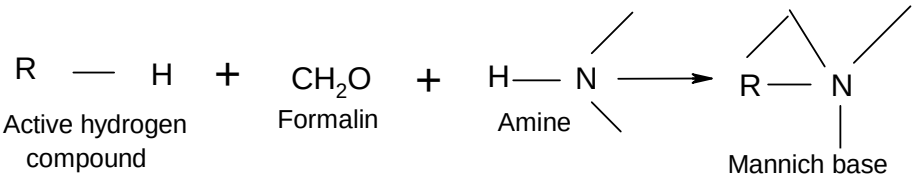
# 1.Introduction

The development of new antimicrobial agents will remain an important challenging task for medicinal chemist[1]. So, there is an urgent need for identification of novel lead structure for the designing of new, potent and less toxic agents[2].

Mannich reaction is a three -component condensation involving active hydrogen containing compound, formaldehyde and a secondary amine[3]. As shown in scheme 1, the Mannich reaction product(theMannich base) has the N-atom of the nitrogen functionality linked to the substrate R through a methylene group. This transformation was first discovered by Carl Mannich in 1912, when he treated a salicylantipyrine pharmaceutical preparation and urotropine with acid [1-4].




Scheme 1: Mannich reaction

It is believed that the Mannich base functional group can increase the lipophilicity of parent amines and amides, which results in the enhancement of absorption through bio-membranes[5] . The lipophilicity of Mannich bases enables them to cross bacterial and fungal membranes [1].

The chemistry of Mannich bases, first studied by Carl Mannich has been the subject of investigations by an ever increasing number of researchers,

several studies which appeared before 1960 together with books by Reichert, Hellman and Optiz, provide an excellent coverage on practically the entire chemistry of Mannich bases up to 1960[4].

Mannich bases have gained importance due to their application in pharmaceutical chemistry. Previous studies have demonstrated that Mannich bases offer a wide range of biological activities[6]. They have been encountered with antibacterial[7] ,anticancer[8] ,analgesic and anti-inflammotry[9] , antimalarial[10] , antiviral[11], and CNS depressant activities[12] .

Two key features render the Mannich reaction and its products very attractive:

(a) The reaction tolerates a large diversity of reactants[13].

(b) The β- amino carbonyl products are valuable synthons for natural products synthesis[14] and can be readily converted to derivatives that possess useful applications in paint and polymer chemistry, plant protection, and particularly medicine and the pharmaceutical industry[15].

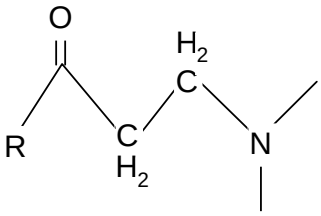
The significant role of iminium salts in many reactions has long been recognized. Thus, the Mannich reaction is one of the most familiar and powerful of synthetic methods. Common substrates for the Mannich reaction are active methylene compounds, amines, thiols, alcohols, alkenes, hydrogen cyanide and electron-rich aromatic amines[16].

The prevalence of heterocyclic ring among drugs and biological agents of mammalian origin can lead to the erroneous assumption that the presence of such rings in drugs means that this moiety necessarily constitutes a part of pharmacophore. Replacement of the particular ring system in such

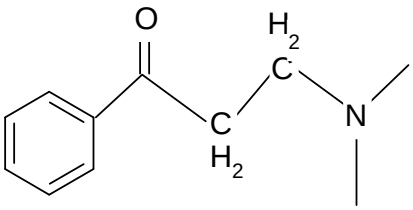
cases leads to loss of desirable biological activity. Recognition of pharmacophoric functions is still largely an empirical art. The diversity of biological effects is possessed by benzo fused six membered heterocyclic ring. It is also interesting to note that range of bio activities involved is different substantially from those seen with the benzo fused five membered heterocyclic[17].

The general structure of Mannich bases could be written as the following[4]:

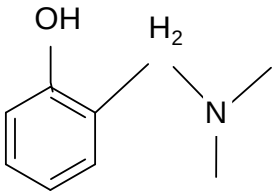
1. C - Mannich bases



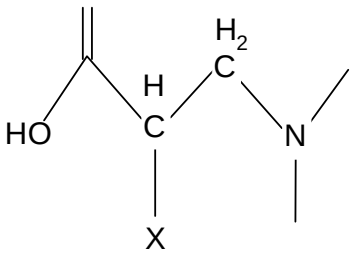

C-Mannich base of aliphatic compound



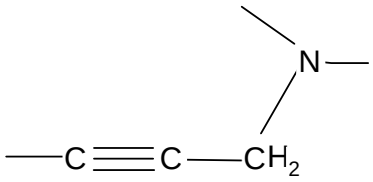

C-Mannich base of aliphatic aromatic compound



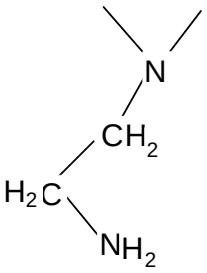

C-Mannich bases of phenols




C-Mannich bases of halides carboxylic acids



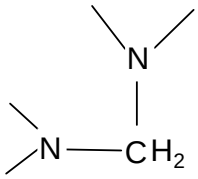

C-Mannich bases of alkynes



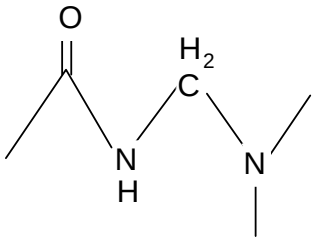

C-Mannich bases of alkyl amines

Heterocyclic compounds which are attached by C-atom afford N-Mannich bases:

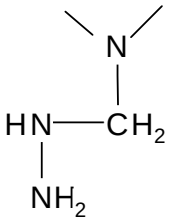
2. N- Mannich bases



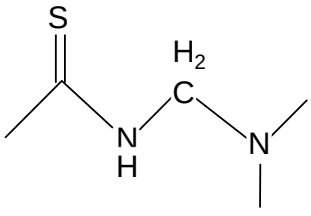

N-Mannich bases of ammonia




N-Mannich bases of amides



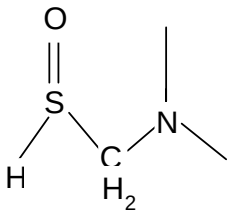

N-Mannich bases of hydrazine

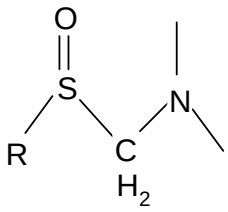



N-Mannich bases of amino sulphide

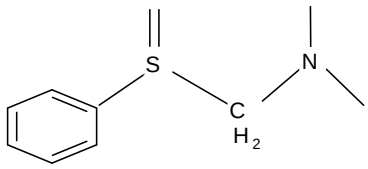
Heterocyclic compounds which are attached by S atom afford:

3. S- Mannich bases

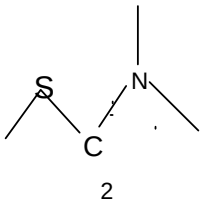


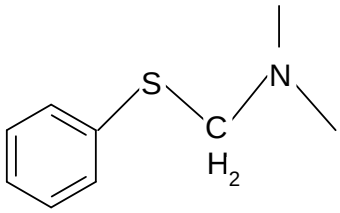

S-Mannich bases of sulphoxy compounds




S-Mannich bases of benzo sulphoxy compound



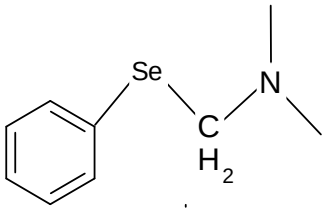

S- Mannich base of Sulphide




S-Mannich bases of benzo sulphide

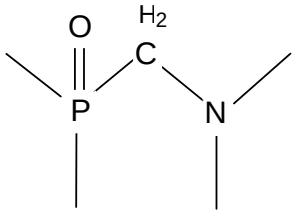
When there is selenium or phosphorus, Mannich bases could also be generated:

4. Se- Mannich bases

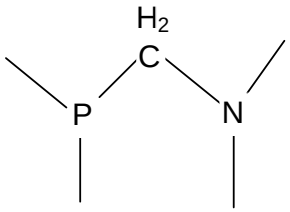



Se-Mannich bases

5. P- Mannich bases




P-Mannich bases of phosphoxy compounds




P-Mannich bases of phosphide compounds

## 1.2. Synthesis of Mannich bases

### 1.2.1 Reactants and Reaction conditions

Formaldehyde, either as aqueous solution (Formalin), paraformaldehyde or 1, 3, 5 trioxane, is most frequently used. The amines are employed either as free bases or as hydrochloride[18].

