easy because they are classical and widely used transformations, thionyl chloride followed by ammonia, which is capable of converting the carboxylic acid and sulfonyl chloride into amide and sulfonamide, respectively. The third step requires a little more attention since an intramolecular cyclization occurs in an acid medium, with the formation of the indole nucleus. The reaction using ammonia can not be done with an excess of this reagent and heating, because an aromatic nucleophilic substitution reaction between the chlorine atom and the ammonia could occur.



EXERCISES

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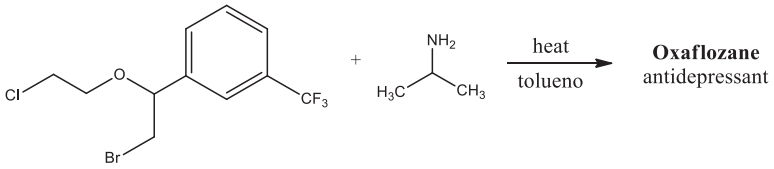

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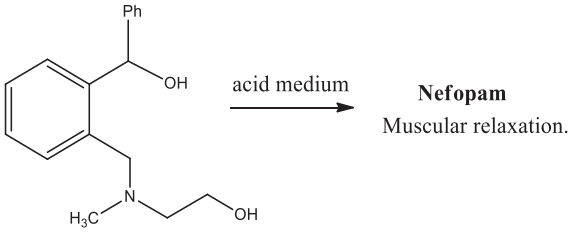

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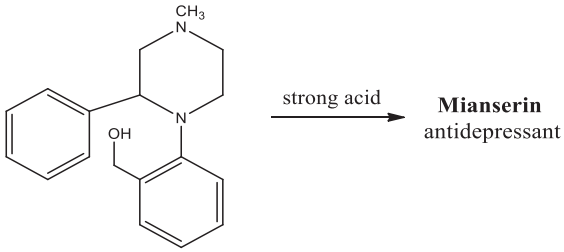


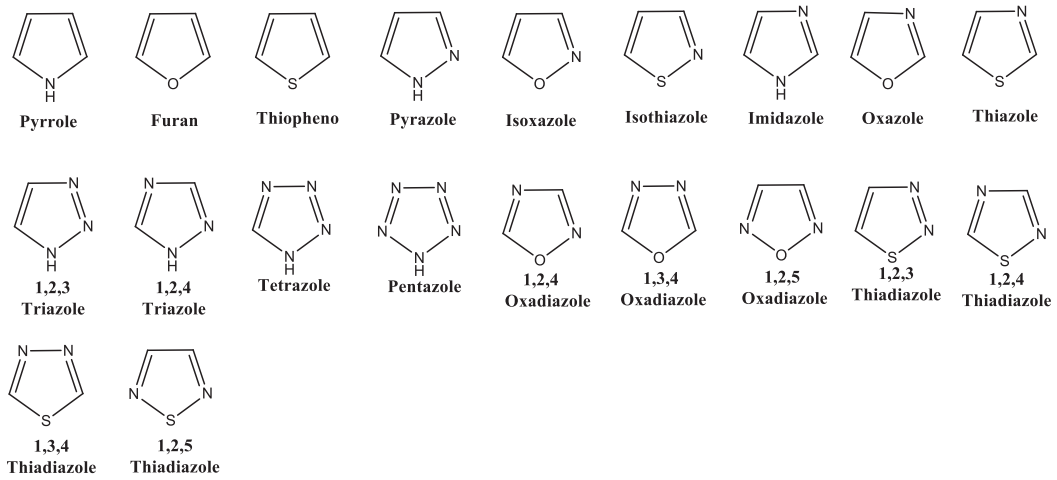
CHAPTER 4

Heteroaromatic Substances

Abstract: Heteroaromatics are substances having one or more atoms in the aromatic ring other than the carbon atom. This class of compounds is fundamental in developing new drugs, being present in a large number of drugs and bioactive compounds. Some of these cores are listed below, and it is worth noting that due to their immense structural variety, we mentioned only the most common ones. The exercises of this item we based on the formation of different heteroaromatic substances, and it is up to the reader to identify the respective nuclei.

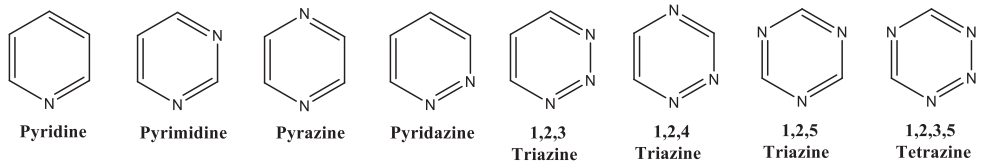
Keywords: Bioactive compounds, Chemical transformations, Drugs, Exercises, Heteroaromatic compounds, Medicinal chemistry, Molecules, Reaction conditions, Reagents, Synthesis, Retrosynthetic analysis, Substances, Synthons.

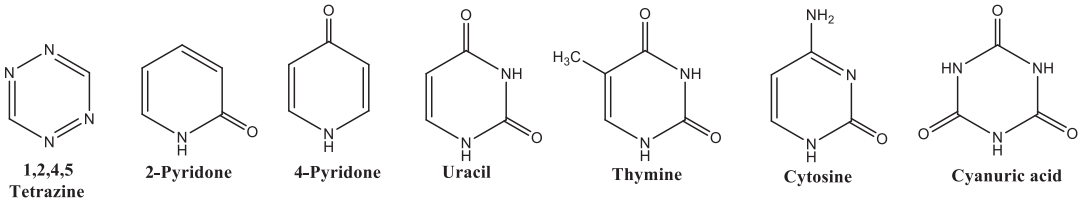
FIVE-MEMBERED RINGS



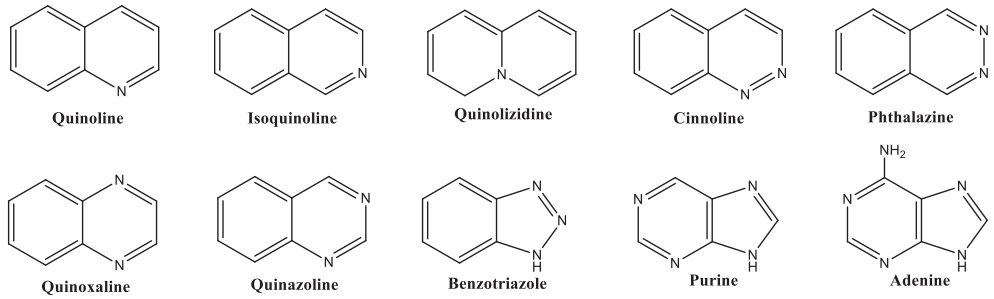
Marcus Vinícius Nora de Souza

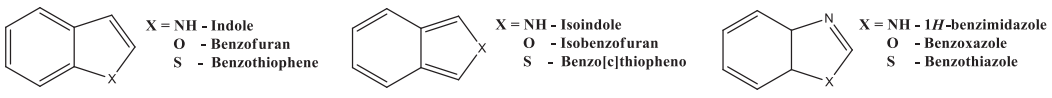
SIX-MEMBERED RINGS

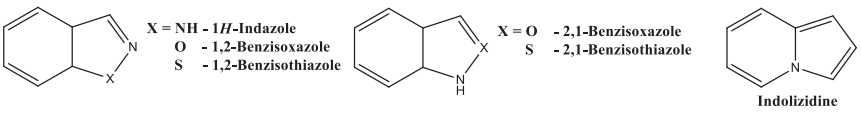


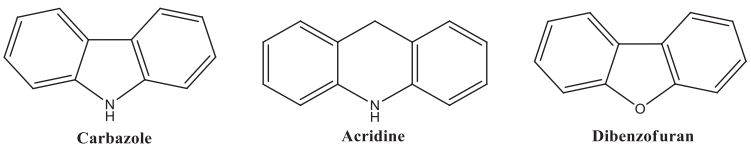


FUSED SYSTEMS



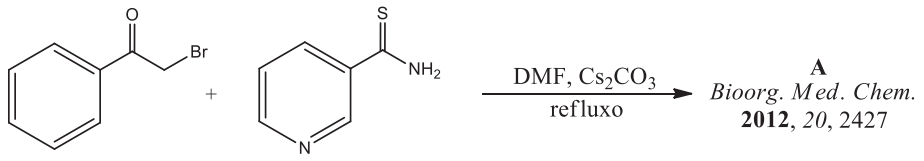






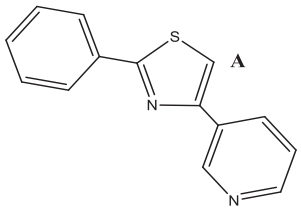
Example

The exercises below indicate the chemical structures of the nuclei formed.

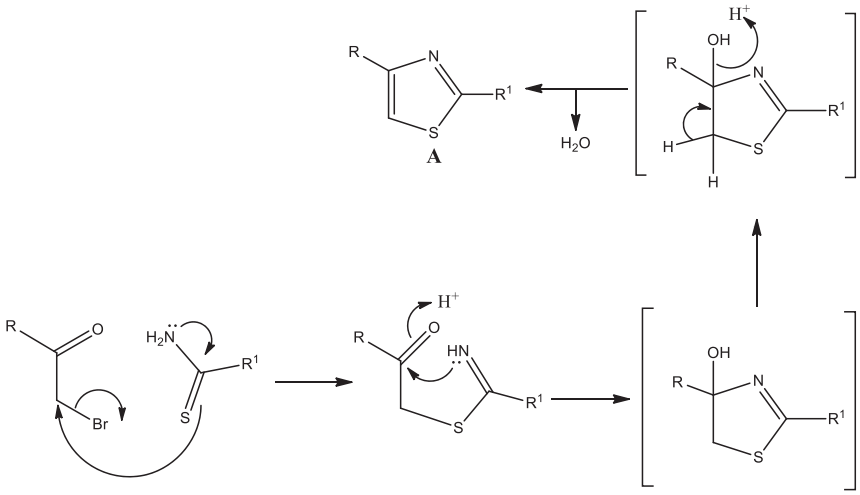


Answer

An important point concerning heteroaromatics is that despite their diversity, the mechanisms of their formation are somewhat similar, so it is fundamental to understand these mechanisms since the reader can easily propose the formation of a specific heteroaromatic nucleus. For example, in general, the structure of these nuclei is almost always related to an intramolecular cyclization reaction followed by the aromatization of the water loss system or an excellent leaving group. The formation of the thiazole nucleus **A** could have occurred according to the mechanism below.



MECHANISM OF REACTION



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CHAPTER 5

Hydrazine and its Derivatives

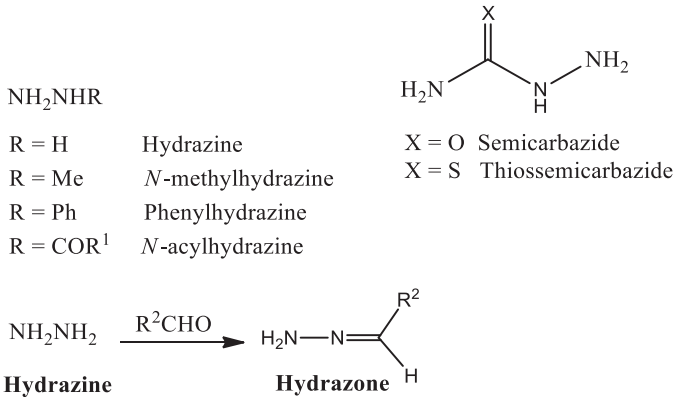
Abstract: The chemical hydrazine (NH_2NH_2) and its derivatives have several applications being also responsible for a large number of chemical transformations. This class has applications as rocket fuel and being present in the composition of explosives, in the control of corrosion, and the area of polymers. They also have full use in the development of bioactive substances being of great importance in medicinal chemistry. In the exercises of this chapter, we can synthesize several rings using hydrazine and its derivatives, and it is up to the readers to identify them.

Keywords: Bioactive compounds, Chemical transformations, Drugs, Exercises, Heteroaromatic compounds, Hydrazine, Medicinal chemistry, Molecules, Reaction conditions, Reagents, Retrosynthetic analysis, Substances, Synthesis, Synthons.

INTRODUCTION

The chemical hydrazine (NH_2NH_2) and its derivatives have several applications, being also responsible for a large number of chemical transformations. This class has applications as rocket fuel and being present in the composition of explosives, in the control of corrosion, and the area of polymers. They also have full use in the development of bioactive substances being of great importance in medicinal chemistry. Some examples of hydrazine derivatives such as, methylhydrazine, phenylhydrazine, *N*-acylhydrazide, semicarbazide, and thiosemicarbazide are listed below. It is noteworthy that the condensation of these substances above listed with aldehydes produces the respective hydrazones, methylhydrazones, phenylhydrazones, *N*-acylhydrazones, semicarbazones, and thiosemicarbazones (Scheme **1**).

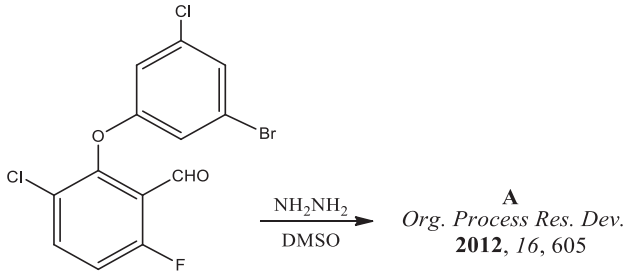
Marcus Vinícius Nora de Souza



Scheme 1. Hydrazine and its derivatives.

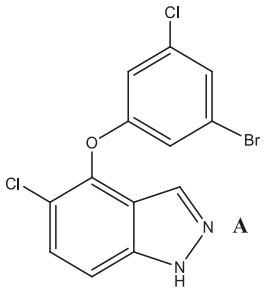
Example

After the reaction with the hydrazine (NH_2NH_2), what will be the target molecule formed?



Answer

The use of hydrazine was responsible for the formation of the indazole nucleus due to the position of the aldehyde chemical function (hydrazone formation) and the fluorine atom acting as a leaving group.

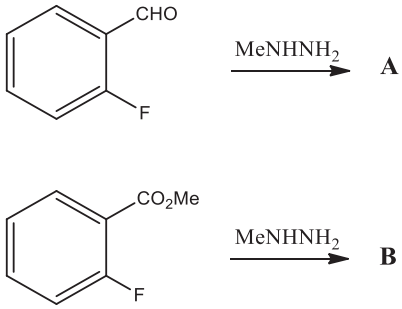


A

In the exercises below, we can synthesize several rings using hydrazine and its derivatives, and it is up to the reader to identify them.

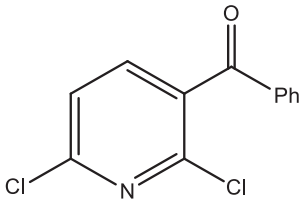
EXERCISES

1)



Org. Process Res. Dev.
2011, *15*, 565

2)



$H_2NNH_2.H_2O$
EtOH/THF

A
Bioorg. Med. Chem. Lett.
2019, *29*, 912

CHAPTER 6

Nitriles

Abstract: Nitrile is a chemical function found in several drugs in the market for different kinds of diseases and can be transformed into several other functional groups such as ketones, aldehydes, carboxylic acids, amines, amides, and other functional groups. The use of nitriles is also advantageous in forming heteroaromatic nuclei with important applications in medicinal chemistry. In this chapter, the exercises are based on the use of nitriles to form a different nucleus.

Keywords: Bioactive compounds, Chemical transformations, Drugs, Exercises, Heteroaromatic compounds, Hydrazine, Medicinal chemistry, Molecules, Nitriles, Reaction conditions, Reagents, Retrosynthetic analysis, Substances, Synthesis, Synthons.

