

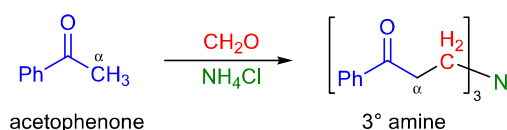
## MANNICH REACTION

(References are on page 623)

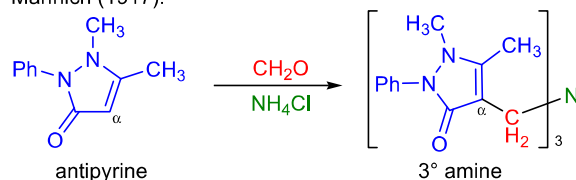
**Importance:**[Seminal Publications<sup>1-3</sup>; Reviews<sup>4-23</sup>; Modifications & Improvements<sup>24-36</sup>; Theoretical Studies<sup>37-49</sup>]

In 1903, B. Tollens and von Marle made the observation that the reaction of acetophenone with formaldehyde and ammonium chloride led to the formation of a tertiary amine.<sup>1</sup> In 1917, C. Mannich also isolated a tertiary amine by exposing antipyrine to identical conditions and recognized the generality of this reaction.<sup>2,3</sup> The condensation of a CH-activated compound (usually an aldehyde or ketone) with a primary or secondary amine (or ammonia) and a non-enolizable aldehyde (or ketone) to afford aminoalkylated derivatives is known as the *Mannich reaction*. More generally, it is the addition of resonance-stabilized carbon nucleophiles to iminium salts and imines. The product of the reaction is a substituted  $\beta$ -amino carbonyl compound, which is often referred to as the Mannich base. The general features of the reaction are: 1) the CH-activated component (activated at their  $\alpha$ -position) is usually an aliphatic or aromatic aldehyde or ketone, carboxylic acid derivatives,  $\beta$ -dicarbonyl compounds, nitroalkanes, electron-rich aromatic compounds<sup>12</sup> such as phenols (activated at their *ortho* position) and terminal alkynes;<sup>13</sup> 2) only primary and secondary aliphatic amines or their hydrochloride salts can be used since aromatic amines tend not to react; 3) the non-enolizable carbonyl compound is most often formaldehyde; 4) when the amine component is a primary amine, the initially formed  $\beta$ -amino carbonyl compound can undergo further reaction to eventually yield a *N,N*-dialkyl derivative (a tertiary amine); however, with secondary amines overalkylation is not an issue; 5) the reaction medium is usually a protic solvent such as ethanol, methanol, water, or acetic acid to ensure sufficiently high concentration of the electrophilic iminium ion, which is responsible for the aminoalkylation; 6) unsymmetrical ketones usually give rise to regioisomeric Mannich bases, but the product derived from the aminoalkylation of the more substituted  $\alpha$ -position tends to be dominant; and 7) Mannich bases are useful synthetic intermediates, since they can undergo a variety of transformations:  $\beta$ -elimination to afford  $\alpha,\beta$ -unsaturated carbonyl compounds (Michael acceptors), reaction with organolithium, or Grignard reagents to yield  $\beta$ -amino alcohols and substitution of the dialkylamino group with nucleophiles to generate functionalized carbonyl compounds. There have been several improvements to the original three-component *Mannich reaction*. The use of preformed iminium salts is the most significant modification because it allows faster, more regioselective, and even stereoselective transformations under very mild conditions.<sup>18</sup>

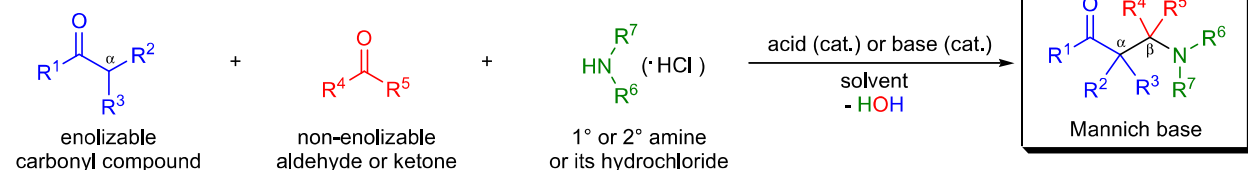
Tollens and von Marle (1903):



Mannich (1917):



Mannich reaction:

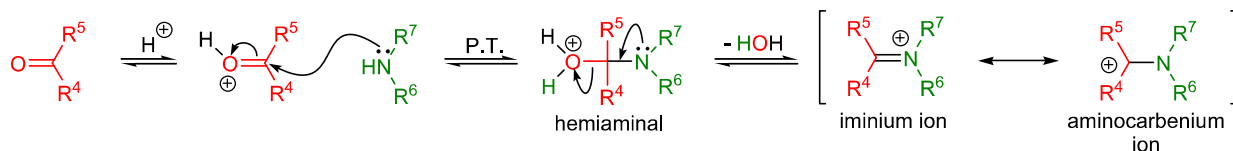


$\text{R}^1 = \text{H, alkyl, aryl, OR}$ ;  $\text{R}^{2-3} = \text{H, alkyl, aryl}$ ;  $\text{R}^{4-5} = \text{H, alkyl, aryl}$ ;  $\text{R}^6 = \text{H, alkyl, OH, NH}_2$ ;  $\text{R}^7 = \text{H, alkyl}$ ; solvent = ROH, H<sub>2</sub>O, AcOH

**Mechanism:** <sup>6,50,12-14</sup>

The mechanism of the *Mannich reaction* has been extensively investigated. The reaction can proceed under both acidic and basic conditions, but acidic conditions are more common. Under acidic conditions the first step is the reaction of the amine component with the protonated non-enolizable carbonyl compound to give a hemiaminal, which after proton transfer loses a molecule of water to give the electrophilic iminium ion.<sup>50</sup> This iminium ion then reacts with the enolized carbonyl compound (nucleophile) at its  $\alpha$ -carbon in an *aldol-type reaction* to give rise to the Mannich base.

Formation of the reactive iminium ion under acidic conditions:



Alkylation of the enolized carbonyl compound:

