1. **Introduction**

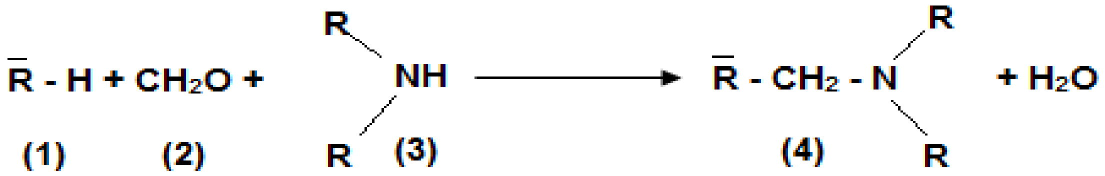
1.1- Mannich Reaction

The Mannich reaction is three component condensation in which a compound containing an active hydrogen atom is allowed to react with formaldehyde and an NH-amine derivative . Secondary amines rather than primary amines and ammonia are employed , the resulting product (Mannich Base) is an amine compound having the N atom linked to the R substrate through a methylene group [1,2].

The aminoalkylation of CH-acidic compounds was described by several authors as early as the 19th. century. However, it was Carl Mannich who was the first to recognize the enormous significance of this reaction , and it was he who extended the chemistry into a broad based synthetic methodology through systematic research. Since then this reaction that now carries his name has developed into one of the most important C-C bond-forming reactions in organic chemistry[3,4].

The Mannich reaction is a classical method for the preparation of β -aminoketones and aldehydes (Mannich bases) and, as such, is one of the most important basic reaction types in organic chemistry. It is the key step in the synthesis of numerous pharmaceuticals and natural products[3,4].

The Mannich reaction can be presented by the following equation:

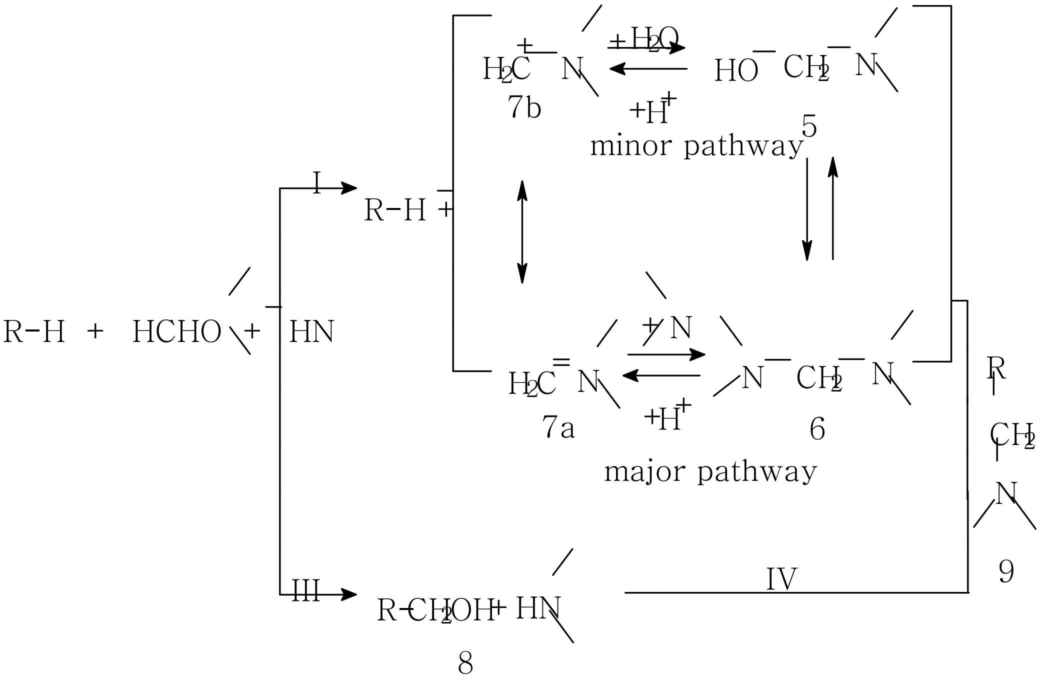


$$\underset{(1)}{\bar{R}-H} + \underset{(2)}{CH_2O} + \underset{(3)}{\overset{R}{\underset{R}{NH}}} \longrightarrow \underset{(4)}{\bar{R}-CH_2-\overset{R}{\underset{R}{N}}} + H_2O$$

The essential feature of the reaction is the replacement of the active hydrogen atom by an aminomethyl or substituted aminomethyl group. The $\bar{R}-H$ symbolizes the active hydrogen component which includes ketones, aldehydes, acids, esters, phenols, acetylenes, $\alpha-$picolines, nitroalkanes and quinolines[1,2].

1.2- Mechanism of the Mannich reaction

The mechanism of the Mannich reaction has been well investigated, the condensation reaction occurs in two steps: first, the amine reacts with formaldehyde to give condensation product (5), (6), (7) (step I) which then attacks the substrate R-H (step II) .The reaction does not normally follow the other possible route (step III and IV) ; however, some successful reaction between hydroxymethyl derivatives (8) and alkylamines to give Mannich bases (9) should be mentioned .



The reactive species in acidic medium is the imonium ion (7a and 7b) derived principally from methylene-bis-amine (6) and secondarily from hydroxymethylamine(5). The electrophilic attack of (7a and 7b) on alkylcarbonyl substrates is postulated to occur by an S_E2 mechanism on the enol , rather than on the carbanion.

In the basic medium , the reactant is postulated to be hydroxymethylamine (5) or, more probably ,methylene-bis-amine (6); however , the participation of the O,N-acetal(alkyl-O-CH_2-N) in the reaction in alcoholic solvents cannot be excluded[1].

1.3- Aminomethylation Reactants

1.3.1- Substrates

Substrates usually employed in Mannich reaction are general XH compounds having nucleophilic properties , with X being equal to C,N or other hetroatom . In particular , CH compounds are suitably activated saturated derivatives ,and NH substrates may be amine ,amides,hetrocycles,etc.Out of OH substrate alcohol are mainly able to give stable Mannich products[5].C-,N-,O- and S-Mannich bases are known.

C- Mannich bases such as :

R-(C=O)-C-CH_2N ,Z-C (Z= carboxy ,Nitro,N-hetroaryl,etc),Z=C ($Z=R_2C$,RN) , R-C=C-, phOH , Z-C-(hetrocycle) (Z=N,O,etc)

N- Mannich bases such as :

R_2N-CH_2-N , R-(C=Z)-N (Z=S,O)

O-,S- Mannich bases such as :

R-O-CH_2-N , R-S- ,R-SO_2- ,R-PO- , R-As-

Substrates have been divided into two main catogeries: CH substrates and XH substrates .CH substrates are compounds having the reactive hydrogen atom linked to carbon affording C-aminomethylationm , substrates are further grouped according to SP^3,SP^2 or SP hybridization of the reaction site[5].

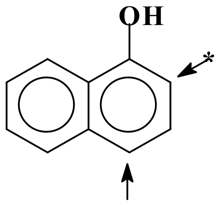
CH substrates are alkenes, homocyclic aromatic (phenols, phenol derivitives, phenol ethers, arylamines, sulfonamides, azulenes, tropolones, metallocenes) , alkynes, aliphatic aldehydes, alkyl ketones, alkyl carbonyl derivitives (acid , este r and lactones), nitro toluenes, Schiff bases, hydrazones, oximes, alkyl nitriles, nitro alkenes and alkyl sulfones[5]. XH substrates are compounds having the reactive hydrogen atom linked to a hetro atom (X= N,P,S,O,etc) affording X-amino methylationm , such as aliphatic and aromatic NH substrates[5].

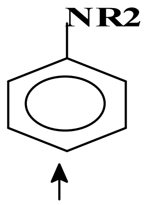
1.3.2- Phenols and NH-Activated Aryl substrates

When aromatic ring is suitably activated by electron – donor substituents (NR_2 ,OH or alkoxy groups) for electrophilic attack, it can easily be subjected to Mannich reaction. Phenols are aminomethylated preferably in the ortho position if available, the para position being alternatively attacked.[6,7] . The sterric effects, electronic effects and the nature of the aminomethylating agents are playing a decisive role in determing the site of attack[5] .

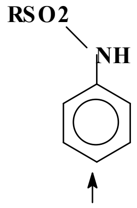
Aromatic rings activated by secondary or tertiary aminic or amidic groups give the Mannich reaction in para position ,as observed in the aminomethylation of arylamines[8,9] and sulfonamides.

For example:





R=H,alkyl

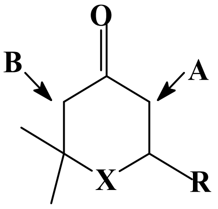


R= alkyl or phenyl

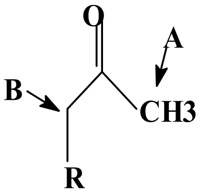
* Arrow and arrow* indicate to experimentaland expected position of attack respectively.

1.3.3- Aliphatic ketones and other activated alkyl substrates

Several studies reported the aminomethylation of dialkyl ketones of the type $R^1R^2CHCOCHR^3R^4(R^1R^2 \neq R^3R^4)$. Both open-chain and cyclic derivatives offer two unequivalent position suitable to Mannich reaction . These are indicated by less substituted C atom and more substituted C atom. Accurataly made investigations [10,11,12,13] concerning the preferred site of reaction lead to the conclusion that enolization of carbonyl group can play a determining role as it may occur at a comparable rate with respect to attack by the reagent[12] such as:



R=H,alkyl & X=(CH_2,O,S)



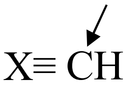
R= alkyl or phenyl

A= slightly in some cases.
B= some results reported with analogous substrates.
* Arrow and indicate to expected position of attack.

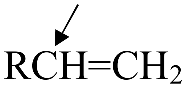
1.3.4- Alkenes and alkynes substrates

Alkenes that lack activating groups or contain carbonyl and thiocarbonyl[14] groups including push-pull olefins and aza alkenes such as oximes and hydrazones , yield unsaturated Mannich bases .Concurrent side reaction may take place with this substrates.Substrate having SP hybridization of the reactive C atom such as alkynes, make it possible to widen considerably the synthetic potential of the Mannich reaction,as it may be applied to variously monosubstituted acetylene derivatives[5].

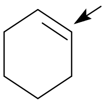
For example:



$X\equiv CH$



$RCH=CH_2$



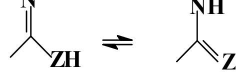
X= C,N

R= alkyl,phenyl

* Arrow and indicate to expected position of attack.

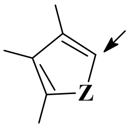
1.3.5-- Aromatic hetrocyclic substrates

Hetrocyclic aromatic substrates constitute a very large and varied group of compounds including five –membered as well as six-membered ring derivatives .The Mannich reaction on these substrates, in particular may be chemo-and/or regioselctive.The presence of a tautomeric keto-enol equilibrium displaced towards the keto form, due to the nature of substituent linked to N atom, as in case of uracil Mannich bases and similar compounds,[15] is also observed. Aromatic N-heterocyclic substrate are divided between five –membered derivatives, having the N-H reactive center not involved in tautomeric equilibria, and five or six-membered derivatives, in which the N-H group in the aminic form participating in a tautomeric imine-amine equilibrium[5].

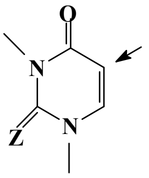


Tautomeric equilibrium in N-heterocyclic derivatives

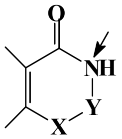
For example:



Z= O,S



Uracils Z=S,O



X,Y= C,N

* Arrow and indicate to expected position of attack.

1.3.6- Amines

The amine must have at least one reactive hydrogen atom thus including ammonia,hydrazine,hydroxylamine derivitives and much frequently aliphatic as well as aromatic primary and secondary amines . Hetroaromatic NH derivitives are also employed.Some general criteria are usually applied to the selection of the amine reagent to be employed when an evaluation of overall feasibility of Mannich reaction on a particular substrate is required. The most relevant features to be considered are steric hindrance and basicity of amine .In some cases it is in fact sufficient to replace dimethylamine with diethylamine for observing a lower reaction yield .The use of secondary bifunctional amines such as piperizine always leads to a bis-Mannich base, due to the raction of both amino groups[16].

NH amides can also behave like amine reagent .Thus ,the resultant aminomethyl derivatives can be then subjected to hydrolysis by means of hydrazine to give the primary amine product[17,18].The amidomethylations play a very important synthetic role , particularly in the production of urea resin and similar derivative, and bis-methyloamides used as cross-linking agents. Anumber of compounds containing the NH residue may behave as either substrates or amine reagents in Mannich reaction, depending on the nature of the co-reagent.Among them, NH-heteroaromatic compounds and hydrazine[19] or hydroxylamine[20,21] derivatives may be considered as amine reagent when allowed to react with more acidic substrates such as alkylthiols affording S-Mannich bases.

1.3.7- Aldehydes

Although formaldehyde (aqueouse formaldehyde , para formaldehyde and trioxane) is usually employed in Mannich aminomethylation . In some circumstances , formaldehyde is replaced in Mannich synthesis by methylene dihalogenides CH_2XY (X or Y= Cl,I)[22,23] or by ether derivitives such as chloro methyl ether[24].

The presence of aldehyde in a Mannich reaction makes it possible to connect substrate and amine moieties through a methylene group. However, when aldehydes other than formaldehyde are used , some other implication have to be considered .First, a reactivity decrease, due to enhanced steric requirements of the aminoalkylation agent related to the increased hindrance of the R group in aldehyde (RCOH), is to be expected . Electronic effects originated by R may also contribute to the lowering of reactivity . Second, the stereochemistry of the resultant product is effected by the creation of a chiral center if the substrate was prochiral,hence, the formation of diastereomeric Mannich bases take place[25,26] . Other aldehyde were used to yield sufficiently stable preformed aminoalkylating agents having the imine structure[27,28].

1.4- Aminomethylation conditions

Formaldehyde,either as aqueous solution (formalin), paraformaldehyde,or 1,3,5-trioxan (trioxy-methylene), is the aldehyde most frequently used .The amines are employed either as free bases or as hydrochlorides.The most widely used solvents are : ethanol , other alcohols such as methanol and isopropanol, water and acetic acid.It is difficult to give general rules concerning the choice of reagents and reaction conditions[29],however the most widely and successfully used reaction conditions for several groups of substrates are as follows:

Alkyl ketones: substrate,amine hydrochloride,and araformaldehyde (sometimes 1,3,5-trioxan or aqueous formaldehyde) are refluxed in alcoholic solvents for several hours.

Phenols: substrate,amine and aqueous formaldehyde (sometimes paraformaldehyde) in alcoholic solvents are heated for a short time (up to several hours), or allowed to stand at room temperature for a longer time (up to a few days).

Carboxylic acid derivatives: substrate,amine, and aqueous formaldehyde are allowed to react in water (sometimes alcoholic solvents) at room temperature.

Heterocyclic compounds : substrate,amine,and aqueous formaldehyde are allowed to react in water or in alcoholic solvents at room temperature(sometimes with brief heating).

Alkynes: various reaction condition as above are used, the reaction is carried out in the presence of copper salts.

The reaction is carried out by mixing the substrate,aldehyde,and amine in equimolar amounts.However, in several cases the amine and aldehyde are condensed first then allowed to react with the substrate, sometimes, the initial condensation products are isolated.In other cases, condensation between aldehyde and substrate (to give R-CH_2-OH) is allowed to take place before addition of the amine.These initial condensation products, usually obtained by use of amidic substrates, indoles,etc., have been investigated for cytostatic activity[30].

Mannich bases often crystallize from the reaction mixture (in some cases, concentration of the reaction mixture or addition of a solvent with low dissolving power is necessary) or the bases can be isolated by extraction with aqueous hydrochloric acid[30].

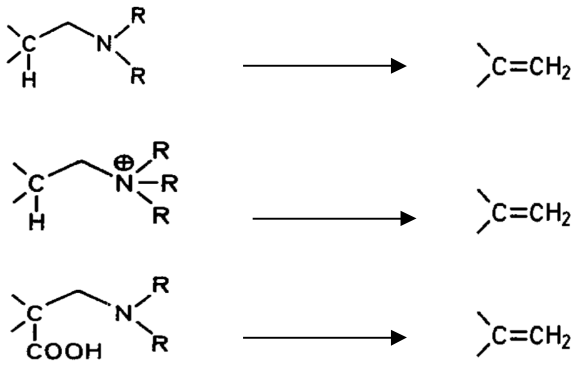
1.5- Reactions of Mannich bases

1.5.1- Deaminomethylation of Mannich bases

Deaminomethylation may be considered a reverse Mannich reaction,which therefore represents an equilibrium.This cleavage reaction has to be regarded as a possible side in all Mannich synthesis.The formation of methylene-bis-derivatives (R-CH_2-R) from Mannich bases[31,32], involve with certainty the deaminomethylation reaction. The interesting cytostatic activity of some Mannich bases derived from succinimide, benzamide and benzenesulfonamide[33] and some other Mannich bases[34], has been studied with respect to their ability to undergo transaminomethylation, deaminomethylation effected by the nature of amino group, reaction medium and steric effect.

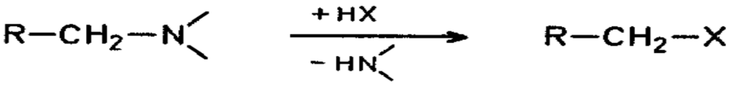
1.5.2- Deamination of Mannich bases

The Deamination reaction involves elimination of a primary or secondary amine from a Mannich base,or of tertiary amine from the mthiodide of a Mannich base, in both cases, the products are vinyl derivatives of the original substrate[35].



1.5.3 - Substitution of other groups for the amino function

One of the most interesting properties of Mannich bases is either ability to undergo substitution of the amino group by a group X.

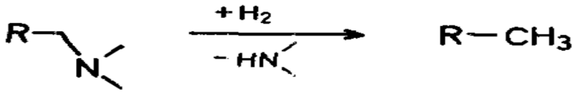


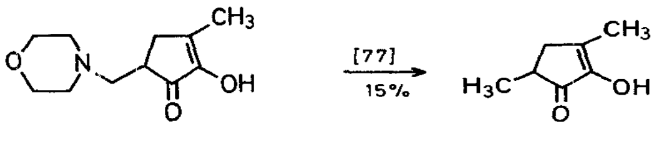
$$R-CH_2-N\langle \xrightarrow[-HN\langle]{+HX} R-CH_2-X$$

This substitution reaction (with elimination of the amino group) can be (when designated as an X-alkylation) an H-alkylation, C-alkylation, N-alkylation, O-alkylation, S-alkylation and P-alkylation[35].

1.5.3.1 H-alkylation

The substitution of an H-atom for an amino group has been obtained either by hydrogenolysis of the free Mannich bases (dimethylamino, piperidino,and morpholino derivatives) or of the corrresponding methiodides. The useful examples are the catalytic hydrogenenolysis of phenolic and steroidal[36] Mannich base to give the corresponding methyl derivatives.



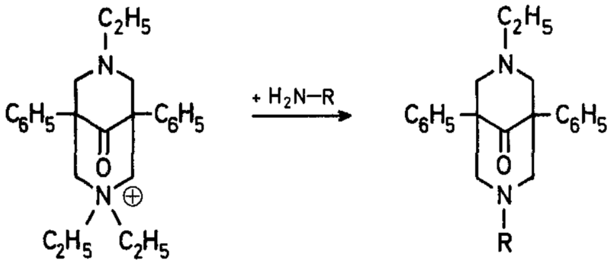


1.5.3.2- C-alkylation

The following compounds have been found to undergo C-alkylation with Mannich bases: hydrogen cyanide, alkylboranes, alkyl ketones, aliphatic carboxylic acid derivatives, enamines, aromatic and heterocyclic substrates, and nitroalkanes[35].

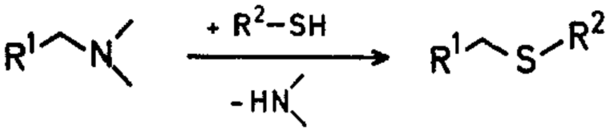
1.5.3.3- N-alkylation

N-alkylation using Mannich bases is successful in the case of most compounds containing an NH group (ammonia, primary and secondary amines, amides, and NH-heterocyclic compounds.for example:



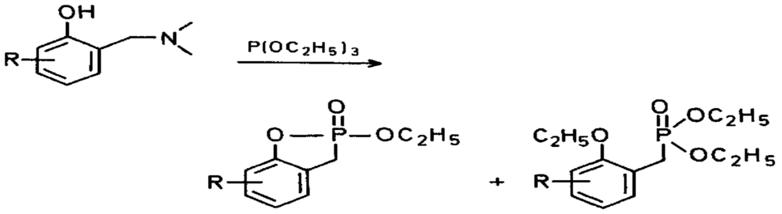
1.5.3.4- S-alkylation

The substitution of the amino group in Mannich bases by an –S-R group to give thioether is carried out by refluxing the Mannich base hydrochlorides with thiols in an aqueous alcoholic medium for a short time. The yields, often high, are affected by the pH of the medium .The reaction has been carried out using bases derived from ketones, phenols, and indoles[37,38] .



1.5.3.5 - P-alkylation

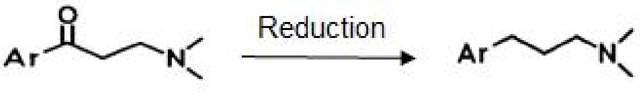
P-alkylation using Mannich bases may be carried out on tertiary phosphines and trialkyl phosphites.Good results are obtained from ketones, phenols, and N-heterocyclic compounds, either as the free bases or as the methiodides[39].



1.5.4- Reduction of Mannich bases

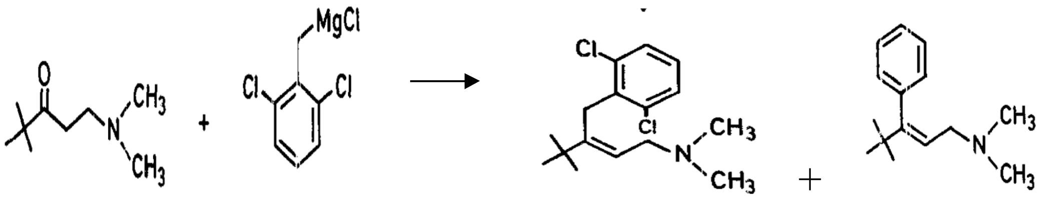
Catalytic hydrogenation or reduction with complex metal hydrides of Mannich bases gives rise to two types of products:

- Products formed by hydrogenation (H-alkylation).
-Products formed by reduction of unsaturated groups present in the molecule.



1.5.5- Reaction of Mannich bases with organometallic compounds

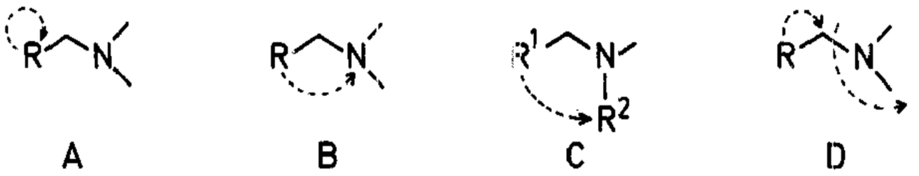
A convenient synthetic route to tertiary β-aminomethylation of suitable ketones is the reaction of resultant Mannich bases with Grignard or organolithim reagents[40,41,42].Usually an excess of organometallic reagent is employed.

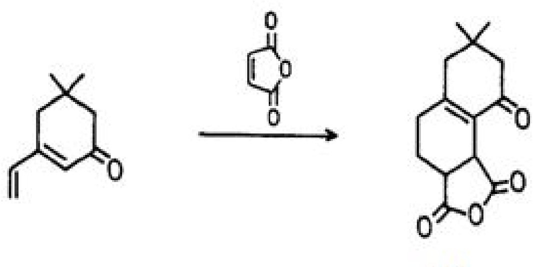


1.5.6- Cyclization reaction of Mannich bases

Mannich bases are useful intermediates for several types of cyclization reactions. These cyclizations are divided into two groups :

- Reactions taking place without elimination of the amino group, and which occur within the group R of the substrate (type A), to the N-atom (type B) or to another position of the amino group (type C), in the latter cases, the reaction affords N-heterocyclic compounds[35].
- Reaction taking place with elimination of the amino group, and involving ring closer at the methylene C-atom (type D) as in (1).

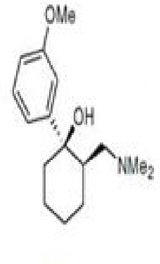




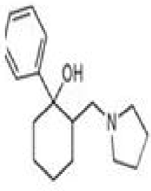
(1)

1.6- Applications of Mannich reaction in bioactive molecule Synthesis

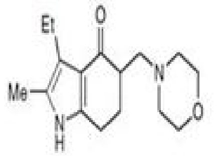
The Mannich reaction and its variants are often employed to access diverse molecules, whose applications are ranging from bioactive skeletons to material science. A representative list of the bioactive/therapeutic molecules obtained by Mannich reaction and the role of Mannich reaction in total synthesis are presented in chart 1. The aminocarbonyl Mannich products are useful in the construction of *β*-peptides and *β*-lactams, which are present in several bioactive molecules such as taxol (antitumour agent), bestatine (immunological response modifier) and SCH48461 (anti-cholesterol agent)[43,44,45,46] Tramadol **(10)**,osnervan **(11)** and moban **(12)** are bioactive *β*-aminocarbonyl derivatives with analgesic, antiparkinson and neuroleptic properties (chart 1).[47] It is believed that the solubility of the Mannich derivatives increases in water due to protonation of basic amine nitrogen atom.[48] Mulundocandin, a class of lipopeptides, showed excellent *in vitro* activity against *Candida* species. However, poor solubility restricts its widespread application. Lal *et al.*carried out a semi-synthetic modification of mulundocandin by Mannich reaction.[49] The Mannich derivatives of mulundocandin **(13)** exhibited significant improvement in solubility, while retaining the activity (chart 1).Mannich reaction was useful for the preparation of zolpidem **(14)**, a hypnotic drug used for the treatment of insomnia (chart 1).[50] The cationic surfactant molecules obtained from Mannich bases possess excellent fungicidal property along with good biocidal property against Gram-positive and Gram-negative bacteria.[51] The quinoline derived Mannich base **(15)** possess vasorelaxing properties (chart 1).[52] Such molecules are useful in the treatment of hypertension. 1,2,4-Triazole derived Mannich bases exhibited anticancer activity.[53] The isothiazolopyridine derived Mannich bases **(16)** were found to be 2 to 10 times more potent than the reference drug acetylsalicylic acid (chart 1).[54] The Mannich reaction is useful for the synthesis of ferrocenyl derived aminohydroxynaphthoquinones **(17)** (chart 1).[55] These products exhibited good activity against *Toxoplasma gondii* and atovaquone resistant strain of *T. gondii*. Mannich reaction also plays a significant role in bioactive skeleton target synthesis. Chernov *et al*. reported the synthesis of alkaloid-like molecules **(18)** and **(19)** from lambertianic acid via Mannich-type intramolecular ring closure reaction (chart 1).[56] Martin *et al.* employed vinylogous Mannich reaction to synthesize bicyclic lactam(20), a key intermediate used in the total synthesis of alkaloid pumiliotoxin 251D (chart 1).[57] Proline- catalysed asymmetric Mannich reaction played a vital role in the synthesis of *N*-terminal amino acid equivalent moiety **(21)** of peptide antibiotic, nikkomycin (chart 1).[58 ,59]



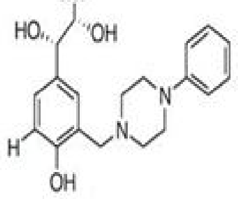
10



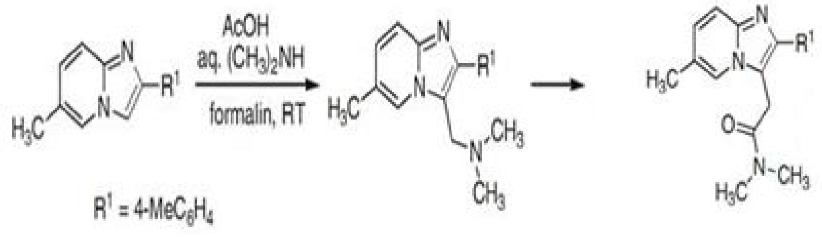
11



12

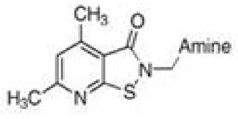


13

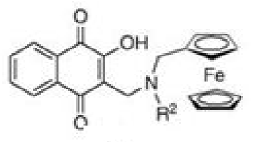


14

15

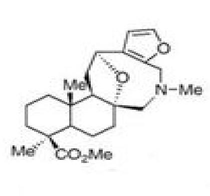


16

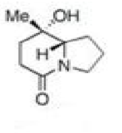


17

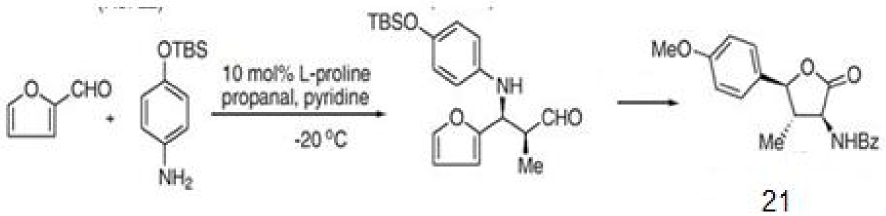
18



19



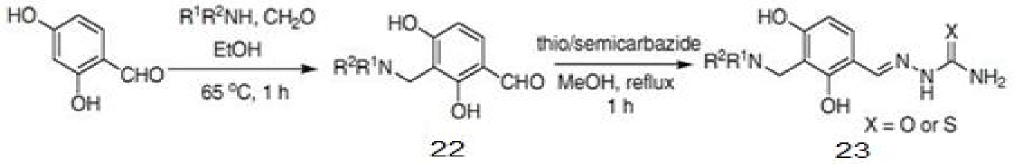
20



21

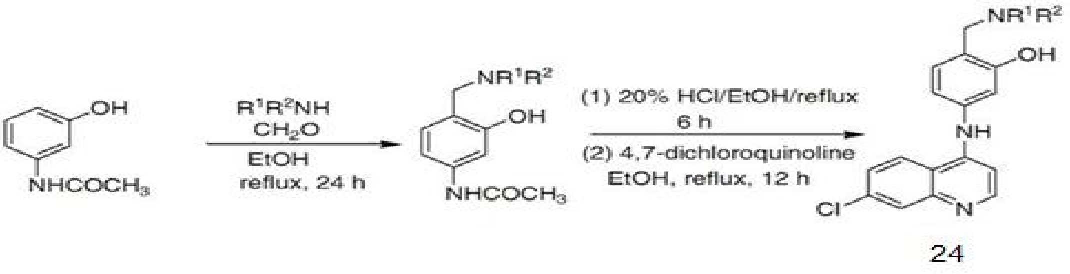
Bioactive Mannich derivatives

The phenolic Mannich bases possess good biological activity partially due to the liberation of α,β–unsaturated ketones by deamination. The α,β–unsaturated ketones have good affinity toward thiols and hence they may selectively bind and inhibit the cysteine proteases. Chipeleme *et al*. synthesized phenolic Mannich bases **(22)** by treating equimolar quantities of 2,4-dihydroxybenzaldehyde, formaldehyde and secondary amine in ethanol solvent[60]. Reaction of the resultant Mannich base with thiosemicabazide afforded (23).



NR^1R^2 = NEt_2, pyrrolidino, piperidino, morpholino, methylpiperazino, 4-(7-Cl-quinolinyl)-piperazino

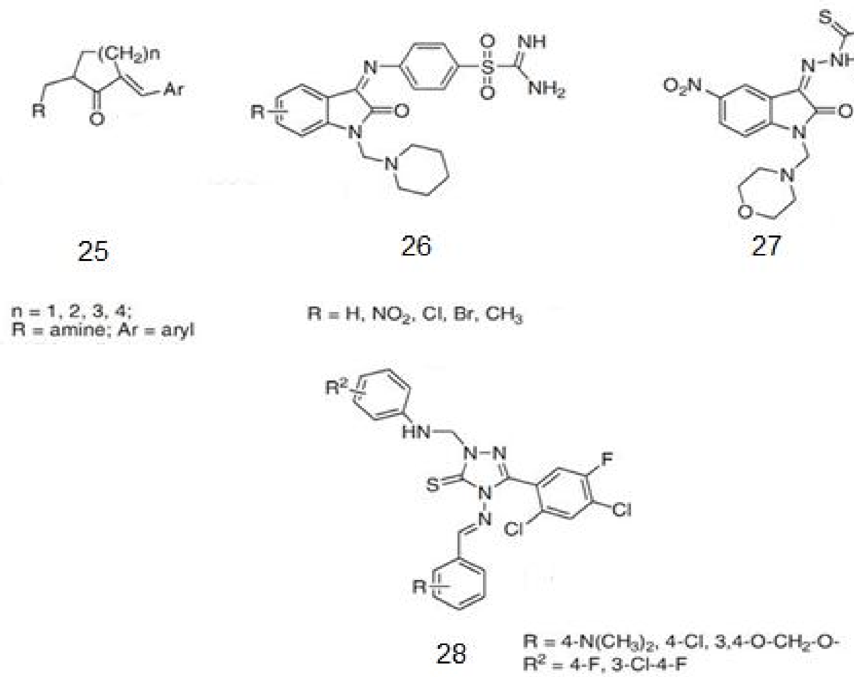
O’Neill *et al*. reported the synthesis of quinoline analogues(24) by coupling chloroquinoline with phenolic Mannich bases [61].



R^1, R^2 = methyl, ethyl, *n*-propyl, *n*-butyl, $(CH_2)_4$, $(CH_2)_2O(CH_2)_2$, $(CH_2)_5$
R^1 =H, R^2 = Et or *i*-propyl or *t*-butyl

Synthesis of quinoline analogues by Mannich reaction

Karthikeyan *et al*. reported the synthesis and biological activity of 2,4-dichloro-5-fluorophenyl substituted Mannich base derivatives(25-28)[62]. TheMannich base derivatives showed good antibacterial and antifungal properties.



25

n = 1, 2, 3, 4;
R = amine; Ar = aryl

26

R = H, NO_2, Cl, Br, CH_3

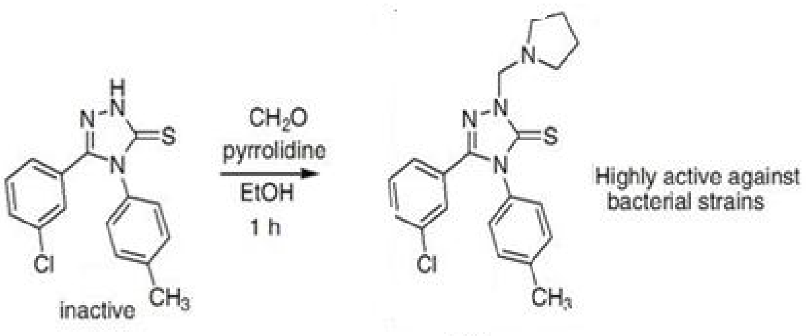
27

28

R = 4-$N(CH_3)_2$, 4-Cl, 3,4-O-CH_2-O-
R^2 = 4-F, 3-Cl-4-F

Representative list of antimicrobial Mannich bases

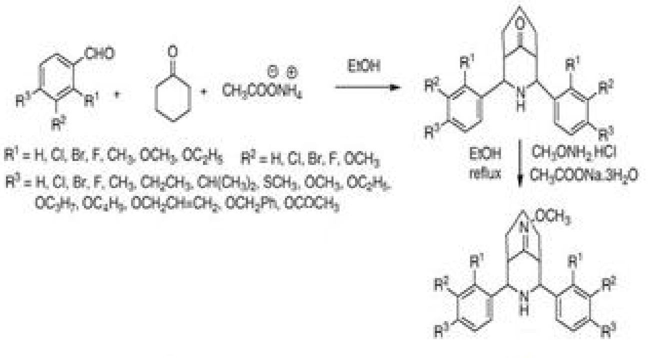
Plech *et al*. reported the synthesis of triazolinothione Mannich bases **(29)**, by reacting 1,2,4-triazolino-3-thione , pyrrolidine and formaldehyde in ethanol solvent.[63] The studies revealed that the introduction of a Mannich side chain in the reacting substrate imparts several-fold increase in antibacterial activity.



29

Triazolino-3-thione Mannich derivatives

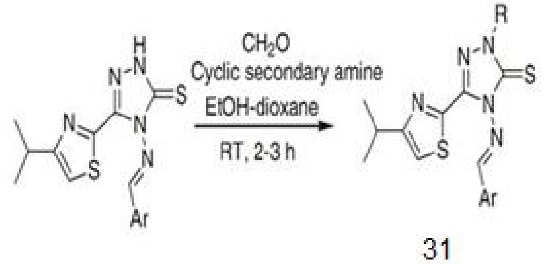
Parthiban *et al.* reported the synthesis of 2,4-diaryl-3azabicyco[3.3.1]nonan-9-one *O*-methyloximes **(30)** and the corresponding *N*-methyl analogs through modified Mannich reaction.



30

Antitubercular Mannich derivatives-

The Mannich reaction of substituted triazole, formaldehyde and cyclic amines in ethanol-dioxane solvent mixture gave the corresponding triazole Mannich derivative **(31)**.[64]



31

Antitubercular Mannich derivative

1.7- Schiff bases

Imines, known even as azomethines or Schiff bases [65,66,67,68] are compounds that are represented by the general formula $R_3R_2C=NR1$. The substituents R_2 and R_3 may be alkyl, aryl, heteroaryl, hydrogen.The substituent at the *N*-imino (C=N) may be alkyl, aryl, heteroaryl, hydrogen or metallo (usually Si,Al, B, Sn).

The most common method for preparing imines is the original reaction discovered by Schiff [65,69,70,71]. Basically it consists in the reaction of an aldehyde (respectively a ketone) with a primary amine and elimination of one water molecule . This reaction can be accelerated by acid catalysis and is generally carried out by refluxing a mixture of a carbonyl compound and an amine, in a Dean Stark apparatus in order to remove the water. This removal is important as the conversion of aminal into the imine is reversible. From this point several dehydrating agents have been successfully used including sodium sulphate and molecular sieves [72]. Alternatively, some *in situ* methods, involving dehydrating solvents such as tetramethyl orthosilicate or trimethyl orthoformate, have been reported as well [73,74]. As far as the use of acid catalyst is required [75,76,77], mineral acids, like H_2SO_4 or HCl, organic acids such as *p*-toluene sulphonic acids or pyridinium *p*-toluenesulphonate, acid resin, montmorillonite or even Lewis acids like $ZnCl_2$, $TiCl_4$, $SnCl_4$, BF_3Et_2O, $MgSO_4$, $Mg(ClO_4)_2$, *etc*., have been reported.

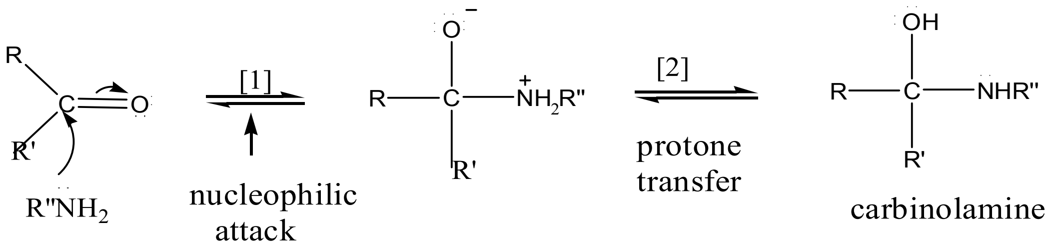
Aliphatic ketones react with amines to form imines more slowly than aldehydes, therefore, higher reaction temperatures and longer reaction time are required. Acid catalysts and water removal from the reaction mixture can significantly increase the reaction yields, which can reach 80%–95% values.

Aromatic ketones are less reactive than aliphatic ones and require harsh conditions to be converted into imines [78]. Recently, several new techniques to produce imines have been published, including solvent-free, clay, microwave irradiation, water suspension medium, liquid crystals, molecular sieves, infrared and ultrasound irradiation [79,80,81,82].

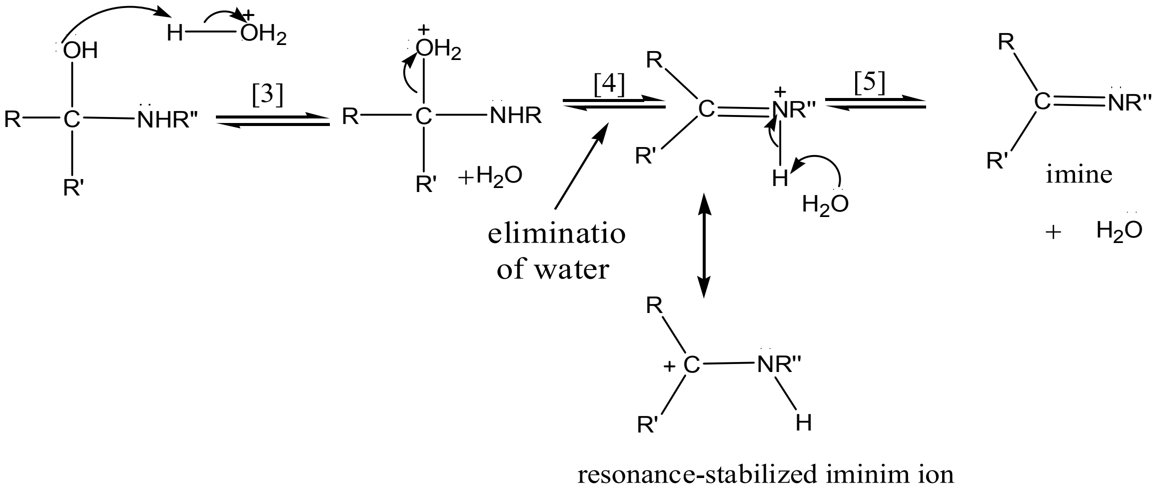
The mechanism of imine formation can be divided into two distinct parts: nucleophilic addition of the primary amine, followed by elimination of water. Each step involves a reversible equilibrium, so that the reaction is driven to completion by removing water[83].

Imine formation is most rapid at pH 4–5. Mild acid is needed for protonation of the hydroxyl group in Step (3) to form a good leaving group. Under strongly acidic conditions, the reaction rate decreases because the amine nucleophile is protonated. With no free electron pair, it is no longer a nucleophile, and so nucleophilic addition cannot occur[83].

Part[1] Nucleophilic addition forms a carbinolamine:



Part[2] Elimination of water forms an imine:



Mechanism of Schiff formation

Since aldehydes and ketones are mostly obtained from the corresponding alcohols via oxidative process, a straightforward preparation of imines from amines and alcohols, through tandem oxidative processes, have recently been developed [83,84,85,86].

$$R^1CH_2OH + R^2NH_2 \xrightarrow{catalyst} R^1CH=NR^2$$

Addition of Grignard or organolithium reagents to aryl cyanides can lead to unsubstituted ketimines which, in turn, can be elaborated to the corresponding ketones depending on the hydrolysis conditions used to decompose the metallo imine intermediate . The reaction has also been extended to aliphatic cyanides [87], producing very high yields of ketimines, provided that the Mg-imine intermediate is treated with anhydrous methanol [88]. The use of heteroaryl lithium reagents affording the corresponding ketimines has also been reported [89].