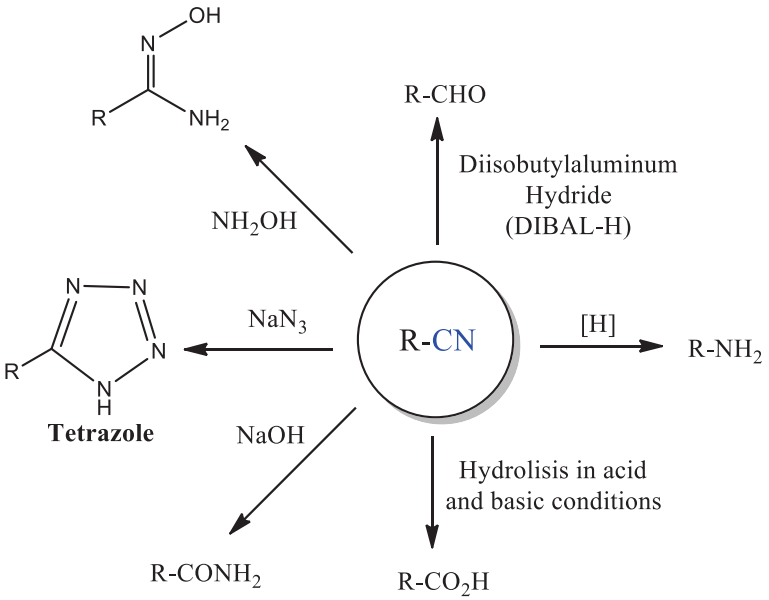
INTRODUCTION

Nitrile is a chemical function found in medicinal chemistry being able to be transformed in several other functional groups such as tetrazoles, ketones, aldehydes, carboxylic acids, amines, amides, different nucleus and other functional groups (Scheme **1**).

Nitrile is a chemical function found in several drugs in the market for different diseases (Fig. **1**).

Saxagliptin, an oral inhibitor class of dipeptidyl peptidase-4 (DPP-4), used against hypoglycemia. Anastrazole used to treat and prevent breast câncer. Escitalopram used against depression is a selective serotonin reuptake inhibitor. Etravirine is an anti-HIV antiviral being the first of a new class of non-nucleoside inhibitors of the reverse transcriptase (NNRTI), an essential enzyme of HIV. Milrinone is used to treat heart failure acting as a phosphodiesterase inhibitor, and Febuxostat is used to treat gout, working against high uric acid levels.

Marcus Vinícius Nora de Souza



Scheme 1. Chemical transformations of nitrile group.

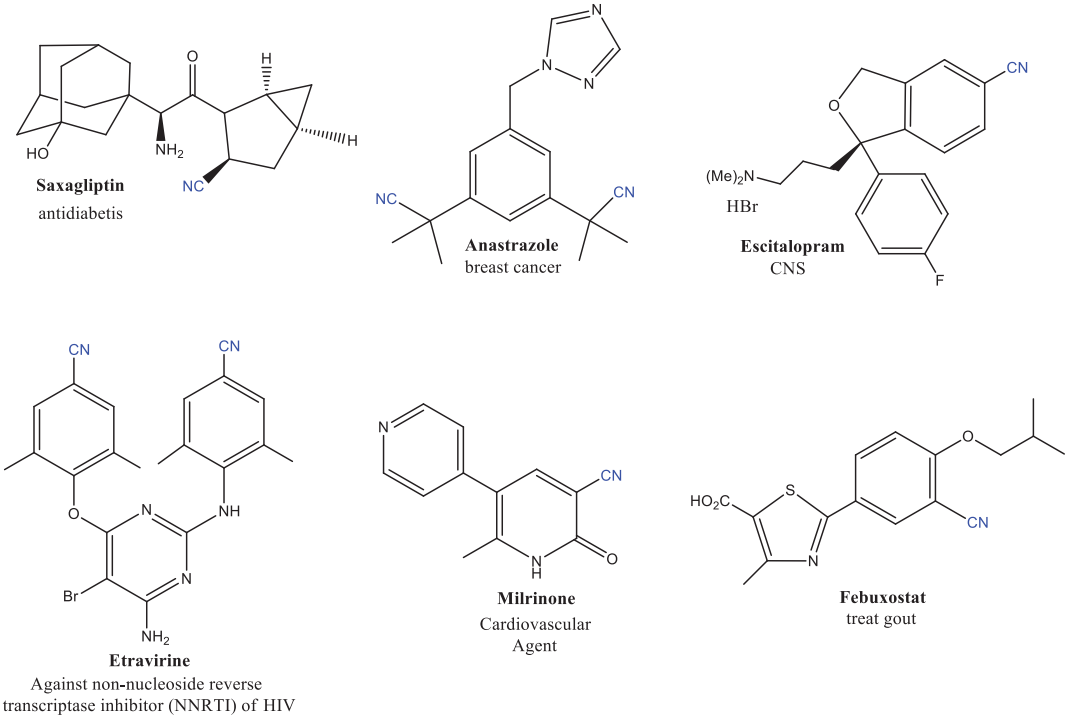
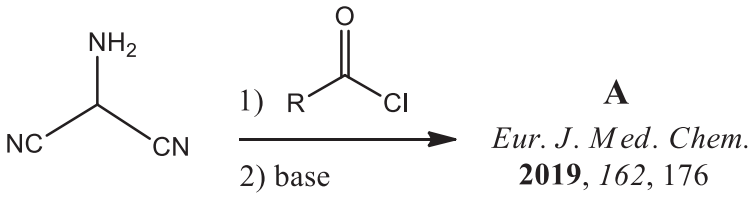


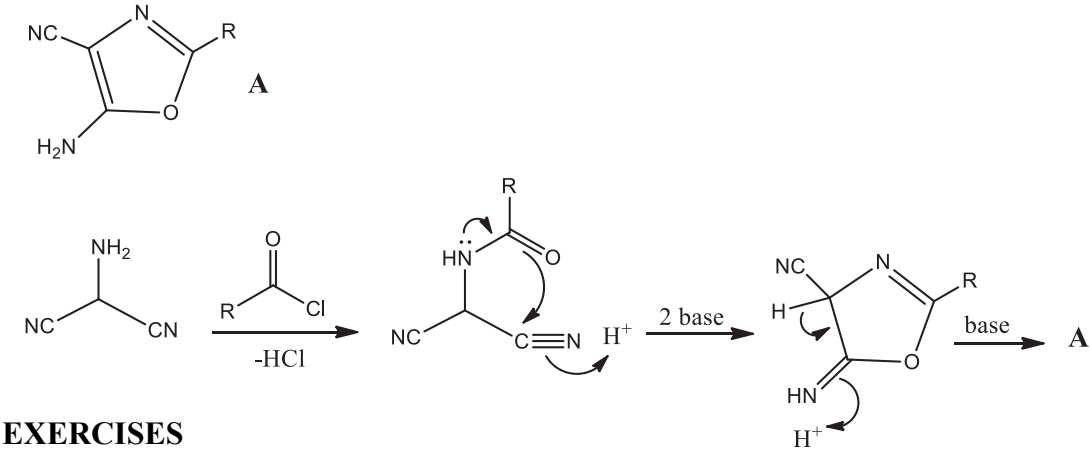
Fig. (1). Drugs containing a nitrile group into its structure.

Example

Which heteroaromatic nucleus is formed using malononitrile and an organic azide?



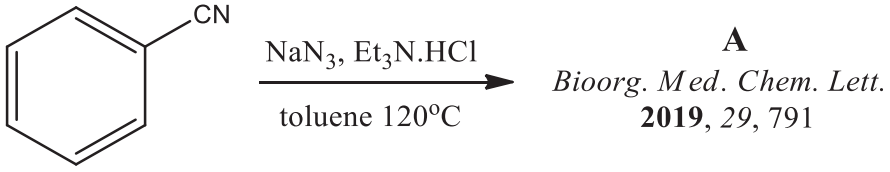
Answer



EXERCISES

Based on the use of nitriles, in the reactions below, the heteroaromatic nucleus formed has been identified.