The most widely used solvents are ethanol, other alcohols such as methanol and isopropanol, water and acetic acid[19]. It is difficult to givegeneral rule concerning the choice of reagents and reaction conditions[19,20].However, the most widely and successfully used reaction conditions for several groups of substrates are as follows[21]:

-Alkyl ketones: substrate, amine hydrochloride and paraformaldehyde are refluxed in alcoholic solvents for several hours.

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

-Carboxylic acid derivatives: substrate, amine and aqueous formaldehyde are allowed to react in water or in 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).

-Alkenes: various reaction conditions as above are used; the reaction is carried out in the presence of copper salts,

The reaction is generally carried out by mixing substrate, aldehyde and amine in equimolar amounts. However, in several cases the amine and aldehyde are condensed first and then allowed to react with the substrate; sometimes, the initial condensation products are isolated[21].

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 [22].

Mannich bases frequently crystallize from the reaction mixture (in some cases, concentration of the reaction mixture or addition of solvent with low dissolving power for the product is necessary) or the bases can be separated by extraction with aqueous hydrochloric acid[23.]

Principally concerned are :dialkyl ketones (attack on the more or the less substituted C-atom), phenols (attack on the O- or P- position), NH-

heterocyclic compounds (attack on the N- atom or on heterocyclic C-atom), and in general all compounds having two or more reactive groups (e.g., hydroxyindoles, acetylenic ketones, etc.).

Further, substitution of more than one H- atom on the same C- atom has been observed in the case of compounds containing activated methylene groups( e.g., carbonyl and nitro compounds)[21].

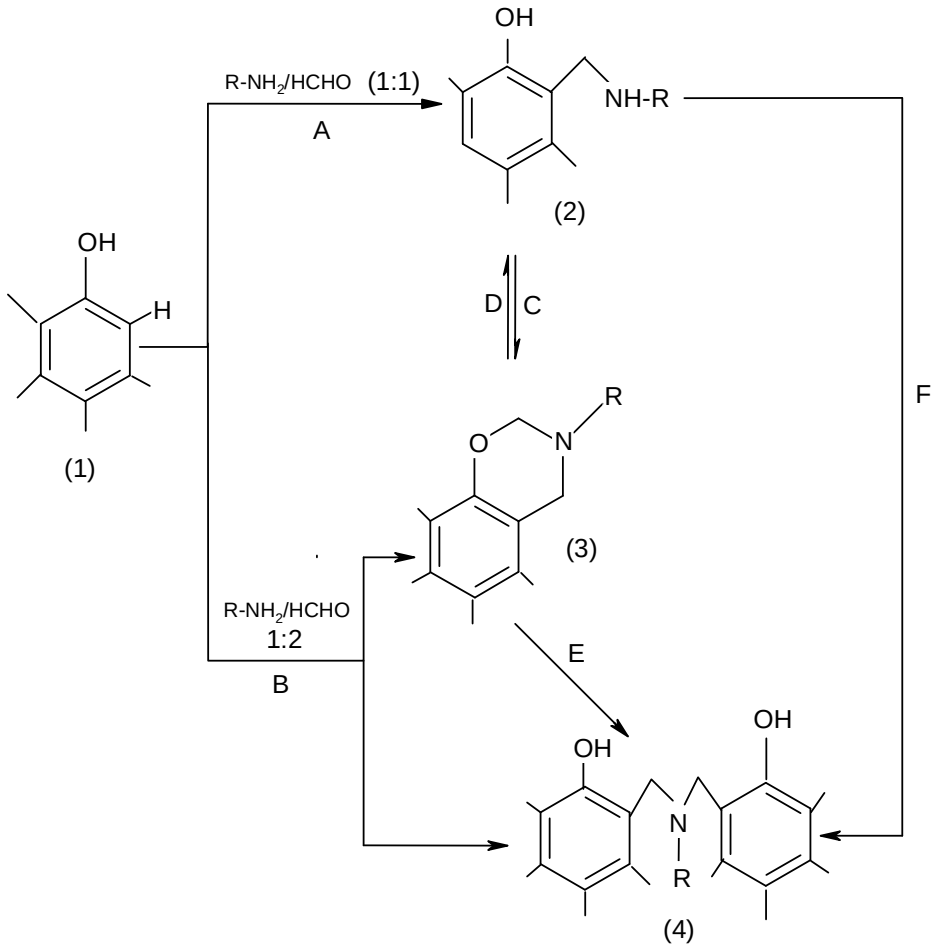
The choice of the amine used in the reaction is important in this context. For example, primary amines can react at both amine H- atoms and it is therefore difficult to obtain secondary Mannich bases free from tertiary derivatives. However, use of the oxalate derivatives of the primary amines instead of the corresponding hydrochlorides makes possible the synthesis of secondary Mannich bases in high yields even when excess formaldehyde is used[24,25].

The use of secondary bifunctional amine such as piperazine always leads to symmetric Mannich bases, in which both of the amino groups have reacted. Attempts to restrict the reaction to only one amine function, or hydrolysis of the Mannich products obtained from mono-N- acetyl-piperazine invariably leads to the formation of disubstitutedpiperazine[26].

### 1.2.2 C-aminomethylation of phenols

Variously substituted phenols and naphthols, as well as phenols condensed with cycloalkenes or heterocyclic ring are commonly used in the Mannich reaction. With a few exceptions, aminomethylation always occurs at the position *ortho* to the hydroxyl group even if the *para* position is unoccupied.

Primary amines can react to give various products, as shown by scheme 2[21].




**Scheme 2**

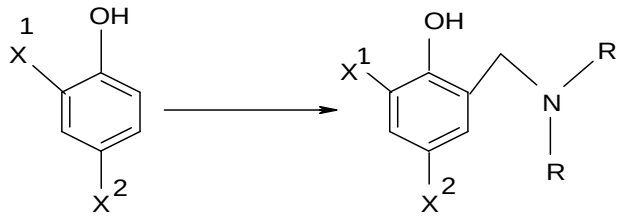
One or both of the amine H- atoms (pathways A and B respectively) can be substituted by use of appropriate reaction conditions. Path A gives secondary bases (2) directly, but the reaction involving acid hydrolysis of dihydrobenzoxazine(3 )(path D) is often preferred. Pathway B usually gives compounds (3) rather than bis-[2- hydroxy benzyl] - amines (4). For this reason, the latter products are best obtained via path F[27.]

Pathway F, leading to bis-[2- hydroxy benzyl] - amines (4) and using compounds (2) as starting material, is only practicable if R represents a linear or a singly-branched alkyl group. When R is a bulky group (e.g., 1-

butyl or 1- octyl), the reaction follows path C and the oxazine derivative (3) is obtained together with considerable amounts of the corresponding α- di hydroxydiaryl methane[28].Unsymmetrical bis-[2- hydroxy benzyl] - amines (4) have been obtained [29] via pathway E.

The preferred position of reaction in this transformation is also *ortho* to the hydroxy group of the phenol residue, and the group R exerts a considerable steric influence;thus, N-methyl compounds (3) ($R=CH_3$) are more reactive than corresponding N- benzyl and N- cyclohexyl compounds[29].

The Mannich reaction of several mono- and poly nuclear phenols with secondary amines also affords *ortho*- substituted products. Thus,*ortho*- and ρ- mono substituted and disubstituted phenols [21,30] react to give *ortho*- aminomethyl phenols.

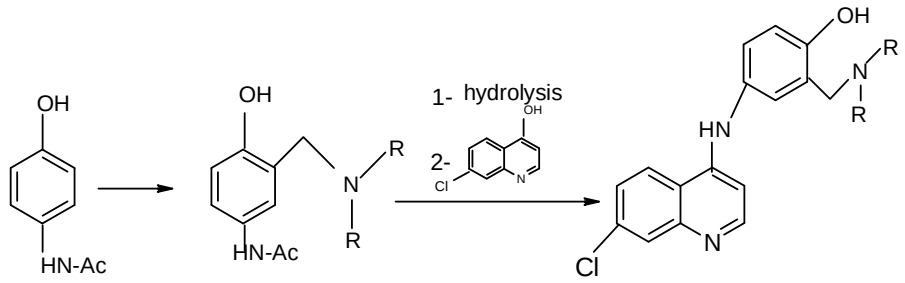



(X=H, X=-NH-Ac)

**Scheme 3**

Only 6- allyl 2- methylphenol is aminomethylatedin theρ- position [30]. The influence of functional group substituents on the orientation of the Mannich reaction in the case phenols is complex; in addition, the reaction conditions play an important role. Thus 2-(2-hydroxy phenyl) benzimidazole is amino- methylated at the phenolic benzene nucleus

rather than at the heterocyclic NH group; on the other hand, salicyamides first react at the amide group and only subsequently at the position *ortho* to the phenolic hydroxygroup[31]. 4- Acetamidophenol ($X^1$=H, $X^2$= -NH-AC) is only aminomethylated at the position *ortho* to the hydroxy group, affording Mannich base (see scheme 4) which are starting material for the synthesis of certain quinolone derivatives possessing anti-malarial activity[32].




**Scheme 4**

Intermolecular aminomethylation[33] has been used to obtain a series of protobeberinederivatives [34-36]. The aminomethylation reaction has also been conducted on polynuclear phenols (including heterocyclic compounds). The reaction of estrone is noteworthy[37].

### 1.2.3 Nature of formaldehyde and reaction time

Formaldehyde is used in the form of a 20-40% aqueous solution or as paraformaldehyde. In certain reactions, such as the condensation oftetralone, formaldehyde, and tetrahydroisoquinoline hydrochloride, aqueous formaldehyde is said to be superior to paraformaldehyde[38].

In a few cases[39-41] enough concentrated hydrochloric acid is added

at the beginning of the reaction to make the mixture acidic to Congo red; in other instances [42-44] the mixture is acidified at the end of thereaction in order to depolymerize unchanged paraformaldehyde andbring it into solution.

The time required for a Mannich reaction depends upon the natureof the ketone and of the amine salt and upon the boiling point of thesolvent employed. The reaction between furfuralacetone, paraformaldehyde,and dimethylamine hydrochloride in alcoholic solution is saidto be complete after the mixture has been boiled for a few minutes[45].

When 3-acetyl-9-methylcarbazole, paraformaldehyde, and diethylamine hydrochloride are heated in absolute ethanolic solution for five hoursthe yield of reaction product is 59% but is increased to 83% when the mixture is heated for eight hours[46].

### 1.2.4 Solvents

When aqueous formaldehyde is used the condensation is ordinarily carried out by shaking or stirring the reactants in the absence of anorganic solvent; in some cases[47] methanol has been added to suchmixtures. When paraformaldehyde is used an organic solvent is required.If the ketone component is a liquid, such as acetone, [40] cyclopentanone,[41]orcyclohexanone, [41] an excess of it may be used as thesolvent. In other cases ethanol (95% or absolute) is added as thesolvent. In condensations involving 2-, 3-, or 9-acetylphenanthrene,paraformaldehyde, and salts of secondary amines, isoamyl alcohol isrecommended as the solvent [46]. The condensations proceed much fasterin the higher-boiling solvent, and the formation of certain by-products,obtained by prolonged heating in ethanol, is avoided. On the otherhand, it is stated that, although in ethanol the condensation

between3-acetyl-9-methylcarbazole, formaldehyde, and a secondary amine saltproceeds more slowly than in isoamyl alcohol, it is less subject to sidereactions associated with instability of the aminoketone salts at thehigher temperature [46].

### 1.2.5 Isolation of product

In a number of cases the salt of the desired product precipitates when the reaction mixture is cooled. Ether may be added to facilitate separation of the product. Occasionally the solvent is removed and crystallization of the residue brought about by washing it with ether or acetone[48]. Sometimes it is advantageous to liberate the basic product from its salt and purify the former by distillation, provided that the material can be distilled without decomposition[48].

### 1.2.6 By-Products

By-products of the reaction have been identified in some instances. They may be formed by some change of the reaction product itself, orthey may be produced by condensation of the formaldehyde with theamine or ketone. Thus, diethylamine may be converted to N,N'-tetraethylmethylenediamine, [49] and piperidine to methylenedipiperidine [46]. From reactions involving cyclohexanone, there have beenisolated 2-methylene cyclohexanone[50] and di-(2-cyclohexanonylmethyl)ether[50].Similarly, methylenedi-3-naphthol [51] and methylenediantipyrine[52] have been produced in reactions involving 3-naphthol andantipyrine, respectively.

### 1.2.7 The use of secondary amines

The secondary amines which have been used successfully are listed in Table 1.1.

Table 1.1: Secondary amines in the Mannich reaction

| | |
|---|---|
| Dimethylamine | Piperidine |
| Diethylamine | 1,2,3,4-Tetrahydroisoquinoline |
| Diethanolamine | 6-Methoxy-l,2,3,4-tetrahydroisoquinoline |
| Dipropylamine | Morpholine |
| Di-n-butylamine | Piperazine |
| Diisoamylamine | α-Methylaminopropiophenon |
| Dibenzylamine | β-Acetylethylbenzylamine |
| Methyldiethylethylenediamine | Benzyl-(2-cyclohexanonylmethyl)-amine |
| Methylaniline | 3,4-Methylenedioxybenzyl-(2-cyclohexanonyl |

Dimethylamine is very reactive and usually leads to excellent yields.Diethylamine appears to be less reactive; it has been reported [53] thatthe typical condensation does not take place with ethyl methylketone,diethylamine, and formaldehyde. On the other hand, formaldehydeand this amine do give normal products with acetone, [54] benzalacetone,[55]acetophenone, [56] and several derivatives of the last[42,39].Ithas been reported that 2-acetylfuran and formaldehyde react normally

with salts of dimethylamine, dipropylamine, di-n-butylamine, anddiethanolamine, but not with the salt of diethylamine[57]. In other cases wheredimethylamine, diethylamine, and dipropylamine have givengood results, di-n-butylamine and diethanolamine have failed to react[57].

The cyclic secondary amines mentioned above generally react about as

well as dimethylamine. However, dicyclohexylamine[58] and tetrahydroquinoline[42,43]are said not to take part in the reaction.

### 1.3. Optically active Mannich bases

Optically active Mannich bases may be divided into two main groups:

1. Products of Mannich synthesis using optically active starting materials (substrates or amines).
2. Products obtained from the resolution of racemic Mannich bases.

   Steroidal derivatives and several β- aminoketones containing optically active alcoholic groups(from an amino alcohol component)[59], or amino acid moieties[60](from an amino acid component) belong to the first group; such, derivatives were occasionally also obtained via amino group exchange[59].

The second group includes several β- aminoketones bearing the asymmetric center in the α- or β- positions, aminoalkylindoles and cyclic β- aminoketoximes; the absolute configuration of a few of these compounds is known[21 .]

The best method of resolution for these bases involves reaction with :*o*,*o*-dibenzyltartaric acid (0.5 mole per 0.5 mole of amine in 4000 ml solvent) in acetone or occasionally in ethanol at room temperature[21]. After afew hours reaction time, aminoketones yield ~ 50% of the corresponding salt; the additional salt which crystallizes after a longer period always contains the same optical isomer as first obtained. The reason for this is that the amine racemizes in solution and reacts to form the original, less soluble salt. It is thus possible to totally transform the aminoketone into a single optical isomer [21]. However, the free bases are not optically pure; thus, either the salt obtained is not homogeneous or the alkaline treatment

necessary to obtain the free base catalyzes the racemization of the unstable product. Recrystallization of the salt often does not increase the optical purity of the base and sometimes leads to decomposition of the amino- ketone. It is probable that carboxylic acids in weakly dissociating media favour the decomposition of the β- aminoketones[21].

### 1.4. Reactions of Mannich bases

The amino types of reactions of Mannich bases are as follows:

1. Deaminomethylation, involving cleavage of the R-$CH_2$ bond.
2. Deamination, involving cleavage of the $CH_2$-N bond.
3. Substitution of the amino group involving cleavage of the $CH_2$-N bond

And formation of a new bond, e.g. $CH_2$-C or $CH_2$-S.

4. Reduction only affecting only on the group derived from the original substrate, the amino group being probably involved in the reaction.

**5.** Reactions with organometallic compounds.

6. Cyclization which deal with ring closure to the amino methyl group, either at the C- atom (with elimination of the amino group residue), at the N- atom, or at a substituent of the amino group[21].

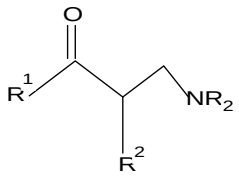
### 1.5 The intermolecular and intramolecular routes in Mannich reaction

Two routes of reaction strategy could occur in Mannich synthesis by the classical procedure which involves direct reaction between the three components of Mannich reaction; and this is called:( direct Mannich reaction or three component Mannich reaction), and reaction here is an intermolecular reaction. On the other hand some of the modern methods were developed to overcome the limitations of classical methods, this modern methods occur by intramolecular reactions for the reactants

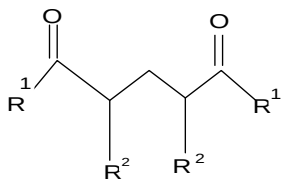
which have ability to this mode of reactions; their reaction methods were called(indirect Mannich reactions)[61-63].

### 1.5.1 Intermolecular Mannich reactions

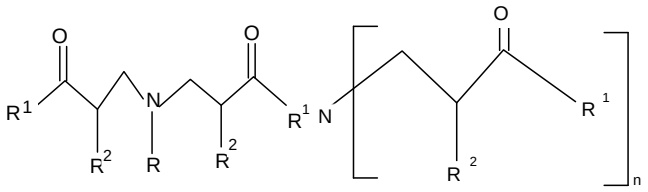
The classical intermolecular Mannich reaction is however, plagued by a number of serious disadvantages[62,64], due to the drastic reaction conditions and long reaction times, unwanted side reactions often take place, major problems here are de-amination and the formation of methylene bis ketones (b). Single products (a) are generally only obtained when secondary amines are used, if one uses a primary amine or ammonia as the amine component reaction can continue until all the H-atoms on the nitrogen are replaced, as a consequence, one obtains, in addition to the desired product (a), the other Mannich bases (c) and (d) as major components. Ketones with two reactive α-position must be used in large excess, in order to avoid the production of bis-Mannich bases (e)[62,63].



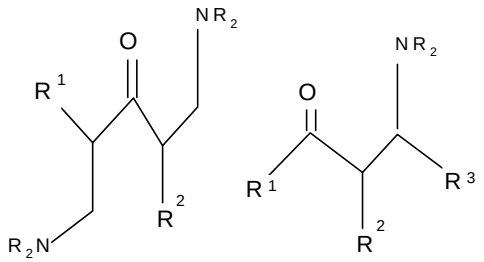

(a)




(b)



(c) (d)



(e) (f)

In the case of the unsymmetrical ketones a further problem is encountered, the regioselectivity cannot be controlled to any significant extent and is often strongly dependent on reaction conditions. Additionally and with very few exceptions; one can only use formaldehyde[62,65], therefore, Mannich bases such as (f) which would very probably also be extremely attractive intermediates are not accessible by this method. A further limitation is that some other carbonyl compounds such as carboxylic acids and their derivatives cannot be aminomethylated, in addition the classical Mannich reaction is not suited to the enantioselective synthesis of β-aminoketones and aminoaldehydes. Thus, the majority of pharmaceutical products, which are derived from Mannich reaction are used in the form of racemate[62,63,66]. This problem becomes more severe when one takes into consideration the increasing

importance of stereochemically pure pharmaceuticals (the avoidance of isomer ballast and of undesirable side effects [62), (66)]). Due to the very attractive nature of Mannich bases, there have been many attempts to find alternative synthetic routes to this compounds, which do not suffer the sever drawbacks of the classical procedure [62,63].

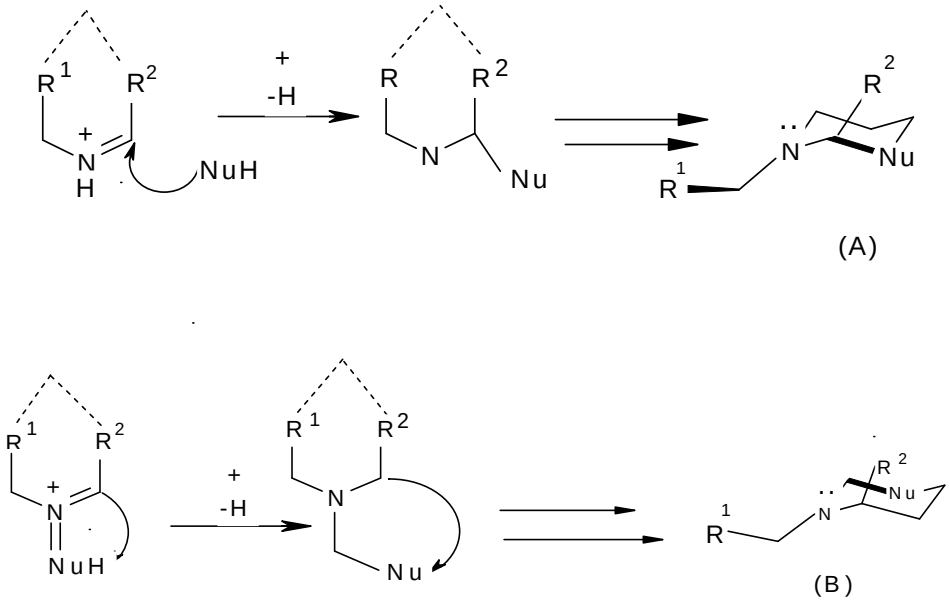
The problems in intermolecular Mannich reaction would be overcomed by using of (Organocatalystic progress), which can play important role in the orientation of one-pot three component Mannich reaction to give enantiochemically products and regioselectivitywould take place in this type of reactions[67] .

### 1.5.2 IntramolecularMannich reaction

IntramolecularMannich reactions possess a significantly wider range of applications than their intermolecular counterparts. Their extremely high value- particularly as the key step in reaction sequence- has long been recognized and used amongst other applications, in biomimetic natural product synthesis. Since the first ground- breaking work, such as Robinson synthesis of tropinone[14,62,63], modern methods such as the combination of [3, 3] sigmatropic rearrangements with intramolecularaminoalkylation, or powerful new methods for the generation of iminium salts under mild reaction conditions have allowed simple highly regio- and stereoselective access to a large number of complex target molecules.

The Intramolecular variant is not restricted to aminomethylation but can be applied in its widest sense to aminoalkylation, its chemoselectivity also offers a much wider range of potential applications. The carbonyl compound, as in the case with the intermolecular variant, can be used in

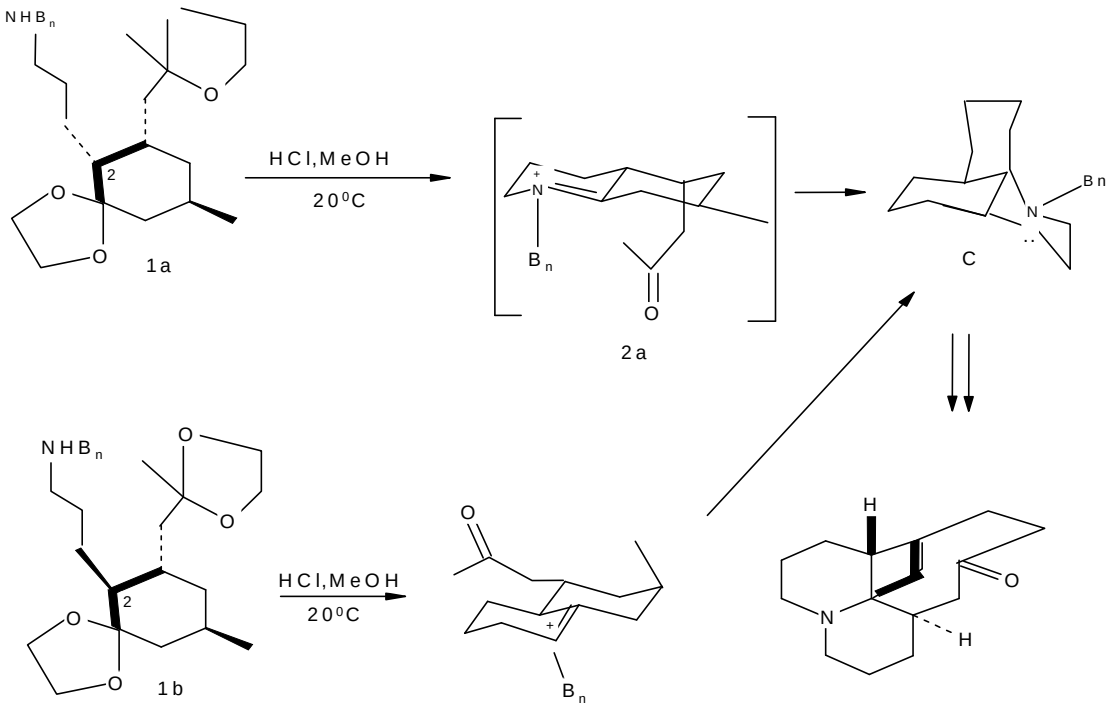
the form of an acetal or a (silyl) enol as in the intramolecular reaction, whereas, in the presence of aqueous mineral acid the protecting group is cleaved and the enol is the reactive species. Thestereochemical pathway of a nucleophilic attack on an iminium ion is often controlled by stereoelectronic factors[62,68]. Because of the anti-perplaner conformation of the product, reliable predictions can therefore be made about the stereoselectivity of the cyclization[62].




**Scheme (5)**: Stereo electronic control in the cyclization initiated by iminium ions form exo-trig (A) and endo-trig (B) products.

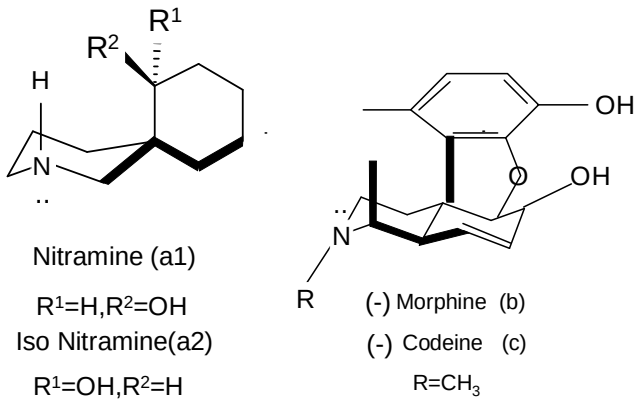
An excellent example of this stereo-controlled reaction is the synthesis oflycopodium alkaloid[62,69], the starting material (1a), which is epimeric at C-2 cyclizes to give the single isomer (c) in 66% yield. This result can

only be explained by assuming an equilibration of the starting material after hydrolysis of the protecting group; a cyclization via the transition state (2b) is impossible on stereoelectronic grounds[62].




**Scheme (6)**represents the redundant synthesis of lycopodium alkaloid.

The above scheme represents the redundant synthesis of lycopodium alkaloid. In this synthetic sequence another major advantage of redundant or degenerate synthesis is exemplified. This is a feature of Mannichcyclization[62]. Further examples of stereo- electronically controlled synthesis of natural products are given by the synthesis of the structurally unusual 2-azaspiro [5.5] undecane alkaloid nitramine (1a) and its regio-isomer isonitramine (2a) [62,70], and the analgesics (-) morphine (b) and (-) codeine (c)[62,63,71].




**Scheme (7):** Alkaloids synthesized by stereo- electronically controlled Mannich reactions.

## 1.6 Preformed Mannich reagents

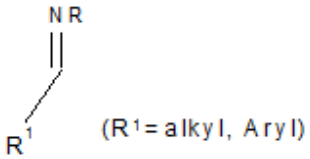
Modern versions of the Mannich reaction usually allow a distinctly simpler entry into β- amino carbonyl compounds through the use of preformed electrophiles (e.g. imnium salts or imines) or nucleophiles (e.g. enolates, enol ether and enamines). Such methods allow; at least in principle, all the limitations of the classical method to be overcomed. The levels of performance and the versatility of these methods have already been powerfully demonstrated in the synthesis of β- amino acid derivatives and β- lactams [62,63,72,73].

In comparison to the classical Mannich conditions, these preformed reagents guarantee a higher concentration of the electrophile leading to lower reaction temperatures and much shorter reaction times, as a consequence many undesired side reactions which so often cause problems in the Mannich reaction are avoided, even with sensitive substrates[62,63]. Furthermore, one can avoid the use of protic solvents, in

this way the carbonyl component can be replaced with much more reactive synthetic equivalents such as enolates. This leads to a greatly extended spectrum of application for the reaction. One can therefore also successfully use reagents which are normally impossible under the classical conditions (e.g. sterically very demanding substrates or carboxylic acid derivatives). In addition; the reaction is not restricted to aminomethylation, but aminoalkylation is also possible. It is also possible to carry out the reaction with high degree of regio- and stereo-selectivity[62,63].

### 1.6.1. Imines

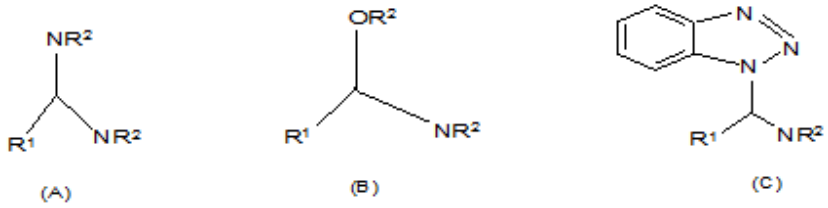
The general form of the amine can be written as follows[62,63,74]:




Amines are generally much less electrophilic than corresponding aldehyde amines. The use of enolizable imines should allow the reaction to proceed under very mild conditions with the avoidance of the aldol-typeself-condensation reactions [62,75]. Formaldehyde amines ($R^1$=H) are generally only stable at low temperature, they are therefore best-generated*insitu* or alternatively, a synthetic equivalent can be used[62,63,75,76].

### 1.6.2 Aminals and N,O- Acetals

The general form of aminals and N,O-acetals can be written as the following:

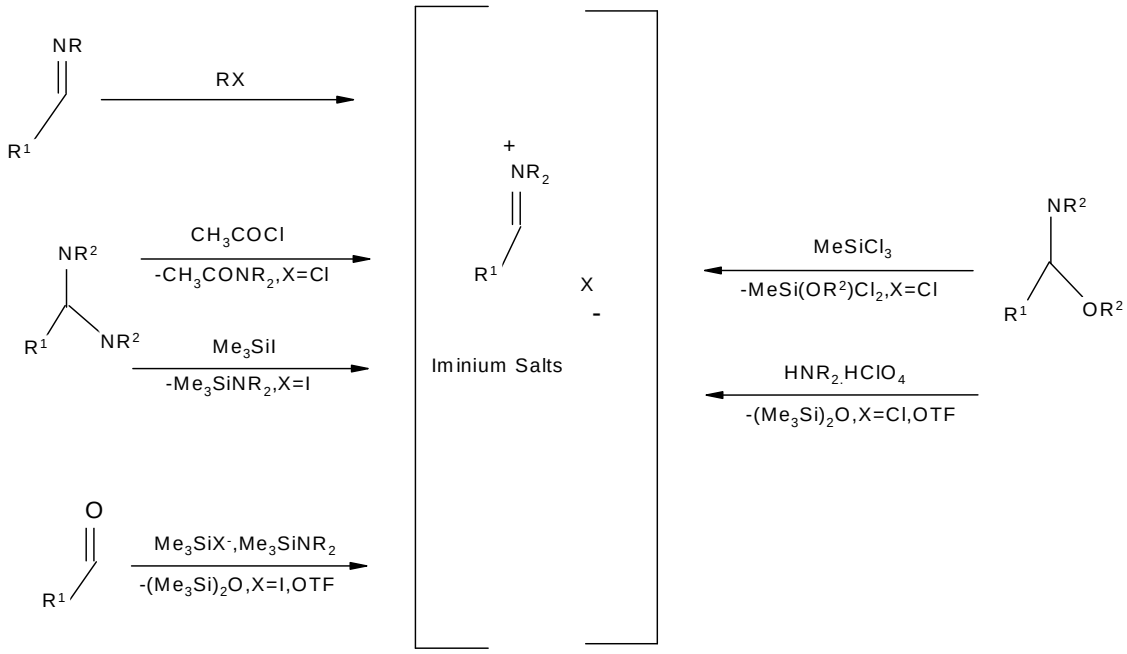



Aminals(A) and N,O-Acetals (B) resemble imines in terms of their electrophilicity. They must therefore normally be activated by Lewis acids in order to react with nucleophiles. The benzotrizoleaminals(C) represent a special case.These easily accessible compounds are very well suited for aminoalkylation, when derivatives of enolizable aldehydes or ketones are used or when derivatives of primary amines are involved[76].Benzotrizoleaminals have been used in the synthesis amongst others β-amino carbonyl compounds[77].

### 1.6.3 Iminium salts

Iminiumsalts are generally readily accessible from basic chemicals[62,78]. The iminium salts are the most commonly applied Mannich reagents in the synthesis of β- amino ketones and aldehydes [75,79], this is because these are more powerfully electrophilic than imines, aminals and N,O-acetals. These are also suitable for the preparation of β-amino- carboxylic acid derivatives[80].Basically, the preparative uses of these materials have been limited to three compounds: eschenmoser's salt $[H_2C{=}NMe_2]^{+}1$-[10] [81,82], the corresponding chloride salt made popular by Kinast and Tietze[62,82.]

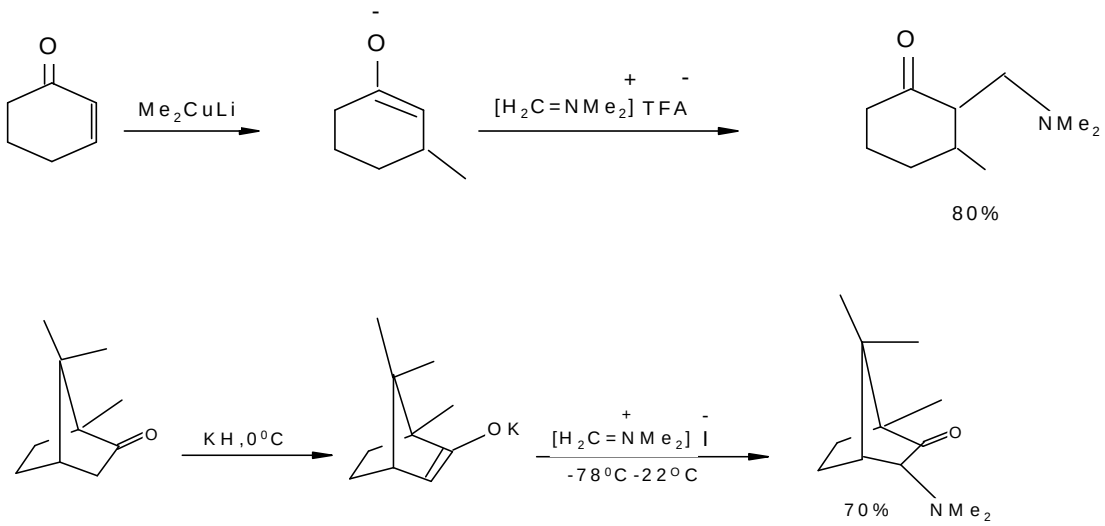
Iminium salts are normally hygroscopic and sensitive towards hydrolysis. Under exclusion of moisture, these can however be stored over long periods, nonetheless; salts with α- H atoms are often less stable[81] .




**Scheme (8)**: Synthesis of iminium salts

### 1.6.4 Enolates

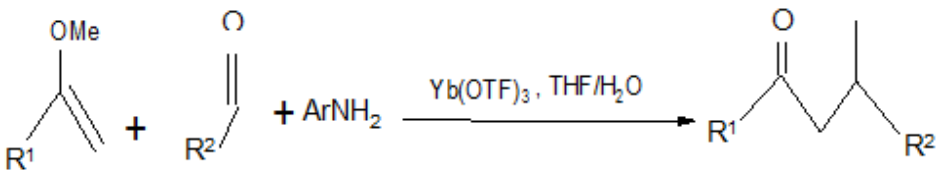
Ketoneenolates react with Mannich reagents not derived from formaldehyde in a similar way to ester enolates[75]. Their use allows the scope of the classical Mannich reaction to be extended from aminomethylation to aminoalkylation.The reaction of lithium enolates(derivatives of cyclohexanone, acetone or acetophenone ) with *in situ*generated,N,O- acetals(derivatives of secondary amines and aromatic or aliphatic aldehyde ) is the first generally applicable method for the amino-alkylation of ketones[83] .




