

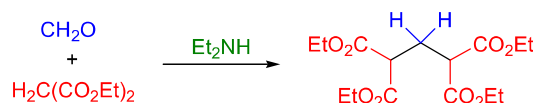
## KNOEVENAGEL CONDENSATION

(References are on page 613)

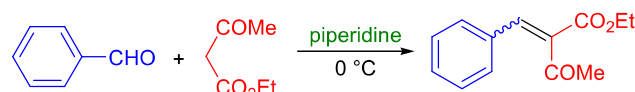
**Importance:**[Seminal Publications<sup>1,2</sup>; Reviews<sup>3-10</sup>; Modifications & Improvements<sup>11-41</sup>]

In 1894, E. Knoevenagel reported the diethylamine-catalyzed condensation of diethyl malonate with formaldehyde in which he isolated the *bis* adduct.<sup>1</sup> He found the same type of *bis* adduct when formaldehyde and other aldehydes were condensed with ethyl benzoylacetate or acetylacetone in the presence of primary and secondary amines. Two years later in 1896, Knoevenagel carried out the reaction of benzaldehyde with ethyl acetoacetate at 0 °C using piperidine as the catalyst and obtained ethyl benzylidene acetoacetate as the sole product.<sup>2</sup> The reaction of aldehydes and ketones with active methylene compounds in the presence of a weak base to afford  $\alpha,\beta$ -unsaturated dicarbonyl or related compounds is known as the *Knoevenagel condensation*. The general features of the reaction are: 1) aldehydes react much faster than ketones; 2) active methylene compounds need to have two electron-withdrawing groups and typical examples are malonic esters, acetoacetic esters, malonodinitrile, acetylacetone, etc.; 3) the nature of the catalyst is important, usually primary, secondary, and tertiary amines and their corresponding ammonium salts, certain Lewis acids combined with a tertiary amine (e.g.,  $\text{TiCl}_4/\text{Et}_3\text{N}$ ), potassium fluoride, or other inorganic compounds such as aluminum phosphate are used; 4) the by-product of the reaction is water and its removal from the reaction mixture by means of azeotropic distillation, the addition of molecular sieves, or other dehydrating agents shifts the equilibrium toward the formation of the product; 5) the choice of solvent is crucial and the use of dipolar aprotic solvents (e.g., DMF) is advantageous, since protic solvents inhibit the last 1,2-elimination step; 6) the dicarbonyl product can be hydrolyzed and decarboxylated to afford the corresponding  $\alpha,\beta$ -unsaturated carbonyl compounds; 7) when  $\text{R}^3$  and  $\text{R}^4$  or  $\text{R}^5$  and  $\text{R}^6$  are different, the product is obtained as a mixture of geometrical isomers, and the selectivity is dictated by steric effects; and 8) usually the thermodynamically more stable compound is formed as the major product.

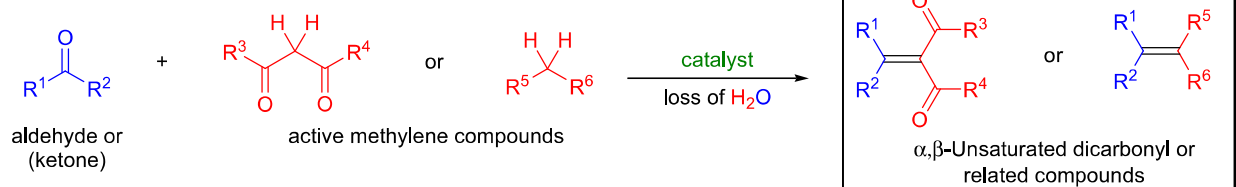
Knoevenagel (1894):



Knoevenagel (1896):



Knoevenagel condensation:

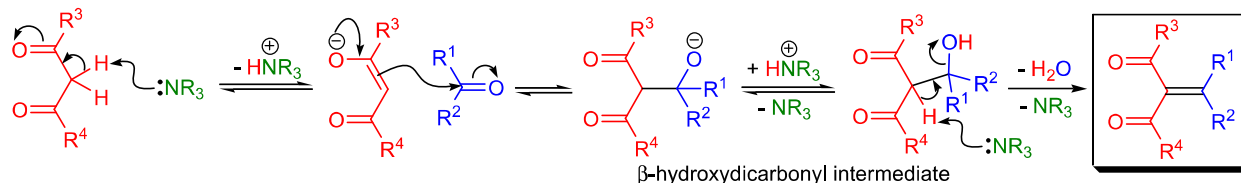


$\text{R}^1 = \text{H}$ , alkyl, aryl;  $\text{R}^2 = \text{H}$ , alkyl, aryl;  $\text{R}^{3-4} = \text{alkyl}$ , aryl, OH, O-alkyl, O-aryl, NH-alkyl, NH-aryl *N*-dialkyl, *N*-diaryl;  $\text{R}^{5-6} = \text{CO}_2\text{H}$ ,  $\text{CO}_2^-$ -alkyl,  $\text{CO}_2^-$ -aryl,  $\text{C}(\text{O})\text{NH}$ -alkyl,  $\text{C}(\text{O})\text{NH}$ -aryl,  $\text{C}(\text{O})\text{N}$ -dialkyl,  $\text{C}(\text{O})\text{N}$ -diaryl,  $\text{C}(\text{O})$ -alkyl,  $\text{C}(\text{O})$ -aryl, CN,  $\text{CNNR}_2$ ,  $\text{PO}(\text{OR})_2$ ,  $\text{SO}_2\text{OR}$ ,  $\text{SO}_2\text{NR}_2$ ,  $\text{SO}_2\text{R}$ ,  $\text{SOR}$ ,  $\text{SiR}_3$ ; **catalyst**: 1°, 2° or 3° amines,  $\text{R}_3\text{NHX}$  such as  $[\text{H}_3\text{NCH}_2\text{CH}_2\text{NH}_3](\text{OAc})_2$ , piperidinium acetate/AcOH,  $\text{NH}_4\text{OAc}$ ,  $\text{KF}$ ,  $\text{CsF}$ ,  $\text{RbF}$ ,  $\text{TiCl}_4/\text{R}_3\text{N}$  (*Lehnert modification*), pyridine/piperidine (*Doebner modification*), dry alumina (*Foucaud modification*),  $\text{AlPO}_4/\text{Al}_2\text{O}_3$ , xonotlite with  $\text{KOH}$ -Bu,  $\text{Zn}(\text{OAc})_2$

**Mechanism:** 42,4,43-49,7,50-55

The *Knoevenagel condensation* is a base-catalyzed *aldol-type reaction*, and the exact mechanism depends on the substrates and the type of catalyst used. The first proposal for the mechanism was set forth by A.C.O. Hann and A. Lapworth (*Hann-Lapworth mechanism*) in 1904.<sup>42</sup> When tertiary amines are used as catalysts, the formation of a  $\beta$ -hydroxydicarbonyl intermediate is expected, which undergoes dehydration to afford the product. On the other hand, when secondary or primary amines are used as catalyst, the aldehyde and the amine condense to form an iminium salt that then reacts with the enolate. Finally, a 1,2-elimination gives rise to the desired  $\alpha,\beta$ -unsaturated dicarbonyl or related compounds. The final product may undergo a *Michael addition* with the excess enolate to give a *bis* adduct.

Hann-Lapworth mechanism with tertiary amines as catalysts:



Mechanism with primary or secondary amines as catalysts:

