

# Mannich reaction

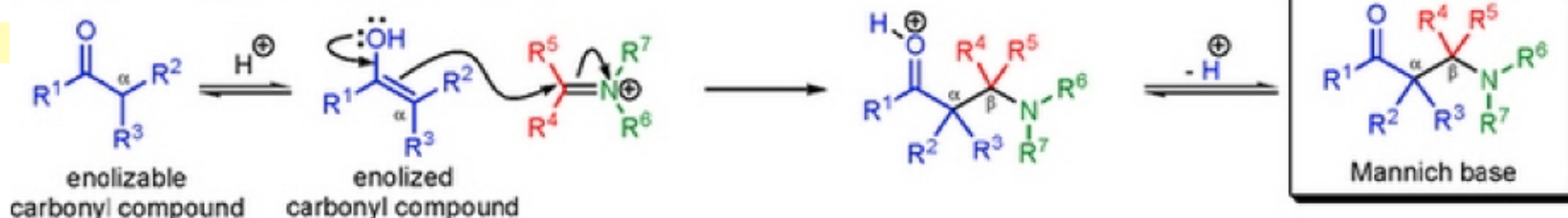
## Mechanism: 6,50,12-14

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.<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:



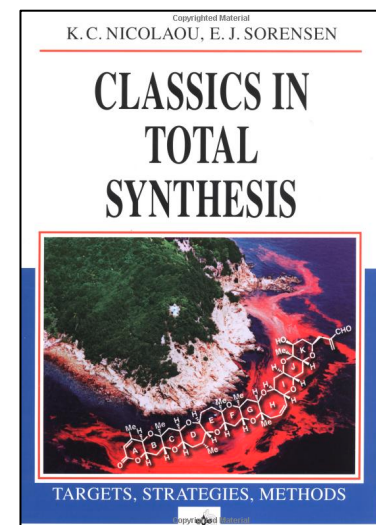
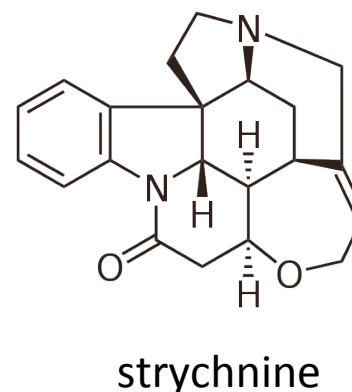
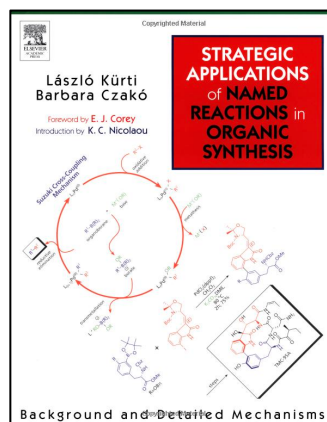
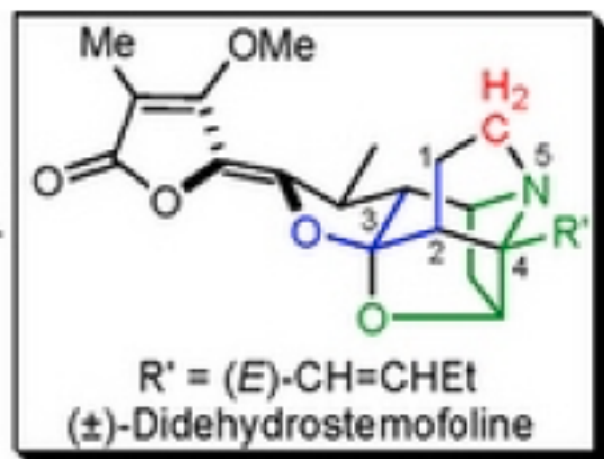
Alkylation of the enolized carbonyl compound:



Taken from: Strategic applications of name reactions in organic synthesis (Kurti and Czako)  
<http://books.google.com/books?id=MdxkSyzhcdcC&printsec=frontcover#v=onepage&q=mannich&f=false>

## Application of Mannich reaction: Pioneering chemistry at UCI

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).<sup>53</sup> 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*.



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