Dia stereo selective amino alkylation of an enolate with a N,O-acetal generated in situ

### 1.6.5 Alkyl Enol Ethers

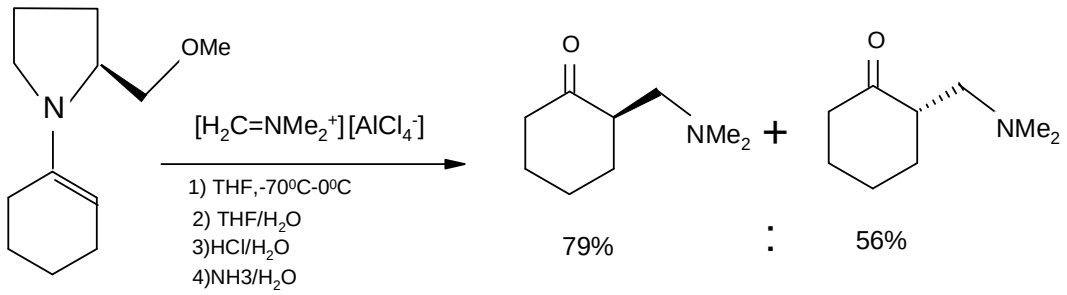
There are relatively few reports of the uses of alkyl enol ethers in the Mannich reaction. Thus; alkyl enol ethers can be aminomethylated with methylene iminium salts under mild conditions[86] .The use of lanthanide triflate catalysts such as ytterbium(III) triflate[$Yb(OTf)_3$] makes possible the synthesis of secondary β-amino ketones by the aminoalkylation of alkyl enol ethers with aldehydes and aromatic amines.Kobayashi and Ishitani have proposed that the reaction proceeds via imines formed *in situ*[86].




Lanthanide triflate-catalyzed aminoalkylation of alkyl enol ethers in aqueous medium

### 1.6.6 Enamines and Imines

So far, iminium salts have been the preferred reagents for the aminomethylation and aminoalkylation of enamines[62,63,87,91] , in comparison to iminium salts, other Mannich reagents such as N,O-acetals[62,92] ,aminals[93,94] and imines[95] have played only a minor supporting role.




Enantioselective Synthesis of B-amino ketones by methylation of enamines with iminium salts

Ternary iminium salts are extremely good in the aminoalkylation of enamines. Iminium salts can be generated *in situ* almost quantitative from secondary amines (or their hydrochlorides) and non-enolizable aldehydes. These iminium salts can then be used directly, without isolation or purification, in the reaction with enamines or other nucleophiles such as imines or electron-rich arenes(silylogousMannnich reaction), the experimental effort required can be dramatically reduced with such approach [62,87,89]. The results (yields, diastereoselectivities) are essentially indistinguishable from those obtained with preformed iminium salts [88,96].

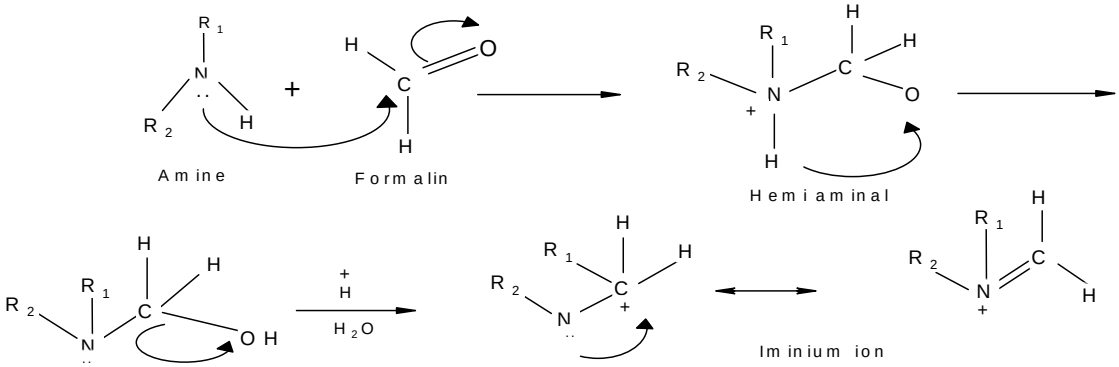
A further benefit is that iminium salts that are otherwise difficult or impossible to obtain can easily be generated (e.g. derivatives of benzyl amine) [96].

### 1.7. Mechanism of Mannich reaction

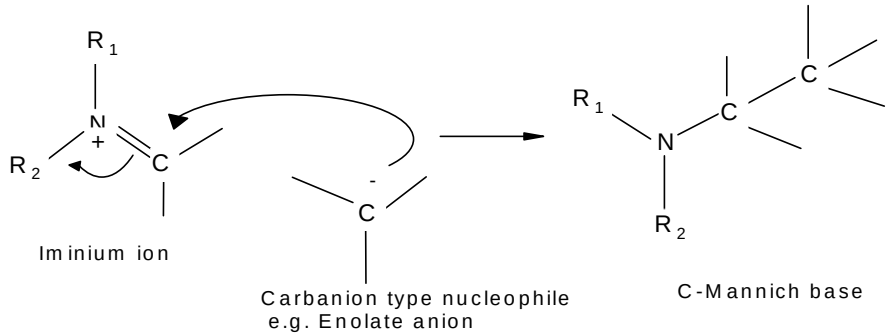
The Mannich reaction apparently proceeds through a variety of mechanisms depending on the reactants and conditions that are employed. Modern recent progress in asymmetric Mannichreaction took place such as the use of organo-catalysis systems [97,98].

### 1.7.1 The Pathways and Orientation in Mannich reaction

Many pathways were proposed to the mechanism of the Mannich reaction through the kinetic studies in various conditions. Reaction of the secondary amine with the aldehydes forms a hemiaminalswhich loses molecule of water to form iminiumcation in the first step. In the second step of the reaction a carbanion is generated from CH acidic compounds (enol from of the active hydrogen compound) which reacts with the iminiumcation to form a β-amino carbonyl compound (aMannich bases)[99,100].



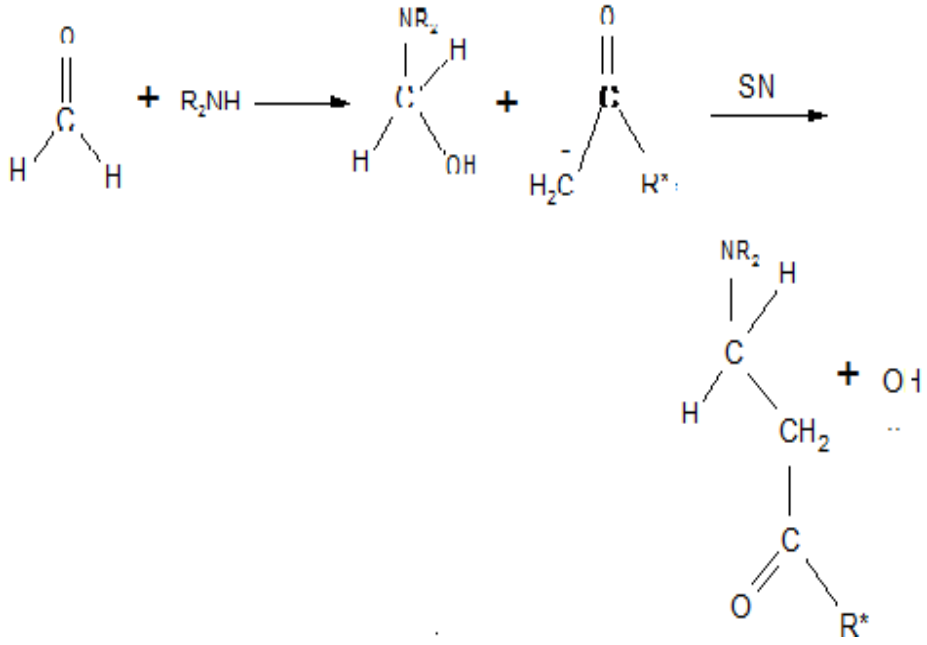

The first step in the Mannich reaction mechanism:formation of iminium ion.



