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Recent Scenario: Knoevenagel Condensation in Organic Synthesis: A Review

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ABSTRACT

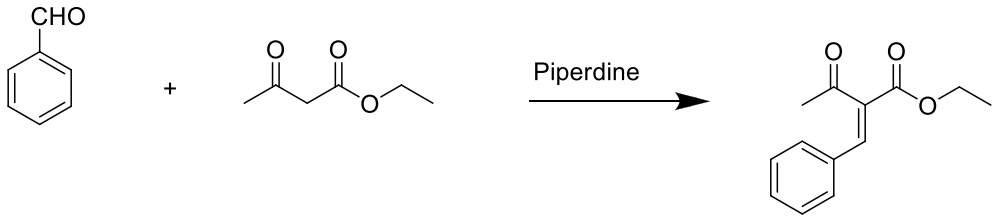
"Modern organic synthesis emphasizes sustainability, selectivity, and efficiency. Carbon-carbon bond formation is crucial in organic synthesis, and the Knoevenagel condensation reaction is one of the most powerful tools for this purpose. Green methodologies—including solvent-free conditions, water/ionic liquids, and bio-based solvents—along with metal-free or earth-abundant metal catalysis (e.g., cobalt, copper, single-atom catalysts) are increasingly preferred. This review provides a comprehensive overview of recent developments in Knoevenagel condensation, highlighting key synthetic pathways, catalytic systems, and applications."

Key Words: Knoevenagel condensation, ethyl acetoacetate, Di isopropyl ethyl ammonium acetate (DIPEAc)

INTRODUCTION

Historical Background, Mechanism & Scope:

In 1894, Emil Knoevengel[1] a German scientist reported a condensation reaction between benzaldehyde and ethyl acetoacetate in the presence of catalytic amount of piperidine to yield ethyl-2-benzylidene-3-oxobutanoate as a product (**Scheme 1.1**). Later this reaction was named as Knoevenagel condensation reaction. Knoevenagel condensation is one of the best tools for C-C bond construction in organic synthesis. It has innumerable applications in fine chemical synthesis, carbocyclic, hetero Diels-alder reactions and heterocyclic compounds of biological significance.



Scheme 1.1: Synthesis of Ethyl-2-benzylidene-3-oxobutanoate

Cope et al. [2-4] extended this reaction to various active-methylene substrates, including malonic acid, acetyl acetic acid, cyanoacetate, malononitrile, Meldrum's acid, and their derivatives. It was applied to carbonyl groups such as aromatic and aliphatic aldehydes and ketones to participate in this reaction.

In recent decades, the development of homogeneous catalyzed transformations has played a vital role in organic synthesis. In recent years, the use of ionic liquids, either as catalysts or reagents, in homogeneous media has been found in organic synthesis[5-7]. Ionic liquids showed good and alternative reagent in the organic synthesis and key intermediates has generated tremendous interest from an academician, and industrial perspective

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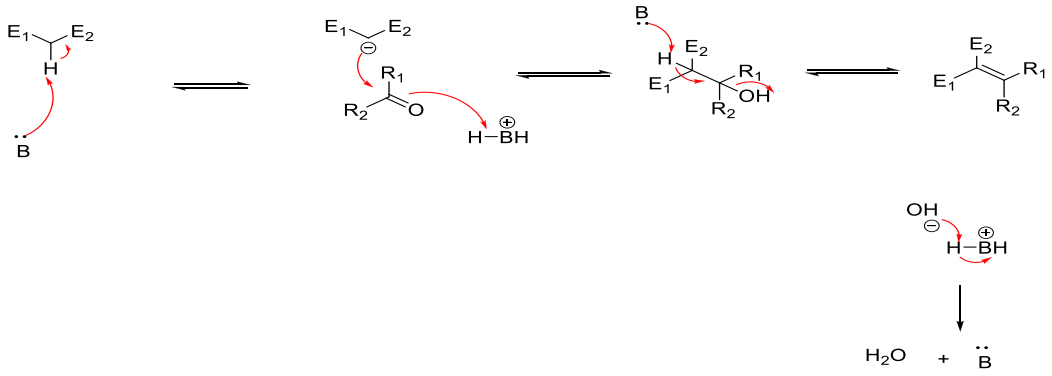
as well as specifically in the synthesis of pharmaceutical compounds[8]. The solubility of ionic liquids can be changed by altering cations and anions to improve their catalytic activity and solubility differences in an aqueous medium and a less polar solvent system. At the end of the reaction, the ionic liquid catalyst/reagent easily separated from the reaction mass and it can be regenerate and recycle[9-10].

