

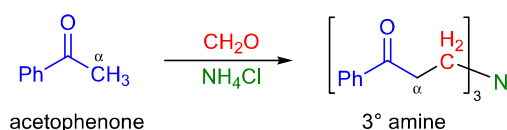
MANNICH REACTION

(References are on page 623)

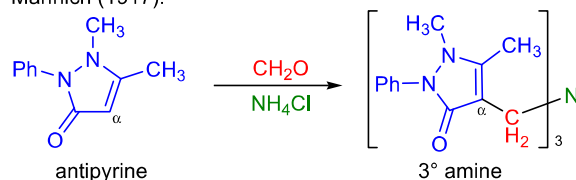
Importance:[Seminal Publications¹⁻³; Reviews⁴⁻²³; Modifications & Improvements²⁴⁻³⁶; Theoretical Studies³⁷⁻⁴⁹]

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.¹ In 1917, C. Mannich also isolated a tertiary amine by exposing antipyrine to identical conditions and recognized the generality of this reaction.^{2,3} 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 β -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 α -position) is usually an aliphatic or aromatic aldehyde or ketone, carboxylic acid derivatives, β -dicarbonyl compounds, nitroalkanes, electron-rich aromatic compounds¹² such as phenols (activated at their *ortho* position) and terminal alkynes;¹³ 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 β -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 α -position tends to be dominant; and 7) Mannich bases are useful synthetic intermediates, since they can undergo a variety of transformations: β -elimination to afford α,β -unsaturated carbonyl compounds (Michael acceptors), reaction with organolithium, or Grignard reagents to yield β -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.¹⁸

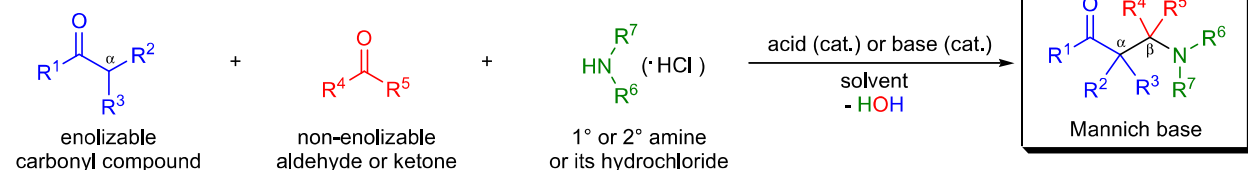
Tollens and von Marle (1903):



Mannich (1917):



Mannich reaction:

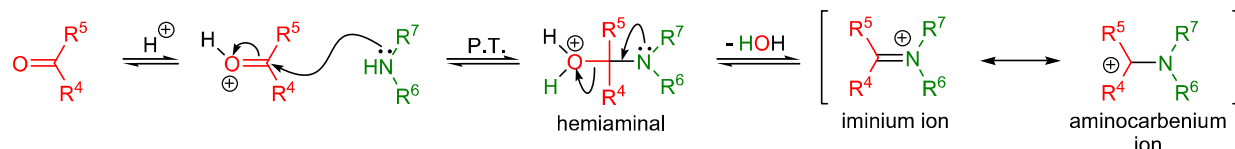


$R^1 = \text{H, alkyl, aryl, OR}$; $R^{2-3} = \text{H, alkyl, aryl}$; $R^{4-5} = \text{H, alkyl, aryl}$; $R^6 = \text{H, alkyl, OH, NH}_2$; $R^7 = \text{H, alkyl}$; solvent = ROH, H₂O, AcOH

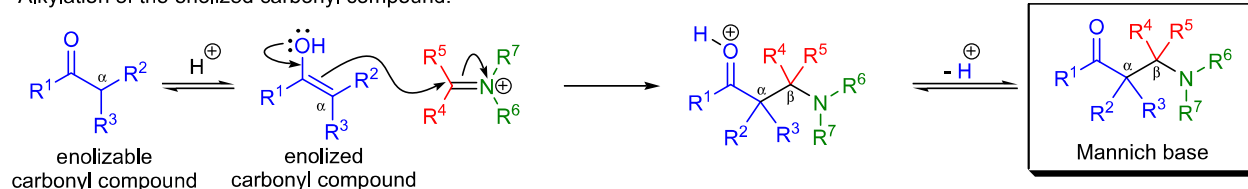
Mechanism: ^{6,50,12-14}

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.⁵⁰ This iminium ion then reacts with the enolized carbonyl compound (nucleophile) at its α -carbon in an *aldol-type reaction* to give rise to the Mannich base.

