KNOEVENAGEL CONDENSATION

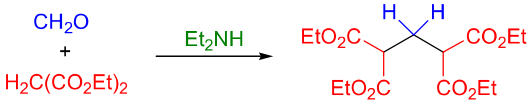
(References are on page 613)

Importance:

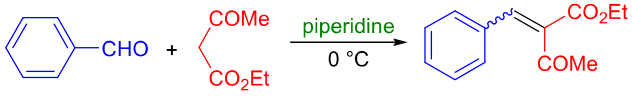
[*Seminal Publications*[1,2]; *Reviews*[3-10]; *Modifications & Improvements*[11-41]]

In 1894, E. Knoevenagel reported the diethylamine-catalyzed condensation of diethyl malonate with formaldehyde in which he isolated the *bis* adduct.[1] 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.[2] The reaction of aldehydes and ketones with active methylene compounds in the presence of a weak base to afford α,β-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., $TiCl_4/Et_3N$), 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 α,β-unsaturated carbonyl compounds; 7) when R^3 and R^4 or R^5 and 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.

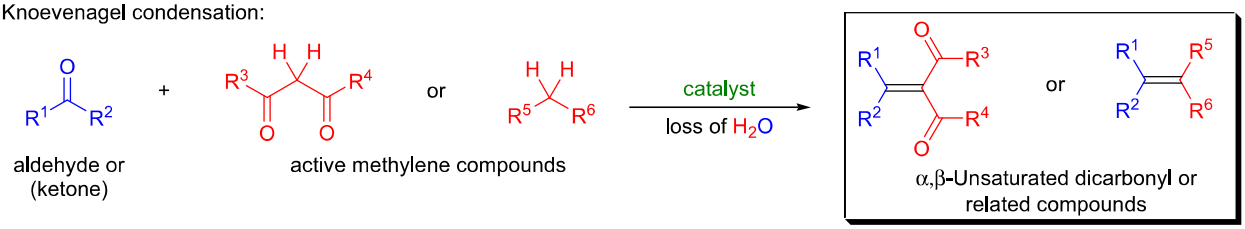
Knoevenagel (1894):



Knoevenagel (1896):



Knoevenagel condensation:



aldehyde or (ketone)

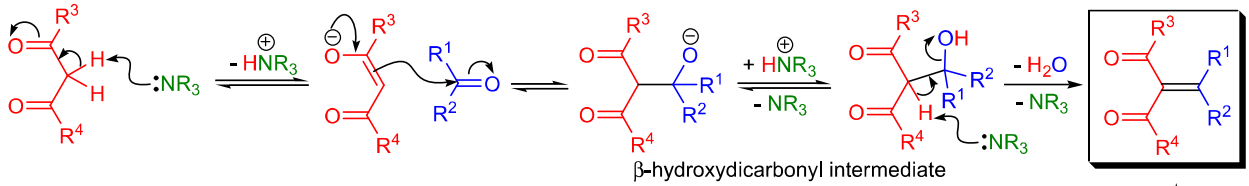
active methylene compounds

R^1 = H, alkyl, aryl; R^2 = H, alkyl, aryl; R^{3-4} = alkyl, aryl, OH, *O*-alkyl, *O*-aryl, NH-alkyl, NH-aryl *N*-dialkyl, *N*-diaryl; R^{5-6} = CO_2H, CO_2-alkyl, CO_2-aryl, C(O)NH-alkyl, C(O)NH-aryl, C(O)N-dialkyl, C(O)N-diaryl, C(O)-alkyl, C(O)-aryl, CN, $CNNR_2$, $PO(OR)_2$, SO_2OR, SO_2NR_2, SO_2R, SOR, SiR_3; catalyst: 1°, 2° or 3° amines, R_3NHX such as $[H_3NCH_2CH_2NH_3](OAc)_2$, piperidinium acetate/AcOH, NH_4OAc, KF, CsF, RbF, $TiCl_4/R_3N$ (*Lehnert modification*), pyridine/piperidine (*Doebner modification*), dry alumina (*Foucaud modification*), $AlPO_4/Al_2O_3$, xonotlite with KO*t*-Bu, $Zn(OAc)_2$

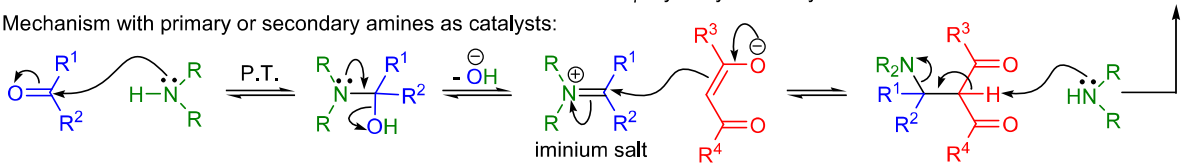
Mechanism:[42,4,43-49,7,50-55]

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.[42] When tertiary amines are used as catalysts, the formation of a β-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 α,β-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:



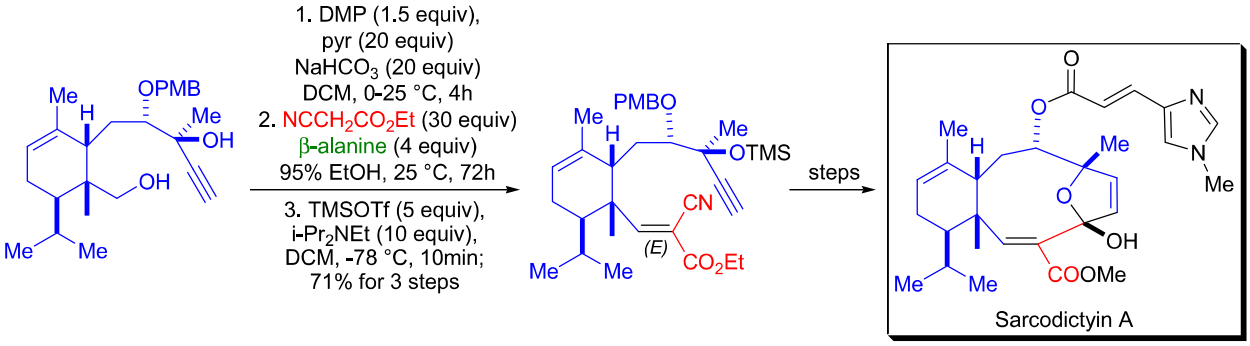
Mechanism with primary or secondary amines as catalysts:



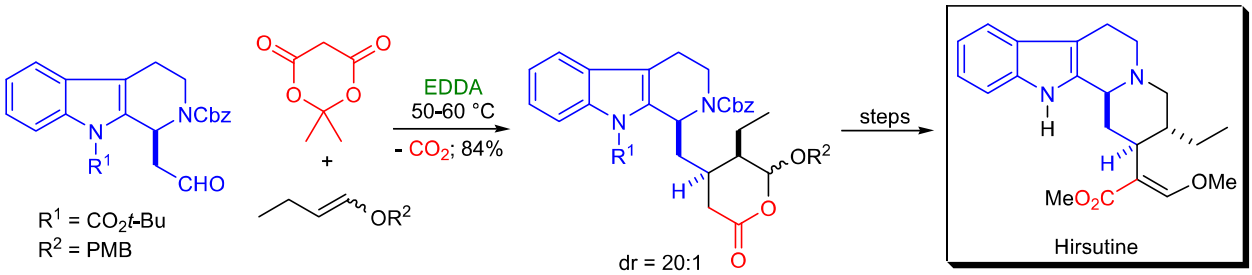
KNOEVENAGEL CONDENSATION

Synthetic Applications:

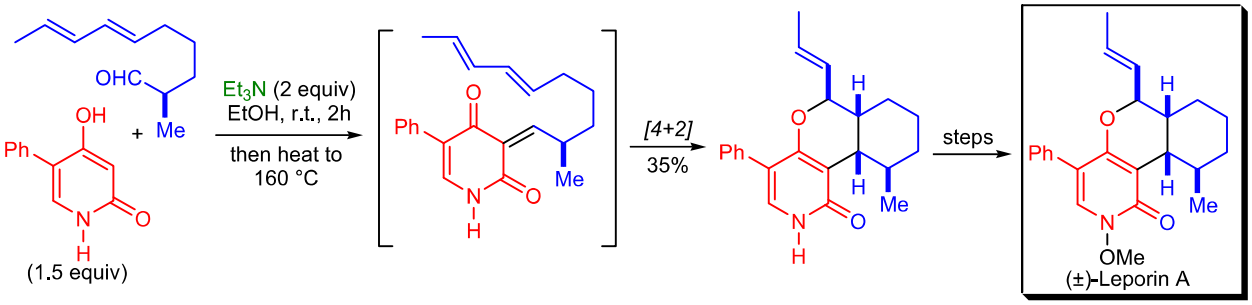
The total synthesis of the marine-derived diterpenoid sarcodictyin A was accomplished in the laboratory of K.C. Nicolaou.[56] The most challenging part of the synthesis was the construction of the tricyclic core, which contains a 10-membered ring. This macrocycle was obtained by the intramolecular 1,2-addition of an acetylide anion to an α,β-unsaturated aldehyde. This unsaturated aldehyde moiety was installed by utilizing the *Knoevenagel condensation* catalyzed by β-alanine. The Knoevenagel product was exclusively the (*E*)-cyanoester.



The domino *Knoevenagel condensation/hetero-Diels-Alder reaction* was used for the enantioselective total synthesis of the active anti-influenza A virus indole alkaloid hirsutine and related compounds by L.F. Tietze and co-workers.[57] The *Knoevenagel condensation* was carried out between an enantiopure aldehyde and Meldrum's acid in the presence of ethylenediamine diacetate. The resulting highly reactive 1-oxa-1,3-butadiene underwent a *hetero-Diels-Alder reaction* with 4-methoxybenzyl butenyl ether (*E*/*Z* = 1:1) *in situ*. The product exhibited a 1,3-asymmetric induction greater than 20:1.



During the total synthesis of (±)-leporin A, a tandem *Knoevenagel condensation/inverse electron demand intramolecular hetero-Diels-Alder reaction* was employed by B.B. Snider et al. to construct the key tricyclic intermediate.[58] The condensation of pyridone with the enantiopure acyclic aldehyde in the presence of triethylamine as catalyst afforded an intermediate that underwent a [4+2] cycloaddition to afford the tricyclic core of the target.



The stereocontrolled total synthesis of (±)-gelsemine was accomplished by T. Fukuyama and co-workers using the *Knoevenagel condensation* to prepare a precursor for the key *divinylcyclopropane-cycloheptadiene rearrangement*.[59] The use of 4-iodooxindole as the active methylene component allowed the preparation of the (*Z*)-alkylidene indolinone product as a single stereoisomer.