In the Knoevenagel condensation reaction, the catalyst plays a key role. Common catalysts include primary, secondary, and tertiary amines, quaternary ammonium salts, inorganic bases, Lewis's acids, metal catalysts, and acid-base pairs that stabilize the reaction pH by acting as buffers. In recent years, the scope of catalysts has expanded to include ionic liquids, microwave irradiation, organ base mediation, and homogeneous catalysts.

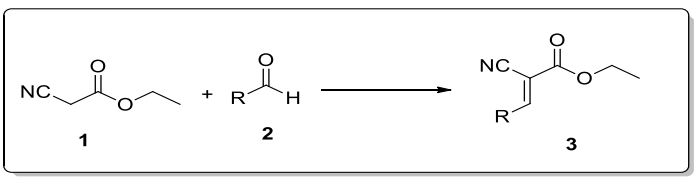
In the general mechanism of the Knoevenagel condensation reaction shown in (**Scheme 1.2)** the initial base abstracts the proton from the active methylene group, forming an anion. Nucleophilic attack on the carbonyl carbon of the aldehyde or ketone forms a tetrahedral intermediate. Elimination of water from the tetrahedral intermediate yields the Knoevenagel condensation product and regenerates the base catalyst. In the reaction, R1, R2, E1, and E2 are different, and a mixture of isomers may form. The outcome depends on the type of catalyst, temperature, and steric factors of R1 and R2.

"The Knoevenagel condensation typically yields the thermodynamically more stable E-isomer, although Z-isomers can be obtained under kinetic control or through specific catalyst systems. The E/Z selectivity is influenced by several factors, including the nature of the catalyst, reaction temperature, solvent polarity, and steric effects of substituents on the aldehyde/ketone and active methylene components. For example, reactions catalyzed by secondary amines often favour E-isomers due to the formation of iminium intermediates, while Lewis acid catalysts may exhibit different selectivity patterns. The stereochemical outcome has important implications for subsequent transformations, as the configuration of the double bond can affect the reactivity and stereochemistry of products derived from cyanoacrylates. Computational studies have provided insights into the transition states and energy profiles of Knoevenagel condensation, enabling prediction of selectivity and rational design of catalysts. A deeper understanding of these mechanistic aspects is essential for developing selective and efficient Knoevenagel condensation reactions."



Scheme 1.2: General mechanism of the Knoevenagel condensation

In this reaction, the byproduct is a water molecule. It will participate in the backward reaction. Some amount of the starting materials will be observed in the reaction. To avoid the backward reaction, water should be removed by using azeotropic distillation, molecular sieves, or dehydrating agents like sodium sulphate, magnesium sulphate, and phosphorus pentoxide, etc.



Scheme 1.3: Synthesis of cyanoacrylates

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Classification of Synthetic methods based on Catalytic Systems:

Among these catalytic systems, piperidine and other secondary amines remain the most commonly used organo catalysts due to their high activity and selectivity for Knoevenagel condensation. However, their toxicity, volatility, and difficulty in recovery have prompted the development of alternative catalysts. Ionic liquids offer advantages including tunable solubility, thermal stability, and recyclability, but their high cost and potential environmental concerns limit widespread application. Heterogeneous catalysts such as Al_2O_3, CaO, and silica-supported systems facilitate product separation and catalyst recovery, although they may exhibit lower activity compared to homogeneous systems. Recent developments have focused on earth-abundant metal catalysts and single-atom catalysts that combine high activity with sustainability.

