CHAPTER 4

Knoevenagel condensation in aqueous medium at neutral pH
4.1 Introduction

The Knoevenagel condensation is one of the most powerful strategies for the construction of carbon–carbon double bonds in organic chemistry.\(^1\) The condensation products were found to be useful intermediates for the synthesis of fine chemical, as well as carbocyclic and heterocyclic compounds of biological significance.\(^2\) This reaction is generally carried out in organic solvents in the presence of bases such as piperidine, pyridine, ammonia, amines or sodium ethoxide.\(^3\) But use of these homogeneous base catalysts often leads to the complicated work-up procedure and undesired side-reactions such as oligomerizations.\(^4\) Although the reaction seems easy, it may undergo simultaneous addition (1,2)-elimination-addition (1,4) reactions to generate byproducts under acidic and basic conditions (Fig. 1).

\[ \text{Figure 1} \]

Therefore, the reactivity of nitrile containing Knoevenagel product has recently been exploited to a great extent in multicomponent reactions (MCRs) by adding other competitive nucleophiles to synthesize heterocycles in one step (Figure 2). But such MCRs has hardly been used for stereoselective reactions. Given the fact that Knoevenagel product is an excellent Michael acceptor, its application in stereoselective synthesis of pharmacologically important heterocycles cannot be ignored.
Current interest in the Knoevenagel condensation is shifted towards the development of environmentally as well as economically benign reaction conditions such as employment of heterogeneous catalysts or ionic liquids. However, many of these procedures associated with multiple disadvantages such as a use of large amount of catalysts and organic solvent, long reaction time, harsh reaction conditions, cumbersome purification process, and poor catalyst recovery. Additionally, the utilization of volatile, hazardous, carcinogenic and costly solvents has limited the application of the reaction in large scale synthesis. Owing to the environmental issues associated with the organic solvents recently many research groups developed Knoevenagel condensation in aqueous media, which is usually catalyzed by Lewis acids or bases, and requires drastic conditions. Some reactions are performed on solid supports, promoted by infrared, ultrasound or microwave.

Zhang and co-workers recently reported the Knoevenagel condensation of aromatic aldehydes with active methylene compounds in water. Authors employed 5 mol% of a polyacrylonitrile fibre catalyst to enhance the reactivity of the active methylene compounds at 50 °C. In most of the cases, they observed excellent yield of the products except the compound 406 containing –CF<sub>3</sub> group at the ortho position. On the other hand, when the reaction was carried out in water at 50 °C for 1.5 h only 5% of the product was obtained (Scheme 4.1).
Xie and co-workers employed MCM-41/Schiff base as catalyst for Knoevenagel condensation reactions of malononitrile with aromatic aldehydes.\textsuperscript{12} The reaction afforded the corresponding products in excellent yields (up to 99\%) within 3 h using water as solvent. But the protocol was ineffective for generation of Knoevenagel product from aliphatic aldehyde (Scheme 4.2).
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Phukan et al. reported cobalt ferrite magnetic nanoparticle catalysed Knoevenagel condensation reaction in aqueous medium. A 1:3 mixture of water and ethanol was suitable for the condensation of aldehyde and ethyl cyanoacetate in the presence of 5 mol% of the catalyst (Scheme 4.3).

To avoid the oligomerization issue Stark et al. reported a base free Knoevenagel condensation catalysed by elemental copper. The authors have used commercially available semi-noble copper in ethanol at 56 °C to obtain the desired product.

![Scheme 4.4](image)

4.2 Objective

Volatile organic compounds (VOC) are a major concern in industry and academia; therefore use of environmentally benign solvents such as water gained tremendous attention in recent years. In the process of elimination of volatile organic solvents, different research groups explored the Knoevenagel condensation of aldehyde and active methylene compound in aqueous media in presence of various catalysts. However, most of the currently used methods suffered from one disadvantage or another; these include the use of non-recoverable catalysts, complicated procedures involved in the catalyst preparation or the multiple steps of characterization of the catalyst.

