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MINISTRY OF HIGHER EDUCATION AND SCIENTIFIC RESEARCH
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DEPARTEMENT OF CHEMISTRY

Speciality : Organic Chemistry

Topic:

Polycyclic compounds by Multicomponent Reactions A mini review

Thesis submitted for the award of Master's degree

Presented by: **Ms Meriem Houche**

Defended on in front of the jury:

President:	N. Bouider	M.C.B.	MSBY University, Jijel
Supervisor:	N. Merabet-Bouraoui	Pr.	MSBY University, Jijel
Examiner:	H. Bounar	M.C. B	MSBY University, Jijel

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DEDICATION

For their diligence in providing the appropriate conditions besides everything I need, for their encouragement during my course of study,

*For all their sacrifices, I dedicate this dissertation to my father "**HOUCHE ABED EL HAFID**" and my mother "**NEGHIZ NABILA**".*

Thank you for everything.

List of Abbreviations

AFIR	artificial force-induced reaction
AIBN	azobisisobutyronitrile
°C	degree Celsius
CONC	concentrated
DFT	density Functional Theory
DHP	dihydropyridin
DHPM	dihydropyrimidinone
DMF	dimethylformamide
GGA	generalized gradient approximation
h	hour(s)
HF	hartree fock
LDA	local density approximation
MCR	multicomponent reaction
MM	molecular modeling
MTSA	melamine trisulfonic acid
PA-Sc-TAD	polyallylscandium trifylamide ditriflate
PEG	polyethylene glycol
PG	Protecting group
QUIN	Quinoline
TFA	trifluroacetic acid
THF	tetrahydrofurane
THQ	tetrahydroquinoline

TMSCl	trimethylsilyl chloride
TS	transition state
3D	3 dimensions

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General Introduction

Introduction

Cascade (domino) reactions provide an efficient way to construct complex structures; most interesting are drugs, from available organic compounds [1]. The complexity of bioactive drugs is meanly due to the presence of polycyclic moieties in their structure.

The first purpose of the present work is to review the cascade reactions with a focus on multicomponent reactions (MCRs) leading to cyclic moieties (bicyclic, tricyclic and polycyclic) and by the way to complex structures, as they are a subgroup of cascade reactions [2]. This is developed in Chapter I and Chapter II, where the most important MCRs, Hantzsch; Biginelli, Passerini, Pavarov…are presented.

The second purpose is to explore the contribution of computational methods in the comprehension of the aspects of MCRs, especially their mechanisms. Chapter III is devoted to reviewing the application; in organic synthesis; of Molecular modelling (MM), which is a collection of computer-based techniques involving theoretical calculation methods (DFT, AFIR…) to cover several issues of organic reaction. Passerini reaction and Biginelli reaction are discussed.

Chapter I:
MCRs, a bibliographic review

I. Introduction

The synthesis and the design of bioactive compounds such as drugs, natural products and analogs was very challenging to modern chemistry, as they are complex molecules, their synthesis requires a long and multistep process which increase the consumption of resources and the amount of waste formed.

As a solution, the chemists found a green and efficient process that access the necessary complexity and diversity in one pot transformation starting from simple substrates, this process was described by different names: “cascade, domino , tandem ,zip or multicomponent reaction». In fact these processes are slightly, different from each other [2].

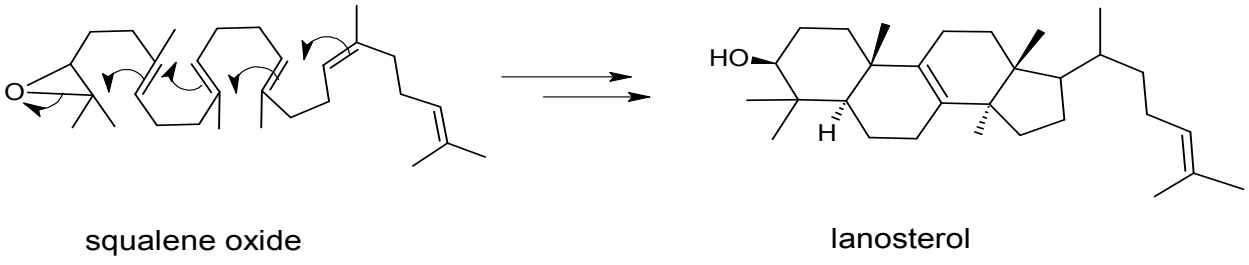
The main purpose of this study is to focus on MCRs that lead to cyclic (bicyclic, tricyclic and polycyclic) complex molecules possessing pharmaceutical properties.

II. Cascade reaction or Multicomponent reaction?

The words tandem, domino, cascade…, sometimes communicate ambiguities, although they are used as synonyms., Tandem means "one after another" Cascade means that each subsequent stage happens under structural change provided by the previous step under the same reaction conditions [3]. As for domino, the name has been taken from the famous game [4].

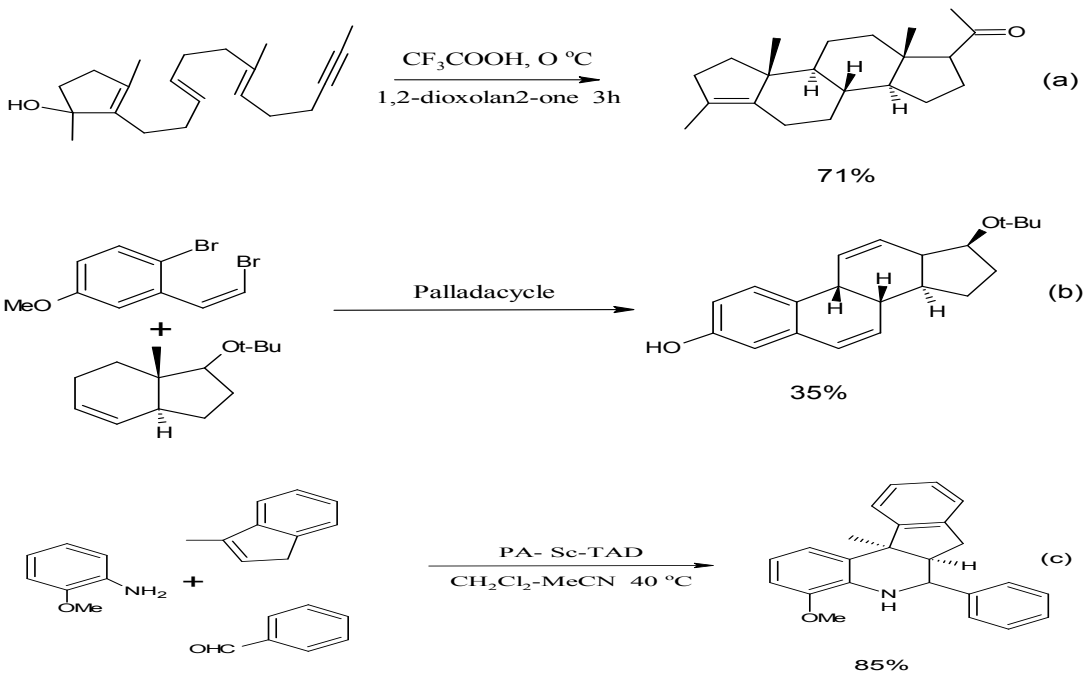
In 1996, Tietze defined the domino reaction as following: a domino reaction is a process involving two or more bond-forming transformations (usually C-C bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step [4].

Cascade reactions are very common in nature, especially in enzymatic pathways. The enzymatic cyclisation of squalene 2, 3-oxide to lanosterol is a very illustrating example to the domino process.



Scheme I.1. Enzymatic cyclisation of squalene 2, 3-oxide to lanosterol.

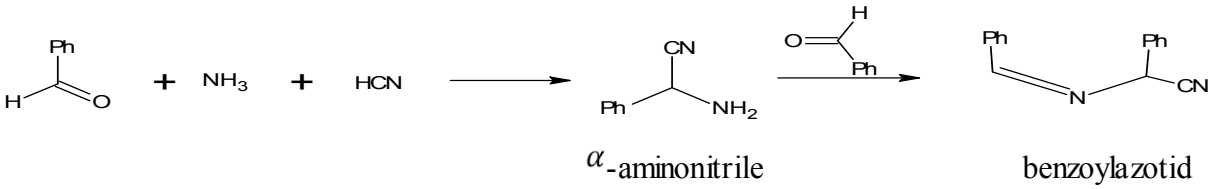
The quality and the importance of a cascade reaction can be correlated to the number of bonds generated and the increase of complexity. They can be performed as single-component (a), two-component (b), and multicomponent transformations (c).



Scheme I.2. Single component, two component and multicomponent cascade reaction [5].

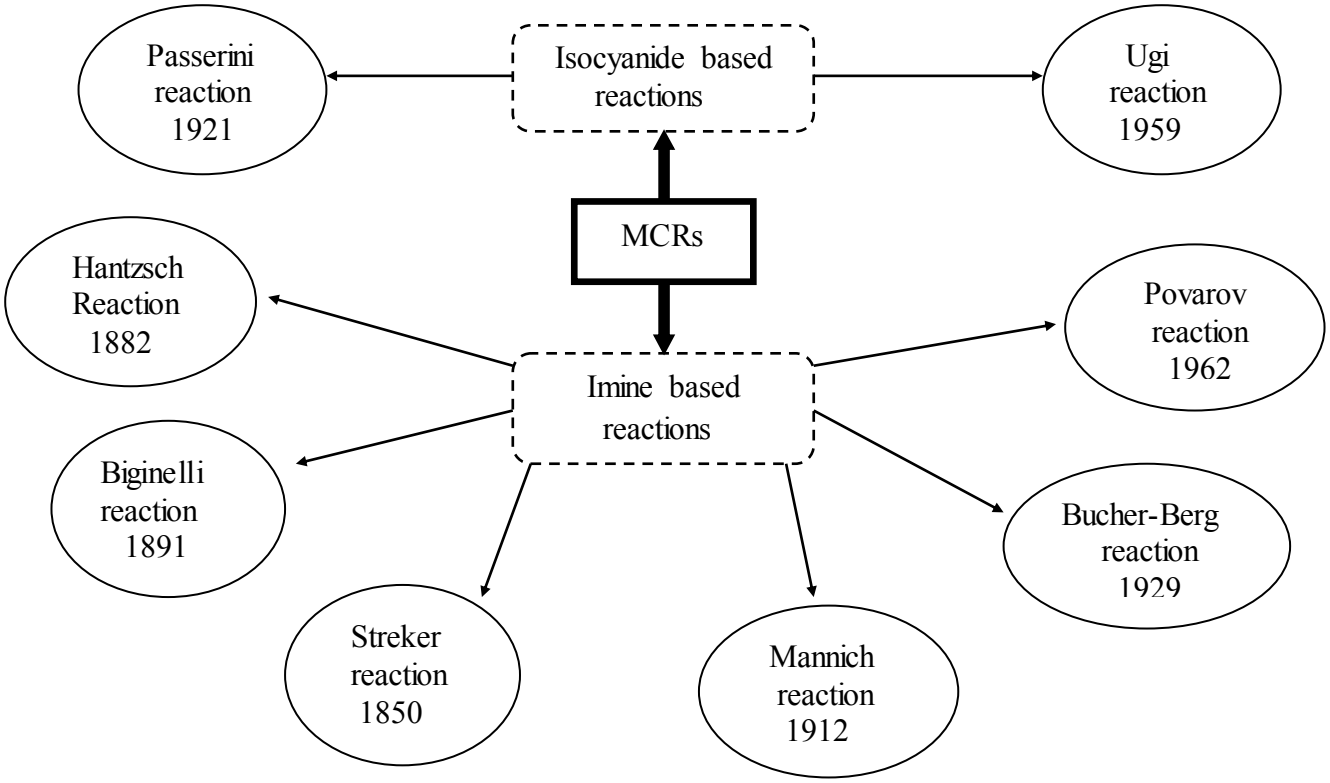
Most of the known multicomponent reactions can be defined as a subgroup of domino reactions [9], as they respect the domino principle: subsequent transformations are a consequence of the functionalities produced in the previous one.

MCR is a convergent process, in which three or more starting materials react in a single reaction vessel to form a product which contains portions of all the components [7], they are classified into two main families: imine based and isocyanide based. In 1838, the first MCR was reported by Laurent and Gerhardt [6], it was a reaction between benzaldehyde, hydrocyanic acid and ammonia which formed the intermediate: α-aminonitrile who reacts with a second molecule of benzaldehyde to produce the "benzoylazotid". Since that discovery, chemists were very interested in this type of reactions called later: "ideal synthesis" as they combine both efficiency and environment safety in chemical production.



α-aminonitrile benzoylazotid

Scheme I.3. Laurent and Gerhardt MCR.



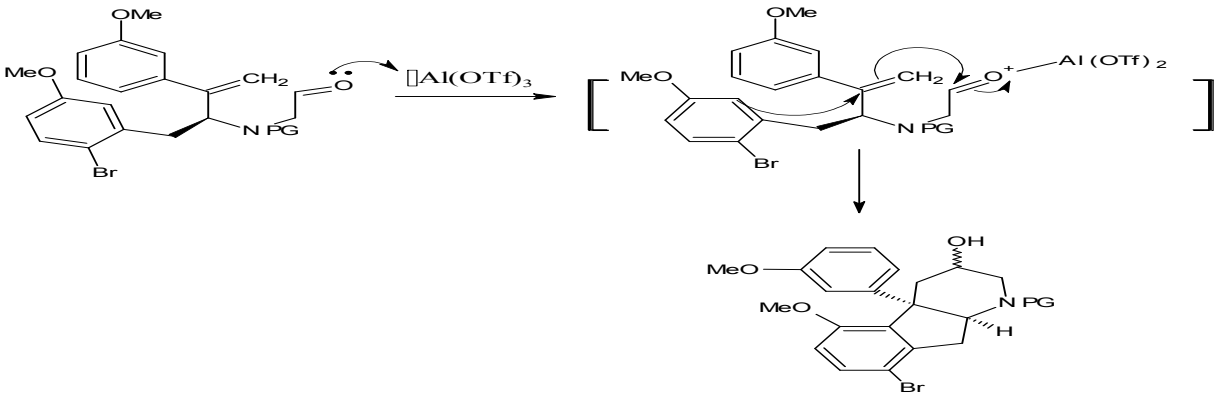
Scheme I.4. Classification of MCRs based on imines and isocyanides [8].

III. An overview on cascade reaction types

Cascade reactions have been classified into four types: cationic, anionic, radical, and pericyclic depending on the nature of the first step of the process.

III.1. Cationic cascade reaction

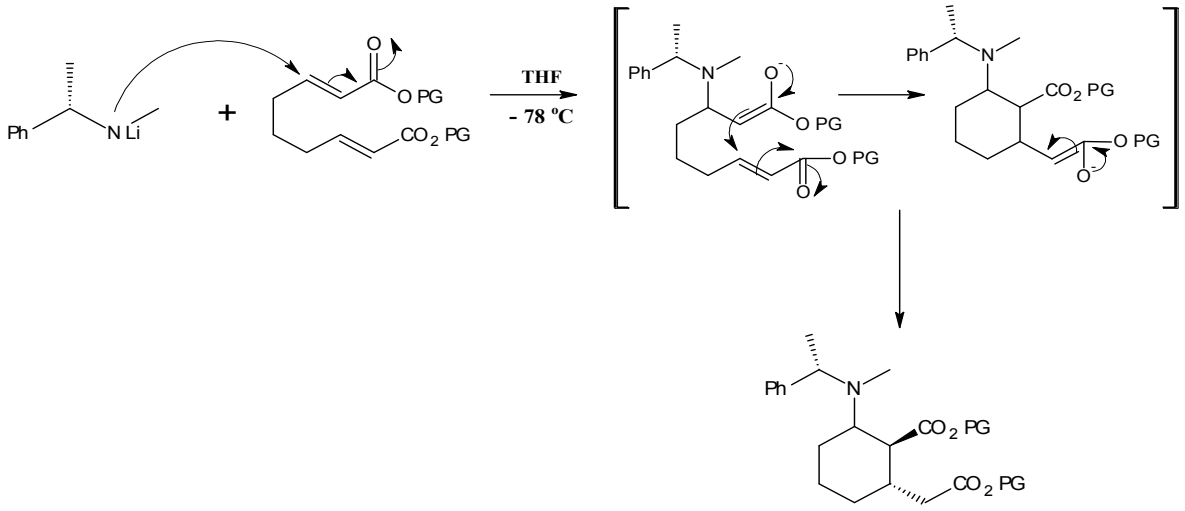
In this type, a cationic ion appears in the first step of the reaction. The tandem Prins/Friedel Crafts reaction useful for the construction of the indeno-tetrahydropyridine core of the haouamine alkaloid is a good example of a cationic cascade reaction where the first cation is formed when the oxygen attacks the aluminum, this last one is attacked by the alkene (Prins reaction) leading to a six membered ring, while the second appeared cation is attacked by the aromatic pair in a Fridel Craft process building the five membered ring.



Scheme I.5. Example of cationic cascade reaction [10].

III.2. Anionic cascade reaction

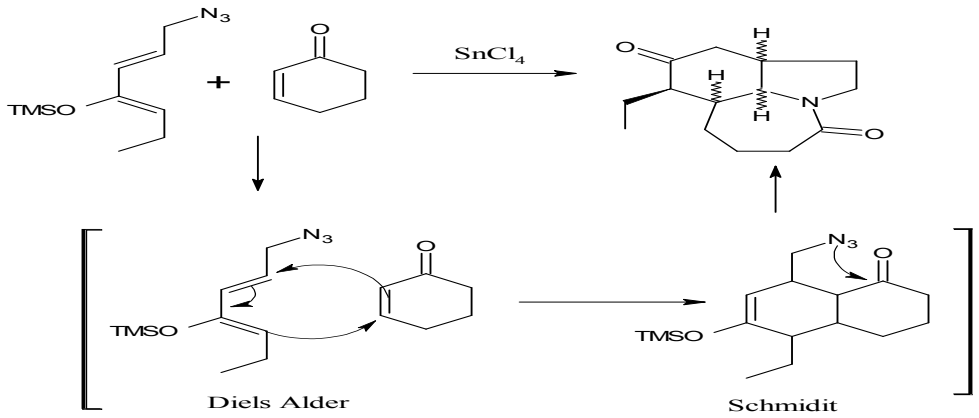
Similarly, a cascade reaction is considered as anionic, when the first step of the process leads to the formation of an anionic ion. The synthesis of Precursor of (-) Pumiliotoxin C through Domino aza-Michael/Michael reaction is one of the examples that illustrate this kind of process. At first, an aza-Michael reaction between the amine group and the α,β unsaturated carbonyl offers the anion ion, then a second intramolecular Michael reaction cyclizes the compound.



Scheme I.6. Example of anionic cascade reaction [11].

III.3. Pericyclic cascade reaction

A pericyclic reaction is a concerted reaction in which all bonds are made or broken around a circle [12] they are very useful for building complex ring systems, the most known is The Diels-Alder reaction. **Scheme I.7** shows an example of a tricyclic compound which is produced by a pericyclic cascade process in the total synthesis of Stenine, where a Diels Alder reaction forms a bicyclic compound followed by Schmidt reaction and rearrangement.



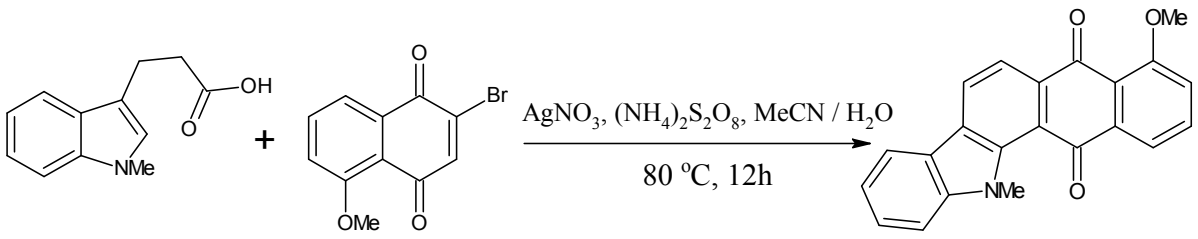
Scheme I.7. Example of pericyclic cascade reaction [13].

III.4. Radical cascade reaction

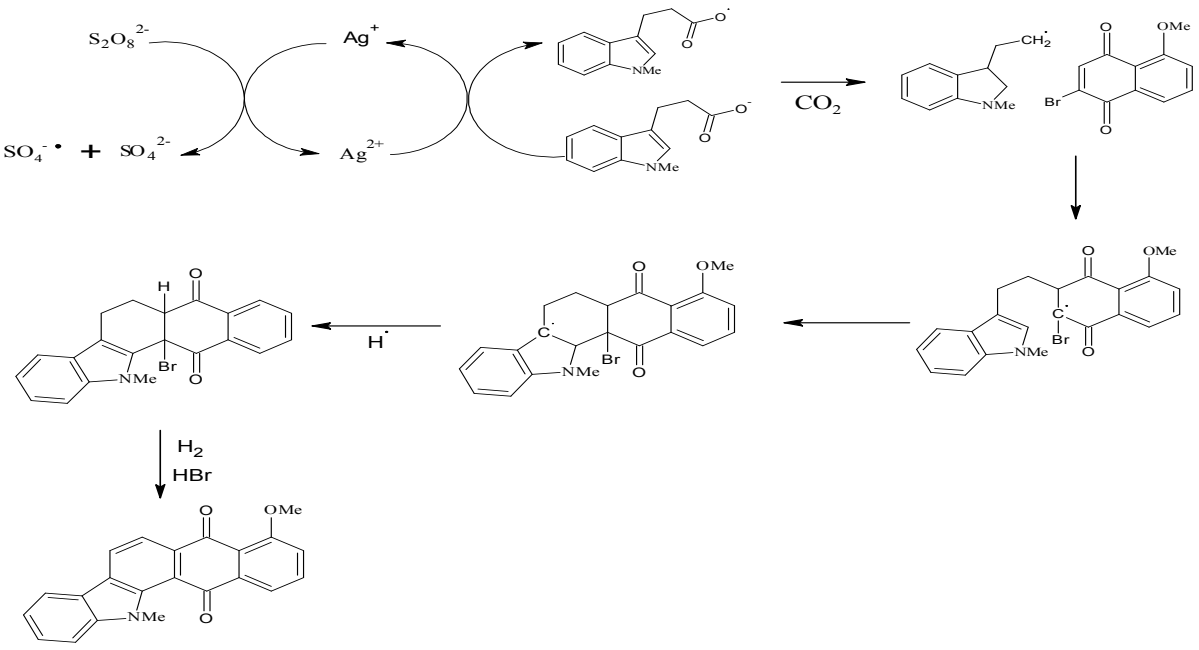
Radical cascade reactions can be defined as a rapid series of inter and intramolecular different processes: cyclization, fragmentation, addition, ring-expansions, and rearrangements depending on the reaction's conditions and the nature of the substrates [14].