1)



CHAPTER 7

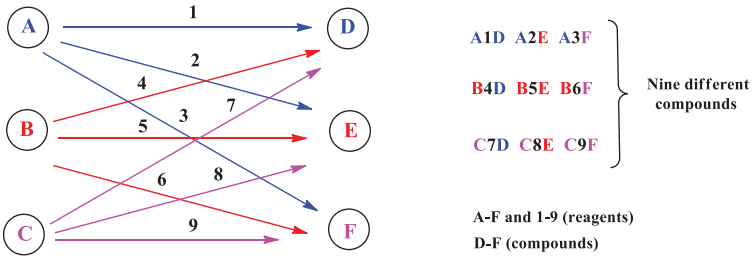
Combinatorial Chemistry

Abstract: Combinatorial chemistry is a methodology developed based on the synthesis of many compounds (hundreds, thousands, or even millions) in a simple chemical process building libraries of these compounds. In medicinal chemistry, an essential factor is the number of different molecules to be produced. For obtaining a leading compound and later a candidate drug, the biological evaluation of thousands of compounds is necessary. Therefore, the exercises below are based on combinatorial chemistry.

Keywords: Bioactive compounds, Combinatorial chemistry, Chemical transformations, Drugs, Exercises, Heteroaromatic compounds, Medicinal chemistry, Molecules, Reaction conditions, Reagents, Retrosynthetic analysis, Substances, Synthesis, Synthons.

INTRODUCTION

In medicinal chemistry, an essential factor is the number of different molecules to be produced. For obtaining a leading compound and later a candidate drug, the biological evaluation of thousands of compounds is necessary, previously provided by using organic syntheses. Combinatorial chemistry is a methodology developed with this purpose and based on the synthesis of a large number of compounds (hundreds, thousands or even millions) in a simple chemical process building libraries of compounds. Scheme **1** shows an example of the concept of combinatorial chemistry by using A-C and 1-9 as reagents using all these reagents together in a single reaction we produced at the same time nine different compounds.



Scheme 1. Example of combinatorial chemistry.

Marcus Vinícius Nora de Souza

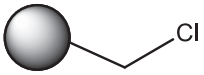
Combinatorial chemistry is a methodology developed in the 1960s by Professor Bruce Merrifield (1921-2006) (Scheme **2**). He studied solid-phase of peptides, which introduced the use of insoluble and chemically inert polymers (commonly referred to as resins) as carriers, which are covalently bound to the substrate, in this case, the peptides. The great advantage of solid support synthesis is the simplicity of the purification of the products obtained. The use of a simple filtration followed by successive washing of the solid support with different types of solvents is sufficient for the purification of the product obtained. After the discovery of Merrifield, other researchers developed resins to improve the synthesis in solid support, among which Wang resin is one of the most commonly used. Due to his important work, Merrifield was awarded the Nobel Prize in 1984. In the 1990s, combinatorial chemistry had a major impact on the pharmaceutical industry in the development of new drugs. However, combinatorial chemistry has some disadvantages, such as the production of a mixture of compounds, and it is difficult to isolate and identify the biologically active compound.

Robert Bruce Merrifield

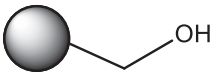
(1921 – 2006)

Nobel Prize 1984

Source of the picture: The nobel prize website
https://www.nobelprize.org/prizes/chemistry/1984/merrifield/biographical/

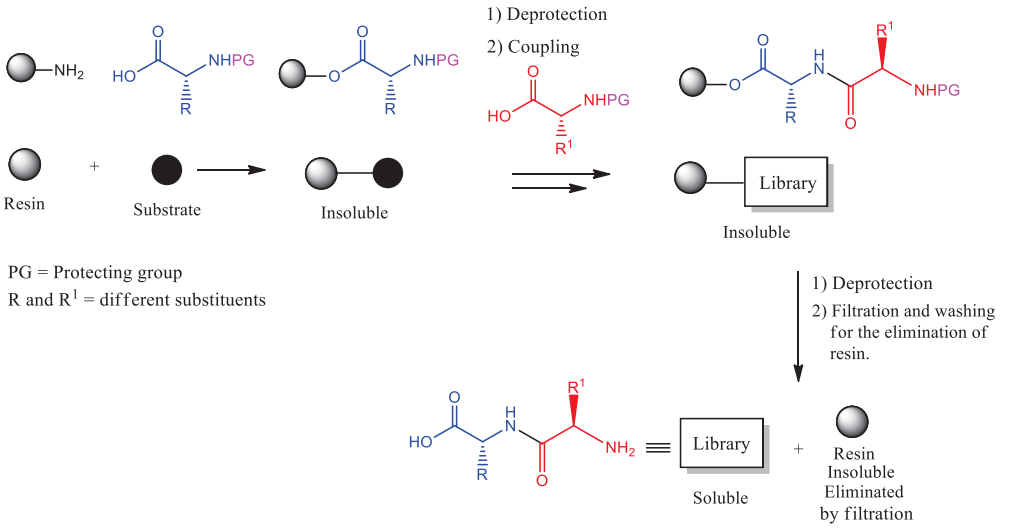


Resin de Merrifield



Resin de Wang

Due to the structural complexity this is usually the representation of the resin.

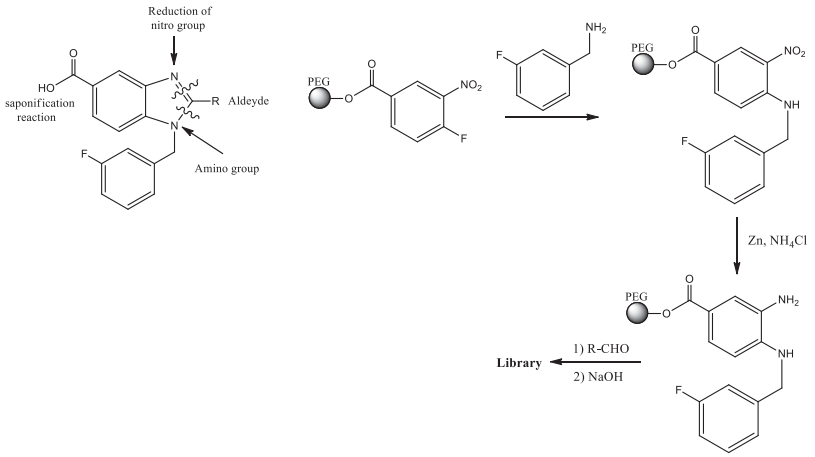


Scheme 2. Principle of solid support synthesis and resins commonly used in solid support synthesis.

Example

Using 4-fluoro-3-nitrobenzoic acid as start material, the product of this reaction was 4-fluoro-3-nitro-benzoate PEGester. The reagents used by the introduction of this resin were *N*,*N*′-dicyclohexylcarbodiimide (DCC) as the esterification agent and 4-dimethylaminopyridine (DMAP) as a catalyst. The 4-fluoro-3-nitro-benzoate PEGester is a key intermediate for the preparation of a library of 1,2,5-trisubstituted benzimidazole derivatives in some steps. What are these steps?

Answer



CHAPTER 8

Multicomponent Reaction (MCR)

Abstract: Multicomponent reaction (MCR) is a type of reaction based on a mixture of three or more compounds or reagents leading only to one or a major molecule being able to form complex molecules with a high degree of control of the stereogenic centers in only one step. This methodology is also a useful tool in medicinal chemistry to produce a diversity of compounds for biological evaluation. Due to its importance, the exercises below focus on this technique.

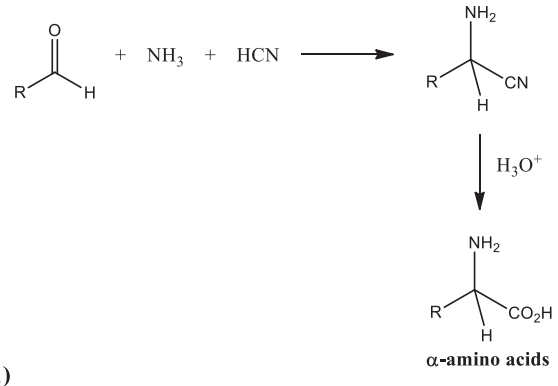
Keywords: Bioactive compounds, Chemical transformations, Combinatorial chemistry, Drugs, Exercises, Heteroaromatic compounds, Medicinal chemistry, Molecules, Multicomponent reaction (MCR), Reaction conditions, Reagents, Retrosynthetic analysis, Substances, Synthesis, Synthons.