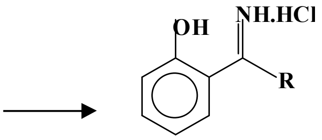
$$\mathrm{ArC \equiv N + RM} \longrightarrow \mathrm{ArC(R){=}NM} \longrightarrow \mathrm{ArC(R){=}NH} \longrightarrow \mathrm{ArC(R){=}O}$$

M = MgX or Li

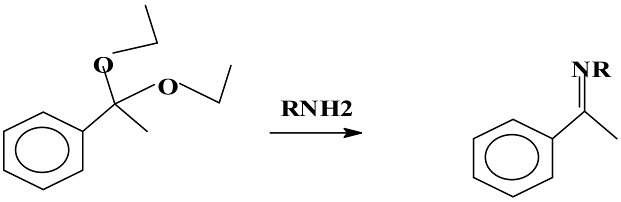
Ketimine has been produced by the addition reactions of alkali metal (or calcium amine salts) to aromatic ketones .The scope of this reaction has been widely extended [90].

$$\mathrm{Ar_2C{=}O} + \mathrm{ArNHNa} \longrightarrow \mathrm{ArC{=}Nar}$$

Alkyl and aryl cyanides react smoothly with phenols and their ethers producing ketimines in very good yields in the presence of an acid catalyst[91,92,93]. The reaction is performed by mixing the nitrile and phenol in ether and saturating the solution with gaseous HCl, whereas, for less reactive phenols, $ZnCl_2$ must be used.

ArOH + RC≡N HCl 

Ketimine can be prepared in high yield using aryl ketone diethyl ketals and arylamines, while alkylamines give only low yields [94]. Similarly, imines can react with higher boiling point amines to give the exchange products. The latter can be distilled driving the equilibrium towards the formation of the desired product [95].



Olefins and tertiary alcohols can be converted into ketimines [96] by reaction of hydrazoic acid in sulfuric acid .

$$(R)_2C{=}CHR \xrightarrow{NH_3} (R)_2C{=}NCH_2R + N_2$$

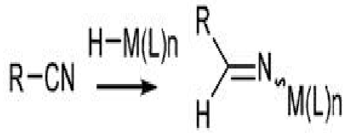
$$(R)_3COH \xrightarrow{NH_3} (R)_2C{=}N + N_2$$

Imines can also be formed by reaction of amino acids with sodium . The first step of this reaction is the formation of a chloramine intermediate that gives rise to the imine via elimination of carbon dioxide and sodium chloride[97].

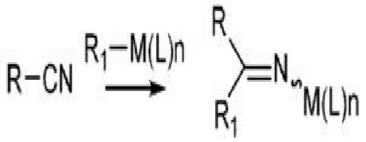
1.8- N-metallo-imines as stable synthetic equivalents of N-unsubstituted Schiff bases

N-metallo-imines constitute a young family of organometallic compounds congeners of Schiff bases [98,99] They have found synthetic applications in the last few decades as relatively stable analogues of the corresponding Schiff bases. Their elaborations to azadiene have been fully explored by the Barluenga [100,101,102], Ghosez [103,104] and Panunzio groups [105,106,107] Generally speaking, they are monomeric compounds reasonably stable under anhydrous conditions. Since the metal-nitrogen bond is easily hydrolysed, the *N*-metalloimines may be considered a protected, stabilized form of the corresponding elusive imines of ammonia, which are known to be very unstable readily trimerizing to triazines [70]. Although some metalloimines, e.g., the silylimines of certain aldehydes, can be isolated in a pure form by distillation under reduced pressure, for synthetic purposes it is in general more convenient to prepare them *in situ* just before the use. In this case it is possible to ascertain their structure by a combined use of IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopic techniques.

A General procedure used to prepare metalloimines is starting from nitriles and a suitable organometallic reagent either by hydrometallation to give schiff compounds or by alkylation to give also schiff compounds .

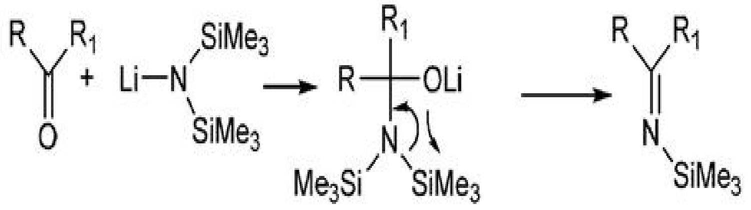


R= alkyl or aryl, M= Al , B



R, R_1 = alkyl or aryl, M= Mg, Li

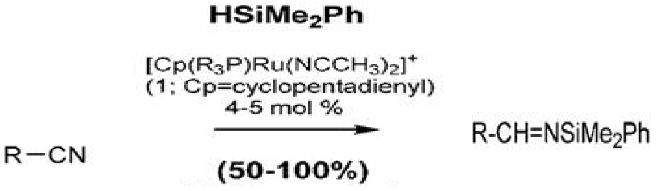
Among different metalloimines, *N*-trialkylsilyl imines must be considered the most popular and the most used intermediates in the preparation of nitrogen containing organic compounds, with special emphasis to the potentially bioactive ones. [106,108] Silyl imines have been prepared, for the first time, by Rochow [109] starting from aromatic aldehydes and non-enolizable ketones by treatment of the carbonyl compounds with one equivalent of lithium hexamethyldisilylamide in tetrahydrofuran [108]. The reaction proceeds by an addition-elimination sequence probably involving a four centers cyclic transition state (Scheme 12).



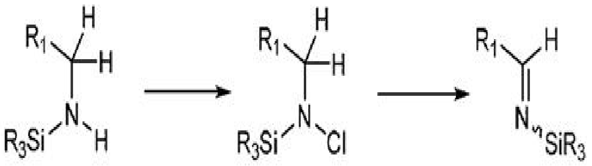
R=alkyl or aryl , R_1= H, alkyl or aryl

Ketones, bearing a hydrogen atom in α-position to the carbonyl group, failed to produce the silylimines since in this case the strongly basic organometallic reagent attacks an α-hydrogen affording the corresponding lithium enolate. Enolizable aldehydes were supposed to behave in the same way [110,111].

Few competitive methods, to the above cited, have been reported in the last few years on the preparation of *N*-alkylsilyl imines. Nikonov and co-workers [112] reported an elegant preparation of *N*-silyl-aldimines via a chemoselective hydrosilylation of nitriles catalysed by ruthenium complex

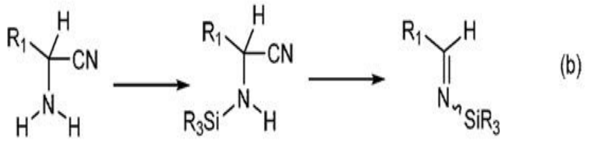


Formation of silylimines via elimination of vicinal groups. (**a**) from *N*-chloro silylamines; (**b**) from α-cyano silylamines is shown below:



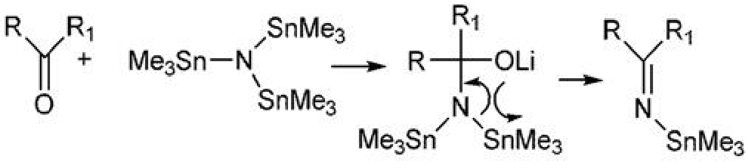
(a)

R_1=ph,2-furyl,COOEt,-CH=CH_2



R_1=H,Me,Et,n-prop.

The preparation of tin imines from enolizable and non-enolizable aldehydes and ketones, in good yield and under very mild conditions was reported[113]. The organometallic reagent is, in this case, the tris(trimethylstanny1)amines which can be easily prepared from trimethyl tin chloride and lithium amide. Since the tris(trimethylstanny1)amine does not show strong basic properties, the α-deprotonation is completely suppressed thus allowing a facile preparation of tin-imines even in the case of enolizable ketones and aldehydes. An interesting feature of the tin-imines is the possibility to undergo transmetallation reactions with trialkylsilyl chlorides (e.g., chloro *tert*-butyldimethylsilane) to give the corresponding *N*-silylimine and tris(trimethyltin)onium chloride that spontaneously precipitates from the solution. Removal of this precipitate by filtration allows the preparation of almost pure solution of silylimines [113].

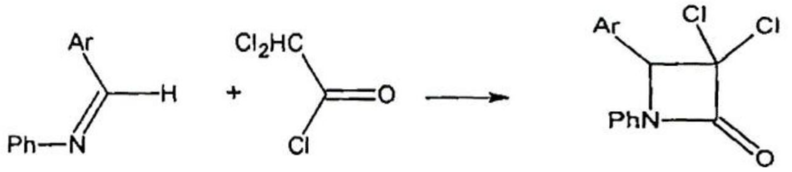


R=alkyl or aryl , R_1= H, alkyl or aryl

1.9- Some reactions of Schiff bases

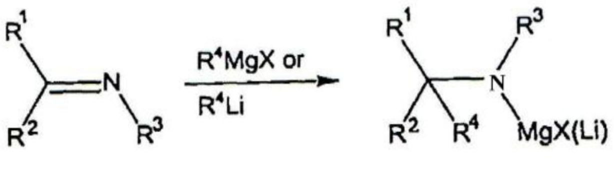
1.9.1- Reaction of Schiff bases with ketenes

The base catalyzed condensation of acetyl chlorides (bearing an electron withdrawing group and at least one hydrogen atom at the α-position) with *N*-arylaldimines occurs by initial acylation at the nitrogen atom and leads to β-lactams[114,115,116] of interest in penicillin chemistry .