III.4.1. Using transition metal catalysis

Metal catalysis is a powerful tool that improves the efficiency of one-pot processes, as example, the Ag-catalyzed Minisci/cyclization of fused pentacycles compounds from indolylpropanoic acids and quinones [14].



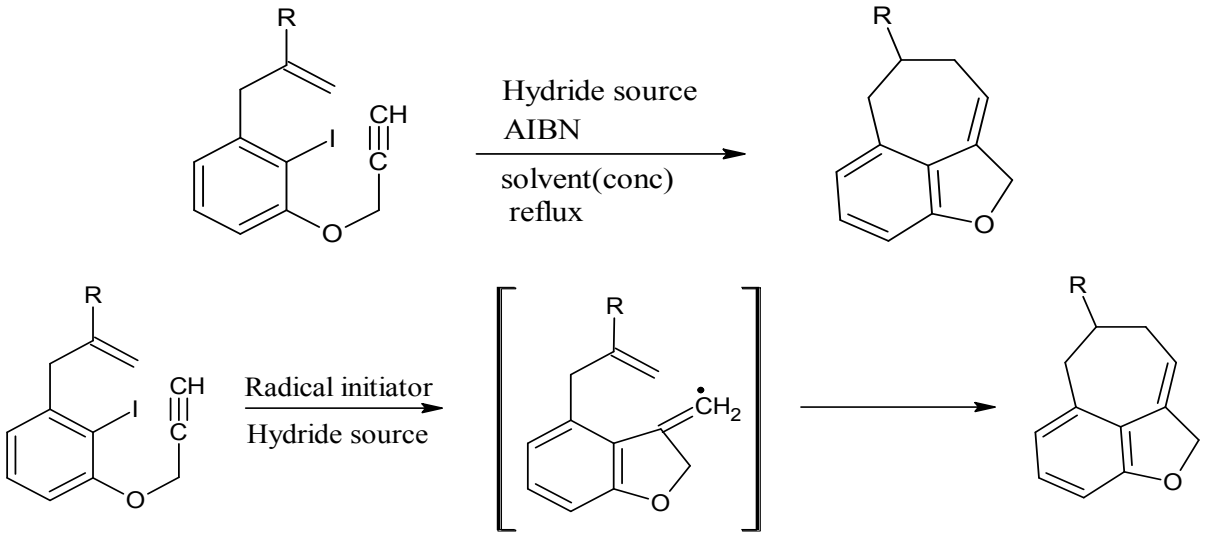
Scheme I.8. Example of a radical cascade reaction catalyzed by a transition metal (Ag).



Scheme I.9. Mechanism of the radical cascade reaction catalyzed by a transition metal (Ag).

III.4.2. Using radical initiator

AIBN is usually used as a radical initiator in radical cascade reactions, as an example, the radical cascade synthesis of 3,4-fused tricyclic 3-alkylidene dihydrobenzofuran derivatives is achieved by the treatment of propargyl iodophenol derivatives with a tethered alkene [15].



Scheme I.10. Example of a radical cascade reaction by a radical initiator (AIBN).

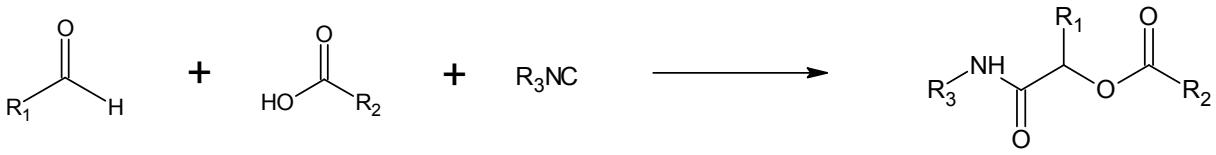
IV. The most known MCRs that lead to cyclic compounds

IV.1. Isocyanides based reactions

The classical isocyanides multicomponent reactions were first recognized by Passerini and Ugi. They have extensive applications in the synthesis of drug libraries. However, neither the classical Passerini nor the Ugi reactions are able to generate different scaffolds or producing cyclic systems [16]. Further modifications achieved on these reactions allowed them to form cyclic and polycyclic compounds (**chapter II**).

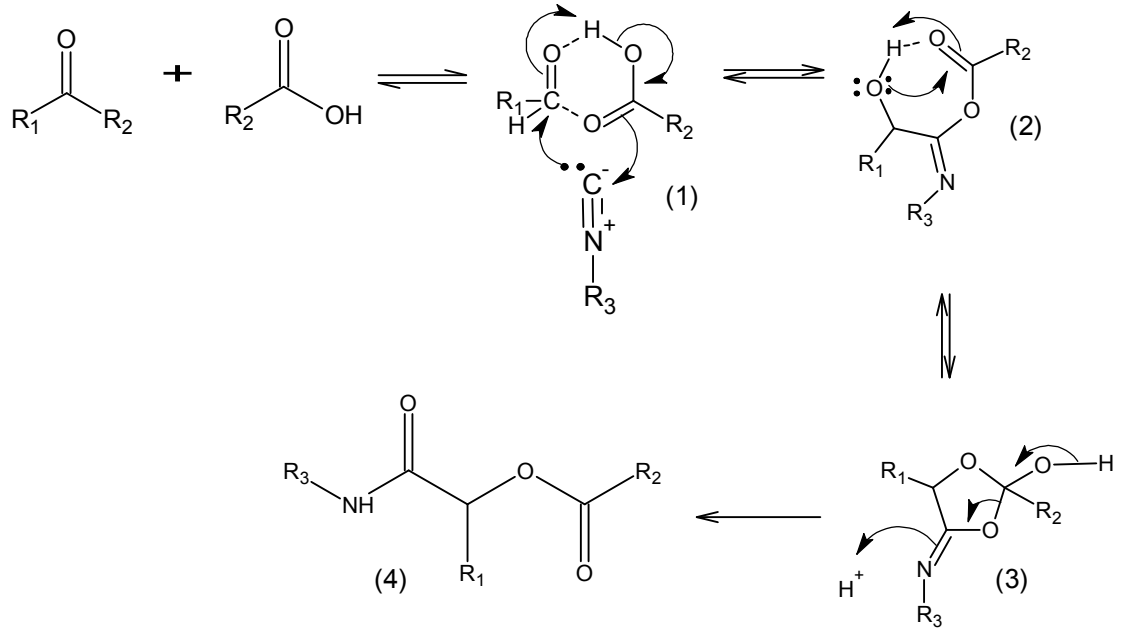
IV.1.1. Passerini reaction

The first synthetically useful reaction of isocyanides, also known isonitriles was described by Mario Passerini in 1921, who reported that isocyanides react with acids and carbonyl compounds in one step to provide α-acyloxycarboxamide [17].



Scheme I.11. Passerini MCR.

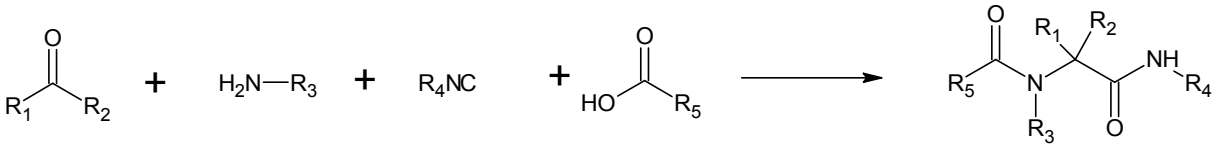
A hydrogen bond is formed between the carbonyl compound and the carboxylic acid giving a six membered transition state (1). Then, the nucleophilic addition of the isocyanide to the electrophilic carbonyl carbon followed by the nucleophilic attack of oxygen to the electrophilic isocyanide carbon leads to a seven membered and second transition state (2). An intramolecular rearrangement gives a five membered intermediate (3) which undergoes a second intramolecular rearrangement that produces the α-acyloxycarboxamide (4).



Scheme I.12. Passerini MCR mechanism [16].

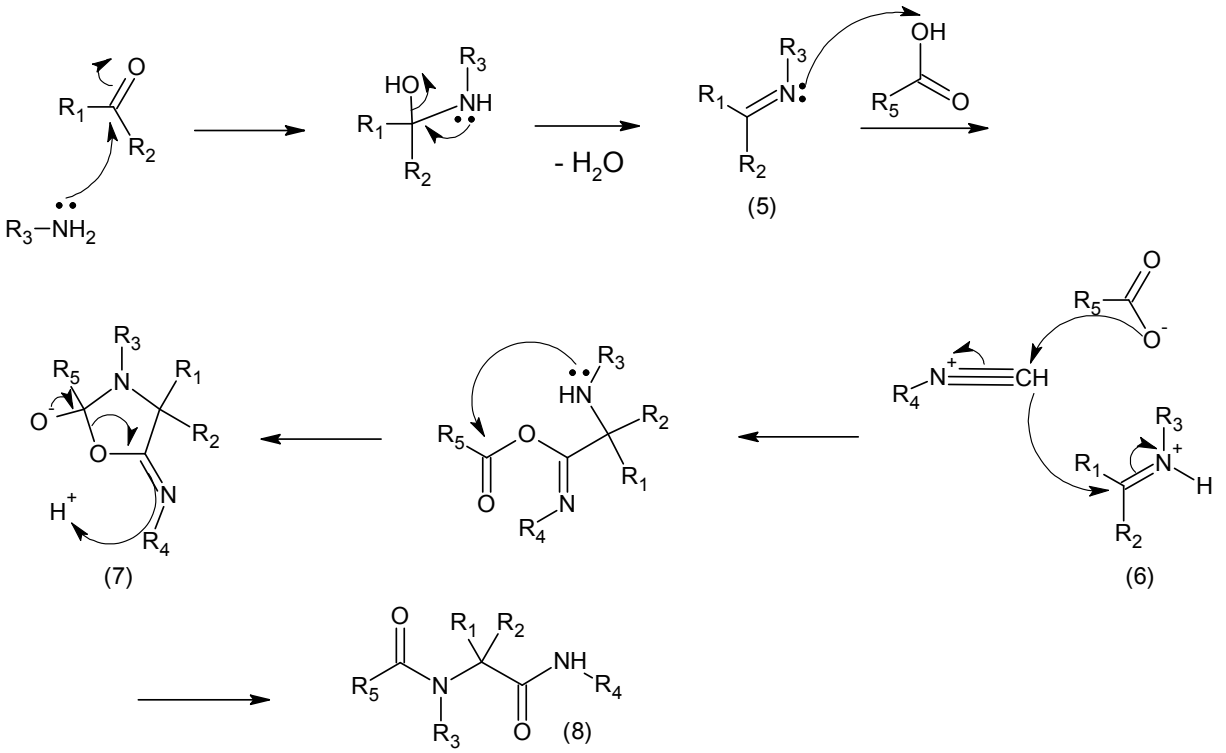
IV.1.2. Ugi reaction

In 1959, Ivar Karl Ugi reported that isocyanides undergo a four-component reaction in the presence of an amine, a carbonyl compound (aldehyde or ketone) and carboxylic acid, which allows the rapid preparation of α-aminoacyl amide derivatives [17].



Scheme I.13. Ugi MCR.

The carbonyl compound (ketone or aldehyde) reacts with amine to form the imine (5) which is protonated by the carboxylic acid offering the activated iminium ion (6); this one undergoes a nucleophilic addition of isocyanide. The carboxylic acid anion formed previously attacks the isocyanide carbon and a Mumm rearrangement (7) leads to the final product: α-aminoacyl amide (8).

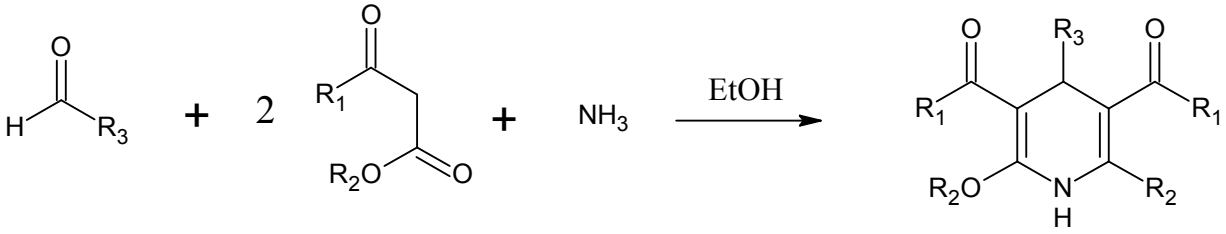


Scheme I.14. Ugi MCR mechanism [17].

IV.2. Imines based reactions

IV.2.1. Hantzsch reaction

The combination of aldehyde, β-keto-ester and ammonia in an alcoholic solvent gives the 1,4-DHP, commonly known as the Hantzsch reaction. It was discovered for the first time in 1882 by Arthur Rudolf Hantzsch [17].



Scheme I.15. Hantzsch MCR.

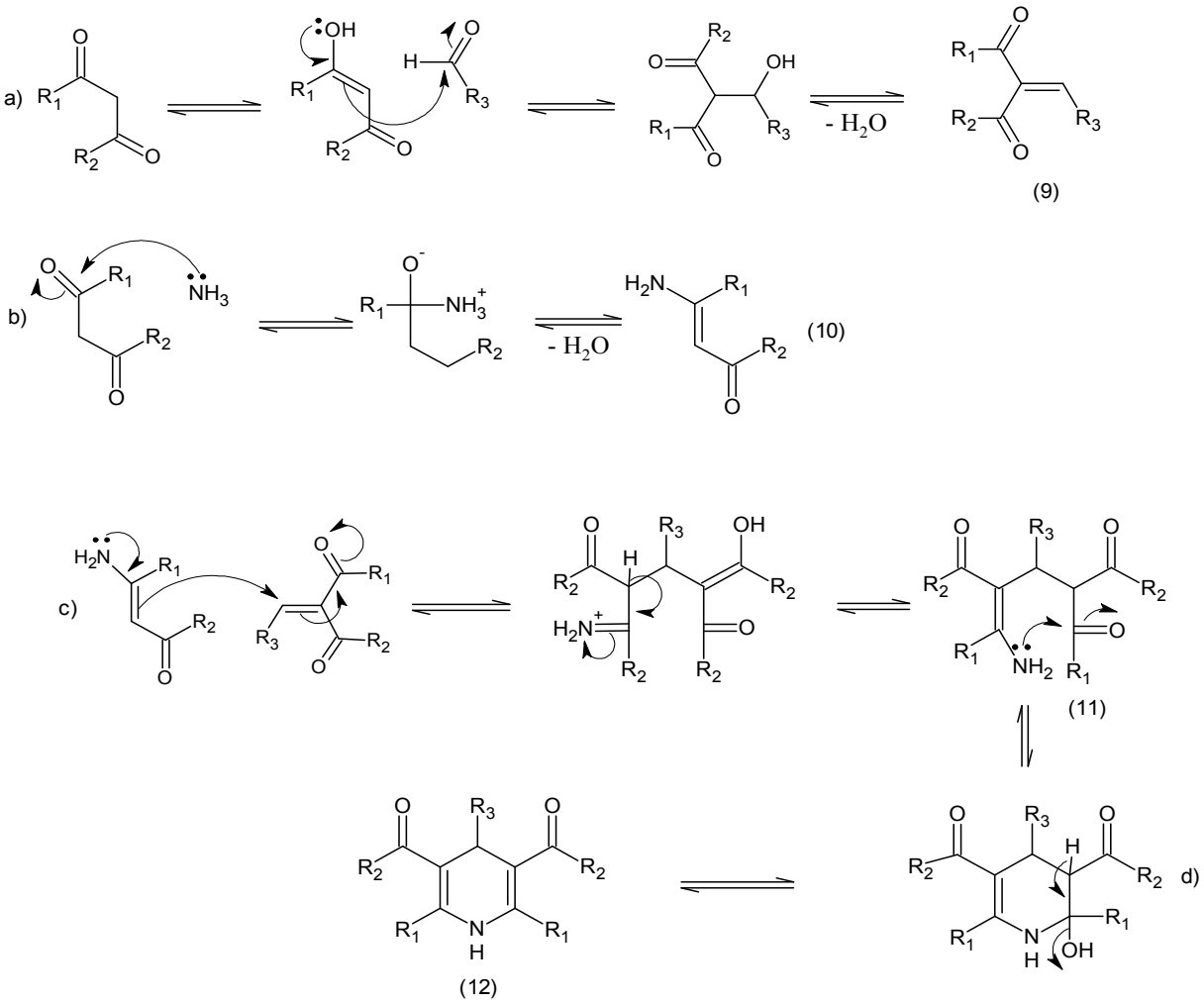
In the mechanism of Hantzsch reaction, there are four principal steps:

a) Knovenagel condensation: between 1,3 dicarbonyl and the aldehyde offering an α,β unsaturated carbonyl (9).

b) Enamine formation: in this step the second equivalent of the 1,3 dicarbonyl reacts with ammonia to produce the enamine (10).

c) Mickael addition: of the enamine to the α,β unsaturated carbonyl compound wich leads to intermediate (11).

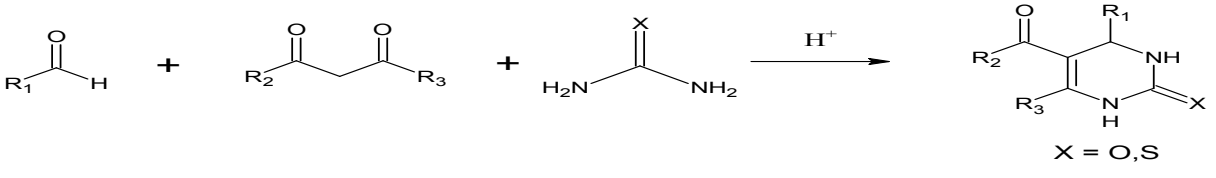
d) Intramolecular condensation: between the amino group and the carbonyl group in intermediate (11) gives the final product: 1, 4-DHP (12).



Scheme I.16. Hantzsch MCR mechanism.

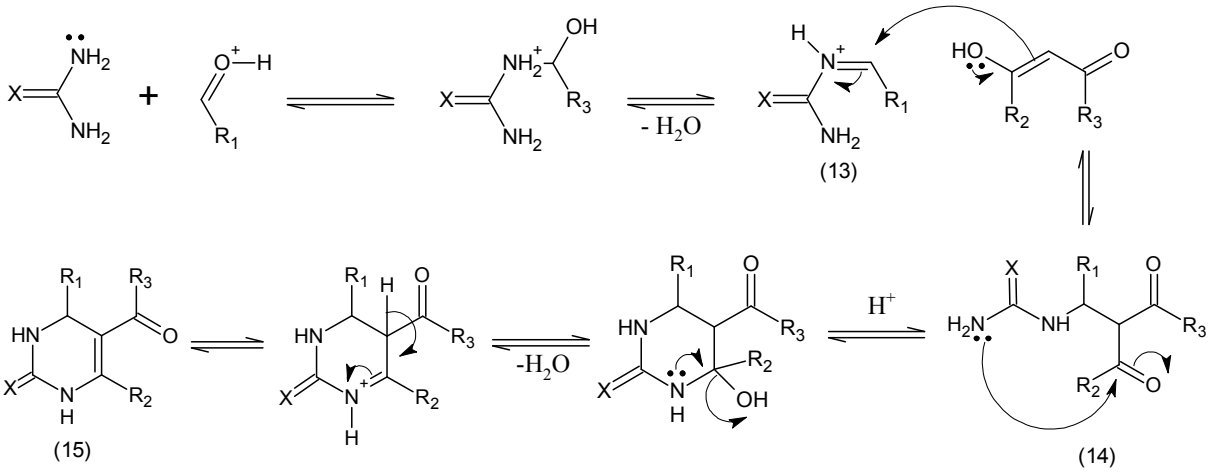
IV.2.2. Biginelli reaction

The three component Biginelli reaction was described for the first time in 1893 by Pietro Biginelli. This reaction produces dihydropyrimidinone (DHPM) derivatives by the combination of β-keto-ester with aldehyde and urea (or thiorea) in the presence of acid catalyst [17].



Scheme I.17. Biginelli MCR.

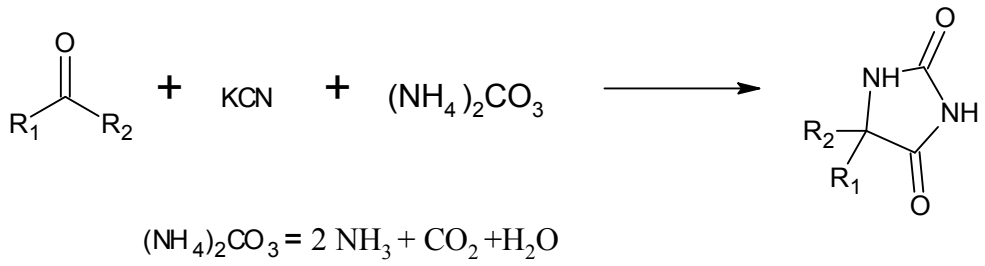
N-acyliminium ion intermediate (13) is firstly obtained when the urea reacts with the aldehyde after the dehydratation of the aminal. Next, intermediate (13) is attacked by the enol form of the β-keto-ester to give intermediate (14) wich undergoes an intramolecular cyclization between the amino and the carbonyl groups after a second dehydratation, the Bigenilli compound (15) is formed.



Scheme I.18. Biginelli MCR mechanism.

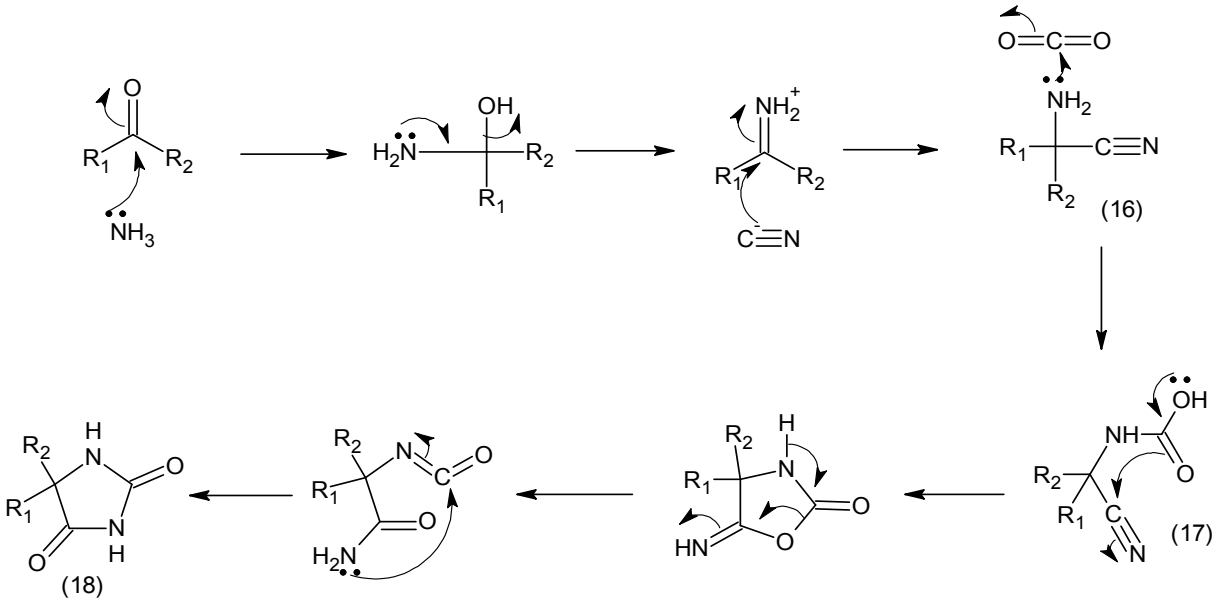
IV.2.3. Buchrer Bergs reaction

Formation of hydantoin derivative from carbonyl compounds reaction with potassium cyanide (KCN) and ammonium carbonate [(NH4)2CO3] was discovered by Buchrer and Bergs in 1929 [19].



Scheme I.19. Buchrer Bergs MCR.

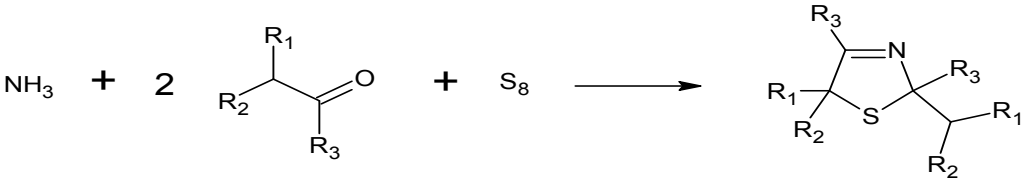
The carbonyl compound reacts with the ammonia producing the imine which is attacked by the isocyanide to form the aminonitrile (16). Afterward, the addition of CO_2 to the aminonitrile (16) leads to the intermediate: "cyano-carbamic acid" (17). An intramolecular ring closing followed by a rearrangement gives the hydantoin product (18).



Scheme I.20. Buchrer Bergs MCR mechanism.

IV.2.4. Asinger reaction

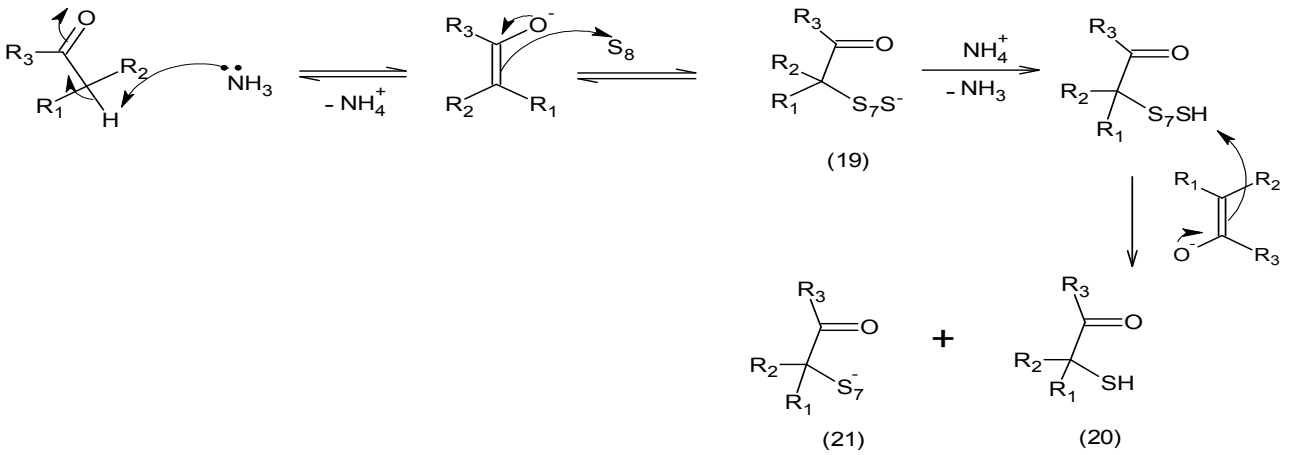
Reported by Friedrich Asinger in 1956 [20], it is a four component reaction used for the synthesis of 3-thiazoline scaffold when a ketone or aldehyde was treated by sulfur and ammonia.



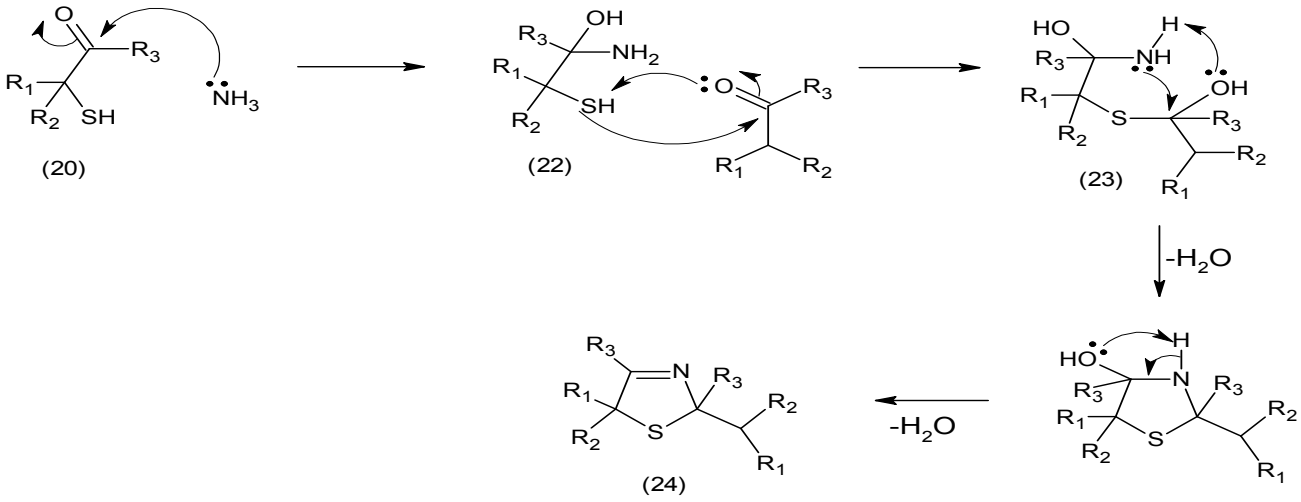
Scheme I.21. Asinger MCR.

The mechanism of the Asinger reaction can be described as following:

- An α-surfhydryl ketone intermediate (20) is formed by a thialation reaction catalysed by the ammonia base wich gives the enolate form. One equivalent of the enolate form attacks, the sulfur to yield intermediate (19) while a second equivalent attacks intermediate (19) after being protonated to produce the α-surfhydryl ketone (20) besides the polysulfur (21).



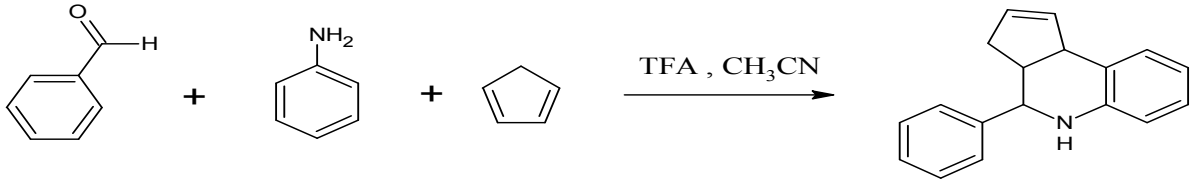
- The ammonia attacks the C_{sp}^2 in the α-surfhydryl ketone (20) to give product (22) deprotonated later by the second carbonyl compound.The nucleophilic sulfer ion attacks the electrophilic carbone appeared in the protonated carbonyl compound and leads to intermediate (23) wich undergoes two succesive dehydrations to give the 3-thiazoline derivative (24). This kind of rings can be found in many molecules used for industriel purposes such as the L-cysteine industrial synthesis.



Scheme I.22. Asinger MCR mechanism.

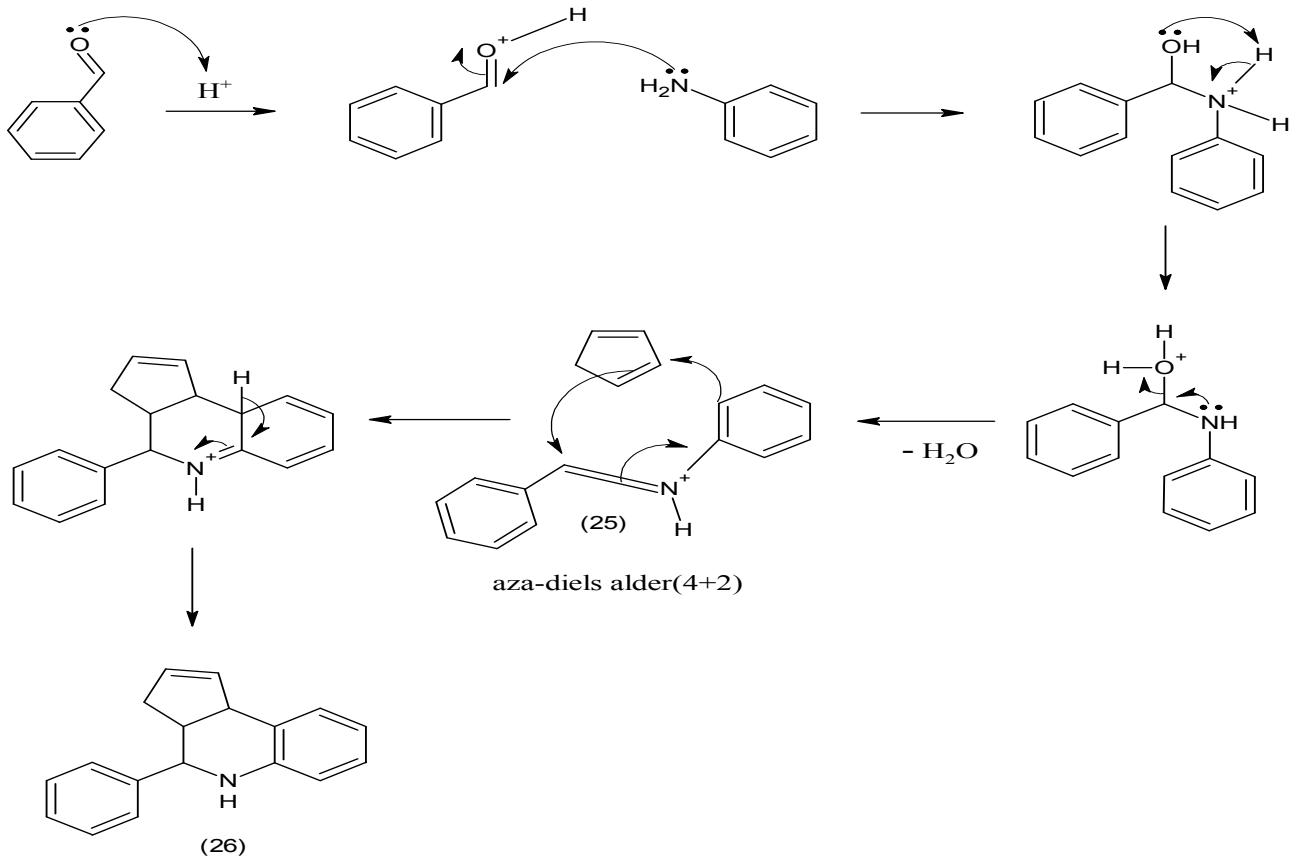
IV.2.5. Grieco reaction

Paul Grieco reported his three component reaction in 1985 [21] for the synthesis of tetrahydroquinolines, it is a condensation between: aldehyde, aniline and an electron rich alken in the presence of equimolar TFA or Lewis acid as catalyst in acetonitrile (CH_3CN) [22]



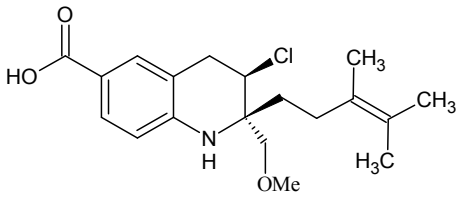
Scheme I.23. Grieco MCR.

For the mechanism of Grieco reaction, the protonated aldehyde reacts with the amine (25) affording after a dehydratation the imine wich undergoes an Aza-Diels Alder [4+2] reaction when it reacts with the electron rich alken, forming the hetero six membred ring of pepiridine (26).

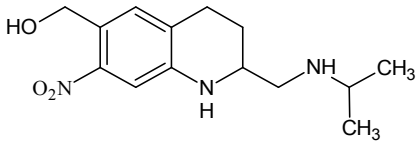


Scheme I.24. Grieco MCR mechanism.

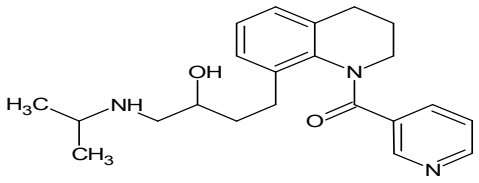
Tetrahydroquinolines (THQ) and Quinolines (QUIN) are very important moieties present in a wide number of natural products, bioactive compounds and drugs, as exemple: Oxamniquine, an oral anthelmintic drug for the treatment of schistosomiasis. Virantmycin is an antiviral antibiotic with antifungal activity and Nicainoprol is a calcium channel antagonist [23].



Virantmycine



Oxamniquine

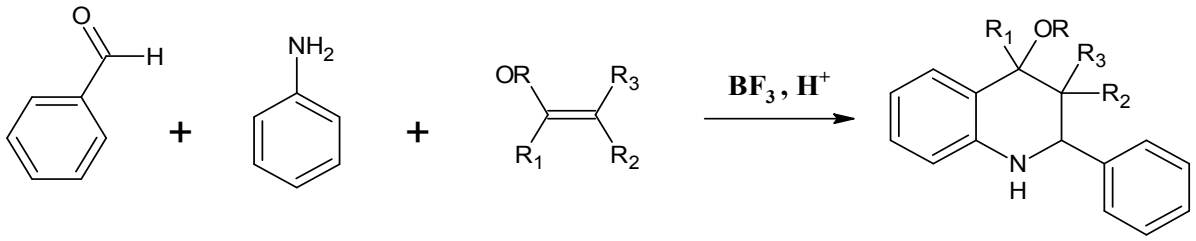


Nicainoprol

Scheme I.25. Some bioactive THQs and QUINs.

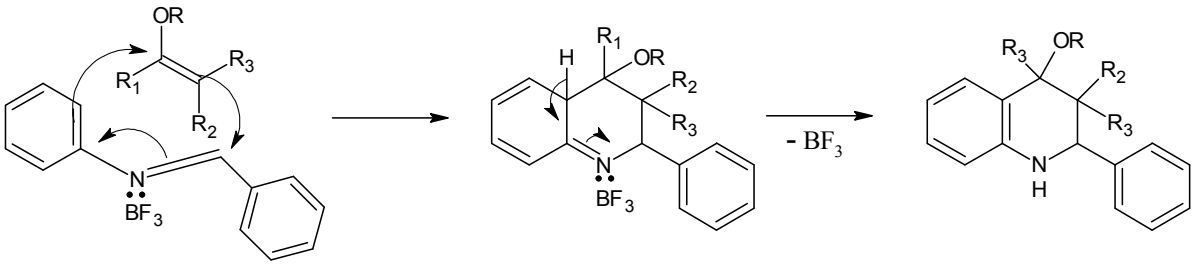
IV.2.6. Povarov reaction

The Povarov three MCR combines aniline, an aldehyde and an olefin to yield a THQ and QUIN. The first example was described by the Russian chemist Povarov in 1962 between vinyl ether and a Schiff base of the N-aryl imine type in the presence of a Lewis acid, trifluoroborane BF_3. It is a very useful reaction especially in medicinal chemistry [24].



Scheme I.26. Povarov MCR.

Povarov reaction has the same mechanism as Grieco reaction.



Scheme I.27. Povarov MCR mechanism.

V. MCR in industry

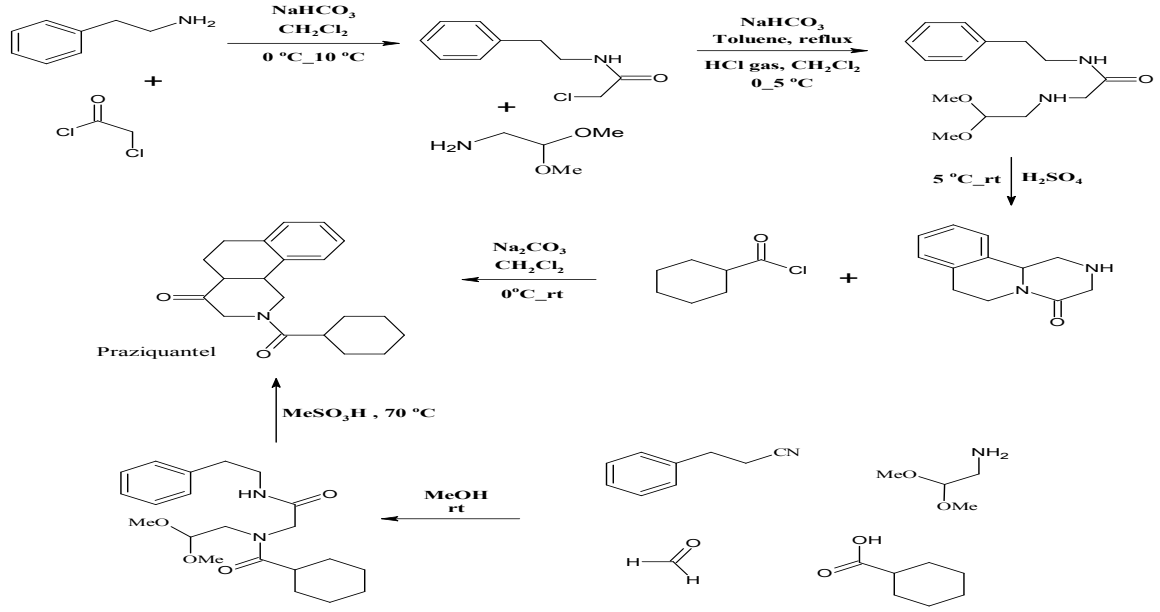
MCR process has diverse applications in biosynthesis, agrochemistry, polymer chemistry …; the most important application is library generation for drug discovery, design and optimization leading to new bioactive compounds necessary in pharmaceutical industry [25].

V.1. Why MCR is a green process?

Pharmaceutical production requires high structure complexity that makes industry with huge waste and long steps in their synthesis. To overcome these issues, MCRs could be a good alternative to access rapidly complexity due to the simultaneous formation of several new bonds and rings. Thus, MCR is considered as a green process due to:

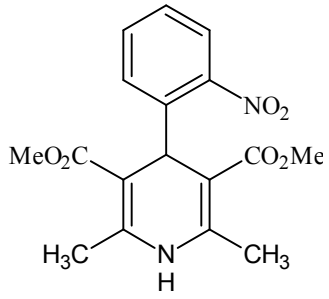
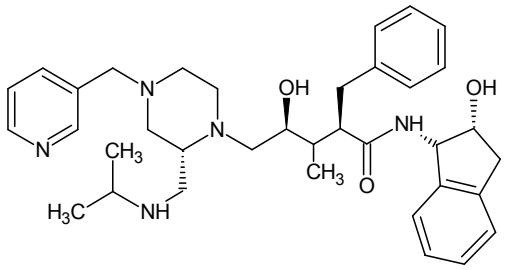
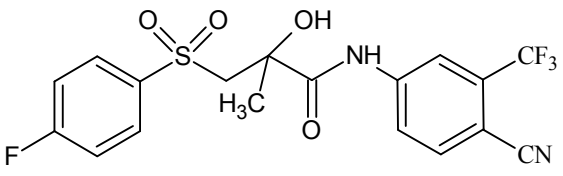
- Atom economy: the majority of atoms in the simple reactants are found in the final product.
- Step economy: the MCR is a one pot operation where the number of steps is extremely minimized.
- Energy saving: MCR requires mild condition (ambient temperature and pressure, under microwave and ultrasound).
- Reducing the waste: fewer steps in the synthesis and the simple isolation of the products means less amount of wastes (reagents and solvents).
- Efficiency: good yields and excellent chemo-regio selectivity.
- Less hazardous synthesis: the reactants used are simple and not hazardous (aldehydes, amines, carbonyls…). Moreover, many eco-friendly solvents are suitable for this process "water, ionic liquids, (PEG) polymers ".