INTRODUCTION

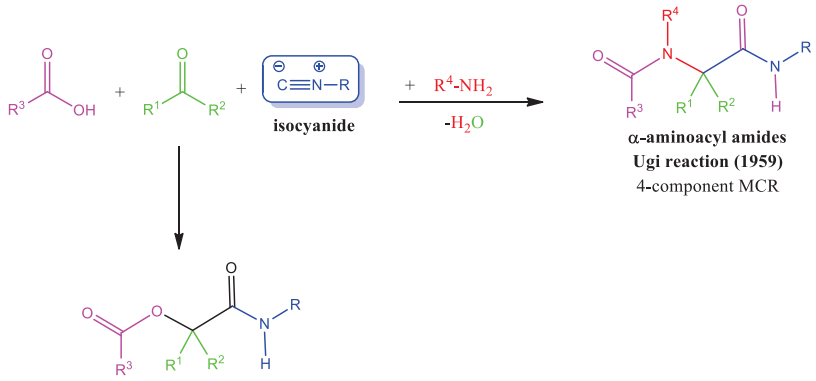
This methodology is a type of reaction based on a mixture of three or more compounds or reagents leading only to one or a major molecule being able to form complex molecules with a high degree of control of the stereogenic centers in only one step. The first reaction described in the literature based on the principles of the MCR was the Streck reaction. This reaction is the synthesis of α-amino acids by using aldehydes, HCN, and NH_3 as reagents described in 1850 by Adolph Strecker (1822-1871) (Scheme **1**). After Strecker´s work, other scientists developed other types of reactions, such as two reactions based on the utilization of the functional group isocyanide. The first one is the Passerini reaction (1921) (Scheme **2**), which is the synthesis of α-acyloxy carboxamides in a one-pot reaction [1]. The reagents of this reaction are aldehyde or ketone, carboxylic acid, and isocyanides in a 3-component MRC. The second is the Ugi reaction (1959) (Scheme **2**), producing α-aminoacyl amides by using primary amines, aldehydes, carboxylic acids, and isocyanides as starting materials in a 4-component MCR [2]. It is essential to mention that this synthesis and its variations are the most known and used MCRs. The proposed mechanisms of these reactions are shown in Schemes **3** and **4**.

Marcus Vinícius Nora de Souza

Adolph Strecker (1822 – 1871)



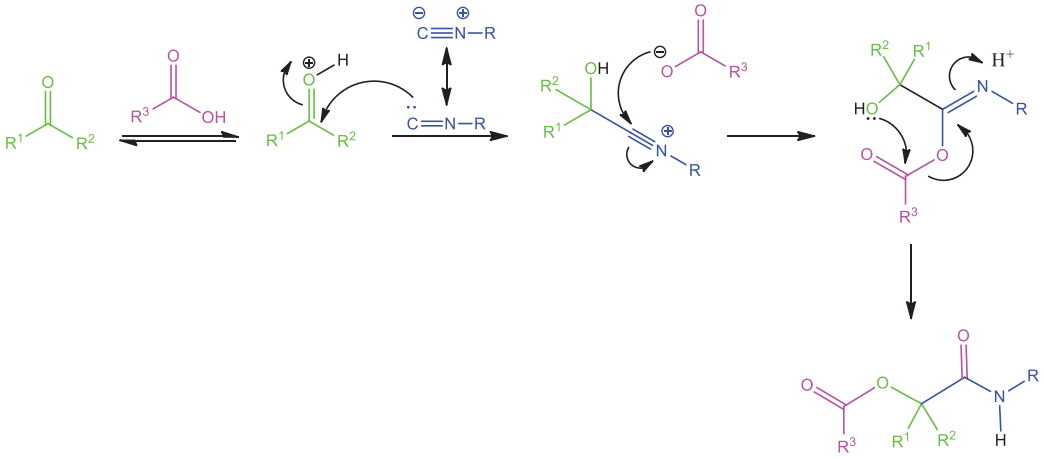
Scheme 1. Synthesis of α-amino acids by using aldehydes, HCN, and NH_3 as reagents, known as Strecker reaction.
Source of the picture: Pedersen, B. Physical Science in Oslo, Phys. Perspect., 2011, 13(2), 215-238.



Scheme 2. MCRs developed by Passerini and Ugi.

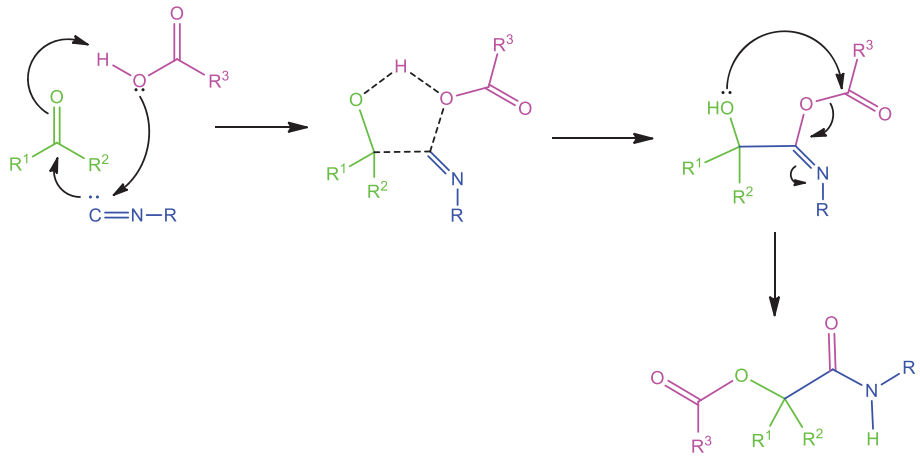
Passerini reaction

Ionic mechanism base on polar solvents such as water and methanol



Passerini reaction

Concerted mechanism base on non-polar solvents and high concentration.



Scheme 3. Mechanism of Passerini reaction.

CHAPTER 9

Click Chemistry

Abstract: The most famous reaction, based on the click chemistry concept, is to obtain 1,2,3-triazoles, employing the 1,3-dipolar cycloaddition reaction between azides and alkynes. This reaction raised intense interest in academics and industrialists and was discovered independently by Sharpless and the Danish Morten Meldal in the year 2002. They demonstrated that the addition of copper as a catalyst has several advantages, such as an increase in the speed of the reaction, regioselectivity, high yields, and reactions are easy to elaborate. Due to its importance in drug discovery, the exercises below are based on this concept.

Keywords: 1,2,3-triazoles, Alkynes, Azides, Bioactive compounds, Catalyst, Chemical transformations, Click chemistry, Combinatorial chemistry, Copper, Drugs, Exercises, Heteroaromatic compounds, Medicinal chemistry, Molecules, Reaction conditions, Reagents, Retrosynthetic analysis, Substances, Synthesis, Synthons, 1,3-dipolar cycloaddition.

INTRODUCTION

The "click chemistry" is a concept proposed the same year that researcher Karl Barry Sharpless won the Nobel Prize in chemistry, *i.e.*, in 2001. This concept resembles the way that mother nature synthesizes its substances, bringing together, in a fast and effective way, small molecules. It is also related to the principles of green chemistry and combinatorial chemistry to have libraries of substances using efficient and straightforward procedures. These procedures should have the following characteristics: reduced numbers of steps, simplicity, the non-use of solvents or water, the non-generation of non-toxic waste or residues, and the use of inexpensive and abundant starting materials. Sharpless, which described the principles and concepts of click chemistry for the first time in one of his articles, enumerated several reactions that follow these principles and concepts. These reactions are Diels-Alder, epoxides, and aziridines opening, dihydroxylation, Michael addition, the formation of heteroaromatic nuclei, hydrazones, amides, ethers, oximes, ureas, and thioureas (Fig. **1**) [1].

