Review in Mannich Bases and Biological Activity

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Abstract- Medicinal chemistry’s roots can be found in the fertile mix of ancient folk medicine and early natural product chemistry and hence its name. As appreciation for the links between chemical structure and observed biological activity grew, medicinal chemistry began to emerge about 150 years ago as a distinct discipline intending to explore these relationships via chemical modification

Index Terms— mannich base , bio , active , drugs

I. INTRODUCTION

Mannich reaction\footnote{Reactions between aldimines and $\alpha$-methylene carbonyls are also considered Mannich reactions because these imines form between amines and aldehydes. The reaction is named after chemist Carl Mannich.\cite{1}} is an important tool for synthesis of novel compounds. Mannich reaction is a three-component condensation reaction involving active hydrogen containing compound, formaldehyde and a secondary amine. The amino alkylation of aromatic substrates by Mannich reaction is of considerable importance for the synthesis and modification of biologically active compounds. A mannich base\footnote{\cite{2,3}} is a beta-amino-ketone, which is formed in the reaction of an amine, formaldehyde (or an aldehyde) and a carbon acid. The Mannich base is an end product in the Mannich reaction, which is nucleophilic addition reaction of a non enolizable aldehyde and any primary or secondary amine to produce resonance stabilized imine (iminium ion or imine salt). The addition of a carbanion from a CH acidic compound (any enolizable carbonyl compound, amide, carbamate, hydantoin or urea) to the imine gives the Mannich base.

The mannich reaction

The Mannich reaction is an organic reaction which consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group by formaldehyde and a primary or secondary amine or ammonia. The final product is a $\beta$-amino-carbonyl compound also known as a Mannich base.\footnote{Reactions between aldimines and $\alpha$-methylene carbonyls are also considered Mannich reactions because these imines form between amines and aldehydes. The reaction is named after chemist Carl Mannich.\cite{1}}
The Mannich reaction is an example of nucleophilic addition of an amine to a carbonyl group followed by dehydration to the Schiff base. The Schiff base is an electrophile which reacts in the second step in an electrophilic addition with a compound containing an acidic proton (which is, or had become an enol). The Mannich reaction is also considered a condensation reaction.

In the Mannich reaction, primary or secondary amines or ammonia, are employed for the activation of formaldehyde. Tertiary amines lack an N–H proton to form the intermediate enamine. α-CH-acidic compounds (nucleophiles) include carbonyl compounds, nitriles, acetylenes, aliphatic nitro compounds, α-alkyl-pyridines or imines. It is also possible to use activated phenyl groups and electron-rich heterocycles such as furan, pyrole, and thiophene. Indole is a particularly active substrate; the reaction provides gramine derivatives.

**Reaction mechanism**

The mechanism of the Mannich reaction starts with the formation of an iminium ion from the amine and the formaldehyde.

**Applications in Medicine and Other Applications:**

The Mannich-Reaction is employed in the organic synthesis of natural compounds such as peptides, nucleotides, antibiotics, and alkaloids (e.g. Tropinone). Other applications are in agrochemicals such as plant growth regulators, paint and polymer chemistry, catalysts and cross linking.

The Mannich reaction is also used in the synthesis of medicinal compounds.

*E.g.*: Roli tetracycline (Mannich base of tetracycline).

Fluoxetine (antidepressant).

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Mannich bases were found to possess potent activities such as antibacterial\(^1\), antifungal\(^4\), anti-HIV\(^2\), antiviral\(^6,7\), anticancer\(^8\), antimicrobial\(^9,10\). They are also used in polymer industry as paints and surface active agents. Mannich bases demonstrated anticonvulsant activities and have been reported as potential biological agents. They also find application as antitubercular\(^11\), antimalarial\(^12\), vasorelaxing\(^13\), analgesic\(^14\), anticonvulsant\(^5,16\) drugs, biological\(^17,18\) and pharmacological\(^19,20\) activity. They are also used in polymer industry as paints and surface active agents.

**Mannich Reaction**

\[
\begin{align*}
\text{H} = \text{O} & + \text{R}_2\text{NH} + \text{R} - \text{C} & \rightarrow \text{R}_2\text{N}^\text{+} \text{R'}^- \\
\end{align*}
\]

This multi-component condensation of a nonenolizable aldehyde, a primary or secondary amine and an enolizable carbonyl compound affords aminomethylated products. The iminium derivative of the aldehyde is the acceptor in the reaction.

**Mechanism of the Mannich Reaction**

\[
\begin{align*}
\text{H} & \text{R} \text{N} & \text{H} & \text{H} & \text{H} & \text{H} & \text{N} & \text{R} & \text{H} & \text{H} & \text{H} & \text{R} & \text{H} & \text{H} & \text{H} & \text{R} & \text{H} & \text{H} & \text{H} & \text{R} & \text{H} & \text{H} & \text{H} & \text{R} & \text{H} & \text{H} & \text{H} & \text{R} \\
\end{align*}
\]

The involvement of the Mannich Reaction has been proposed in many biosynthetic pathways, especially for alkaloids.
A **mannich base** is a beta-**amino-ketone**, which is formed in the reaction of an **amine**, **formaldehyde** (or an **aldehyde**) and a **carbon acid**. The Mannich base is an endproduct in the **Mannich reaction**, which is **nucleophilic addition reaction** of a **non-enolizable** aldehyde and any primary or secondary **amine** to produce resonance stabilized **imine** (iminium ion or imine salt). The addition of a carbanion from a CH acidic compound (any enolizable carbonyl compound, amide, carbamate, hydantoin or urea) to the imine gives the Mannich base.

With primary or secondary amines, Mannich bases react with additional aldehyde and carbon acid to larger adducts HN(CH₃CH₂COR)₃ and HN(CH₂CH₂COR)₃. With multiple acidic hydrogen atoms on the carbon acid higher adducts are also possible. Ammonia can be split off in an **elimination reaction** to form **enals** and **enones**.

Progress has been made towards **asymmetric** Mannich reactions. When properly functionalized the newly formed ethylene bridge in the Mannich adduct has two **prochiral** centers giving rise to two diastereomeric pairs of enantiomers. The first asymmetric Mannich reaction with an unmodified aldehyde was carried with (S)-**proline** as a naturally occurring **chiral catalyst**.
The reaction taking place is between a simple aldehyde, such as propionaldehyde, and an imine derived from ethyl glyoxylate and p-methoxyaniline ($PMP = \text{paramethoxyphenyl}$) catalyzed by $(S)$-proline in dioxane at room temperature. The reaction product is diastereoselective with a preference for the syn-Mannich reaction 3:1 when the alkyl substituent on the aldehyde is a methyl group or 19:1 when the alkyl group the much larger pentyl group. Of the two possible syn adducts $(S,S)$ or $(R,R)$ the reaction is also enantioselective with a preference for the $(S,S)$ adduct with enantiomeric excess larger than 99%. This stereoselectivity is explained in the scheme below.

Proline enters a catalytic cycle by reacting with the aldehyde to form an enamine. The two reactants (imine and enamine) line up for the Mannich reaction with Si facial attack of the imine by the Si-face of the enamine-aldehyde. Relief of steric strain dictates that the alkyl residue $R$ of the enamine and the imine group are antiperiplanar on approach which locks in the syn mode of addition. The enantioselectivity is further controlled by hydrogen bonding between the proline carboxylic acid group and the imine. The transition state for the addition is a nine-membered ring with chair conformation with partial single bonds and double bonds. The proline group is converted back to the aldehyde and a single $(S,S)$ isomer is formed.
By modification of the proline catalyst to it is also possible to obtain anti-Mannich adducts.\(^5\)

An additional methyl group attached to proline forces a specific enamine approach and the transition state now is a 10-membered ring with addition in anti-mode. The diastereoselectivity is at least anti:syn 95:5 regardless of alkyl group size and the \((S,R)\) enantiomer is preferred with at least 97% ee.\(^5\)

**Applications in Drugs and Pharmaceutical Field:**

The Mannich-Reaction is employed in the organic synthesis of natural compounds such as peptides, nucleotides, antibiotics, and alkaloids (e.g. tropinone). Other applications are in agrochemicals such as plant growth regulators,\(^6\) paint- and polymer chemistry, catalysts and main mechanism of formalin tissue crosslinking.

The Mannich reaction is also used in the synthesis of alkyl amines, converting non-polar hydrocarbons into soap or detergents. This is used in a variety of cleaning applications, automotive fuel treatments, and epoxy coatings. Similar methods of substituted branched chain alkyl ethers into polyetheramines are achieved via a number of reactions.\(^9\)

**REFERENCES**