Scheme I 28 shows the synthesis of Praziquantel by the linear synthesis and the convergent synthesis as well. The advantage of MCR process over linear one is clearly illustrated.



Scheme I.28. Linear vs. multicomponent synthesis of Praziquantel.

In the following table, some examples for available medicaments produced by MCR's:

Medicament's name	Reaction's name	Therapeutical uses
Nifedipine 	Hantzsch	It's a calcium channel blocker for treating high blood pressure.
Indinavir 	Ugi	Anti-HIV (anti-retroviral) drug called a protease inhibitor or IP.
Bicalutamide 	TiCl4-mediated Passerini-type reaction	Prostate cancer drug.

V.2. Challengs of MCR processes

Despite the fact that MCRs could be a beneficial solution to overcome some issues in pharmaceutical industry, they are still marginally applied for many reasons. For example, Ugi and isocyanides-based reactions which are among the most important MCRs, are known for their bad smell, instability and toxicity. Moreover, they are not available as building blocks but they should be prepared, which implies additional steps and reactants. On the other hand, most of the aromatic and heterocycles produced are not degradable.

As solutions to the previous issues, chemists have developed "isocyanide free process" using activated halides and cyanide nontoxic resources such as potassium hexacyanoferrate (II) [25]. Furthermore TMSCN could be successfully used as isocyanides in MCRs besides microreactors for safe operations.

VI. Conclusion

In this chapter, attention was focused on MCRs as a subgroup of cascade reactions some of important MCRs (Hantszch, Biginelli, Passerini…) leading to polycyclic compounds s were highlighted. The choice of the various cyclic partners used in these reactions along with the mechanisms were discussed.

Chapter II:
Polycyclic compounds by MCRs

I. Introduction

Cascade reactions, in which several new bonds are formed sequentially in a single operation with a rapid increase in the molecular complexity, have recently been the focus of considerable interest in the field of synthetic chemistry, they provide extremely powerful methods for the synthesis of interesting polycyclic compounds [26].

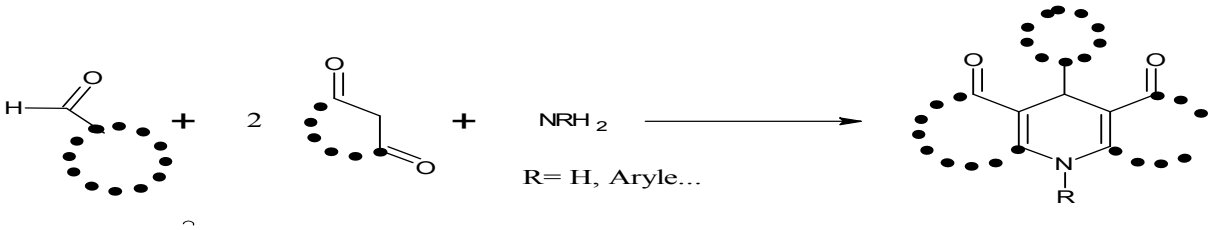
II. Polycyclic compounds by MCRs

In the interest of accessing polycyclic compounds by multicomponent reactions studied in the first chapter, several variations of building blocks are proposed in this part. The idea is to use cyclic building blocks or building blocks bearing cycles to get the largest possible number of rings in the product, as it was mentioned previously, there are many types of cycle linkages, our focus will be on fused scaffolds, but other cases will be also discussed.

II.1. Hantzsch reaction

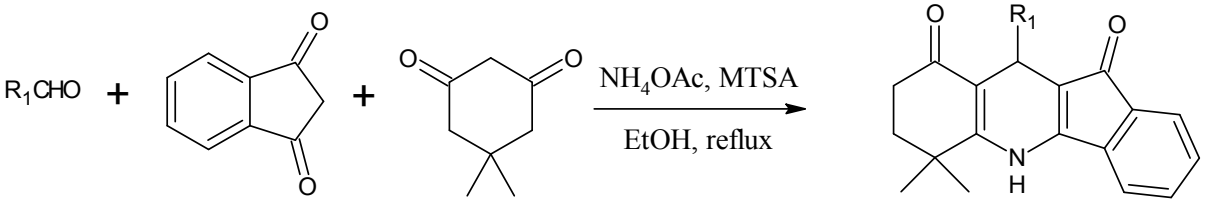
II.1.1. Synthesis of 1,4-dihydropyridine derivatives by four* component Hantzch reaction

Using cyclic 1,3 diketones lead at least to two cyclic ketones fused to the main 1,4 DHP scaffold, while aromatic and heterocyclic aldehydes offer tethering rings to the 1,4 DHP in position 4.



Scheme II.1. Cyclic scaffolds obtained by Hantzch reaction.

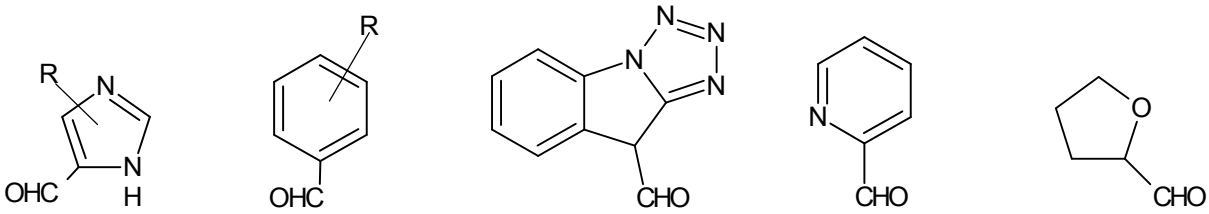
The following example shows the ability of synthesizing polycyclic compounds by four component Hantzsch reaction [28].



*In comparison to Hantzch-like reaction: wich is a three component reaction where an enamine is used instead of amine.

Aldehydes used in Hantzsch reaction

Various types of aromatic and heterocyclic aldehydes are used in Hantzsch reaction:

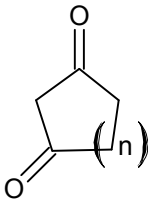


Scheme II.2. Some Aldehydes used in Hantzsch reaction [27].

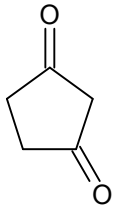
1, 3 diketones used in Hantzsch reaction

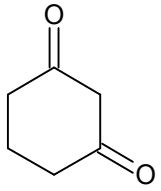
Dihydropyridin derivatives possessing two cyclic ketones fused to the main Scaffold are obtained by using wide groups of cyclic 1,3 diketones (a-c) [28] and (d) [29] in **scheme II.3.** In addition, some cyclic ß-ketoesters such as pyran 3,5-dione (e) [30] and barbituric acid (f) [31] or 2-thiobarbituric acid **scheme II.4** can be used to produce fused 1,4 DHP with interesting pharmaceutical properties.

a)



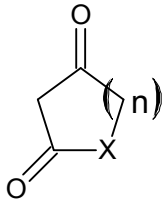
Examples



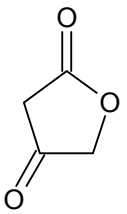


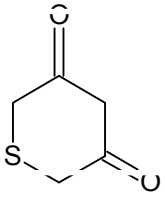
n = 1,2 n = 1 n = 2

b)



Examples



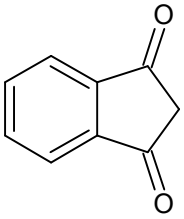


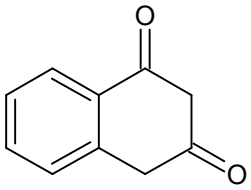
n = 1,2
X = O,S

n = 1
X = O

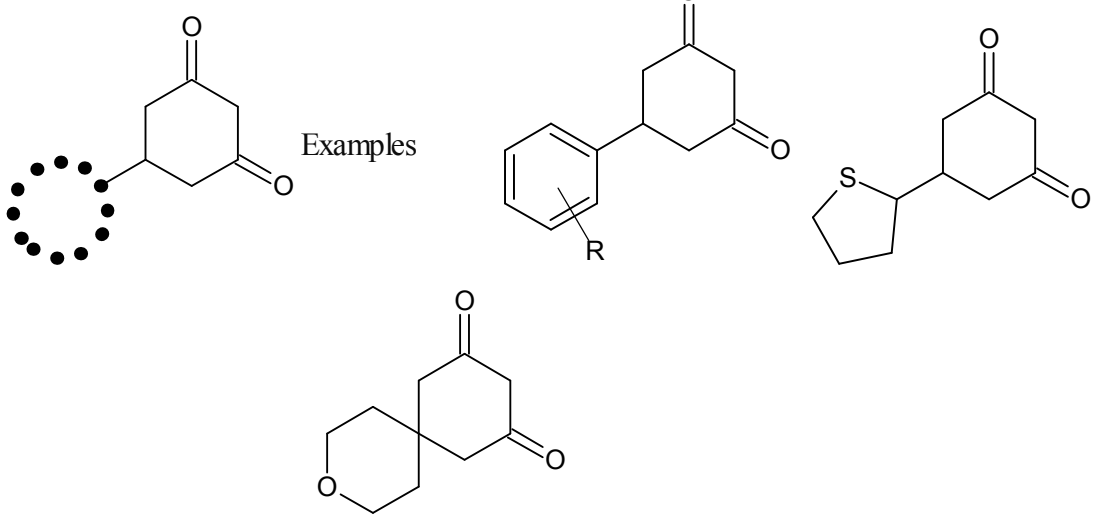
n = 2
X = S

c)

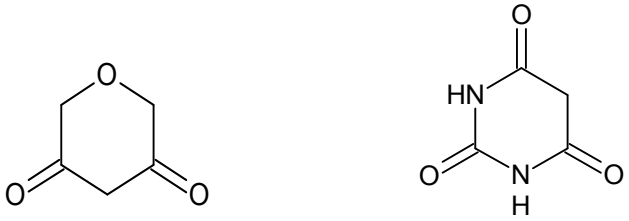




d)



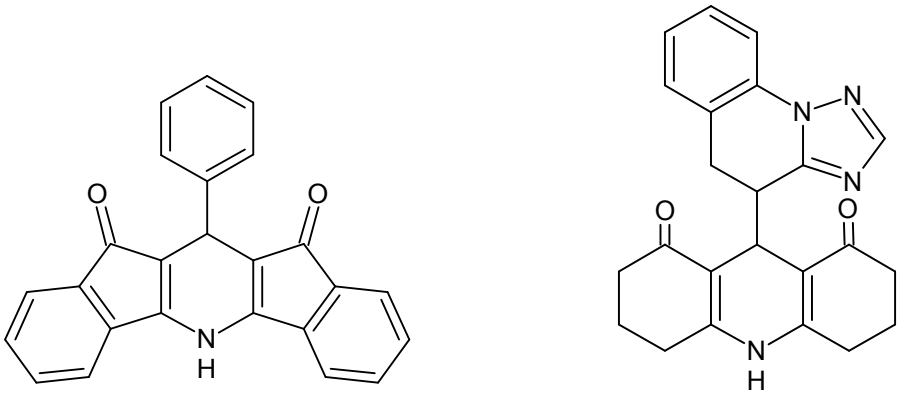
Scheme II.3. Some 1,3 diketones employed in Hantzsch reaction.



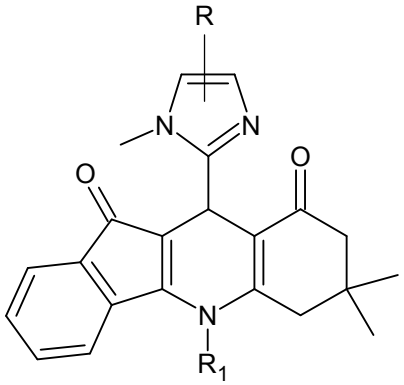
e f

Scheme II.4. Pyran-3,5-dione (e) and barbituric acid (f) used in Hantzsch reaction.

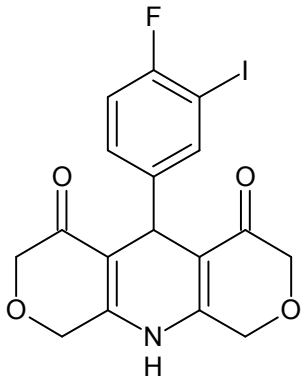
1,4-dihydropyridines have a great impact on pharmacology and medicinal fields due to their various therapeutic applications, some polycyclic DHPs examples [27] presented in **scheme II.5** illustrate accessing structural complexity by Hantzsch reaction.



Antimicrobial 1,4-DHPs



Anticancer 1,4-DHPs

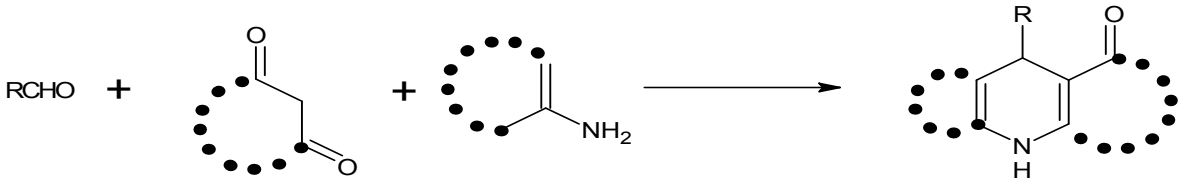


ABT-598

Scheme II.5. Fused-ring bioactive 1,4-DHPs.

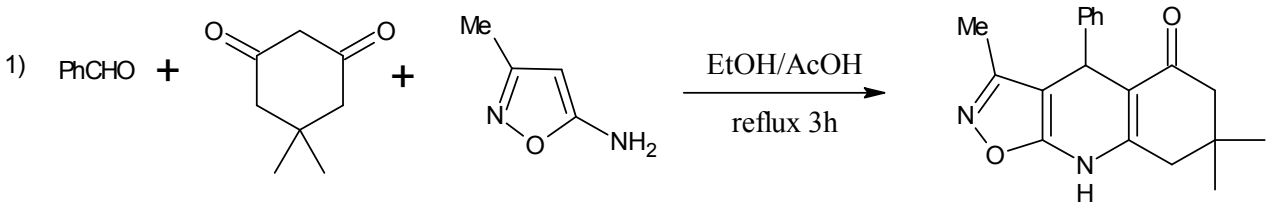
II.1.2. Synthesis of 1,4-dihydropyridine derivatives by three-component Hantzch-like reaction

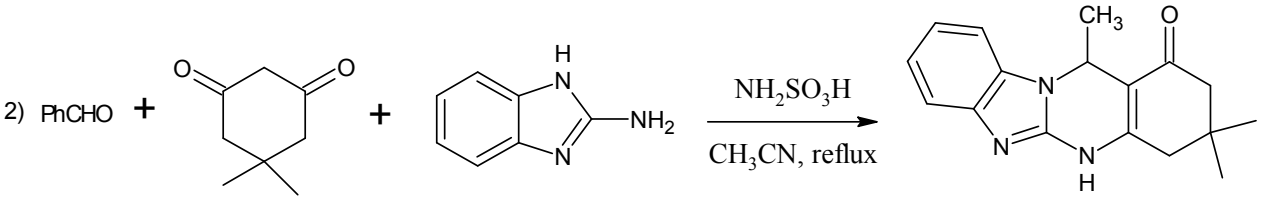
A modified three-component Hantzch protocol utilizing 1,3-dicarbonyl compounds, aldehydes, and enamines has been reported affording 1, 4-dihydropyridine derivatives [28].



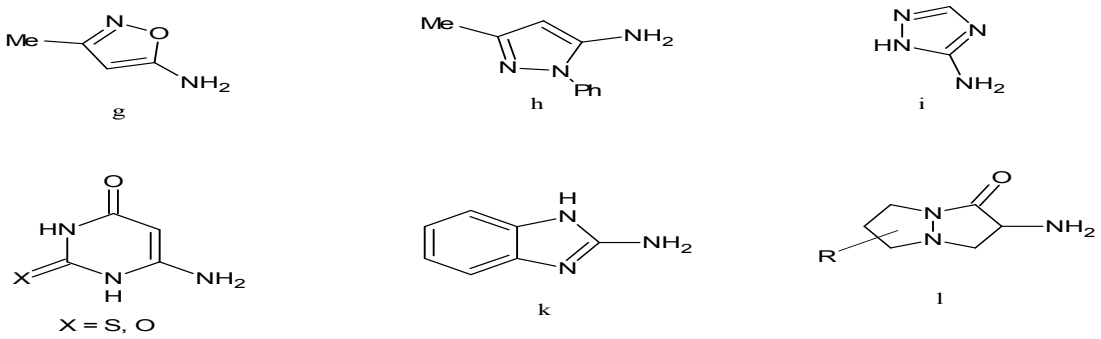
Scheme II.6. Fused cyclic scaffolds obtained by Hantzch-like reaction.

These are some examples that show the ability of synthesizing polycyclic compounds by Hantzch-like reaction [28].





Many electron rich aminoheterocycles (g-k) [28] and (l) [32] **scheme II.7** can be used for this version of Hantzsch reaction.

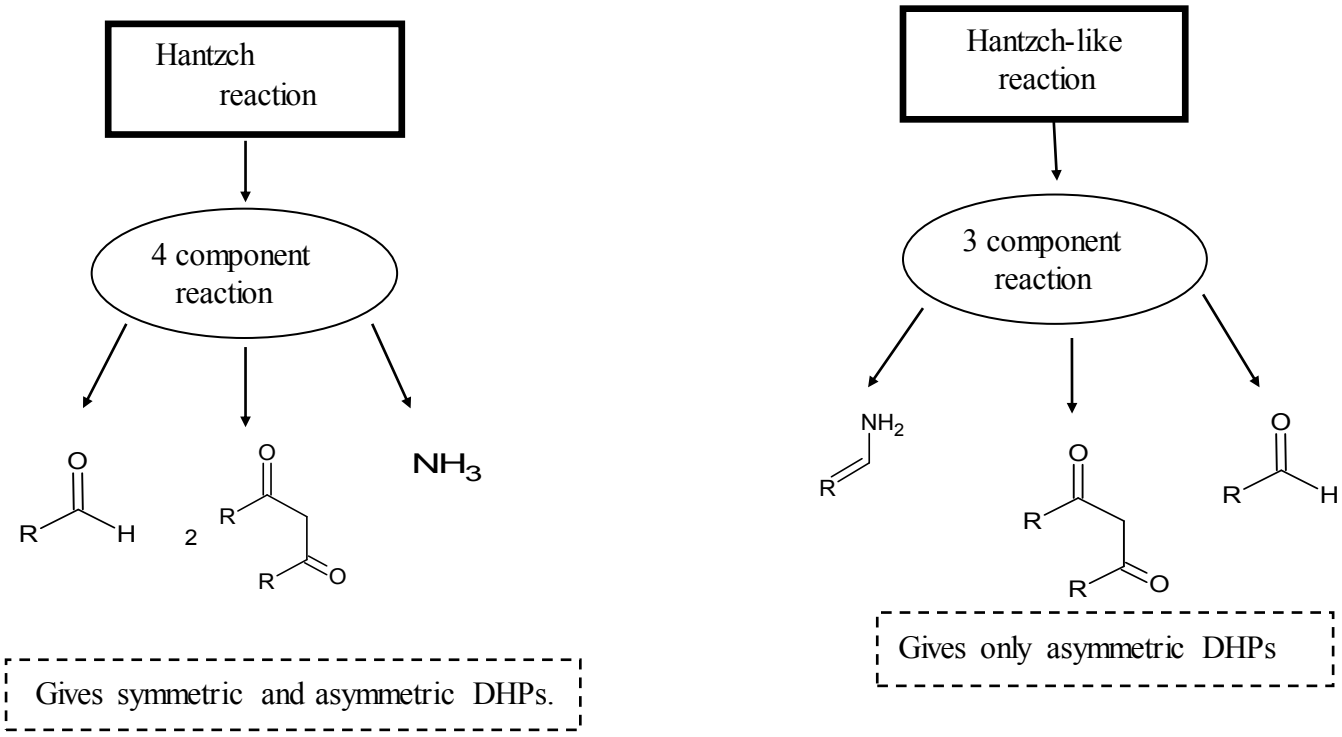


Scheme II.7. Some aminoheterocycles used in. Hantzch-like reaction.

Scheme II.8. 1,4 DHPs synthesized by the Hantzch-like reaction [28].

Hantzch reaction Vs Hantzch-like reaction

Hantzsch reaction is a four component process, where the enamine is formed in situ to give symmetreic and assymmetric DHPs. While Hantzch-like reaction is a three component process involving an already available enamine to give only assymmetric DHPs **Scheme II.9.**



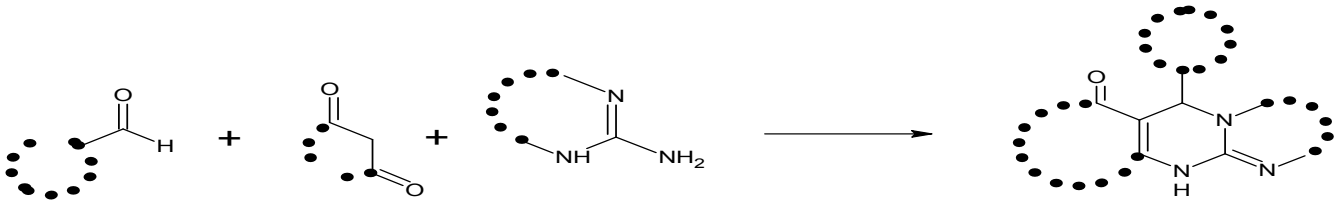
Scheme II.9. Comparison between Hantzch reaction and Hantzch-like reaction.

II.2. Biginelli reaction

Fused dihydropyrimidinones are synthesized by the utilization of cyclic C-H carbonyl compounds: 1, 3 diketones as in Hantzsch reaction, cyclic ketones and cyclic ß-ketoesters. Moreover, cyclic urea like 2-aminobenzimidazole, 3-amino-triazole and 5-aminotetrazole derivatives can be used in Biginelli-like cyclocondensations to get fused DHPMs scaffolds.

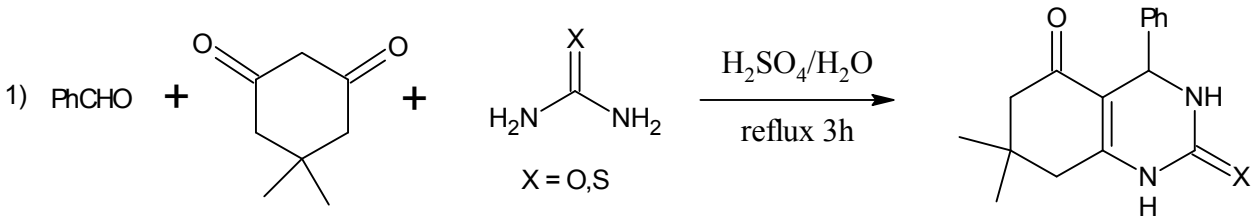
Furthermore, intramolecular or tethered Biginelli reaction presented in **Scheme II.17** is a special case that leads to fused products.

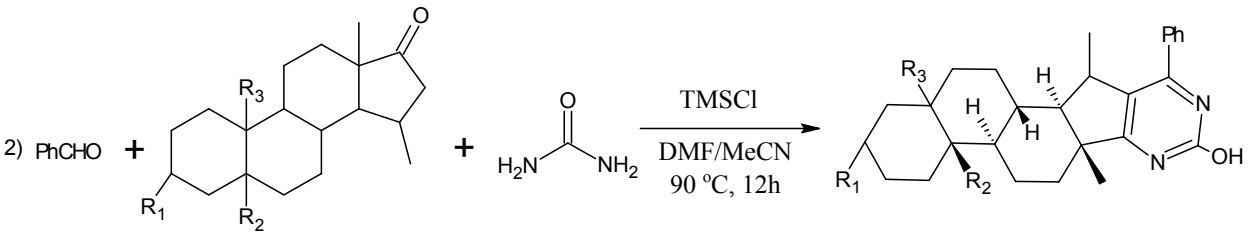
As for aldehydes, a wide range bearring cycles and fused rings are available but they only permit to build tethered cycles.

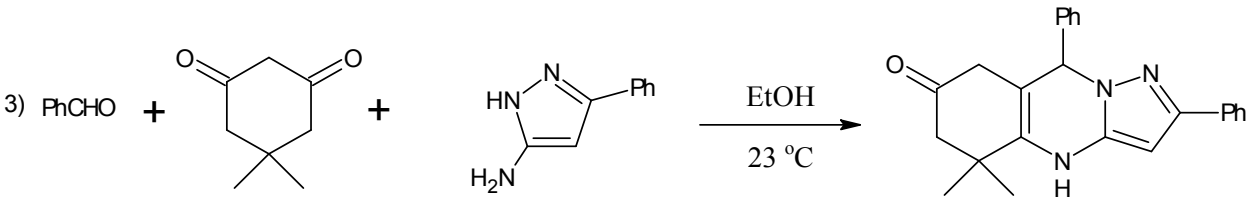


Scheme II.10. Biginelli scaffold general variations.

These are some examples show the ability of synthesizing polycyclic compounds by four Biginelli reaction (1) and (2) [33] and Biginelli-like reaction (3) [34]

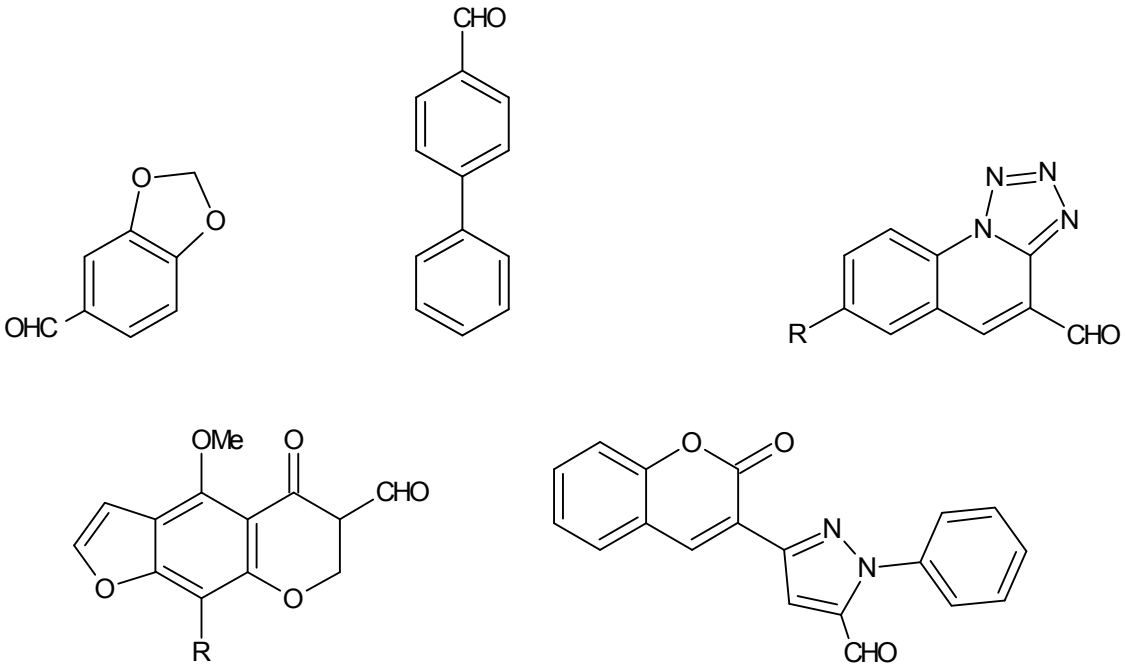






Aldehydes employed in Biginelli reaction

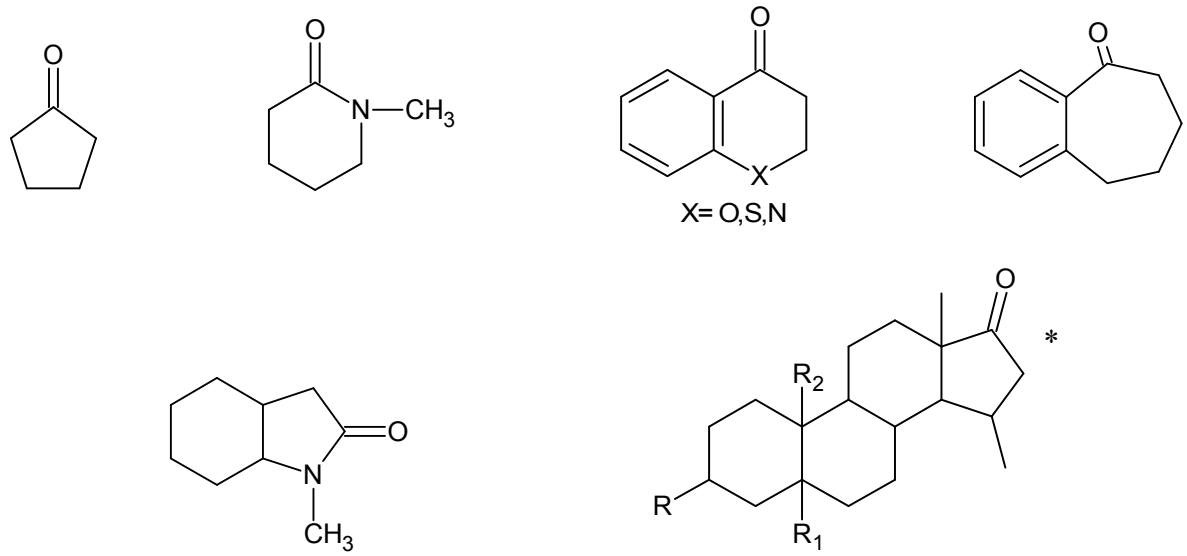
Same to Hantzsch reaction; the Biginelli reaction can employ many aromatic and heterocyclic aldehydes.



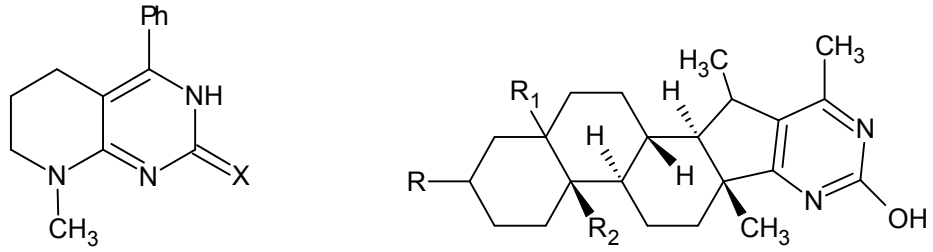
Scheme II.11. Structure of some aldehydes used in Biginelli reaction [29].

Cyclic ketones used in Biginelli reaction

Cyclic ketones can be employed in Biginelli reaction instead of cyclic 1,3 diketones, they are of different and diverse structures.



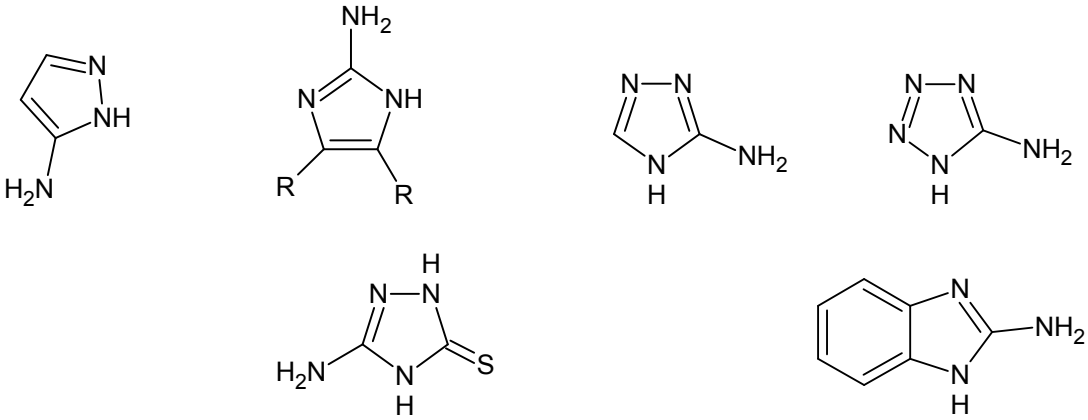
Scheme II.12. Cyclic ketones used in Biginelli reaction [33].



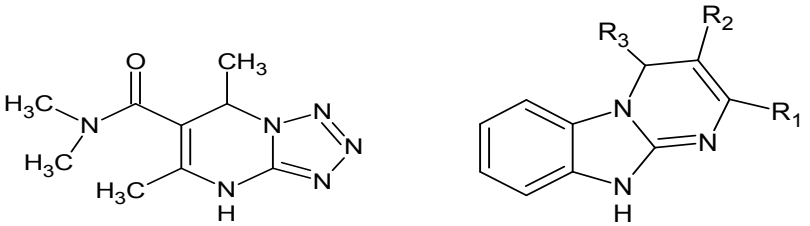
Scheme II.13. Examples of Biginelli products using cyclic ketones [33].*steroid-17-ones.

II.2.1. Biginelli-like reaction

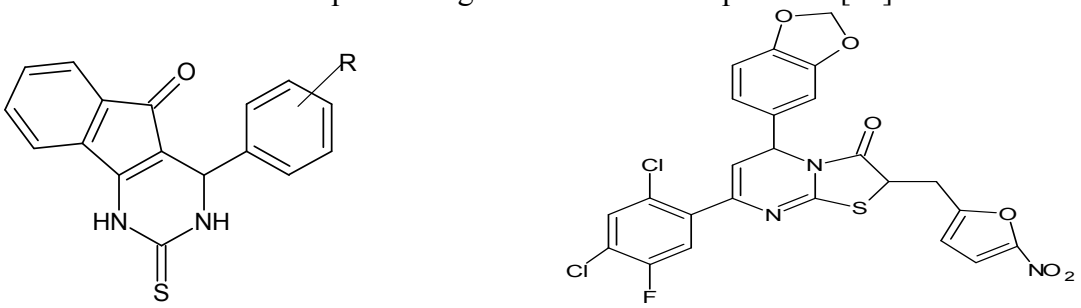
Biginelli-like cyclocondensations based on three-component treatment of 3-amino 1,2,4-triazole or 5-aminotetrazole, beside to others with aldehydes and 1,3-dicarbonyl compounds have been investigated to produce a number of novel derivatives of dihydrotriazolo and tetrazolopyrimidines [27].



Scheme II.14. Examples of cyclic urea derivatives used in Biginelli-Like reaction [33].



Scheme II.15. Examples of Biginelli-like reaction products [33].

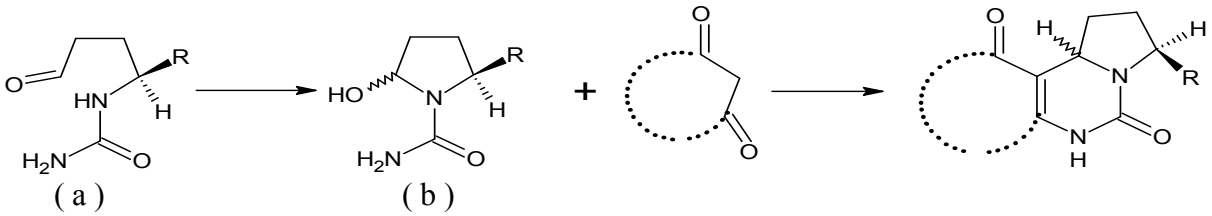


The structure of TRPA1 antagonists DHPM against blood cancer

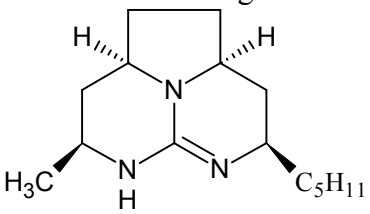
Scheme II.16. Some bioactive DHPMs structure [35].

II.2.2.Tethered Biginelli reaction

The intramolecular Biginelli reaction requires a special building block (b) where the aldehyde and the urea components are linked together (a) [36]. This interesting reaction has been used to synthesis various polycyclic guanidinium alkaloids isolated from marine sponges like: batzelladines K; they have wide range of biological activities due to the tricyclic system.



Scheme II.17. Intramolecular Biginelli reaction.



batzelladine K

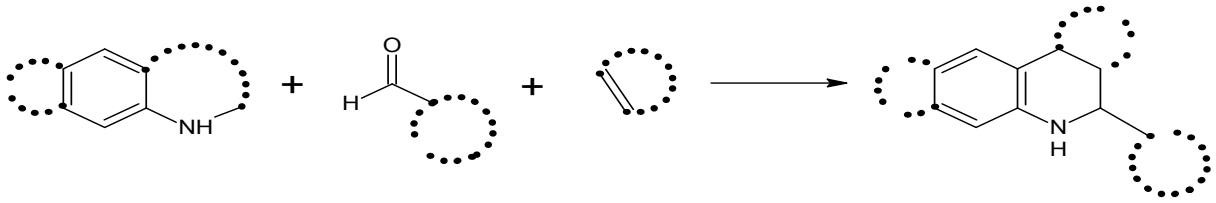
Scheme II.18. Batzelladine K structure.

II.3. Povarov reaction

Povarov reaction is the best example of MCR offering polycyclic products. It is the most common method used in synthesizing THQ, one of the most important nitrogen heterocyclic. Povarov reaction has many types; it can be two component reaction between imines and electron rich olefins, three component reaction between aldehydes, arylamines (even N-heterocycles) and electron rich olefins under a wide variety of catalysts: acid catalysit (Lewis or Bronsted) and metal salt related catalysts. In addition to intramolecular povarov reaction in which substituted arylamines and aldehydes bearing tethered dienophiles undergo imine formation by an intramolecular [4+2] cycloaddition sequences, and four component reaction, where two equivalents of 3,5-dimethylaniline were used under CAN-catalysis [41]. Only three component Povarov reaction will be discussed as it is the most suitable one to construct fused- THQ scaffolds.

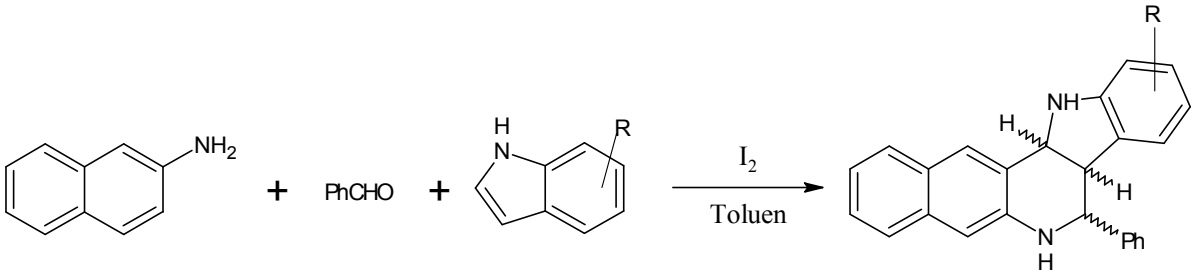
Povarov three component reaction

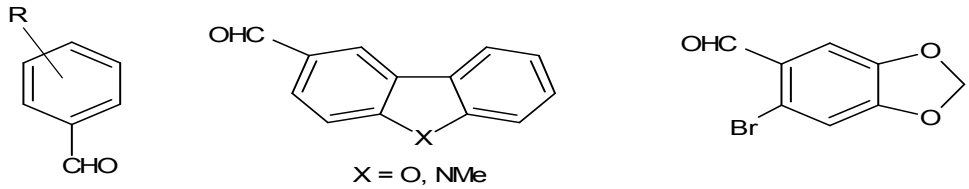
In this type, it is possible to use cyclic olefins, arylamines and N-heterocycles to produce polycyclic systems that contain from bi to hexa fused cycles. As for aldehydes, some aryl and heterocyclic aldehydes can be used; however, the rings will be only tethered to the THQ motif.



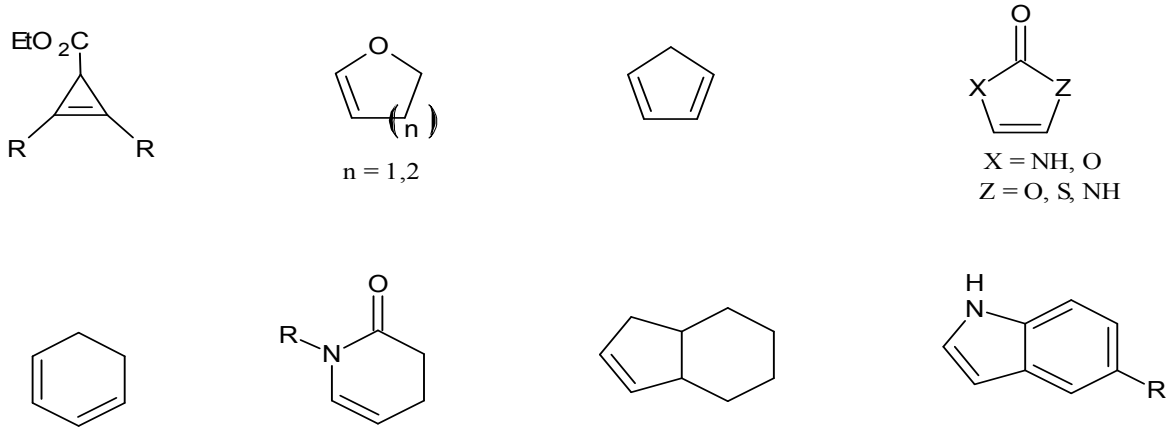
Scheme II.19. Povarov scaffold general variations to give polycyclic scaffolds.

These examples show the ability of synthesizing polycyclic compound by Povarov reaction [41].

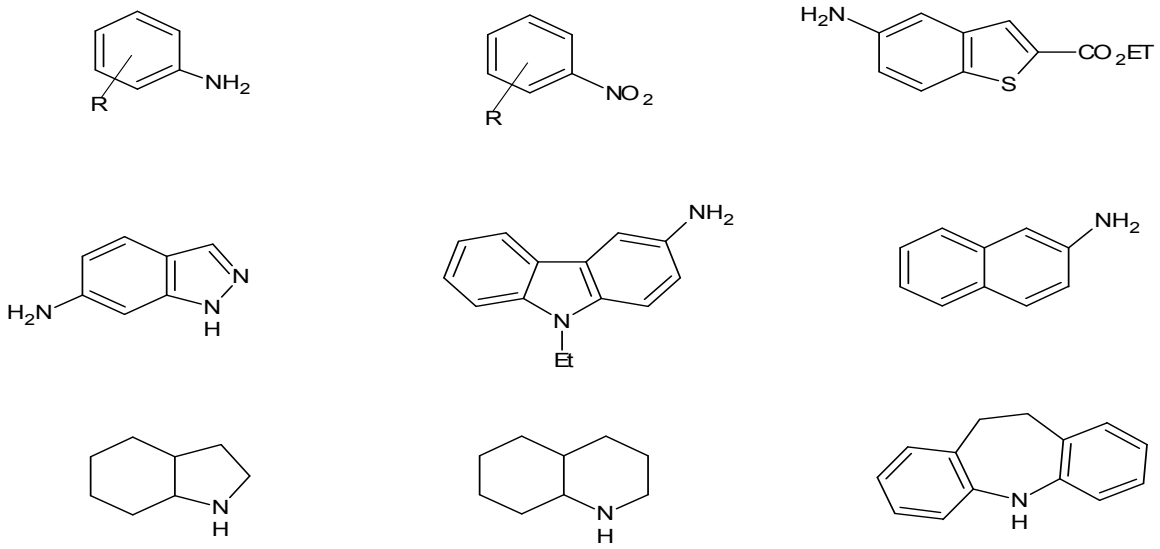




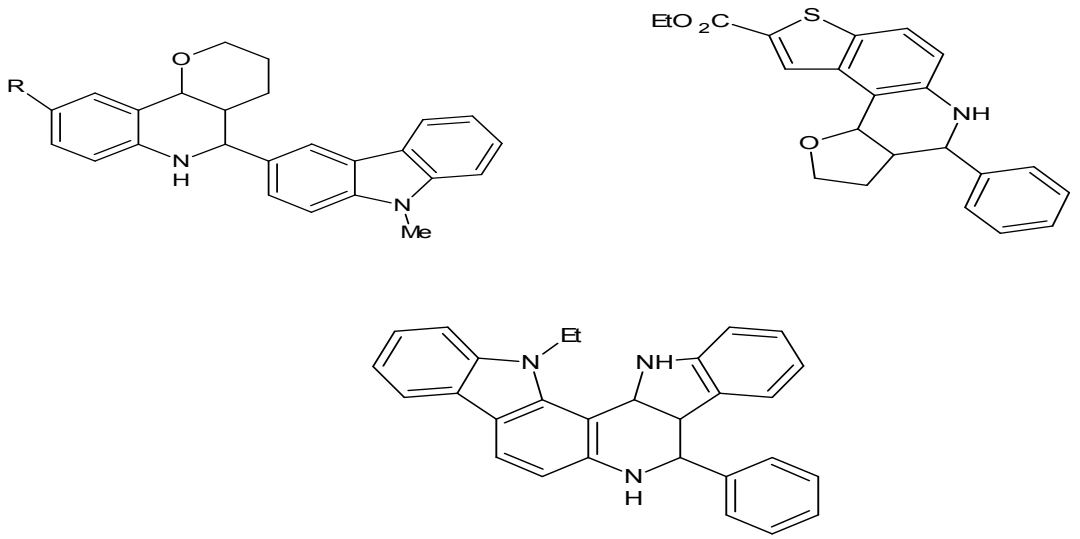
Scheme II.20. Some aldehydes used in Povarov reaction [41].



Scheme II.21. Some Cyclic olefins used in Povarov reaction [41].



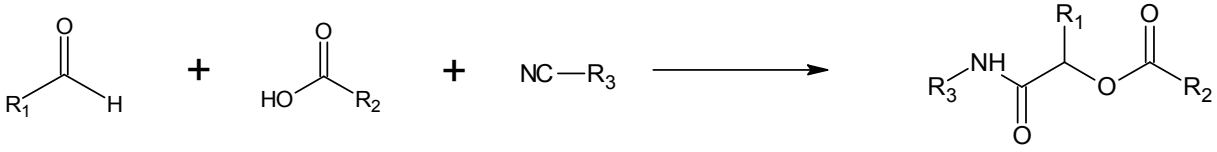
Scheme II.22. Arylamines and N-heterocycles used in Povarov reaction [41].



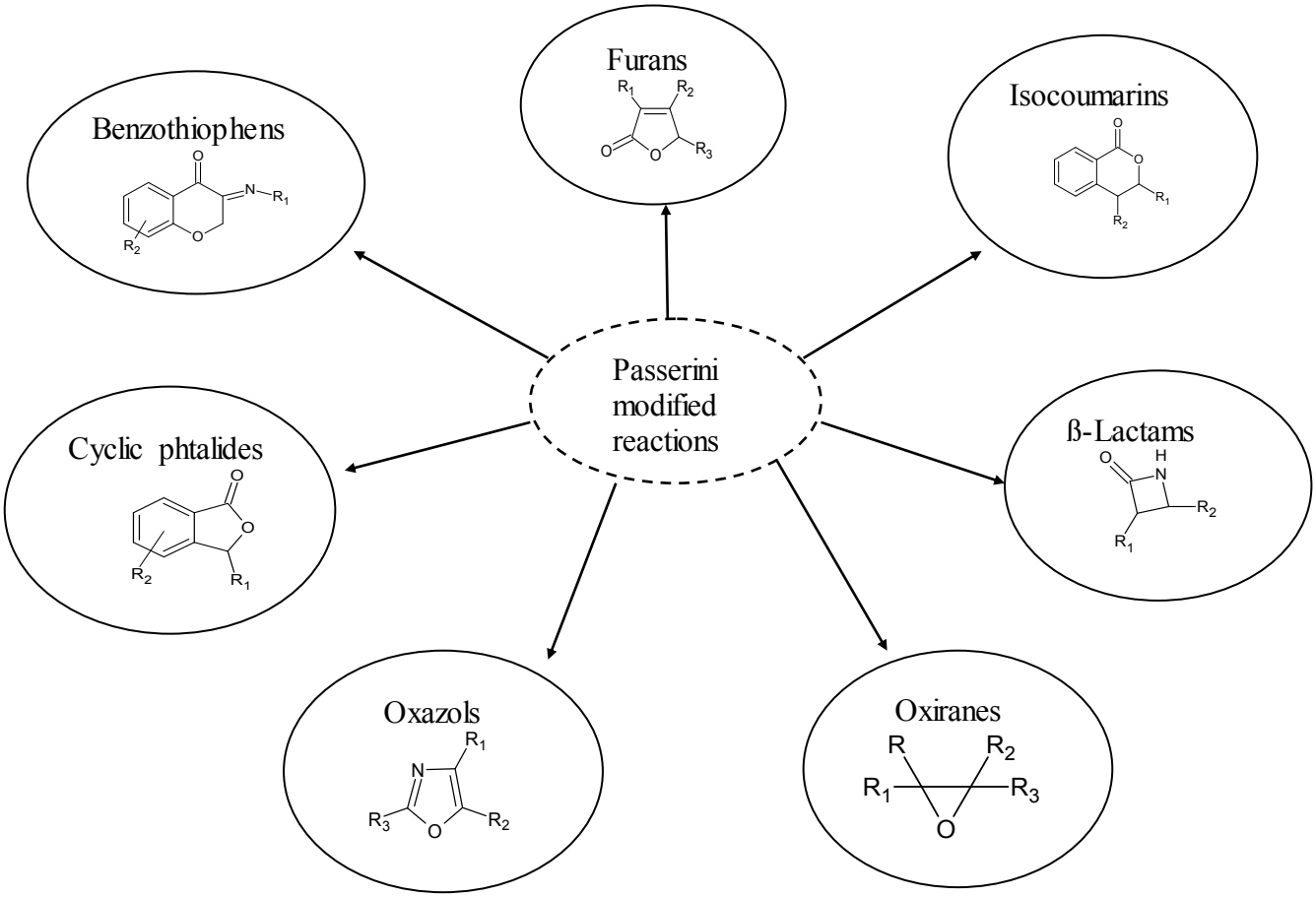
Scheme II.23. Examples of Povarov reaction products [41].

II.4. Passerini reaction

The classical Passerini reaction is not suitable to produce cyclic compounds, although, chemists have made changes to this reaction so it gives different cyclic compounds as it is shown in **scheme II.25.**



Scheme II.24. Passerini MCR.

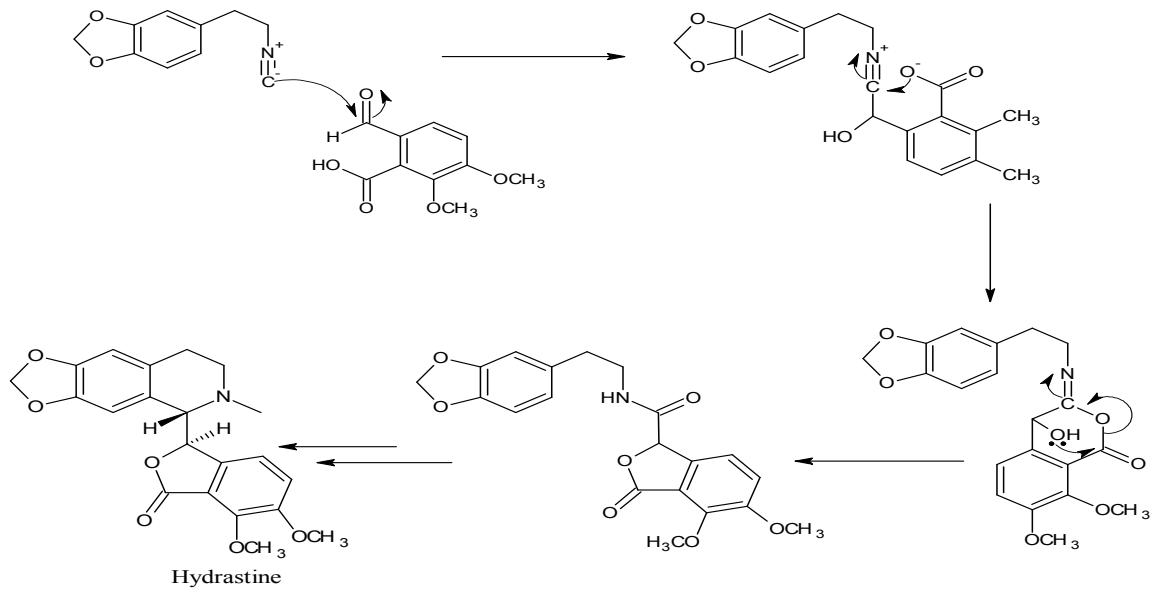


Scheme II.25. Different heterocycles prepared by Passerini modified reactions.

In the Passerini reaction as well as the Ugi reaction, it is difficult to deduce the reactants that can be manipulated to have polycyclic compounds as it was done in Hantzsch and Biginelli reactions, where the main idea was to look after cyclic reactants and reactants bearing cycles in order to use theme for building a fused scaffolds of DHPs and DHPMs, the situation here is different because every modified Passerini and Ugi reaction is independent; although, the key in every one is to use reactants that bear cycles with a view to form an intermediate that undergoes an intramolecular cyclization.

II.4.1. Hydrastine synthesis

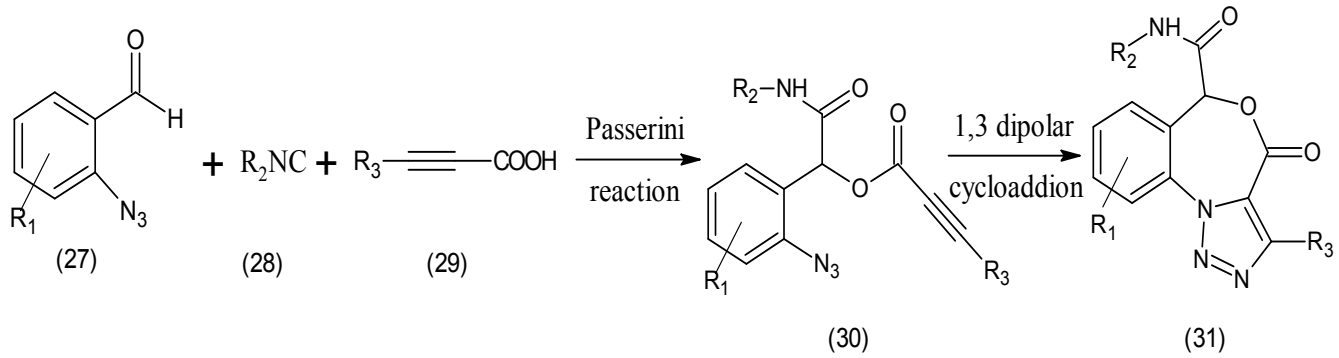
Hydrastine is an alkaloid extracted from roots of golden seal plants, rich in biological activities; the key step to synthesis hydrastine is the intramolecular Passerini reaction between 3,4-methylenedioxyphenethyl isocyanide and opianic acid which constructs a lactonic amide intermediate.



Scheme II.26. Hydrastine synthesis mechanism [37].

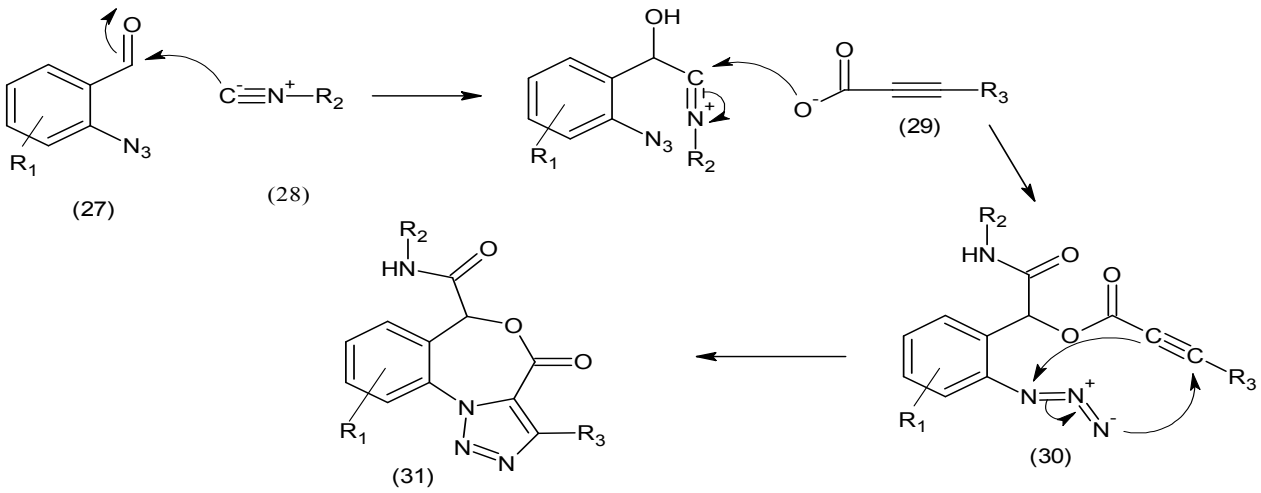
II.4.2. Synthesis of triazolo-fused benzoxazepinones

A Passerini reaction between 2-azidobenzaldehyde (27), isocyanide (28) and propargylic acid (29) forms an intermediate (30) which undergoes a 1,3 dipolar cycloaddition reaction under the heat to produce the challenging scaffold "triazolo-fused benzoxazepinones (31)."



Scheme II.27. Synthesis of benzoxazepinones by Passerini reaction [38].

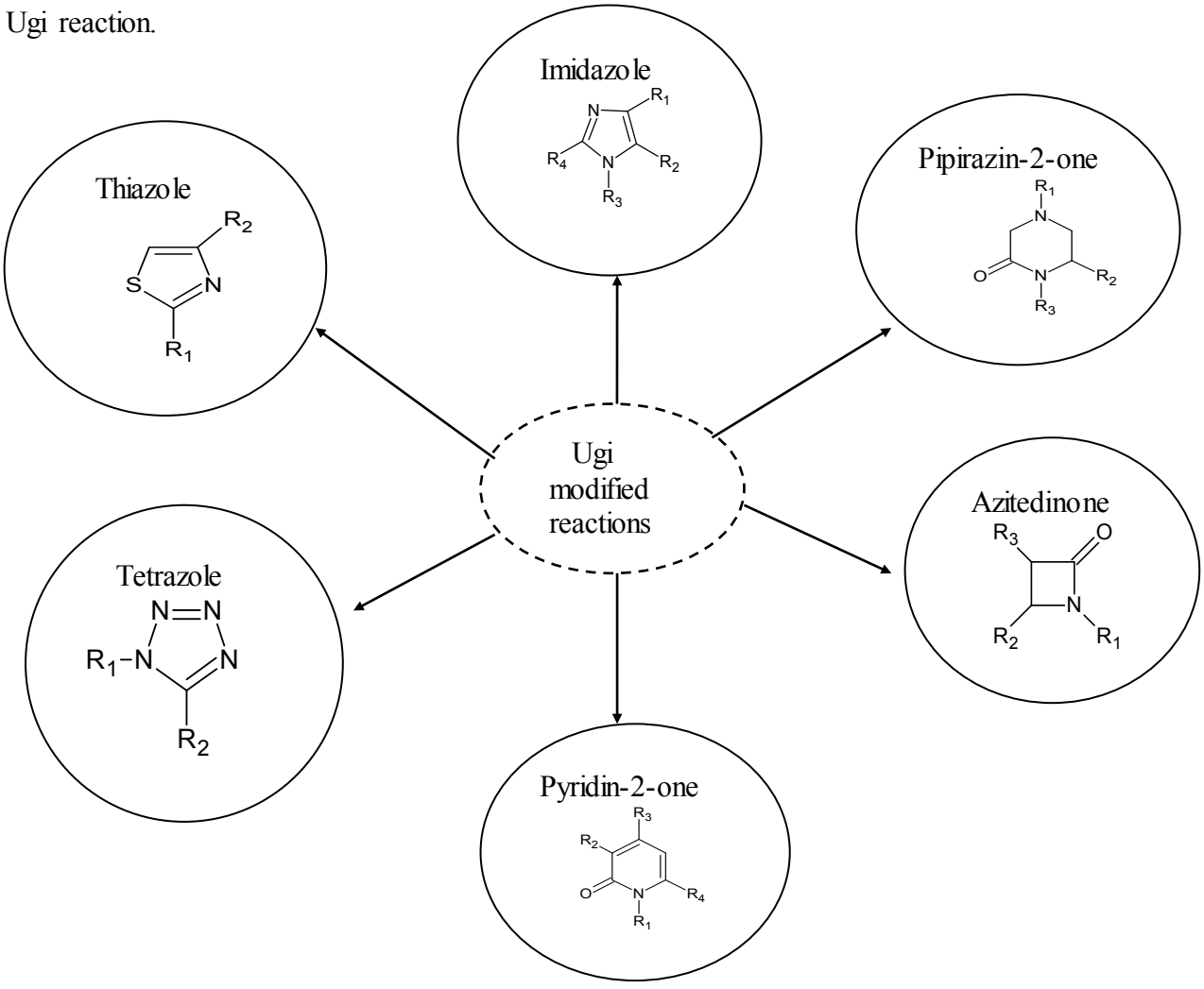
The tricyclic structure in the final product (31) is obtained by the formation of two new heterocycles; the oxazepinone and the triazole, while the benzene was originally present in the benzaldehyde derivative.



Scheme II.28. Proposed mechanism for the synthesis of triazolo-fused benzoxazepinones.

II.5. Ugi reaction

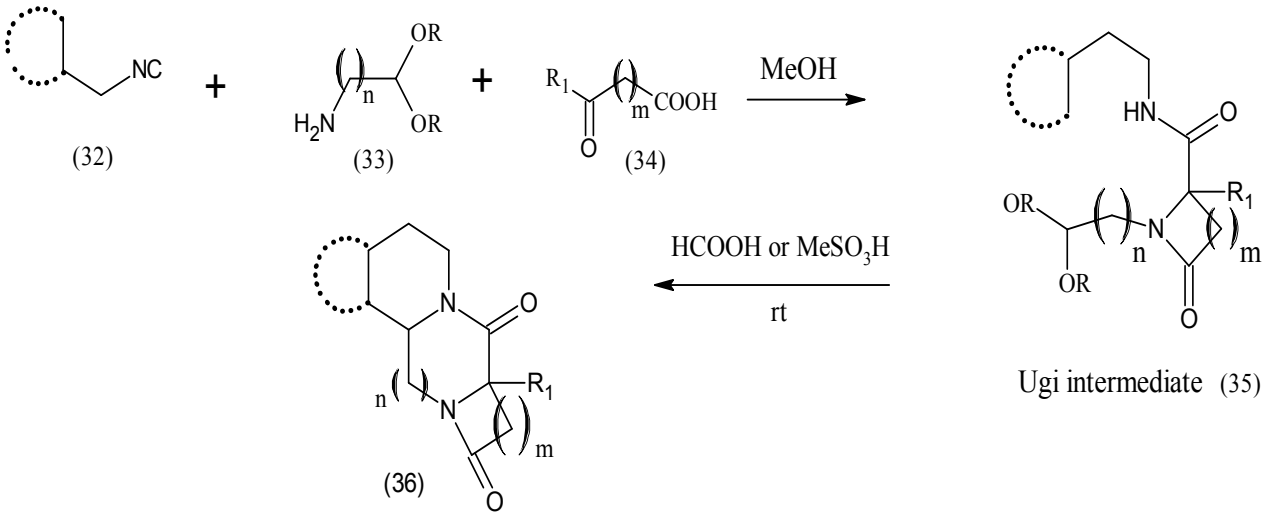
Ugi reaction has been modified to form cyclic and polycyclic compounds; in fact, it is more important than the Ugi reaction due to the nature and the number of libraries produced by Ugi reaction.



Scheme II.29. Different cyclic compounds prepared by Ugi modified reactions.

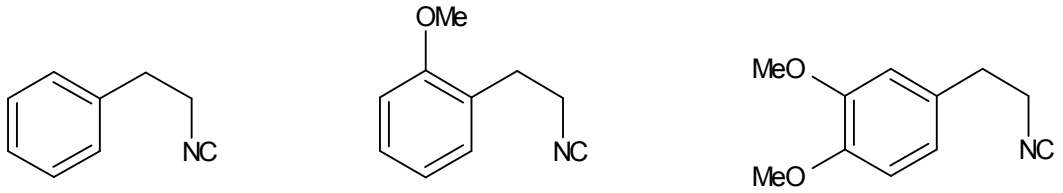
Ugi-Pictet-Spengler Sequence

The Ugi reaction of a phenylethylamine-derived isocyanide (32), aminoacetaldehyde dimethyl acetal (33) and oxocarboxylic acid derivatives (34) combined to a subsequent Pictet-Spengler reaction permit to access a condensed tetra and pentacyclic fused systems (36) with interesting biological activities: anticancer, antiparasital and antifungal [39].

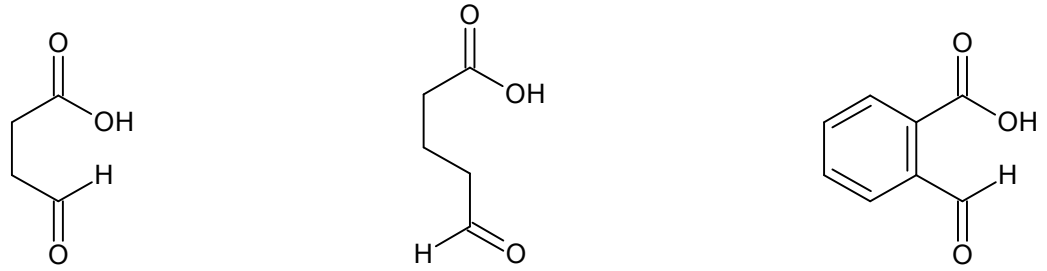


Scheme II.30. Ugi and Pictet–Spengler Reaction Strategy [40].

In all the reactions that have been experienced, n = 1, however, many isocyanides and oxocarboxylic acid derivatives have been used.