The C-C bond formation is crucial in organic synthesis. Knoevenagel condensation reaction is one of the most powerful tools to form a C-C bond in organic synthesis. First, Knoevenagel condensationwas developed by Emil Knoevenagel between formaldehyde and diethylmalonate with diethylamine as catalyst in 1894. Later several improvements have emerged with different reagents as reported by different research groups such as piperdine[11](Rodionow),L-Proline[12](Wang), *β*-alanine[13](Zhu), TBAB[14], $[MeHMTA]BF_4$[15], resin poly (propylene imine)dendrimer[16], *nano*-Fe_3O_4[17], 2,4,6-trichloro-1,3,5-triazine (TCT)[18], $[bmim(NTf_2)]$[19], Al_2O_3-SiO_2[20] and other conditions.

1) Base catalyzed reactions:

Initially, the Knoevenagel condensation reaction developed with a piperidine base as a catalyst. Later different research groups extended this method to various bases including Triethylamine, Diisopropylethylamine, pyridine, N-methyl pyrrolidine, ethylene diamine, DABCO[21], DBU, K_2CO_3 etc.

2) Acid catalyzed reactions:

Several acid catalysts are reported by different research groups in the synthesis of Knoevenagel condensation reaction including Al_2O_3[22], CaO[23], Silica[24], $ZnCl_2$[25], CuCl[26], $TiCl_4$[27], $MgBr_2$[28] etc.

3) Amino acid catalyzed reactions:

Aminoacids like glycine, alanine, and proline[29] were used as catalysts in Knoevenagel reaction condition

4) Metal catalysts:

Metal catalysts reported including CdI_2[30], $Ti(OiPr)_4$[31] inKnoevenagel condensation reaction.

5) Ionic liquids:

Different research groups reported ionic liquid promoted Knoevenagel condensation using various catalysts including 1-methoxyethyl-3-methyl imidazolium trifluoroacetate, $[MeOEtMIM]^+[CF_3COO]$ [32], [Bmim][OAc] Ionic Liquids[33]

6) Miscellaneous:

Many research groups reported different catalysts including Triphenylphosphine[34], triethylbenzyl ammonium chloride[35], I_2-K_2CO_3[36], Methoxypropylamine acetate[37] etc.

7) Knoevenagel condensation between ethyl cyanoacetate and aromatic aldehyde in the presence of diisopropylethyl ammonium acetate (DIPEAc) for the formation of cyanoacrylates in good to excellent yields

8) A catalyst free and Green solvent water- Mediated Process: some of the research groups reported different green solvents especially water[38], aldehyde/ketone react with active methylene compounds to produce desired product in good to excellent yield

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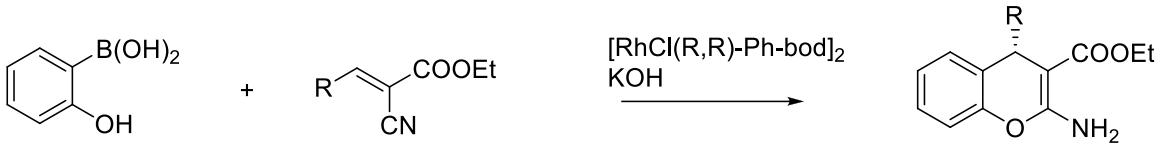
Synthetic applications:

Cyano acrylate (Knoevengel condensation product) has taken attention of the chemical community because dynamic, inexpensive intermediate for significant to make analogues of pharmaceutical and biological prominence is in demand.

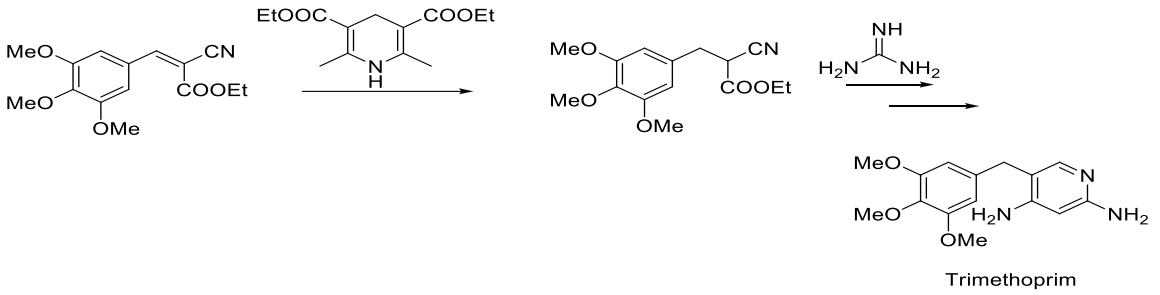
Thrope-Ziegler reaction:

(E)-ethyl-2-cyano-3-phenylacrylate reaction with 2-hydroxylated phenylboronic acid in the presence of chiral diene (R, R)-bod$_{12}$ coordinated rhodium catalyst to form Thrope-Ziegler condensed product[39] 4-phenyl-2-amino-4H-chromene (**Scheme 1.4**) with 90% ee.



Scheme 1.4: Synthesis of 4-phenyl-2-amino-4H-chromene

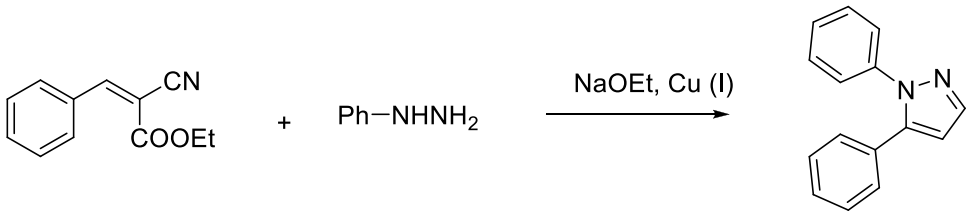
3,4,5-Trimethoxy phenyl ethyl cyanoacrylate reduction with Hantzch ester to afford saturated ester, which was further converted into Trimethoprim[40] natural product (**Scheme 1.5)**.



Scheme 1.5: Synthesis of Trimethoprim

Synthesis of 1,5-disubstituted pyrazoles:

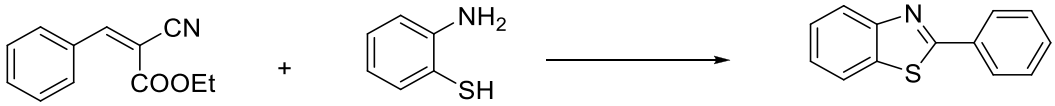
Cyanoacrylates react with phenylhydrazine, and sodium ethoxide in the presence of Cu(I) catalyst to form 1,5-disubstituted pyrazoles[41] (**Scheme 1.6**).



Scheme 1.6: Synthesis of 1,5-disubstituted pyrazoles

Synthesis of benzthiazoles:

Cyanoacrylates couple with 2-amino thiophenol to afford benzthiazoles[42](**Scheme 1.7**).



Scheme 1.7: Synthesis of benzthiazoles

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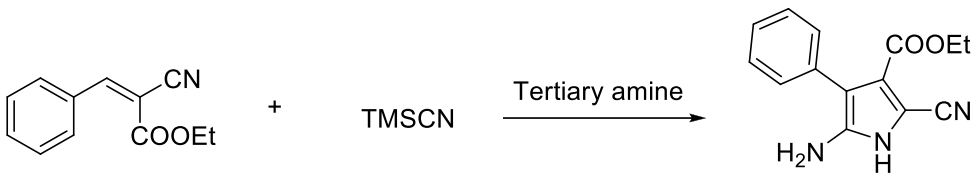
Synthesis of pyrroles:

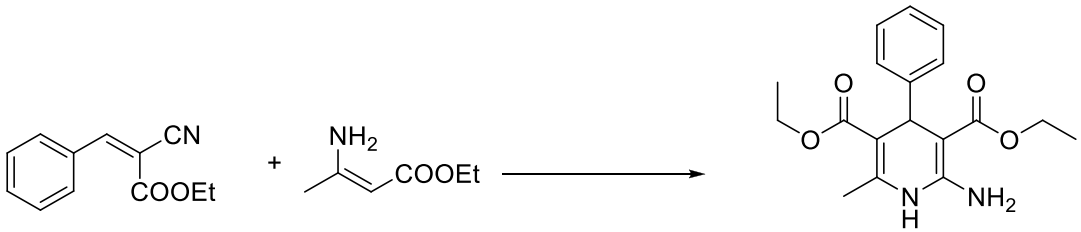
Cyanide mediated Michael addition on cyanoacrylates in the presence of tertiary amine form dinitrile compound, which undergoes cyclocondensation to form tetra substituted pyrrole derivative[43] (**Scheme 1.8**).



Scheme 1.8: Synthesis of substituted pyrroles

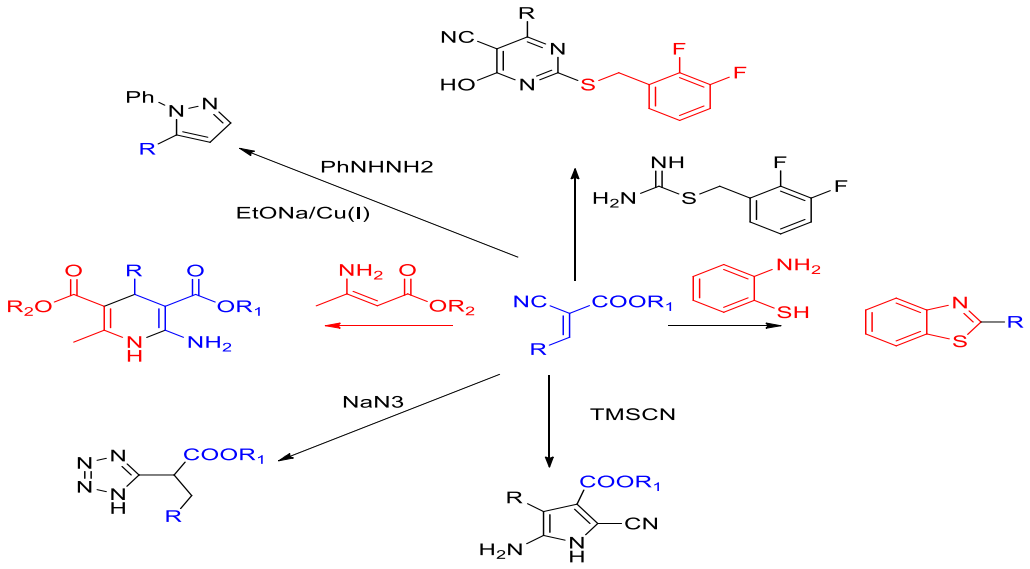
Synthesis of dihydropyridines:

Cyanoacrylate react with methyl-3-amino crotonate at higher temperature to afford 2-aminodihydropyridine[44] derivative (**Scheme 1.9**).



Scheme 1.9: Synthesis of substituted amino dihydropyridine

Cyanoacrylate has several applications, which undergoes several transformations with different reagents to produce a variety of biologically active scaffolds (**Scheme 1.10**), including 1,5-Disubstituted pyrazoles[45], substituted tetrazoles[46], 2-amino dihydropyridine derivatives[47], 2-amino pyrrole derivatives[48], pyrimidine-5-carbonitrile[49]and benzothiazole derivatives[50].



Scheme 1.10: Applications of cyanoacrylates

Recently Gill *et al*used diisopropyl ethyl ammonium acetate (DIPEAc) as an ionic liquid catalyst for various synthetic applications including Bignellidihydropyrimidines, and dihydrothiophenes synthesis.

Room temperature ionic liquid (RTILs) supported catalysts are used in the organic synthesis in a homogenous system, that has higher catalytic activity and selectivity compared to a homogenous parent

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catalytic system. The advantages of the ionic liquids, which has designed to be a soluble polar organic solvent by adding a nonpolar organic solvent to be recovered and reused. Ionic liquids have several advantages 1) high polarity and ionic character 2) ionic liquid supported catalysts have better loading capacity than solid supported catalysts 3) high selectivity.

CONCLUSION

However, numerous methods are available in the literature for Knoevenagel condensation but still have several disadvantages such as strong acidic, hazardous, expensive reagents, toxic nature, longer reaction time and lower yields. The continuous effort of many researchers has been made development of the efficient synthesis of cyanoacrylates using Knoevenagel condensation but still improvements are needed.

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