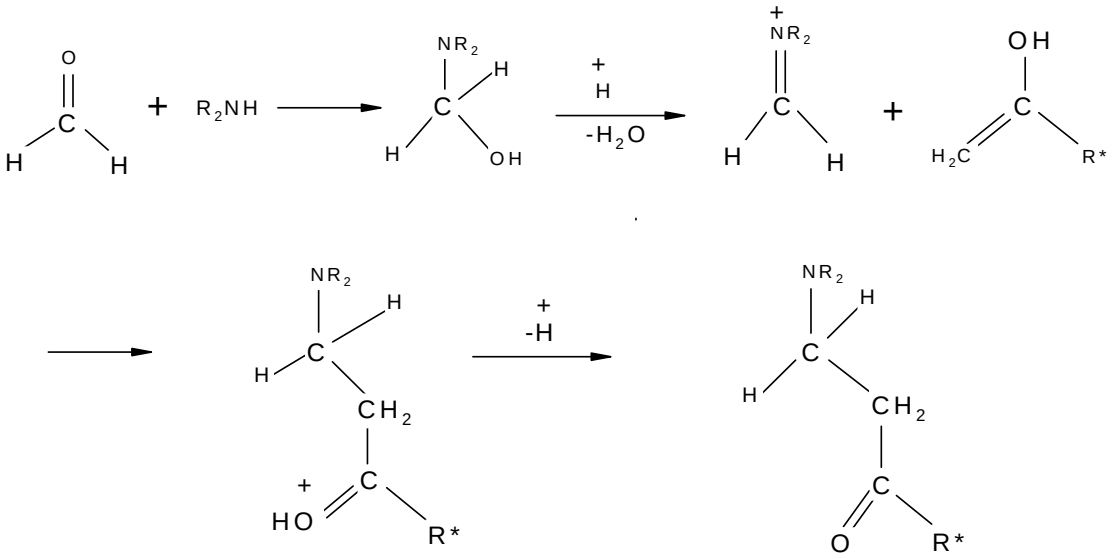

The second step in the Mannich reaction mechanism: nucleophilic addition on to iminium ion.

Studies of the reaction kinetic have led to the following proposal for the mechanism of the Mannich reaction:

### 1.7.2 The base- catalyzed reaction:

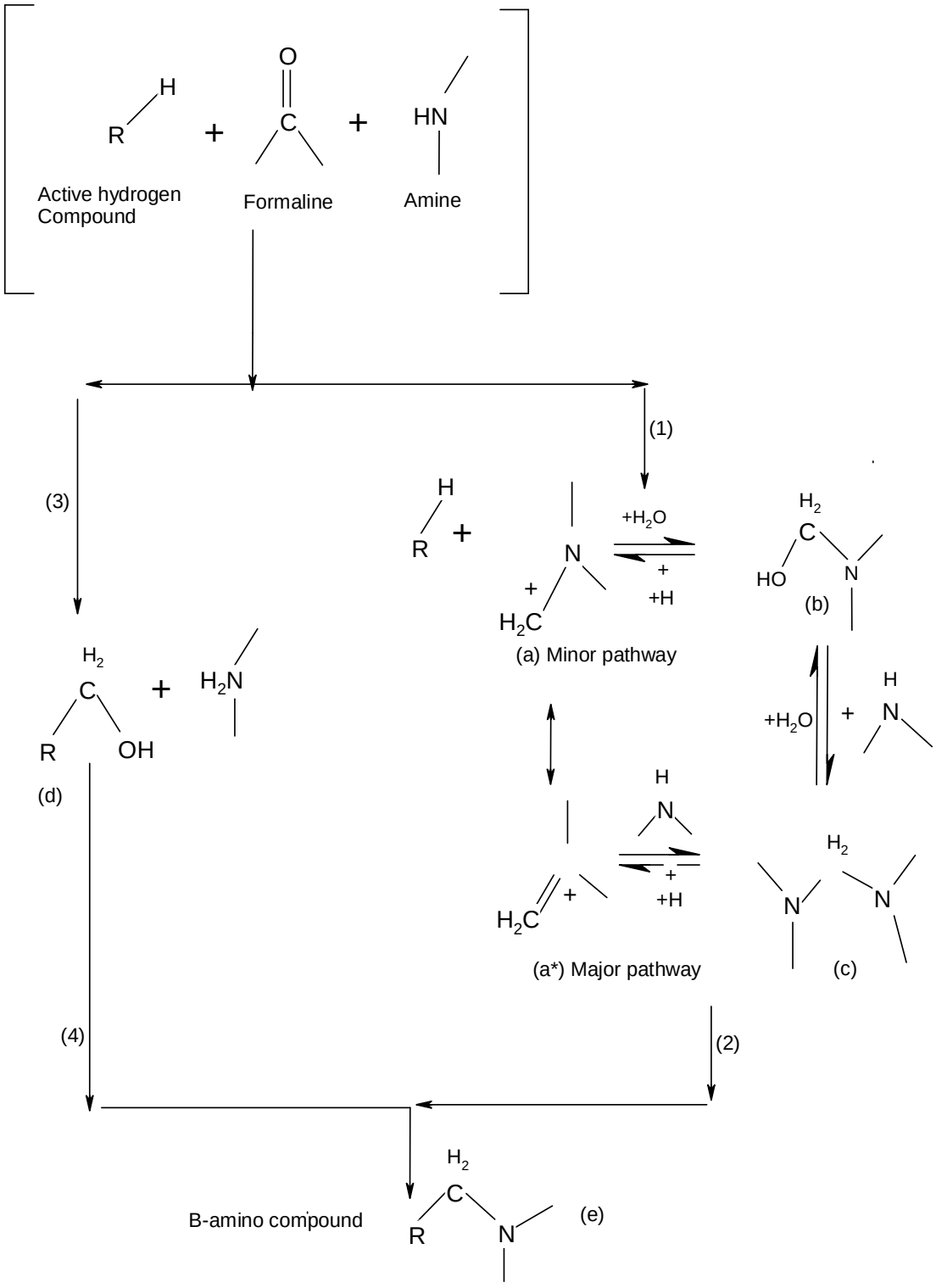


### 1.7.3 The acid- catalyzed reaction



According to this mechanism, it is the free amine; not the salt that react, even in acidic solution; and the active hydrogen compound ( in the acid-catalyzed process), reacts as the enol when that is possible, there is kinetic evidence for the intermediacy of the iminium ion [97,100].

The following scheme illustrated the pathways and bearing compounds in the Mannich reaction[4].


Active hydrogen Compound
Formaline
Amine
(1)
(2)
(3)
(4)
(a) Minor pathway
(a*) Major pathway
(b)
(c)
(d)
(e)
B-amino compound

**Aim of this study**

This study was aimed to:

(i) Synthesis of some phenolic Mannich bases and their acetylated derivatives.

(ii) Elucidation of structures of targeted molecules via spectroscopic tools.

(iii) Screening of targeted molecules for their biological activity.