Research Article

Knoevengel Condensation: A Review on cyanoacrylates and their synthetic applications

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Abstract

Strong and quick-acting adhesives belong to the cyanoacrylate family. These are widely used in industry, healthcare, and domestic settings. Moreover, they can be found in various topical skin adhesives as well as glues, plastics, paints, and inks. The authors of this mini-review provided a brief overview of Knoevengel condensation in addition to highlighting the crucial synthetic uses of ethyl cyanoacrylates in the production of numerous key heterocyclic compounds.

Keywords

Emil Knoevengel; ethylacetoacetate; Condensation; cyanoacrylates

Introduction

In 1894, Emil Knoevengel[1] a German scientist reported a condensation reaction between benzaldehyde and ethylacetoacetate in the presence of catalytic amount of piperidine to yield ethyl-2-benzylidene-3-oxobutanoate as a product (**Scheme 1**). Later this reaction was named as Knoevengel condensation reaction. Knoevengel 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.

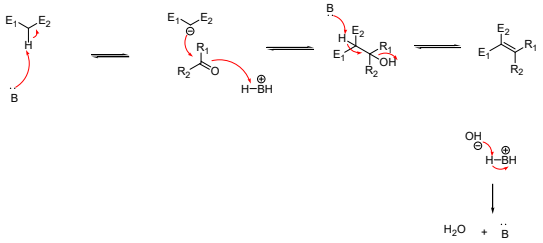
Scheme 1: Synthesis of Ethyl-2-benzylidene-3-oxobutanoate

Cope *et.al*[2-4] extended this reaction to different active methylene group substrates like malonic acid, acetylacetic acid, cyanoacetate, malononitrile, meldrum acid and their derivatives. It was applied different carbonyl groups such as aromatic/aliphatic aldehydes and ketones to participate in this reaction.

In the Knoevengel condensation reaction catalyst play key role, usually primary, secondary, tertiary amine, quaternary ammonium salts, inorganic bases, Lewis acids, metal catalysts, and acid-base pair to stabilize the pH of the reaction act as buffer. In recent years, the scope of catalyst extended to ionic liquids, microwave irradiation, organo-base mediation and homogenous catalysts.

In the general mechanism of the Knoevengel condensation reaction shown in **Scheme 2**, the initial base abstracts the proton from active methylene group, which leads to form an anion of the active methylene group. Nucleophilic attack on carbonyl carbon of aldehyde or ketone to resulting tetrahedral intermediate. Eliminate the water molecule from the tetrahedral intermediate resulting in Knoevengel condensation product and regenerated base catalyst.

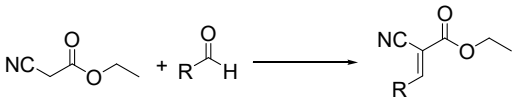
In the reaction, R_1, R_2, E_1, E_2, groups are different, and a mixture of isomer formation is possible. It depends on the type of catalyst, temperature condition, and steric factors of R_1, and R_2.



Scheme 2: General mechanism of the Knoevengel condensation

In this reaction, the byproduct is water molecule. It will help to participate in backward reaction resulting will observe some amount of starting materials 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 phosphouspentaoxide etc.

This Knoevengel condensation provides an important intermediate known as cyanoacrylate (**Scheme 3**) which is useful to synthesize various industrially and pharmaceutically important products.



Scheme 3: Synthesis of cyanoacrylates

Among the particular cyanoacrylates are methyl 2-cyanoacrylate (MCA), ethyl 2-cyanoacrylate (ECA, often marketed under trade names like "Super Glue" and "Krazy Glue"), octyl cyanoacrylate, 2-octyl cyanoacrylate (used in first aid, veterinary, and medical applications) and n-butylcyanoacrylate (n-BCA). Adhesives containing cyanoacrylate are commonly referred to as superglues, power glues, or instant glues. Industrial-grade cyanoacrylate is frequently referred by the abbreviation "CA".

2. Synthetic methods

a) Base catalysed reactions: Initially, Knoevengel 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[5], DBU, K_2CO_3 etc.

b) Acid catalysed reactions: Several acid catalysts are reported by different research groups in the synthesis of Knoevengel condensation reaction including Al_2O_3[6], CaO[7], Silica[8], $ZnCl_2$[9], CuCl[10], $TiCl_4$[11], $MgBr_2$[12] etc.

c) Aminoacidcatalysed reactions: Aminoacids like glycine, alanine, and proline[13] were used as catalysts in Knoevengel reaction condition

d) Metal catalysts: Metal catalysts reported including CdI_2[14], $Ti(OiPr)_4$[15] in Knoevengel condensation reaction.

e) Ionic liquids: Different research groups reported ionic liquid promoted Konevengel condensation with different catalysts including 1-methoxyethyl-3-methyl imidazolium trifluoroacetate, $[MeOEtMIM]^+[CF_3COO]^-$ [16-18]

f) Miscelounous: Many research groups reported different catalysts including Triphenylphosphine[19], triethylbenzylammonium chloride[20], I_2-K_2CO_3[21], Methoxypropylamine acetate[22] etc.

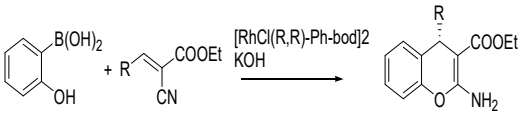
3. Synthetic applications

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.

3.1 Thrope-Ziegler reaction:

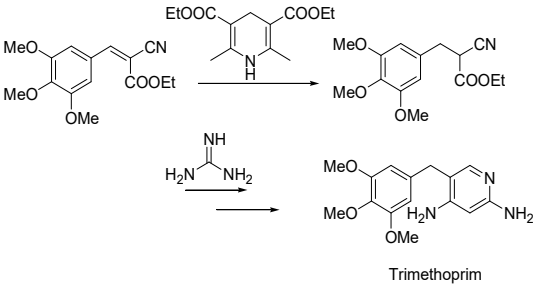
(E)-ethyl-2-cyano-3-phenylacrylate reaction with 2-hydroxylated phenylboronic acid in the presence of chiral diene (R, R)-bod_{12} coordinated rhodium catalyst to form Thrope-

Ziegler condensed product[23] 4-phenyl-2-amino-4H-chromene (**Scheme 4**) with 90% ee.



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

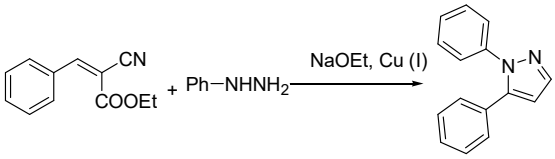
3,4,5-Trimethoxy phenyl ethyl cyanoacrylate reduction with Hantzch ester to afford saturated ester, which was further converted into Trimethoprim[24-25] natural product (**Scheme 5**).



Scheme 5: Synthesis of Trimethoprim

3.2. Synthesis of 1,5-disubstituted pyrazoles:

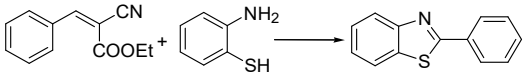
Cyanoacrylates react with phenylhydrazine, and sodium ethoxide in the presence of Cu(I) catalyst to form 1,5-disubstituted pyrazoles[26] (**Scheme 6**).



Scheme 6: Synthesis of 1,5-disubstituted pyrazoles

3.3. Synthesis of benzthiazoles:

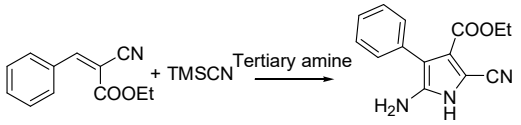
Cyanoacrylates couple with 2-amino thiophenol to afford benzthiazoles[27] (**Scheme 7**).



Scheme 7: Synthesis ofbenzthiazoles

3.4. Synthesis of pyrroles:

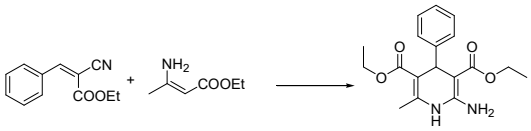
Cyanide mediated Michael addition on cyanoacrylates in the presence of tertiary amine form dinitrile compound, which undergoes cyclocondensationto form tetrasubstitutedpyrrole derivative[28] (**Scheme 8**).



Scheme 8: Synthesis of substituted pyrroles

3.5. Synthesis of dihydropyridines:

Cyanoacrylate react with methyl-3-amino crotonate at higher temperature to afford 2-aminodihydropyridine[29] derivative (**Scheme 9**).



Scheme 9: Synthesis of substituted amino-dihydropyridine

Conclusions

A brief review on Knoevengel condensation was provided with mechanism. Further, the synthetic approaches for the cyanoacrylates and their significant applications were well reviewed in systematic manner.

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Conflict of interest

The authors declare that there are no potential conflicts of interest in the present work.

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