Given the fact that phosphate buffer at neutral pH to be an excellent catalyst for Henry and Michael addition reaction, we proposed to employ phosphate buffer at neutral pH Knoevenagel condensation of aldehyde and active methylene compounds (Scheme 4.5). We assumed that the absence of acid and base catalysts will help in reducing the formation of possible byproducts.
4.3 Results and discussion

We started our investigation with 1 mmol of para-chlorobenzyldehyde and 1 mmol of ethyl cyanoacetate in 2mL of phosphate buffer at 80 °C. Under this reaction conditions, the desired product **418** was obtained in 70% isolated yield after 4 h. The IR spectra of the product showed a band at 2223 cm\(^{-1}\) for the CN group and at 1731 cm\(^{-1}\) (C=O str.) for the ester group. The product was characterised by \(^1\)NMR spectra wherein a singlet at \(\delta\) 8.20 ppm integrating one proton was assigned for the –CH=C(CN)CO\(_2\)Et. In the aromatic region, two doublets at \(\delta\) 7.94 \((J = 8.4\) Hz) ppm and 7.48 \((J = 8.4\) Hz) ppm integrating for two protons each was observed. On the other hand, a quartet at \(\delta\) 4.39 \((J = 7.2\) Hz) ppm integrating two protons indicated the presence of –OCH\(_2\)CH\(_3\) group and a triplet at \(\delta\) 1.40 \((J = 7.2\) Hz) ppm integrating three protons signified the presence of –CH\(_2\)CH\(_3\) group. \(^{13}\)C NMR showed two peaks at \(\delta\) 162.1 ppm and 153.3 ppm which were assigned to the carbonyl carbon of –CO\(_2\)Et group and the carbon of the -CN group.

As the yield of the reaction could be improved through optimization of the reaction conditions, we decided to perform the reaction at higher temperature as well. To our delight, the desired product was obtained in 95% yield within 2 h at 100 °C. We also observed that after cooling down the reaction mixture to room temperature solidified products which could be filtered off to achieve almost pure product. The product was further purified by recrystallization from ethanol. Given the fact that, phosphate buffer of pH 7 is a neutral medium and pure water also have neutral pH, we wanted to see whether the reaction could be simply accomplished in water. For that purpose, we vigorously stirred the same reaction mixture in water (2 mL) for 2 h at 100 °C, only a trace amount of the product was detected (table 1, entry 3).
### Table 1: Optimization of reaction condition

![Reaction condition diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction condition</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80 °C, 4h</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>100 °C, 2h</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>100 °C, 2 mL water</td>
<td>trace</td>
</tr>
</tbody>
</table>

*General reaction conditions: phosphate buffer (2 mL), aldehyde (1 mmol), ethylcyanoacetate (1 mmol); †Isolated yields.*

With a simple and efficient protocol in hand, we decided to explore the general applicability of this reaction protocol. The protocol was employed for the synthesis of Knoevenagel products from various aromatic aldehydes and active methylene compounds (table 2). Reaction of 3-nitrobenzaldehyde with ethyl cyanoacetate generated the desired product 422 in excellent yield within 1.5 h. $^1$H NMR showed a singlet at $\delta$ 8.70 integrating for one proton which was assigned to the proton of the $\text{CH}=\text{C}(\text{CN})\text{CO}_2\text{Et}$ group. A quartet at $\delta$ 4.43 ($J = 7.2$ Hz) ppm integrating two protons and a triplet at $\delta$ 1.43 ($J = 7.1$ Hz) ppm integrating three protons were observed for the ethyl group of the ester. In $^{13}$C NMR two peaks at $\delta$161.4 and 151.9 supported the presence of $–\text{CN}$ and $–\text{COOEt}$ carbon in our compound. Similarly other Knoevenagel products (424 to 434) were characterised using IR, $^1$NMR and $^{13}$C NMR spectroscopy. Remarkably, evaluation of the characterised data with literature reveals that the Knoevenagel products obtained from the ethylcyanoacetate was found to be $E$-isomer.$^4,11$

### Table 2: Knoevenagel condensation of aromatic aldehydes with active methylene compounds$^{a,b}$

![Condensation diagram](image)
<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
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<tr>
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<tr>
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<td><img src="438" alt="Image" /></td>
<td>96</td>
</tr>
</tbody>
</table>
General reaction conditions: phosphate buffer (2 mL), aldehyde (1 mmol), ethylcyanoacetate or malononitrile (1 mmol), 100 °C. Isolated yields.

4-Chlorobenzaldehyde also reacts efficiently with malononitrile to produce the desired product 438 under the optimized reaction conditions. In IR analysis, the compound showed a peak at 2227 cm$^{-1}$ which indicates the presence of –CN group. A singlet at $^1$H NMR analysis of the compound show a δ 7.74 ppm integrating one proton was assigned to the -CH=C(CN)$_2$ group whereas the aromatic protons were observed at δ 7.87 (d, $J$=8.2 Hz) ppm and 7.53 (d, $J$=8.4 Hz) ppm integrating two proton each. In $^{13}$C NMR of the compound, a peak at δ 158.3 was observed for the carbon of the -CN group. Similarly, 436, 440 and 442 was also characterised from the IR, $^1$H NMR and $^{13}$C NMR spectroscopy.

4.4 Conclusion

In conclusion we developed an efficient Knoevenagel condensation reaction of aldehyde and active methylene compounds in aqueous phosphate buffer at neutral pH. The reaction worked excellently without any added base catalyst. The yield of the products were found to be good to excellent. Remarkably, the product was purified by without column chromatography.
4.5 Experimental
4.5.1 Materials and instruments

The commercially available chemicals and reagents were used without further purification. The IR spectra were recorded on a Perkin Elmer 983 spectrophotometer. $^1$H NMR (400 MHz) ppm and $^{13}$C NMR (100 MHz) ppm spectra were recorded on an FT NMR Bruker advance II 400 MHz spectrometer using CDCl$_3$ as solvent and TMS as internal standard, unless otherwise stated. Data for $^1$H NMR are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, dd = double of doublet, br = broad, m = multiplet), coupling constants (Hz). Silica gel G and Silica gel 60-120 Mesh (E. Merck) were used for Thin Layer Chromatography (TLC) and Column Chromatography, respectively.

4.5.2 General procedure for Knoevenagel condensation reaction

To a 25 mL round-bottom flask containing 1 mmol each of 4-chlorobenzaldehyde and ethyl cyanoacetate, aqueous phosphate buffer (2 mL) solution was added. After the completion of the reaction as monitored by TLC plate, reaction was allowed to cool down to room temperature. At room temperature, the product gets solidified and filtered off. Further purification of the compound was done by recrystallization from ethanol. Notably, same procedure was successfully applied for the gram scale preparation of the Knoevenagel products 420 and 422.

4.5.3 Spectral data of the compounds

**Ethyl 3-(4-chlorophenyl)-2-cyanoacrylate (420):** White solid; m.p. 93-94 °C; IR (KBr): v 3440, 2223, 1731, 1610 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.20 (s, 1H), 7.94 (d, $J = 8.6$ Hz, 2 H), 7.48 (d, $J = 8.6$ Hz, 2 H), 4.39 (q, $J = 7.1$ Hz, 2 H), 1.40 (t, $J = 7.1$ Hz, 3 H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): δ 162.1, 153.3, 139.5, 132.1, 129.8, 129.6, 115.2, 103.3, 62.8, 14.1 ppm; MS (ESI): m/z = 236 [M+H]$^+$

**Ethyl 2-cyano-3-(3-nitrophenyl)acrylate (422):** White solid; m.p. 134-135 °C; IR (KBr): v 3444, 2226, 1719, 1611 cm$^{-1}$ $^1$H NMR (400 MHz, CDCl$_3$) δ = 8.71 (s, 1H), 8.56 – 8.36 (m, 2H), 8.32 (s, 1H), 7.75 (t, $J = 8.1$ Hz, 1H), 4.43 (q, $J = 7.2$ Hz, 2H), 1.43 (t, $J = 7.1$ Hz, 3H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$) δ 161.4, 151.9, 148.5, 135.2,
132.8, 130.5, 127.1, 125.9, 114.5, 106.5, 63.2, 14.1 ppm; MS (ESI): m/z = 247 [M+H]^+

**Ethyl 3-(2-chlorophenyl)-2-cyanoacrylate (424):** White solid; m.p. 53-54 °C; IR (KBr): ν 3433, 2229, 1721, 1618 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 8.70 (s, 1H), 8.31 – 8.13 (m, 1H), 7.59 – 7.33 (m, 3H), 4.41 (q, J = 7.2 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H) ppm; \(^13\)C NMR (100 MHz, CDCl\(_3\)) δ 161.7, 151.1, 136.4, 133.6, 131.0, 129.8, 127.4, 114.8, 106.1, 62.9, 14.1 ppm; MS (ESI): m/z = 247 [M+H]^+

**Ethyl 2-cyano-3-(4-cyanophenyl)acrylate (426):** White solid, m.p. 170-171 °C, IR (KBr): ν 3440, 2227, 1720, 1614 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 8.25 (s, 1H), 8.06 (d, J = 7.8 Hz, 2H), 7.80 (d, J = 7.8 Hz, 2H), 4.40 (q, J = 7.2 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H) ppm; \(^13\)C NMR (100 MHz, CDCl\(_3\)): δ 161.5, 152.2, 135.2, 132.8, 131.0, 117.7, 115.9, 114.6, 106.7, 63.2, 14.1 ppm; MS (ESI): m/z = 227 [M+H]^+