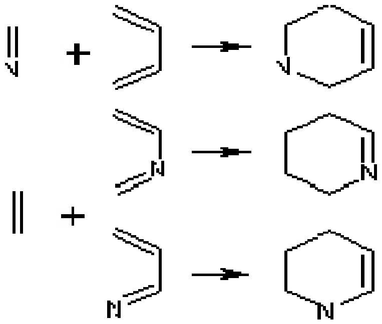
1.9.2- Reaction of Schiff bases with Grignard and organolithium reagents

Schiff bases lacking hydrogen atoms α to the carbon-nitrogen double bond react with Grignard and organolithium reagents (alkyl and aryl) analogously to carbonyl compounds to give adducts which on hydrolytic work-up afford secondary amines in good to excellent yield (60-90%) **.** Reaction occurs best with aryl aldimines and provides the general method for the synthes is of secondary amines[117].



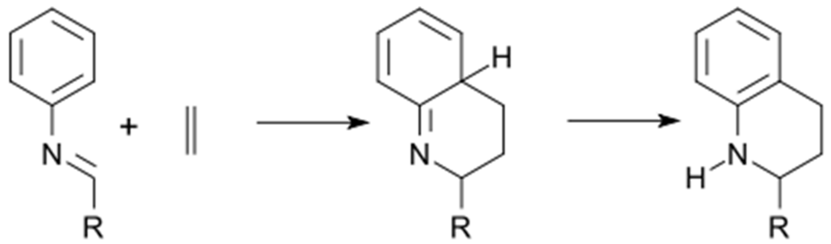
1.9.3- Aza-Diels–Alder reaction

Hetero Diels-Alder reactions afford six -membered nitrogen containing heterocyclic compounds. This reaction converts imines and dienes to tetrahydropyridines. The nitrogen atom can be part of the diene or the dienophile[117].



1.9.4- Povarov reaction

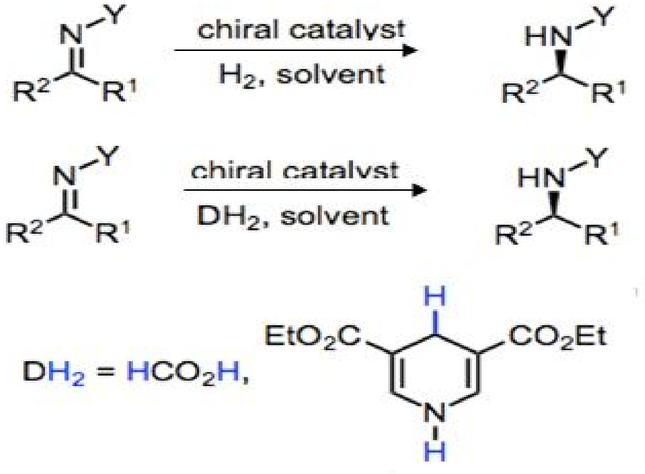
The Povarov reaction is an organic reaction described as a formal cycloaddition between an aromatic imine and an alkene. The imine in this organic reaction is a condensation reaction product from an aniline type compound and a benzaldehyde type compound[1,2]. The alkene must be electron rich which means that functional groups attached to the alkene must be able to donate electrons. Such alkenes are enol ethers and enamines. The reaction product in the original Povarov reaction is a quinoline. Because the reactions can be carried out with the three components premixed in one reactor it is an example of a multi-component reaction[118,119].



1.9.5 -Hydrogenation of Schiff bases

Although a variety of general methods have been developed for the enantioselective hydrogenation of ketones,[120,121] methods for the hydrogenation of carbon–nitrogen double bonds are less general. Hydrogenation of imines is complicated by both *syn*/*anti* isomerization and tautomerization to enamines, which may be hydrogenated with low enantioselectivity in the presence of a chiral catalyst.[122] Additionally, the substituent attached to nitrogen affects both the reactivity and spatial properties of the imine, complicating the development of a general catalyst system for imine hydrogenation. Despite these challenges, methods have been developed that address particular substrate classes, such as *N*-aryl, *N*-alkyl, and endocyclic imines.

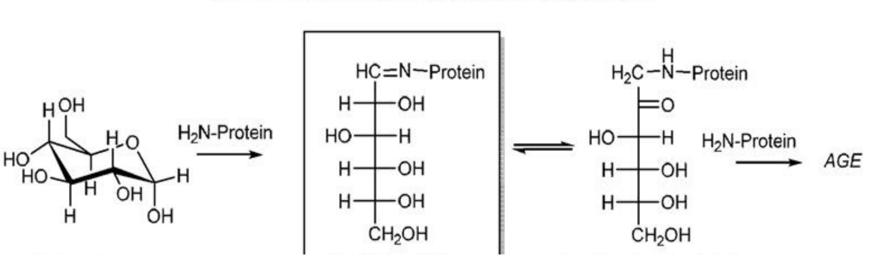
As in hydrogenation reactions of other functional groups, the reductant in C=N hydrogenations is either hydrogen gas or a transfer hydrogenation reductant such as formic acid.[123] The process is usually catalyzed by a transition metal complex.



1.10- Schiff Bases as intermediate of bio-processes

The importance of Schiff bases as intermediates in bio-processes is very well established, suffice it to mention one of the very basic process of life, the transamination reaction [124].

Other important bio-processes, that lately are attracting the interest of chemists and biologists, are related to the glycation of albumin that leads to the formation of important biomarkers, which are predictive of type II diabetes [125] or to the reaction between sugars and biologically relevant amines with the formation of Schiff bases. These intermediate Schiff bases, in turn, evolve to **a**dvanced **g**lycation **e**nd products (**AGE**) .

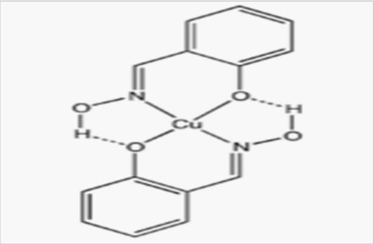


Protein glycation by glucose

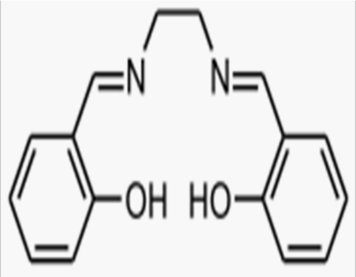
(AGEs) are involved in many pathological conditions such as cardiovascular disease [126], Alzheimer [127] and so on.

1.11- Schiff bases as ligand

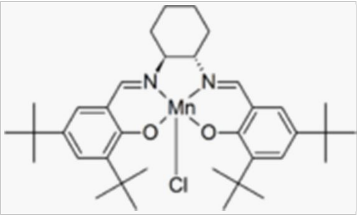
Schiff bases are common ligands in coordination chemistry. The imine nitrogen is basic and exhibits pi-acceptor properties. The ligands are typically derived from alkyl diamines and aromatic aldehydes[128,129].



Copper(II) complex of the Schiff base ligand salicylaldoxime.

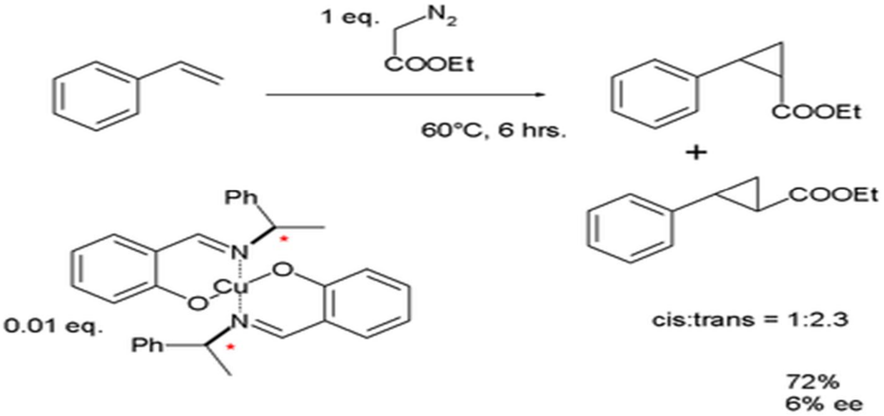


Salen is a common tetradentate ligand, it becomes deprotonated upon complexation.



Jacobsen's catalyst is derived from a chiral salen ligand.