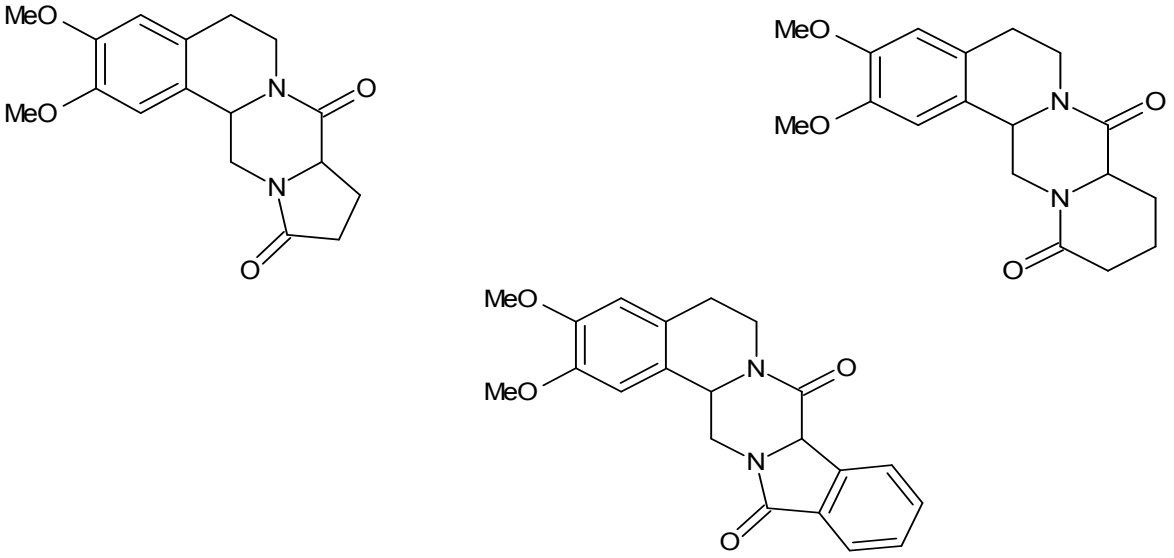


Scheme II.31. Isocyanide derivatives used in Ugi and Pictet–Spengler Reaction.



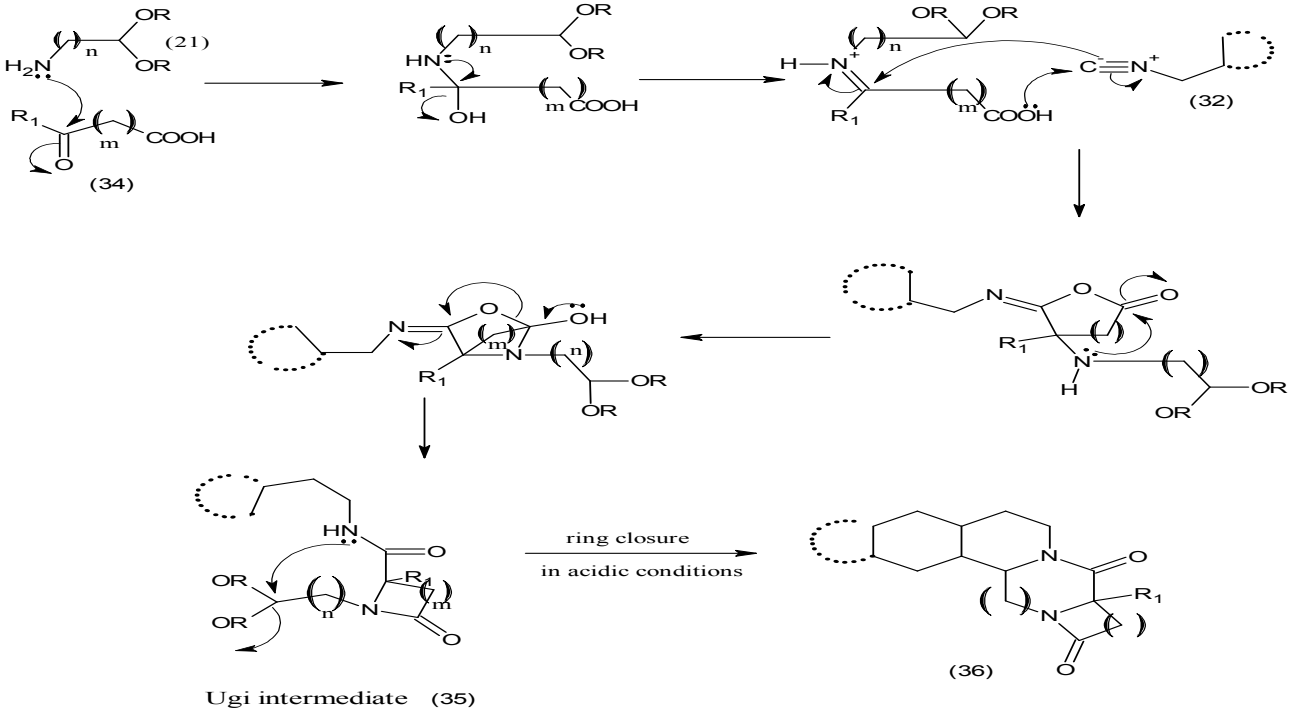
Scheme II.32. Oxocarboxylic acid derivatives used in Ugi and Pictet–Spengler Reaction.

The experiences have shown that the Ugi intermediate had a variant yield from 32%-62% but the pictet-spengler sequences gave a low yield for the penta systems (20%-26%) and high yields for the tetra systems (60%-80%).



Scheme II.33. Some tetra and pentacyclic molecules synthesized by Ugi and Pictet–Spengler reaction [40].

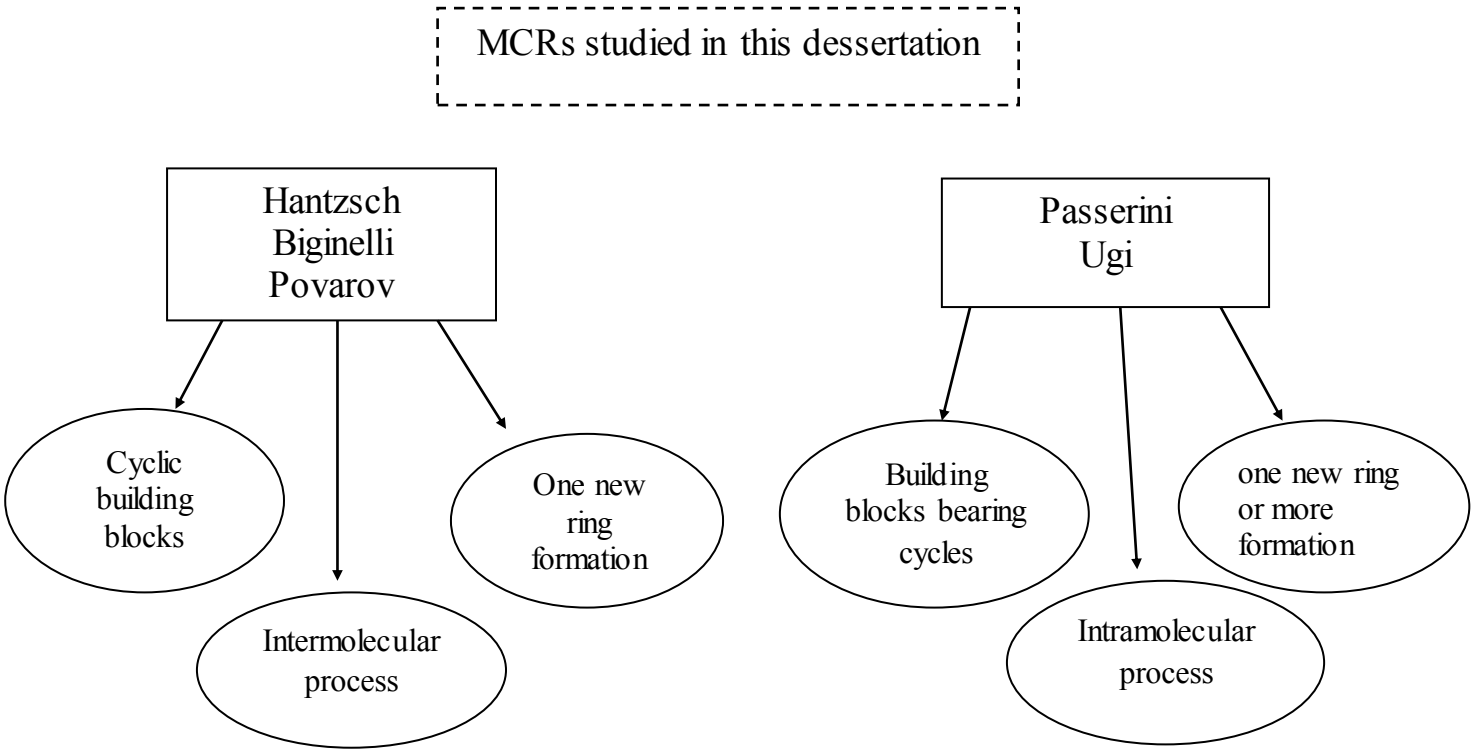
The first step is an Ugi three-component reaction between phenylethylamine-derived isocyanide (32), aminoacetaldehyde dimethyl acetal (33) and oxocarboxylic acid derivatives (34) to offer the dialkyl acetal protected Ugi intermediate (35). Then, it comes the Pictet_Spengler reaction where the intermediate (35) undergoes a ring closure in acidic conditions (formic acid or methanesulfonic acid) at room temperature to yield (36).



Scheme II.34. Proposed mechanism for the Ugi-Pictet–Spengler Reaction.

❖ **Hantzsch,Biginelli, Povarov VS Passerini and Ugi**

It's worth montioning that the MCRs studied in this dissertation could be devided into two groups, the first one involves Hantzsch,Biginelli and Povarov reactions which give polycyclic compounds starting from cyclic building blocks where an intermolecular process leads to the formation of one new ring in the final product. The second group involves Passerini and Ugi reactions which give polycyclic compounds starting from building blocks bearing cycles, where one new ring or more can be formed in the final product by an intramolecular process **Scheme II.35.**



Scheme II.35. Comparison of the reaction process of Hantzsch,Biginelli, and Povarov reactions with Passerini and Ugi reactions.

III.Conclusion

Multicomponent reactions are powerful tools that access high complexity and diversity in few steps and mild conditions to produce different libraries of polycyclic compounds. Even that they have been known since 1838, chemists are still discovering new libraries by simple modifications in the building blocks of known multicomponent reactions.

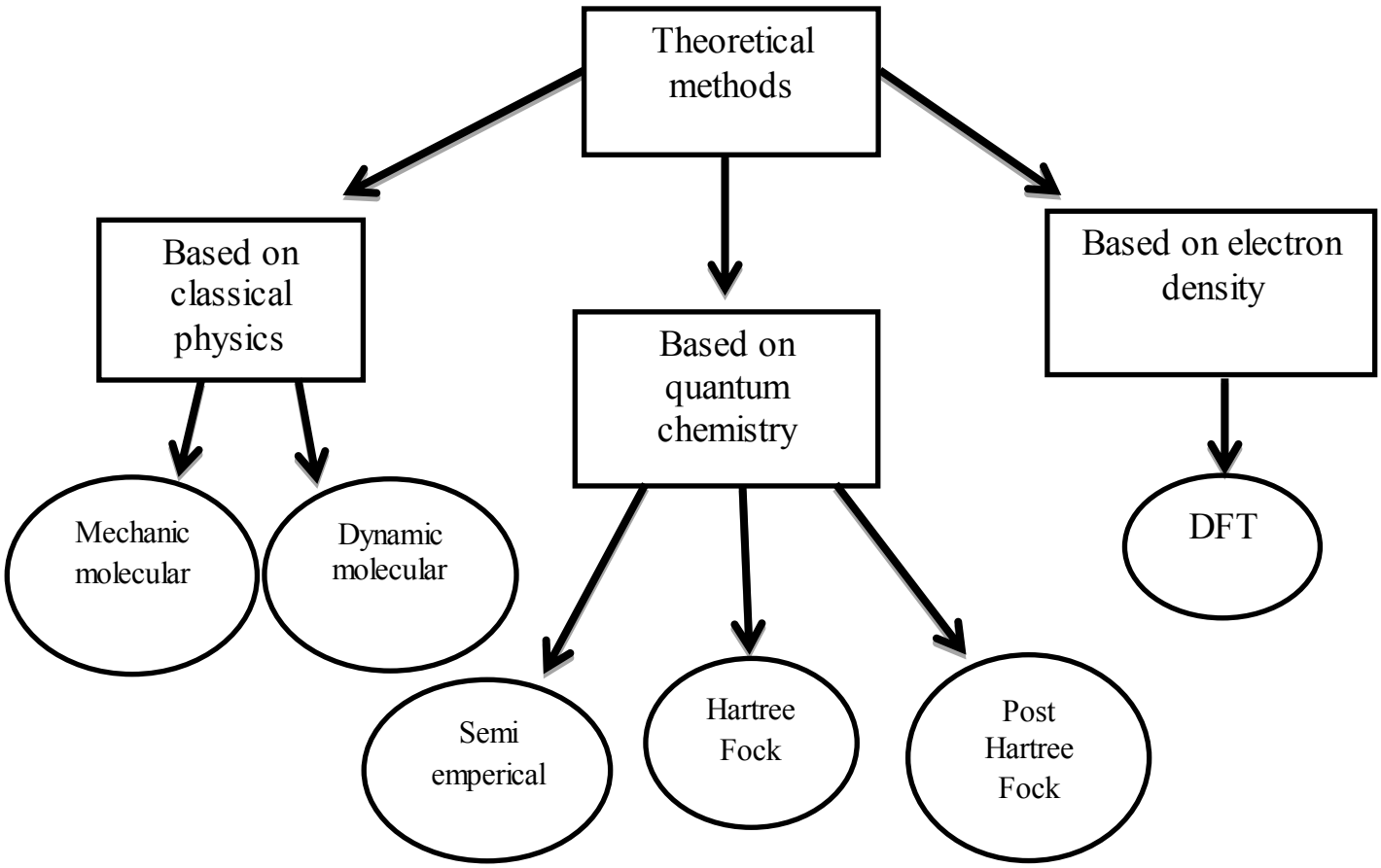
Chapter III
A theoretical study

I. Introduction

Molecular modeling (MM) is the modern branch of science; defined as a collection of computer-based techniques for drawing, representing and manipulating the structures and reactions of molecules, and their properties that are dependent on these 3D structures [42].

It involves the use of theoretical calculation methods (molecular mechanics, molecular dynamics, ab-initio or semi-empirical quantum mechanics, DFT…) **Scheme III.1**.to cover several issues among them computational chemistry, drug design, computational biology, nanostructures, and material science.

In this chapter, a general view on basic principles of density functional theory (DFT) methods and their applications. Furthermore, two MCRs, Passerini and Biginelli are given as examples to show the use of computational methods DFT and AFIR in explaining the mechanism of MCRs.



Scheme III.1. Theoretical methods in computational chemistry.

II. General view on Density Functional Theory (DFT)

II.1. Definition

DFT is a quantum mechanical modelling method, used in physics and chemistry to investigate the electronic structure (principally the ground state) of many-body systems, in particular atoms, molecules, and the condensed phases [43].

II.2. Basic principle of DFT

DFT is a computational method based on the Hohenberg-Kohn theorem which states: the energy of a system is given completely in terms of its electron density [44]. It derives properties of the molecule based on a determination of the electron density of the molecule.
The electron density is a function of only 3 spatial variables x-, y-, and z-position of the electrons and thus independent of the system size so the complexity of the Schrödinger equation decreases.

$$H\Psi = \left[-\sum_{i}^{N} \frac{\hbar^2}{2m} \nabla_i^2 - \sum_{I}^{A} \frac{\hbar^2}{2M} \nabla_I^2 - \sum_{i,I}^{N} \frac{Z_I \ e^2}{\left|\overrightarrow{r_i} - \overrightarrow{R_I}\right|} + \sum_{i<I}^{N} \frac{e^2}{\left|\overrightarrow{r_i} - \overrightarrow{r_I}\right|} + \sum_{I<J}^{N} \frac{Z_I \ Z_J e^2}{\left|\overrightarrow{R_I} - \overrightarrow{R_J}\right|} \right] = E\Psi$$

II.3. Methods of DFT

Methods in DFT are complicated and diverse, but can roughly be divided into three classes:

a) Local density approximation (LDA): assumes that the density of the molecule is uniform throughout the molecule, and is typically not a very popular or useful method.

b) Generalized Gradient Approximation (GGA): looks to account for the non-uniformity of the electron density. The LDA is insufficient to represent the majority of molecular systems because these systems are not found in a homogeneous way thus in practice the real systems cannot be represented by a uniform model. It is for that a second generation of functional which was subsequently developed to better describes the systems; these functional ones called Generalized Gradient Approximation. These functional ones consider exchange-correlation functions depending not only on the density at each point, but also on its gradient, it is described by the form:

$$E_{XC}^{GGA}[\rho_\alpha, \rho_\beta] = \int f(\rho_\alpha, \rho_\beta, \nabla\rho_\alpha, \nabla\rho_\beta) dv$$

The exchange part refers to the names of scientists, it is in general the Becke functional (B), the correlation part that of Lee, Yang and Parr (LYP) or that of Perdew-Wang (PW) with the variants, hence finally the keywords Becke88, PW91, P86 , LYP (34, 35,36,37) and BLYP represent the most used functional in this category [45].

c) Hybrid method: attempt to incorporate some of the more useful features from ab-initio methods (specifically Hartree-Fock methods) with some of the improvements of DFT mathematics, qualified as a hybrid because it takes into account the exact HF exchange energy as well as the DFT exchange and correlation energy [45]: $E_{hybride}^{xc} = c_{HF}\, E_{HF}^{X} + c_{DFT}\, E_{DFT}^{XC}$

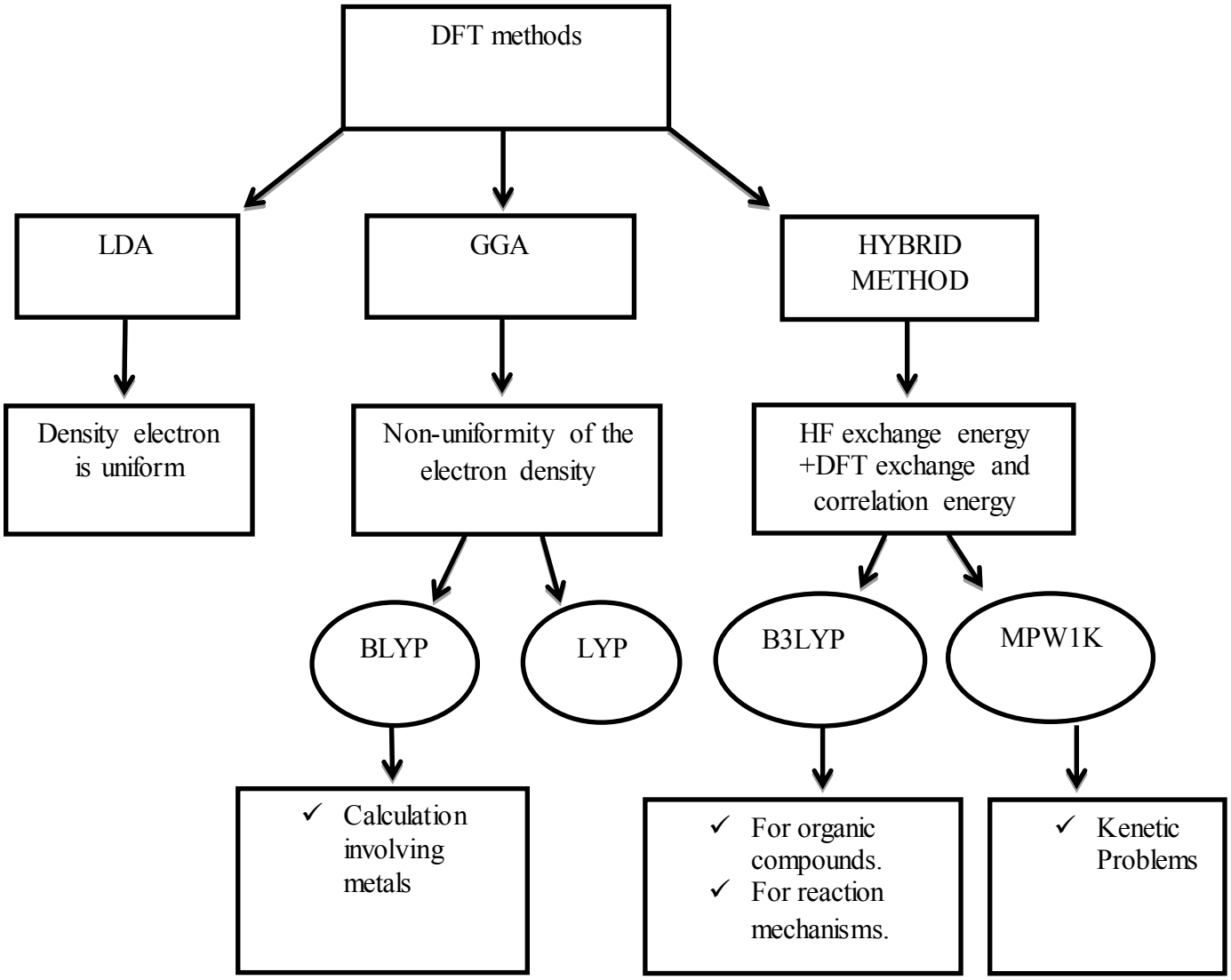
The parameters C_{HF} and C_{DF} are constants to be determined. The most popular hybrid functional is known as B3LYP. It is proposed by Becke as an expression of three parameters denoted by B3 [47] and that of Lee, Yang and Parr (LYP) for the correlation. It allows to correctly describe the magnetic properties of organic molecular compounds [47,48]. Hybrid methods, such as B3LYP, tend to be the most commonly used methods for computational chemistry practitioners, while the MPW1K hybrid method, designed for determination of kinetics problems.