However, the most famous reaction, based on the click chemistry concept, is to obtain 1,2,3-triazoles employing the 1,3-dipolar cycloaddition reaction between

Marcus Vinícius Nora de Souza

azides and alkynes (Scheme **1**). This reaction raised intense interest in both academics and industrialists and was discovered independently by Sharpless and the Danish Morten Meldal in 2002. They demonstrated that the addition of copper as a catalyst has several advantages, such as an increase in the speed of the reaction, regioselectivity, high yields, and reactions are easy to elaborate. The catalytic cycle of this reaction is represented in Scheme **2**. If the reader is interested in the topic, below are some suggestions for reading [2 - 7].

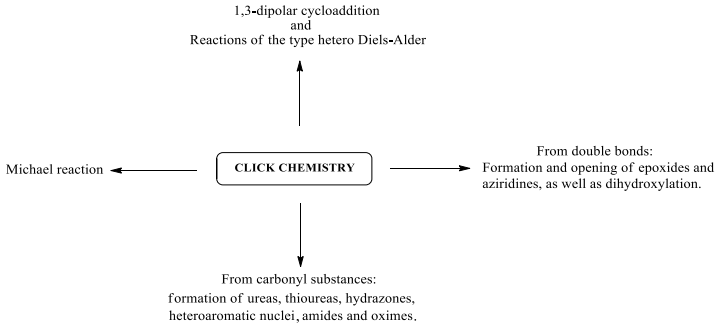
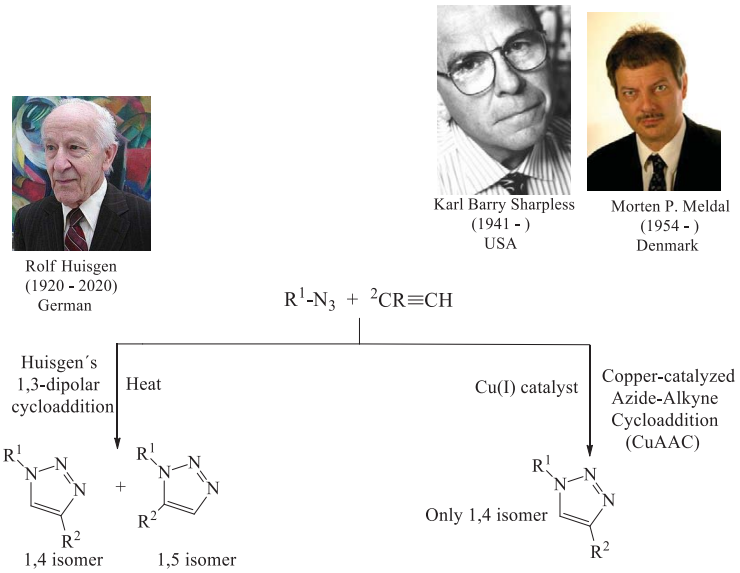
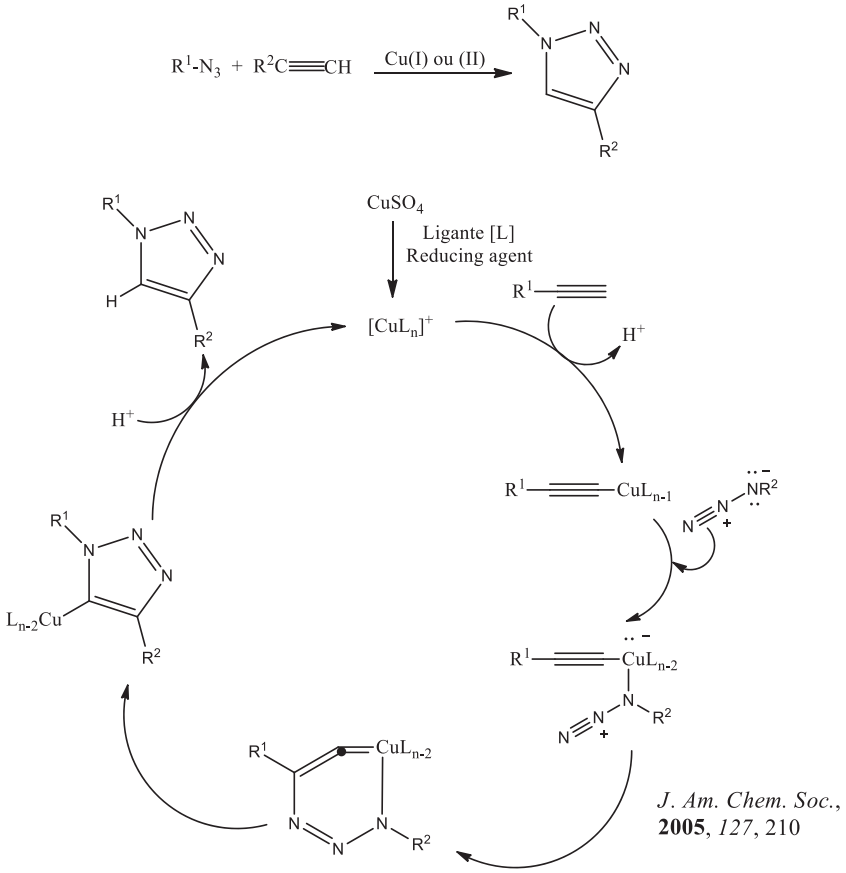


Fig. (1). Reactions related to the concept of click chemistry.



Scheme 1. 1,2,3-triazole formation by Huisgen's reaction and by regioselective copper-catalyzed azide-alkyne cycloadditions (CuAAC).
Source of the picture: Wikipedia
https://en.wikipedia.org/wiki/Rolf_Huisgen
Source of the picture: The Nobel Prize website.
https://www.nobelprize.org/prizes/chemistry/2001/sharpless/biographical/
Source of the picture: University of Copenhagen website.
https://synbio.ku.dk/about/management/ulrik_gether_copy/



Scheme 2. Catalytic cycle of 1,3-dipolar cycloaddition reaction between azides and alkynes to form 1,2,3 triazoles.

Example

a) Based on the two substances below, benzyl 2,6-difluorobromide and propionic acid, how would the reader synthesize the antiepileptic rufinamide using the "click chemistry" reaction?

CHAPTER 10

Fluorine in Drug Discovery

Abstract: Fluorine chemistry is an important area that made a significant impact on drug discovery development, which can be seen by a large number of drugs in the market containing this chemical element. The success of drugs containing fluorine atoms in its structures is due to its chemical properties compared to the other elements, providing several advantages in drug discovery. Some of these advantages are better metabolic stability, avoiding undesired metabolizations, and improving the bioavailability of the drugs, among others. Due to its importance in drug discovery, the exercises below are focused on fluorine chemistry.

Keywords: Bioactive compounds, Catalyst, Chemical transformations, Combinatorial chemistry, Drugs, Exercises, Fluorine, Heteroaromatic compounds, Medicinal chemistry, Molecules, Reaction conditions, Reagents, Retrosynthetic analysis, Substances, Synthesis, Synthons.

INTRODUCTION

Fluorine chemistry is an important area that made a significant impact on drug discovery development, which can be seen by a large number of drugs in the market containing this chemical element (Fig. **1**) [1, 2].

The success of drugs that contain fluorine atoms in its structures and also in other areas, such as materials, agrochemicals, and radiotracers for positron emission tomography (PET), is due to its chemical proprieties compared to the other elements (Table **1**) [3]. The C-F bond (105 Kcal/mol) is stronger than the C-H bond (98 Kcal/mol), providing several advantages on drug discovery. Some of these advantages are better metabolic stability, avoiding undesired metabolizations, and improving the bioavailability of the drugs. The size of the fluorine atom (van der Waals radius 1.47 Å) is close to oxygen (1.52 Å) and hydrogen (1.2 Å) being able to mimic the last one in medicinal chemistry [3]. A fluorine atom is the most electronegative element (4 Pauling units) of the periodic table. Its presence in a molecule provides the ability to modify a series of parameters. Some of these parameters are conformational changes, variations of pKa, formation of hydrogen bonds, and the increase and decrease in lipophilicity.

Marcus Vinícius Nora de Souza

These characteristics can change both the pharmacodynamics and pharmacokinetic parameters of a bioactive compound (Scheme **1**) [4].

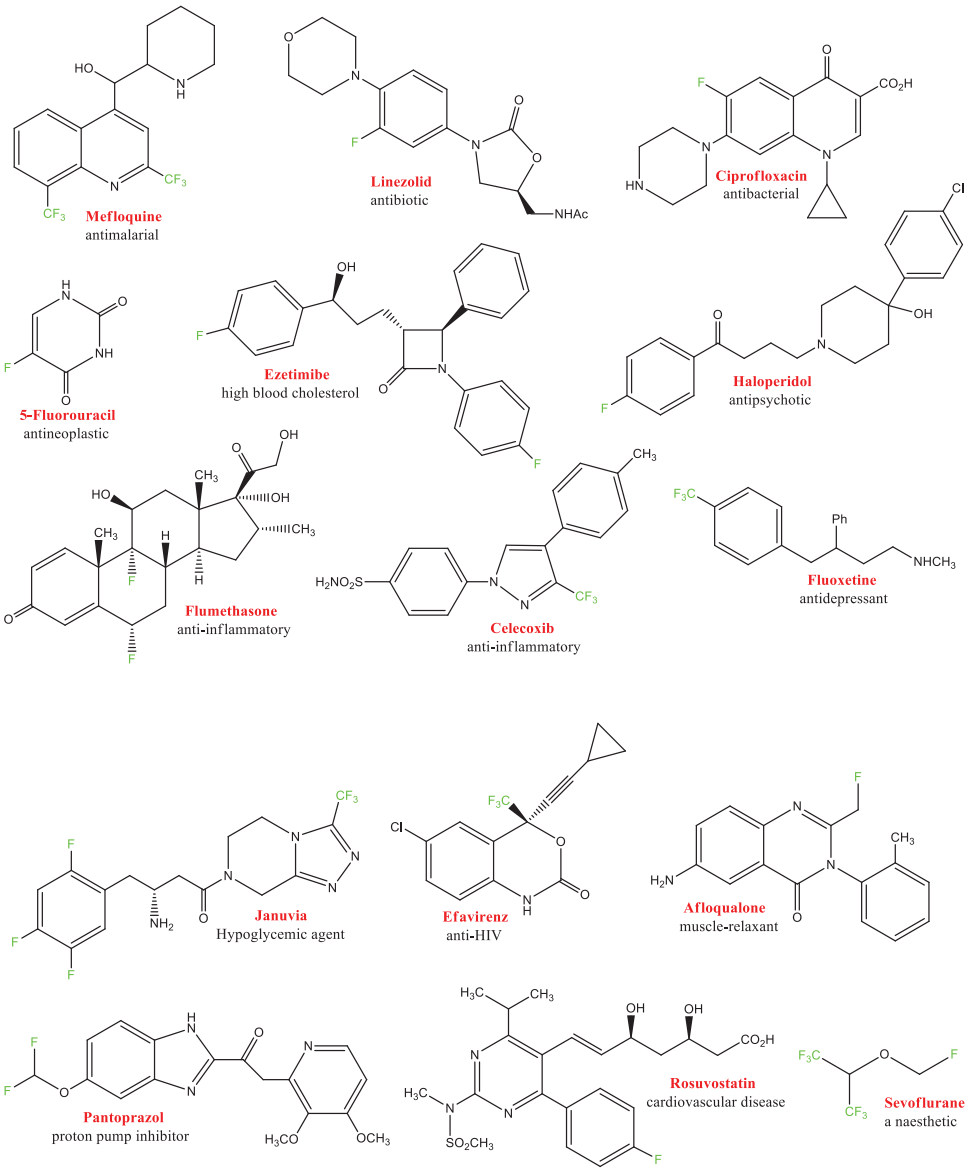
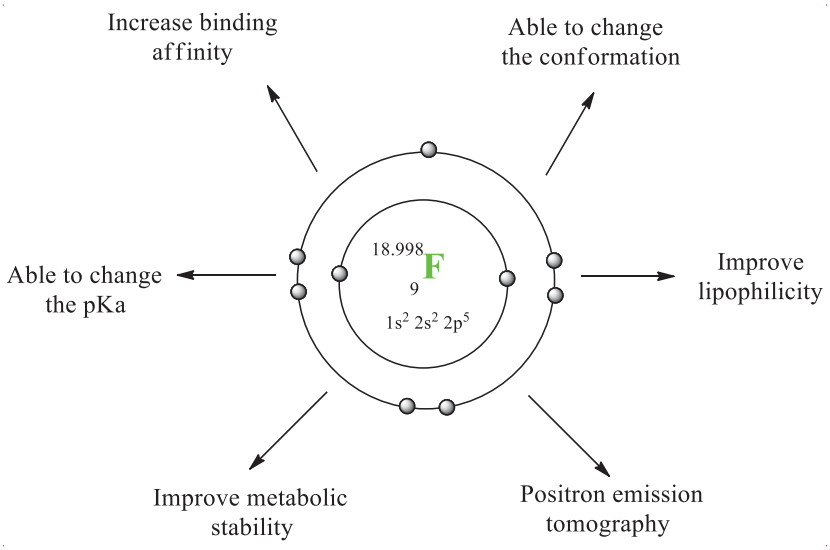


Fig. (1). Drugs that contain fluorine atoms in its structures.

Table 1. Comparison of the fluorine atom with other atoms.

	H	C	N	O	F	Cl
Bond strength to C (Kcal/mol)	**98**	**83**	**70**	**84**	**105**	**77**
Bond length to C (Å)	**1.09**	**1.53**	**1.47**	**1.43**	**1.39**	**1.76**
Van der Waals radius (Å)	**1.2**	**1.7**	**1.55**	**1.52**	**1.47**	**1.75**
Electronegativity (Pauling units)	**2.1**	**2.5**	**3**	**3.5**	**4**	**3**



Scheme 1. The versatility of the fluorine atom in medicinal chemistry.

FLUORINATION REAGENTS

Due to the importance of fluorine atoms in organic molecules, different reagents have been developed. The classification of these reagents is based on nucleophilic and electrophilic fluorination, which are for the introduction of fluorine atom (-F), difluoromethyl (-CF_2H), and trifluoromethyl (-CF_3) group. Below are the most commonly used reagents for fluorination.

Nucleophilic Fluorination for the Introduction of Fluorine Atom NaF, KF, HF, and Bu_4NF

For fluorination, using fluoride ion (F-) as a nucleophile, the commonly used reagents are sodium fluoride (NaF), potassium fluoride (KF), hydrogen fluoride