Chiral Schiff bases were one of the first ligands used for asymmetric catalysis. In 1968 Ryōji Noyori developed a copper-Schiff base complex for the metal-carbenoid cyclopropanation of styrene[130]..

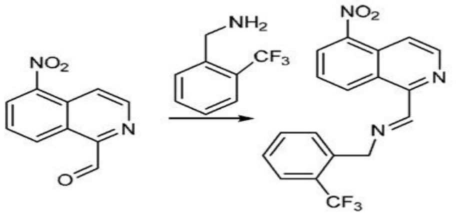


1.12- Some application of Schiff Bases in pharmaceutical field

There are numerous publications covering the use of Schiff bases in therapeutic or biological applications either as potential drug candidates or diagnostic probes and analytical tools. The activity of

Schiff bases as anticancer compounds [131,132] antibacterial [133,134], antifungal [135,136], antiviral agents [137] has been extensively studied. Moreover, Schiff bases are present in various natural, semi-synthetic, and synthetic drugs [138,139].

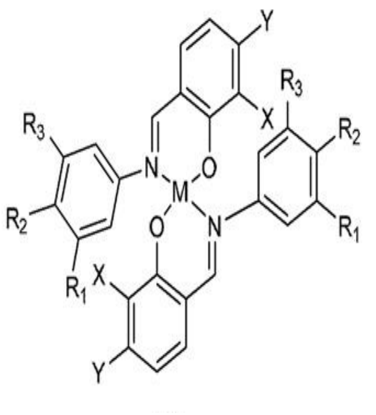
The imino-group of Schiff bases has been shown to be valuable function to confer antimalarial activity. For example, ancistrocladidine, a secondary metabolite produced by plants belonging to the families *Ancistrocladaceae* and *Dioncophyllaceae*, features an imine group in its structure. The compound has shown potent activity against *P. falciparum* K1. Some novel aldimine and hydrazone isoquinoline derivatives, prepared by reacting 1-formyl-5-nitroisoquinoline with amines , showed activity against a chloroquine-resistant *Plasmodium falciparum* strain (ACC Niger). In particular the corresponding Schiff base of formyl-5-nitroisoquinoline (*E*)-*N*-((5-nitroisoquinolin-1-yl)-methylene)-1-(2-(trifluoromethyl)-phenyl) methanamine showed an IC50 of 0.7 µg/mL against *P. falciparium* [136].



Synthesis of some 5-nitroisoquinolines Schiff bases

Salicylidenebenzylamine derivatives have been studied extensively for their biological activities [124]. Schiff base complexes derived from 4-hydroxysalicylaldehyde and amines have strong anticancer activity , e.g., against Ehrlich ascites carcinoma (EAC) [140]. *N*-(salicylidene)-2-hydroxyaniline, in turn, showed activity against *Mycobacterium tuberculosis*
H37Rv [135]. The antibacterial activity of a series of 5-chlorosalicylaldehyde-Shiff bases (Figure) was studied against several strains including *Escherichia coli* and *Staphylococcus aureus* [141]. Cu(II) and Cd(II) complexes of more highly functionalized salicylidenebenzylamines present higher activity with respect to the free molecules [142].

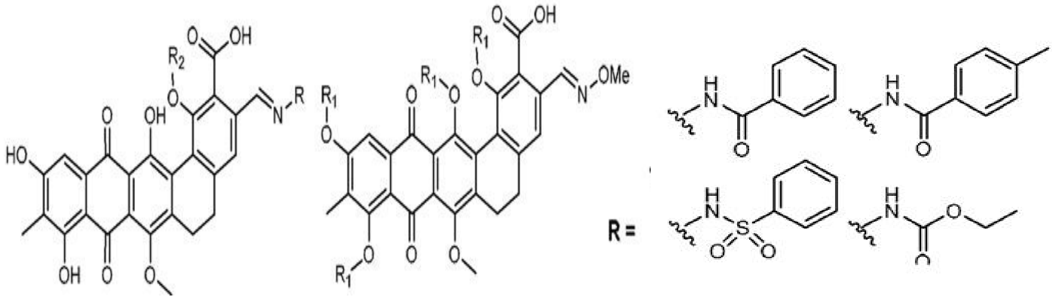
.



	X	Y	R_1	R_2	R_3
a	OH	OH	H	Br	H
b	OH	OH	tBu	OH	tBu
c	OH	H	H	Me	H
d	OH	H	H	Br	H
e	H	OH	tBu	OH	tBu

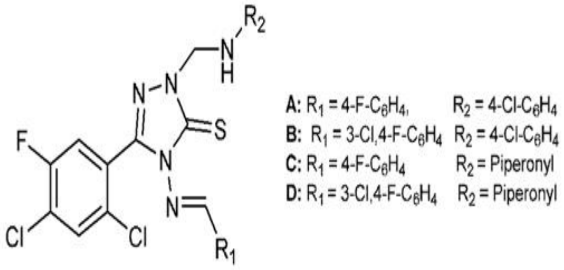
Cu(II) and Cd(II) complexes of salicylidenebenzylamines

Schiff bases characterized by a 2,4-dichloro-5-fluorophenyl moiety completely inhibited the growth of *S. aureus, E. coli, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* with MIC values ranging from 6.3 to 12.5 µg/mL, which are comparable to ciprofloxacin[133]. The secondary metabolites of the plant *Actinomadura rubra*, a hydroxylactones, have been transformed into the corresponding Schiff bases (Figure) [143]. The derived compounds inhibited *in vitro B. subtilis*, *Micrococcus flavus*, *Sarcina lutea*, and *S. aureus* giving MIC values varying from 0.2 to 3.1 µg/mL [144].



The hydroxylactones Schiff bases

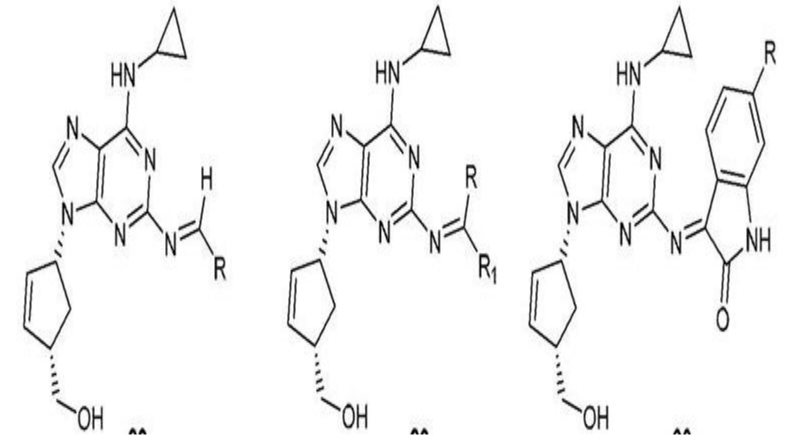
Schiff bases of chitosan have shown antifungal activity against *Botrytis cinerea* and *Colletotrichum lagenarium* [139]. Imine derivatives having a 2,4-dichloro-5-fluorophenyl moiety inhibited the growth of fungal clinical isolates, such as *Aspergillus fumigatus, Aspergillus flavus, Penicillium marneffei, Trichophyton mentagrophytes*. The compounds showed MIC values in the range of 6.3–12.5 μg/mL, which is comparable to that of fluconazole [145]. The isatin-derived Schiff bases. showed an interesting activity against *Microsporum audouinii* (MIC range 2.4–9.7 μg/mL) and *Microsporum gypseum* (MIC range 1.2–9.7 μg/mL) [146].



Antifungal Schiff bases derived from 2,4-dichloro-5-fluorophenyl scaffold.

The compounds reported inhibited also *Candida albicans*, *Aspergillus niger*, *Cryptococcus neoformans*, *T. mentagrophytes*, *E. floccosum*, and *Histoplasma capsulatum* (MIC range 10–79 μg/mL [147].

The Schiff bases of modified 3-hydroxyguanidines [148,149], have been prepared and tested against mouse hepatitis virus (MHV). Similarly, a set of imine derivatives of abacavir [149] have been prepared and tested for their antiviral activity.Such bases were highly effective against the human immunodeficiency virus-type 1 (HIV-1). The molecules, which are reported to be Abacavir prodrugs,showed a 50% protection of human leukemic cells (CEM) at micromolar and even nanomolar concentration.



R= *o*-NO_2-Ph; *p*-NO_2-Ph; *p*-Tolyl;
p-MeO-Ph; *p*-Me_2N-Ph;
2-OH-4-CH_3O-Ph

R= CH_3; Ph;
R_1= *p*-OH-Ph; *p*-Br-Ph

R= H; F; Me

Schiff bases of Abacavir

1.13- Aim of this study

This research was aimed to:

- Synthesis of some ketonic and phenolic Mannich bases.
- Conversion of some of the synthesized Mannich bases into the corresponding Schiff bases.
- Elucidatiotion of structure of intermediates and targeted molecules via sensitive spectroscopic tools.
- Evaluation of the synthesized molecules for their antimicrobial potential.