Formation of the reactive iminium ion under acidic conditions:



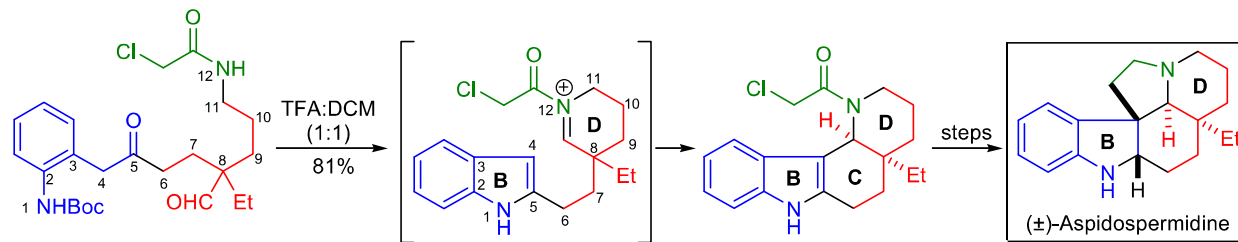
Alkylation of the enolized carbonyl compound:



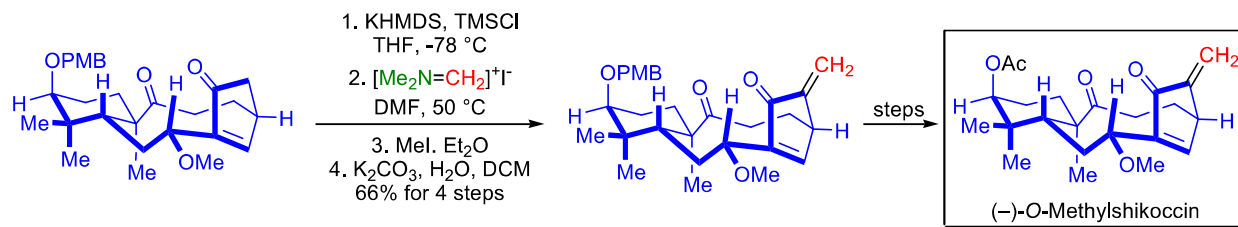
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Synthetic Applications:

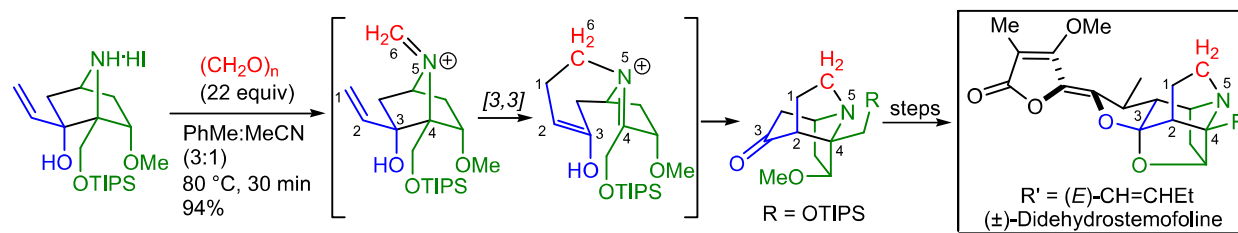
The total synthesis of (\pm)-aspidospermidine was accomplished by C.H. Heathcock and co-workers.⁵¹ The synthetic strategy relied on an intramolecular cascade reaction, which simultaneously formed the B, C, and D rings of the natural product. As we mentioned previously, the CH-activated component of the *Mannich reaction* can also be an electron-rich aromatic ring such as an indole. The starting material was subjected to TFA in dichloromethane which first resulted in the formation of an indole (B ring) and an acylammonium ion (D ring) that *in situ* underwent an *intramolecular Mannich-type cyclization* giving rise to the C ring.



When preformed iminium salts are utilized in *Mannich reactions*, the reaction medium no longer needs to be a protic solvent, so the use of aprotic solvents allows the transformation of sensitive intermediates such as metal enolates. L.A. Paquette et al. carried out the highly regioselective introduction of an *exo*-methylene functionality during the total synthesis of ($-$)-*O*-methylshikoccin by reacting a potassium enolate with the Eschenmoser salt.⁵² The resulting β -*N,N*-dimethylamino ketone was converted to the corresponding quaternary ammonium salt and elimination afforded the desired α,β -unsaturated ketone (*Eschenmoser methenylation*).



One of the most well-known applications of the *Mannich reaction* is its use in a tandem fashion with the *aza-Cope rearrangement* to form heterocycles. This reaction was the cornerstone of the strategy in the research group of L.E. Overman during the total synthesis of (\pm)-didehydrostemofoline (asparagamine A).⁵³ The bicyclic amine hydrogen iodide salt was exposed to excess paraformaldehyde, which led to the formation of the first iminium ion intermediate that underwent a facile $[3,3]$ -sigmatropic rearrangement. The resulting isomeric iminium ion spontaneously reacted with the enol in an *intramolecular Mannich cyclization*.



In the laboratory of S.F. Martin, the *vinyllogous Mannich reaction* (VMR) of a 2-silyloxyfuran with a regioselectively generated iminium ion was utilized as the key step in the enantioselective construction of (+)-croomine.^{54,55} The carboxylic acid moiety of the starting material was converted to the acid chloride which spontaneously underwent decarbonylation to give the corresponding iminium ion. Reaction of this iminium ion with the 2-silyloxyfuran afforded the desired *threo* butenolide isomer as the major product.