LIST OF JOURNALS USED AND THEIR RESPECTIVE ABBREVIATIONS

Acta Chemica Scandinavica (Acta Chem. Scand.)
Angewandte Chemie, International Edition in English (Angew. Chem. Int. Ed.)
Archiv der Pharmazie (Arch. Pharm.)
Arkivoc (Arkivoc)
Beilstein Journal of Organic Chemistry (Beilstein J. Org. Chem.)
Bioorganic & Medicinal Chemistry (Bioorg. Med. Chem.)
Bioorganic & Medicinal Chemistry Letters (Bioorg. Med. Chem. Lett.)
Bioscience, Biotechnology, and Biochemistry (Biosci. Biotechnol. Biochem.)
Biotechnology and Food Science (Biotechnol. Food. Sci.)
British Journal of Pharmacology (Br. J. Pharmacol.)
Bulletin of the Chemical Society of Japan (Bull. Chem. Soc. Jpn.)
Bulletin of the Korean Chemical Society (Bull. Korean Chem. Soc.)
Catalysis Letters (Catal. Lett.)
Chemical Biology & Drug Design (Chem. Biol. Drug Des.)
Chemical and Pharmaceutical Bulletin (Chem. Pharm. Bull.)
Chemical Communications (Chem. Commun.)
Chemical Research in Toxicology (Chem. Res. Toxicol.)
Chemical Society Reviews (Chem. Soc. Rev.)
Chemistry: A European Journal (Chem. Eur. J.)
Chemistry Letters (Chem. Lett.)
Chinese Chemical Letters (Chin. Chem. Lett.)
Current Topics in Medicinal Chemistry (Curr. Top. Med. Chem.)
Drug Metabolism and Disposition (Drug Metab. Dispos.)
European Journal of Chemistry (Eur. J. Chem.)
European Journal of Medicinal Chemistry (Eur. J. Med. Chem.)
European Journal of Organic Chemistry (Eur. J. Org. Chem.)
Green Chemistry Letters and Reviews (Green Chem. Lett. Rev.)
Helvetica Chimica Acta (Helv. Chim. Acta.)
Heterocycle Communications (Heterocycl. Commun.)
Journal of Agricultural and Food Chemistry (J. Agric. Food Chem.)
Journal of American Chemical Society (J. Am. Chem. Soc.)
The Journal of Antibiotics (J. Antibiot.)
Journal of Antimicrobial and Chemotherapy (J. Antimicrob. Chemother.)
Journal of Carbohydrate Chemistry (J. Carbohydr. Chem.)
Journal of Cell Biology (J. Cell. Biol.)
Journal of Chemical Society, Chemical Communication (J. Chem. Soc., Chem. Commun.)
Journal of Enzyme Inhibition and Medicinal Chemistry (J. Enzyme Inhib. Med. Chem.)
Journal of Heterocyclic Chemistry (J. Heterocycl. Chem.)
Journal of Medicinal Chemistry (J. Med. Chem.)

Journal of Nuclear Medicine (J. Nucl. Med.)
Journal of Organic Chemistry (J. Org. Chem.)
Molecular Pharmacology (Mol. Pharmacol.)
Molecules (não possui abreviação)
Organic & Biomolecular Chemistry (Org. Biol. Chem.)
Organic Communications (Org. Commun.)
Organic Letters (Org. Lett.)
Organic Process Research & Developmen (Org. Process Res. Dev.)
Pharmaceutical Research (Pharmaceut. Res.)
Química Nova (Quim. Nova)
RSC Advances (RSC Adv.)
Russian Chemical Reviews (Russ. Chem. Rev.)
Synlett (não possui abreviação)
Synthesis (não possui abreviação)
Synthetic Communications (Synth. Commun.)
Tetrahedron (não possui abreviação)
Tetrahedron: Asymmetry (Tetrahedron: Asymm.)
Tetrahedron Letters (Tetrahedron Lett.)

LIST OF ABBREVIATIONS

Ac	Acetyl
AD-mix-α	It is a commercially available mixture of the reagents used in the asymmetric dihydroxylation of Sharpless = $K_2OsO_2(OH)_4$ (cat.); K_2CO_3; $K_3Fe(CN)_6$ and (DHQ) 2-PHAL (cat.) = Substance containing two moles of hydroquinine and one mole of phthalazine
AD-mix-β	It is a commercially available mixture of the reagents used in the asymmetric dihydroxylation of Sharpless = $K_2OsO_2(OH)_4$ (cat.); K_2CO_3; $K_3Fe(CN)_6$ and (DHQ) 2-PHAL (cat.) = Substance containing two moles of hydroquinine and one mole of phthalazine
AIBN	Azobisisobutyronitrile
DNA	Deoxyribonucleic acid
LA	Lewis acid
PTSA	*Para*-toluenesulfonic acid
aq.	Aqueous
heat.	Heating
Ar	Aromatic substance
RNA	Ribonucleic acid
TFA	Trifluoroacetic acid
AZT	3'-azido-2 ', 3'-dideoxythymidine
BAIB	Bis(acetoxy)iodobenzene
Bn	Benzyl
Boc	Tert-butoxycarbonyl
Boc_2O	Di-*tert*-butyl dicarbonate
Bu	Butyl
Bz	Benzoyl
C	Catalyst
Cap.	Chapter
cat.	Catalytic
Cbz	Benzyloxycarbonyl
CDI	1,1'-carbonyldiimidazole
MIC	Minimal Inhibitory Concentration
1,5-COD	1,5-cyclooctadiene
conc.	Concentrate
CSA	Camphorsulfonic acid

Cy	Cicloexyl
d	Day or days
DABCO	1,4-diazabicyclo [2.2.2] octane
dba	Dibenzylideneacetone
DBU	1,8-diazabicyclo [5.4.0] undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DCU	*N, N'*-dicyclohexylurea
DDQ	Dicyodichloro-*p*-benzoquinone
DEAD	Diethyl azodicarboxylate
DET	Diethyl tartrate
DMG	Direct metalation group
DHP	Dihydropyran
$(DHQ)_2$ and $(DHQD)_2PHAL$	Substance containing two moles of hydroquinine and one mole of phthalazine.
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DiPAMP	(1*S*, 2*S*)-(+)-Bisethane [(2-methoxyphenyl) phenylphosphine]
DIPEA, DIEA or Hunig's Base	*N, N*-diisopropylethylamine
DIPT	Diisopropyl tartrate
DMA-DMF	*N,N*-dimethylformamide dimethylacetal
DMAP ou 4-DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin Periodinane
2,2-DMP	2,2-dimethoxypropane
DMSO	Dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
E^+	Electrophile
EDC	1-ethyl-3-(3-dimethylaminopropylcarbodiimide)
EE	Ethoxyethyl
eq.	Equivalent
Et	Ethyl
FDA	Food and Drug Administration

Fmoc	9-Fluorenylmethoxycarbonyl
PG	Protective group
h	Hour ou hours
HATU	2-(1-*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
hν	Light
HOBt	Hydroxybenzotriazole
HIV	Human immunodeficiency virus
***i*-Pr**	Isopropyl
IBX	2-iodoxybenzoic acid
L	Ligant
LDA	*N, N*-diisopropylamide
LDL	Low-density lipoprotein
L-DOPA	L-3,4-dihydroxyphenylalanine
LHA	Lithium aluminum hydride
LHMDS	Lithium hexamethyldisilylamide
***m*-CPBA**	*Meta*-chloroperbenzoic acid
MCR	Multicomponente reaction
MEM	2-Methoxyethoxymethyl ether
MO	Microwave
MOM	Methoxymethyl ether
MTM	Methylthiomethyl ether
Ms	Methanesulfonyl (mesylate)
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
nm	nanometer
NMP	*N*-methylpyrrolidone
NMO	*N*-methylmorpholine-*N*-oxide
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
Nu	Nucleophile
(O); [O] ou Oxi.	Oxidation
PMB	*Para*-methoxybenzyl
PCC	Pyridinium Chlorochromate

PCy	Cyclohexylphosphine
PDC	Pyridinium dichromate
pg.	Page
Ph	Phenyl
Py	Pyridine
Piv	Pivaloyl
PMHS	Polymethylhydrosiloxane
PPA	Polyphosphoric acid
Pr	Propyl
R^n (n = 0, 1, 2, 3...)	Different substituents
Red-Al	Bis(2-methoxyethoxy)aluminum
RSA	Relationship Structure Activity
rt	Room temperature
NMR	Nuclear magnetic resonance
SEM	β-(trimethylsilyl)ethoxymethyl ether
S_N2	Bimolecular nucleophilic substitution
S_Ni	Substitution Nucleophilic internal
SPhos	2-dicyclohexylphosphino-2,6-dimethoxybiphenyl
TBAI	Tetrabutylammonium iodide
TBDPS	*Terc*-butyldiphenylsilyl
TBAF	Tetrabutylammonium fluoride
TBHP	*Tert*-butyl hydroperoxide
TBS ou TBDMS	*Tert*-butyldimethylsilyl
TEA	Triethylamine
TEMPO	2,2,6,6-tetramethyl-piperidin-1-yl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonate, triflate
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Tr	Trityl
Ts	Tosyl

US ou)))	Ultrasound
X	Halogen or a good leaving group
Xantphos	Bis (diphenylphosphino) -9,9-dimethylxanthene
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbipheny

SUBJECT INDEX

A

B

C

D

E

F

G

H

I

L

M

N

O

P

Q

R

S

T

U

V

W

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