*The most suitable bases in DFT methods for studying organic compounds are: [6-31G (d,p), 6-311G (d,p)]. These bases are a set of atomic orbitals which are mixed in different ways to get the optimum molecular orbitals for the lowest energy of the molecular system under study.

II.4. Applications of DFT

- DFT methods are now standard in virtually all of the most popular software packages, including Gaussian, GAMESS, HyperChem, and Spartan.
- In general, DFT is used for the interpretation and prediction of complex system behavior at an atomic scale. In special, DFT is effective in the determination of kinetic, thermodynamic and electronic proprieties of molecules, beside to reaction calculation and energy transfer and calculation involving metals.
- For organic chemistry, DFT is important for understanding the structure and geometry of compounds, elucidating mechanisms of chemical reactions: as example the reaction mechanisms of the cycloaddition reaction are done using the functional B3LYP method with the standard bases 6-31G * and 6-31 + G * [49]. In addition, it helps in the design of new reactions and catalysts [50].

- B3LYP, running on a 6-31G * base is on average the best choice of a chemical model for most systems. B3LYP / 6-31G * is particularly indicated for organic molecules, but less for molecules containing metals.
- BLYP not particularly accurate with organic compounds, but Provides reasonably good energy values for compounds containing metals.
- Gradient correction methods and hybrid methods provide high levels of precision in determining geometric optimization.



Scheme III.2. DFT methods, their principles and applications.

II.5. Advantages and Disadvantages of DFT

As advantage, the DFT increase the computational accuracy without the additional increase in computing time, beside the fact that DFT methods such as B3LYP/6-31G (d) are oftentimes considered to be standard model chemistry for many applications. Although, determining the most appropriate method for a particular application in DFT is challenging, the practitioner should consult the literature to determine the suitable method for that particular problem or application [50].

II. AFIR method combined with DFT calculations for MCRs theoretical study

It is difficult to study the mechanisms of MCRs, as there can be many possible pathways among the reactants, furthermore, Locating TSs is one of the principal tasks which need a proper initial guess, but it is usually difficult to guess reasonable structures of TSs From the reactants [50].

Recently an automated reaction pathway search method which does not rely on any initial guess has been developed, not only in analysis and prediction of MCRs, but also for many other organic reactions in which often two or more reagents including reactant(s) and catalyst(s) are mixed together and many complex reactions may be taking place simultaneously. The simple idea is just pressing the reactants to each other by a constant force to reach reactive sites, approximate TS structures, and, eventually, products. This method has been called an artificial force-induced reaction (AFIR), it gives not only the lowest pathway but also many higher ones; determination of such pathways strengthens the reliability of a proposed mechanism [50].

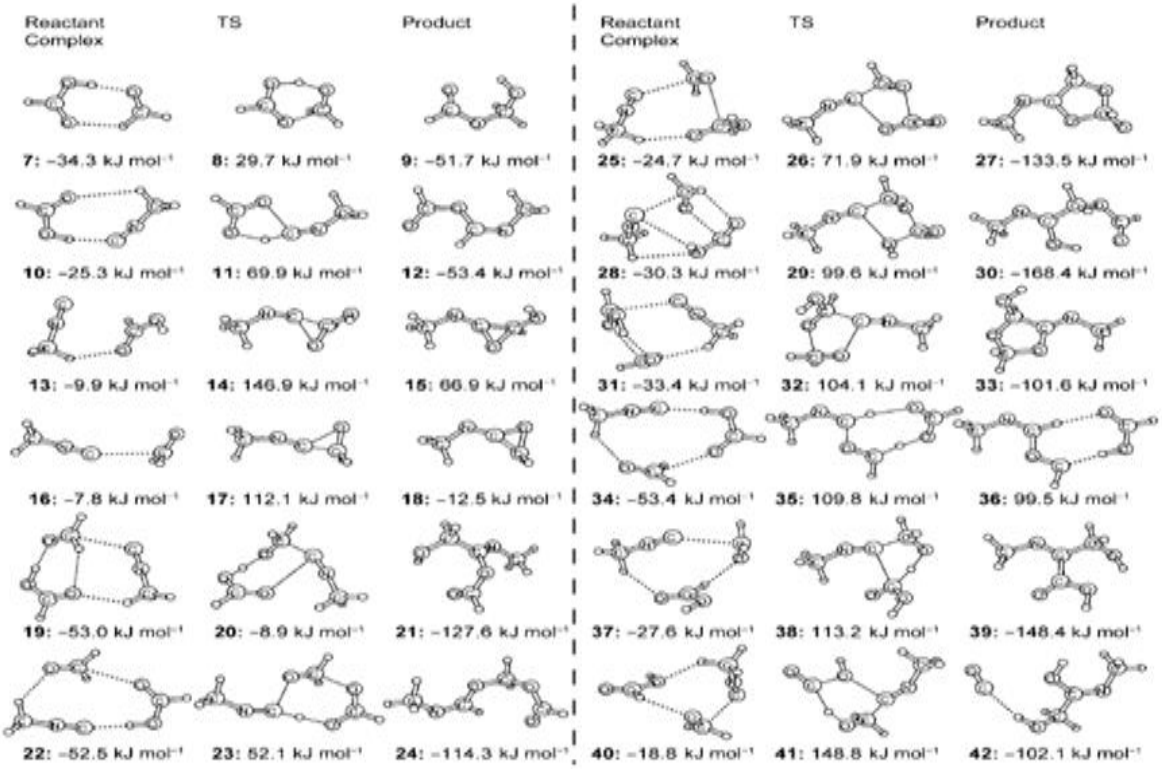
III.1.The Passerini Reaction

In 2010, Satoshi Maeda and co-workers achieved a quantum chemical study on Passerini three component reaction using the AFIR method [51] in order to find transition states (TSs) to determine the most correct and probable pathway in the mechanism.

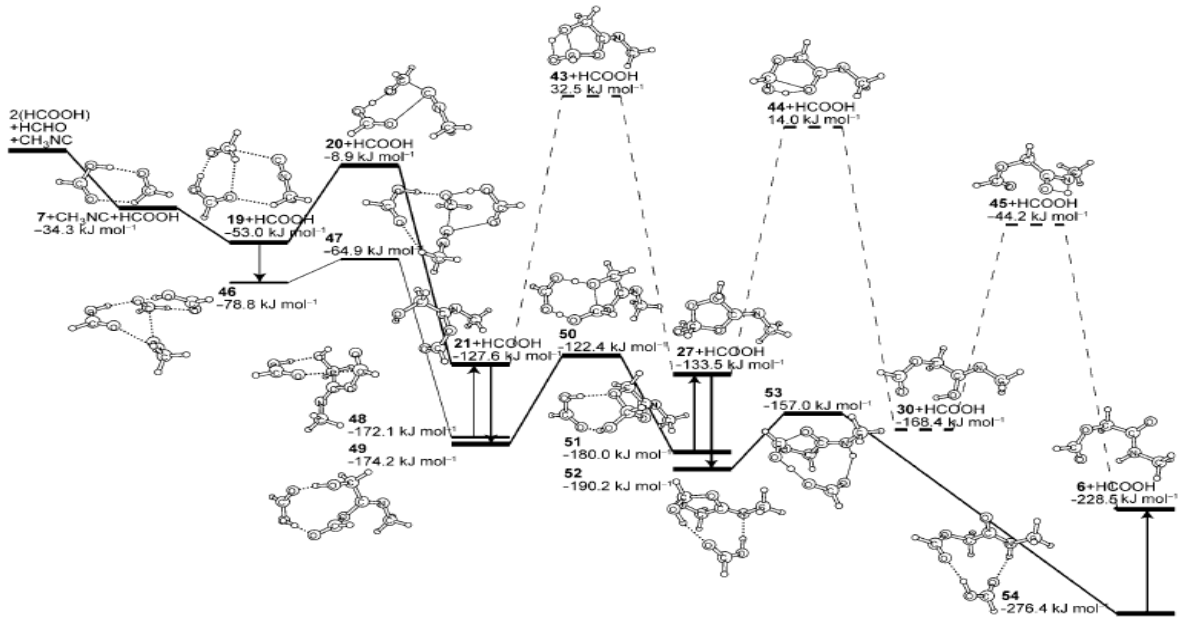
They adopted HCOOH, HCHO, and CH_3NC as the simplest set of reactants of the Passerini reaction and the AFIR method was applied to the trimolecular system and the three bi-molecular systems (i.e., HCOOH+HCHO, HCOOH+CH_3NC, and HCHO+CH_3NC); results are shown in **Scheme III.3**. Among all bi- and trimolecular association pathways, reaction 19→ 21 is the most favorable in terms of the energy of the transition state. However, Reaction of 7 with CH_3NC generates 21 via TS 20. Compound 21 can rearrange into 6 in three steps via

27 and 30 with high barriers at TSs 43, 44, and 45 as shown in **Scheme III.4**, beside to the fact that Compound 21 has never been observed in the Passerini reaction, and it is considered to be a short-lived species which rearranges to 6 immediately. Other pathways have been examined but they all have even higher barriers, pathways that generate a byproduct were more feasible and preferable but its barrier is still too high to explain the efficient mechanism of Passerini reaction.

As no pathway with three-component reaction was satisfactory, they applied a four component Passerini reaction with an extra HCOOH molecule which was not important in the initial associative step from 19 to 21, but in the later bond rearrangement steps it plays a critical role where it lowers the barriers in bond rearrangement steps 49 ⇒ 51 and 52 ⇒ 6. The fourcomponent intermediate 52 directly generates the product 6 in one step, in which the extra HCOOH also participates in the reaction to replace the two original very high barriers [51].

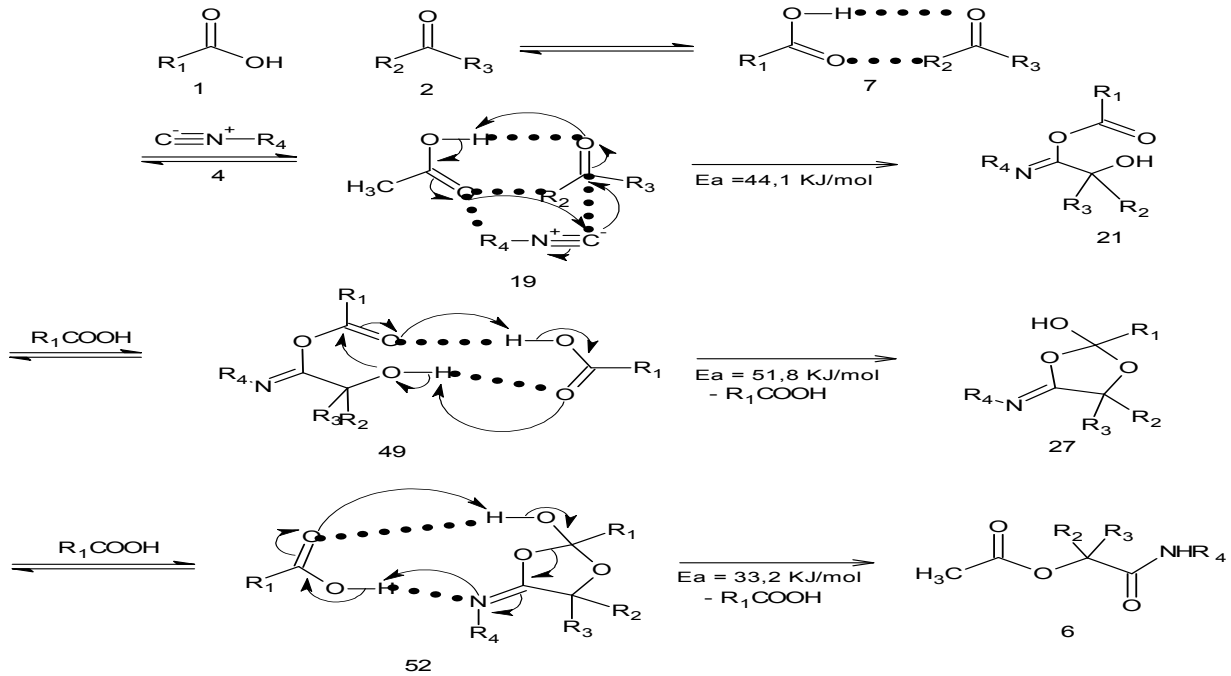


Scheme III.3. All obtained initial association pathways at the M06/6-31+G** level. Energies are relative to the separated three reactant molecules.



Scheme III.4. Potential profile of the most preferable pathway (solid line) leading to product 6 at the M06/6-31+G** level. This pathway involves four components. A minor three-component pathway is also shown (dashed line) for comparison.

As a conclusion for this study, Passerini three-component reaction is actually a four-component reaction via four-component TSs in the final bond rearrangement steps. An extra HCOOH molecule is essential in the mechanism explained in **Scheme III.5**; they authors believe that this mechanism can be applied to real reactions, at least in apolar solvents, which are preferred in conventional Passerini reactions.



Scheme III.5. Detailed mechanism of the Passerini four component reaction.

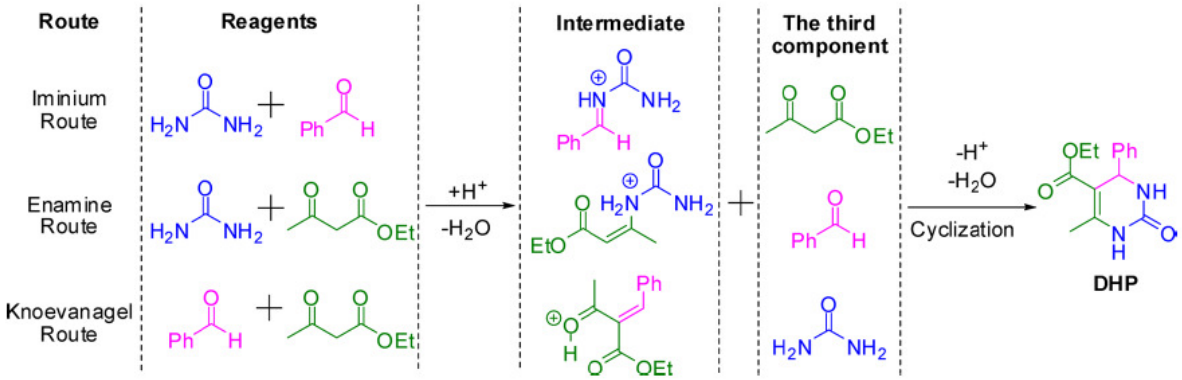
The first step is generated of an H-bonded cluster 7; next, it is the reaction between isocyanide and the H-bond cluster which produces the intermediate 21.

Intermediate 21itself cannot be transformed into 6 because all three bond rearrangement steps have very high barriers. An extra carboxylic acid is necessary as a fourth component to lower the barriers. The second and third rearrangement steps are replaced by a single step via further four-component TS 53.

III.2.The Biginelli Reaction

In 2015, Puripat and co-workers investigated for the first time the entire reaction mechanism of the Biginelli reaction starting from benzaldehyde, urea, and ethyl acetoacetate as reactants by using the recently developed artificial force induced reaction (AFIR) method combined with DFT calculations [52]. Among all possibilities, three main routes were found to be suitable to lead to the expected product, the dihydropyrimidinone, in each route, they followed the initial bond formation step between two reactants (Step I), dehydration step (Step II), bond formation step with the third component (Step III), and final transformation step into dihydropyrimidinone (Step IV):

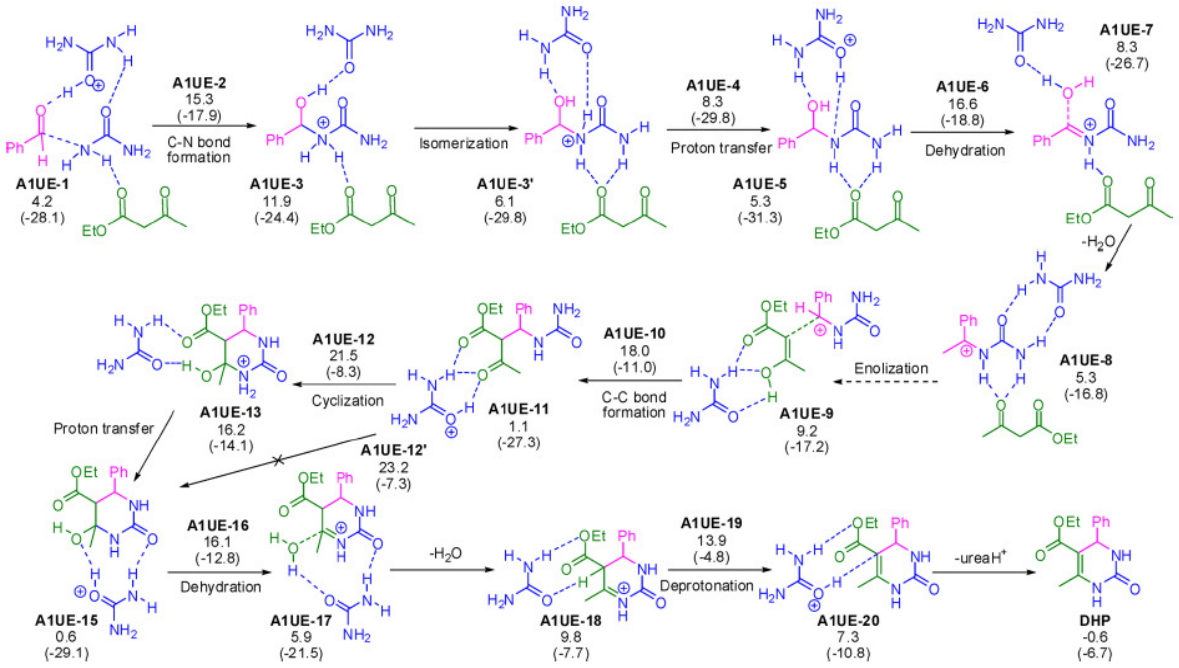
- Route A: the iminium route, which starts the reaction with the protonated urea and benzaldehyde, followed by the condensation of the ethyl acetoacetate.
- Route B: the enamine route, the protonated urea reacts with ethyl acetoacetate, and then condensed with the benzaldehyde.
- Route C: the Knoevenagel route, starts with the condensation of the protonated ethyl acetoacetate with benzaldehyde.



Scheme III.6. Three major possible mechanisms of the Biginelli reaction.

The results of this study can be summarized in two points:

- The most favorable pathway is the iminium route: both resulting barrier in route B and C were higher than that in route A.
- The Biginelli reaction is a urea-catalyzed multicomponent reaction: nearly all steps of all the routes are catalyzed by an extra urea which accepts and releases protons as needed during process and stabilizes the Lewis acid.



Scheme III.7. Best overall pathway for Route A

III. Conclusion

The modern DFT method has succeeded in uncovering the secrets and confusions of the mechanism of multi-component reactions that were discovered a long time ago, some unexpected surprises appeared. DFT still developing so fast and offers a lot of valuable information in different chemistry fields.

General Conclusion

Conclusion

In the present work; an overview on cascade reactions with a focus on MCRs leading to polycyclic compounds is presented. MCRs are a subgroup of cascade reactions. Although they have been discovered since 1838; they still being intensively used in drug design and constitute a powerful tool to access high structural complexity and diversity in few steps and mild conditions to produce different libraries of polycyclic compounds.

Nowadays, chemists have developed new and very interesting MCRs that access high complexity in one pot, especially isocyanide-based reactions which were modified to design polycyclic compounds

Although they present some disadvantages; MCRs could be considered as a green alternative to organic linear synthesis.

The modern DFT method using AFIR has succeeded in rationalizing the mechanism of some multi-component reactions. DFT still developing so fast and offers a lot of valuable information in organic synthesis.

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Summary

In the present work; an overview on cascade reactions is presented. MCRs are considered as a subgroup of cascade reactions. The attention was focused on MCRs leading to polycyclic compounds (bicyclic, tricyclic and polycyclic), this is developed in Chapter I and Chapter II, where the most important MCRs, Hantzsch; Biginelli, Passerini, Pavarov are discussed.

Chapter III is devoted to reviewing the application, in organic synthesis; of modern computational methods. Passerini reaction and Biginelli reaction are given as an example to explain how DFT method using AFIR is used to rationalize the mechanism of MCRs.

Keywords: Cascade reaction, MCRs, Polycyclic compounds, Building blocks, DFT,AFIR.

Résumé

Dans le travail présent; un aperçu des réactions en cascade est présenté. Les RMCs sont considérés comme un sous-groupe de réactions en cascade. L'attention s'est concentrée sur les RMCs conduisant à des composés polycycliques (bicycliques, tricycliques et polycycliques), ceci est développé dans les chapitres I et II, où les RMCs les plus importants, Hantzsch; Biginelli, Passerini, Pavarov sont discutés.

Le chapitre III est consacré à l'examen de l'application, en synthèse organique; des méthodes de calcul modernes. La réaction Passerini et la réaction de Biginelli sont données à titre d'exemple pour expliquer comment la méthode DFT utilisant AFIR est utilisée pour rationaliser le mécanisme des RMCs.

Mots clés: réaction en cascade, RMCs, composés polycycliques, blocs de construction, DFT, AFIR.

ملخص

في هذا العمل يتم تقديم لمحة عامة عن ردود الفعل المتتالية حيث تعتبر التفاعلات متعددة المركبات بمثابة مجموعة فرعية من التفاعلات المتتالية, تم التركيز في هذه الدراسة على التفاعلات متعددة المركبات التي تؤدي الى مركبات متعددة الحلقات (ثنائية, ثلاثية ومتعددة الحلقات), تم التطرق لهذا في الفصل الاول والفصل الثاني اين تمت مناقشة اهم التفاعلات من هذا النوع Hantzsch, Biginelli, Passerini, Pavarov. :

اما الفصل الثالث فقد تم تسخيره لاستظهار تطبيقات الطرق الحسابية الحديثة DFT و AFIR في التركيب العضوي, اين تم اخذ تفاعل Biginelli و Passerini كأمثلة لتوضيح كيف يتم استخدام هذه الطرق في تحديث اليات حدوث التفاعل في التفاعلات متعددة المركبات.

الكلمات المفتاحية: التفاعلات المتتالية, التفاعلات متعددة المركبات, المركبات متعددة الحلقات, وحدات البناء, AFIR,DFT.