**Ethyl 2-cyano-3-(2-methoxyphenyl)acrylate (427):** White solid; m.p. 74-75 °C; IR (KBr): ν 3447, 2225, 1727, 1612 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 8.76 (s, 1H), 8.29 (d, J = 7.2 Hz, 1H), 7.61 – 7.41 (m, 1H), 7.06 (t, J = 7.6 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 4.38 (q, J = 7.2 Hz, 2H), 3.91 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H) ppm; \(^13\)C NMR (100 MHz, CDCl\(_3\)): δ 162.8, 159.2, 149.8, 135.0, 129.3, 120.9, 120.6, 115.9, 111.1, 102.2, 62.5, 55.7 ppm; m/z = 254 [M+Na]^+

**Ethyl 2-cyano-3-(p-tolyl)acrylate (428):** White solid; m.p. 92-93 °C; IR (KBr): ν 3443, 2227, 1733, 1609 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 8.22 (s, 1H), 7.91 (d, J = 7.6 Hz, 2H), 7.31 (d, J = 7.6 Hz, 2H), 4.38 (q, J = 7.2 Hz, 2H), 2.44 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H) ppm; \(^13\)C NMR (100 MHz, CDCl\(_3\)): δ 162.8, 155.0, 144.6, 131.2, 130.0, 128.8, 115.8, 101.5, 62.6, 21.8, 14.1 ppm; m/z = 216 [M+H]^+

**Ethyl 3-(benzo[d][1,3]dioxol-5-yl)-2-cyanoacrylate (429):** White solid; m.p. 106-107 °C; IR (KBr): ν 3446, 2226, 1721, 1606 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 8.11 (s, 1H), 7.71 (s, 1H), 7.40 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.09 (s, 2H), 4.36 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H) ppm; \(^13\)C NMR (100 MHz, CDCl\(_3\)): δ 162.9, 154.3, 152.2, 148.6, 129.7, 125.9, 116.0, 108.9, 108.8, 102.3, 99.7, 62.5, 14.2 ppm; MS (ESI): m/z = 268 [M+Na]^+
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Ethyl 2-cyano-3-(4-(dimethylamino)phenyl)acrylate (430):¹¹ White solid; m.p. 124-125 °C; IR (KBr): v 3440, 2223, 1722, 1611 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.07 (s, 1H), 7.94 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.8 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 3.22 (s, 6H), 1.37 (t, J = 7.2 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 164.3, 154.5, 153.5, 134.0, 119.3, 117.6, 111.4, 93.8, 61.8, 40.0, 14.3 ppm; MS (ESI): m/z = 267 [M+Na]⁺

2-(Furan-2-yl-methylene)malononitrile (432):¹⁵ White solid; m.p. 72-73 °C; IR (KBr): v 3447, 2231, 1607 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.81 (s, 1H), 7.52 (s, 1H), 7.36 (d, J=2.4 Hz, 1H), 6.72 (m, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 150.01, 148.21, 143.11, 123.44, 114.48, 113.81, 77.81 ppm; MS (ESI): m/z = 145 [M+H]⁺

2-(4-Chlorobenzylidene)malononitrile (434):¹⁵ White solid; m.p. 166-167 °C; IR (KBr): v 3446, 2227, 1610 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.87 (d, J=8.4, 2H), 7.74 (s, 1H), 7.53 (d, J=8.4, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 158.3, 141.1, 131.8, 130.0, 129.2, 113.4, 112.3 ppm; MS (ESI): m/z = 189 [M+H]⁺

2-Benzylidenemalononitrile (436):² White solid; m.p. 87-88 °C; IR (KBr): v 3445, 2230, 1609 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.92 (d, J = 6.4 Hz, 2H), 7.78 (s, 1H), 7.63 (d, J = 6.4 Hz, 1H), 7.56 (d, J = 6.4 Hz, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 159.9, 134.6, 130.8, 130.6, 129.5, 113.6, 112.5 ppm; MS (ESI): m/z = 155 [M+H]⁺

2-(4-Methoxybenzylidene)malononitrile (438):¹¹ White solid; m.p. 116-117 °C; IR (KBr): v 3447, 2227, 1610 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.91 (d, J=8.8, 2H), 7.66 (s, 1H), 7.01 (d, J = 8.8, 2H), 3.91 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 164.8, 158.9, 133.5, 124.0, 115.1, 114.4, 113.4, 55.8 ppm; MS (ESI): m/z = 185 [M+H]⁺
REFERENCES


Chapter 4: Supporting information

Representative $^1$H NMR and $^{13}$C NMR spectra of Knoevenagel products
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Representative mass spectra of the Knoevenagel products

![Mass spectrum of a Knoevenagel product with a molecular weight of 420.](image1)

![Mass spectrum of a Knoevenagel product with a molecular weight of 434.](image2)