



Knoevenagel Condensation Reaction Using Ionic Liquid [ADPQ][CF₃SO₃] as Green and Reusable Catalyst

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Knoevenagel condensation reaction of aromatic aldehydes with some active methylene compounds proceeded efficiently without solvent using ionic liquids as catalyst. The experimental results show that these ionic liquids have good catalytic activities to the Knoevenagel condensation with a wide range of reactant. The reactions are carried out in a few minutes with high yields. The ionic liquids can be recycled and reused for 4 times without noticeably decreasing the catalytic activity.

Keywords: Ionic liquids, Knoevenagel condensation, Aromatic aldehydes, Active methylene compounds.

INTRODUCTION

Since Knoevenagel condensation first discovered in 18961, it has become one of the most important synthesis methods for the carbon-carbon double bonds formation. It has been widely used for the preparation of important intermediates in chemical industry and pharmaceutical industry²⁻⁵. Traditionally, Knoevenagel condensation is carried out in organic solvents with acids⁶⁻⁸, bases⁹⁻¹⁰, acid-base bifunctional catalysts¹¹⁻¹³. With special reaction instruments and conditions, this reaction could also be performed by microwave radiation¹⁴ or supersonic wave¹⁵. However, most of the methods have some drawbacks such as long reaction time, harsh reaction conditions, stoichiometric amount of catalysts, toxicity of the organic solvents and unrecyclable for the catalysts.

Recently, ionic liquids (ILs) are receiving much interest for application as innovative solvents or catalysts in a variety of areas due to the advantages of ionic liquids, such as non volatility, high thermal stability, versatile structures and excellent reusability¹⁶. Additionally, the water produced during the reaction was absorbed by the ionic liquid and thus the reaction getting a higher yield in a very short reaction time compared with conventional methods in organic solvents. So research about ionic liquids involved in Knoevenagel condensation has experienced tremendous growth during the past years. Until now, the ionic liquid systems for Knoevenagel condensation were ethylammonium nitrate¹⁷, guanidinium lactate¹⁸, alkylammonium-based^{19,20}, imidazolium-based^{21,22}. Almost all the reported ionic liquids used in Knoevenagel reaction are relatively narrow range for applications and low

yield for some specific reaction, so the optimal ionic liquids for Knoevenagel condensation need to be explored.

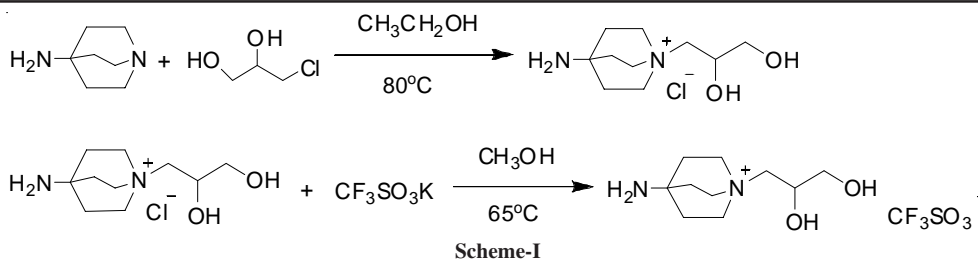
Encouraged by the use of ionic liquids above, we report here in the development of a series of novel ionic liquids and their use as catalysts for the Knoevenagel condensation of various aromatic aldehydes and active methylene compounds.

EXPERIMENTAL

All the chemicals were used as supplied without further purification unless otherwise specified. Melting points were taken on a Gallenkamp melting point apparatus. ¹H and ¹³C NMR spectra were recorded on a Bruker AM-400 MHz spectrometer. HRMS values were measured by a JEOL JMS-SX or JEOL JMS-SX 102A spectrometer. Flash column chromatography was performed on silica gel (200-300 mesh) (Qingdao Haiyang Chemical Co. Ltd, China) and TLC measurements were performed on silica gel GF254 plates (Qingdao Haiyang Chemical Co. Ltd, P.R. China).

Synthesis of ionic liquids: A series of novel amino functionalized ionic liquids was synthesized from commercially available 4-amino quinuclidine and 3-chloro-1,2-propanediol, followed by anion exchange through CF₃SO₃K, NaBF₄, CH₃COOK, KPF₆ (Scheme-I).

Knoevenagel condensation; typical procedure: Benzaldehyde (1 mmol) and ethyl cyanoacetate (1 mmol) were mixed together in the presence of 20 mol % [ADPQ][CF₃SO₃] and then stirred at room temperature. Upon completion of the reaction (monitored by TLC, solvent system: ethyl acetate and petroleum ether), water (2 mL) was added to the mixture. The



product was filtered and the solid, was dried *in vacuo* at 60 °C for 10 h. This gave the desired product in high purity that did not need further purification. The ionic liquid was recovered by removing the aqueous layer using a rotary evaporator. All the products had the E-geometry exclusively and no Z-geometrical isomers were detected in the NMR.

Spectral data of representative compounds

2-Benzylidenemalononitrile (Entry 1, Table-2): (Solid, m.p. 79-81 °C), ¹H NMR (400 MHz, CDCl₃): δ 7.92 (m, 2H), 7.79 (s, 1H), 7.64 (m, 1H), 7.54 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 159.9, 134.6, 130.8, 129.6, 113.6, 112.5, 82.7.

Ethyl 2-cyano-3-phenylacrylate (Entry 2, Table-2): (Solid, m.p. 49-50 °C), ¹H NMR (100 MHz, CDCl₃): δ 8.92 (s, 1H), 8.76 (m, 1H), 8.58 (d, 1H, *J* = 4.0 Hz), 8.27 (s, 1H), 8.48 (m, 1H), 4.41 (m, 2H), 1.41 (m, 3H); ¹³C NMR (400 MHz, CDCl₃): δ 162.4, 155.0, 133.3, 131.4, 131.0, 129.2, 115.4, 102.9, 62.7, 14.1.

2-(4-Methoxybenzylidene)malononitrile (Entry 9, Table-2): (Solid, m.p. 113-114 °C), ¹H NMR (400 MHz, CDCl₃): δ 7.91(d, 2H, *J* = 8.8 Hz), 7.66 (s, 1H), 7.02 (d, 2H, *J* = 8.8 Hz), 3.92 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 164.8, 158.9, 133.4, 123.9, 115.1, 113.3, 55.8.

Ethyl 2-cyano-3-(4-methoxyphenyl)acrylate (Entry 10, Table-2): (Solid, m.p. 79-81 °C), ¹H NMR (400 MHz, CDCl₃): δ 8.17 (s, 1H), 8.00 (d, 2H, *J* = 6.8 Hz), 6.99 (d, 2H, *J* = 6.0 Hz), 4.36 (m, 2H), 3.89 (s, 3H), 1.39 (t, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 164.0, 163.3, 154.6, 133.9, 124.6, 116.5, 115.0, 99.5, 62.6, 55.9, 14.4.

2-(2-Methoxybenzylidene)malononitrile (Entry 11, Table-2): (Solid, m.p. 79-80 °C), ¹H NMR (400 MHz, CDCl₃): δ 8.31 (s, 1H), 8.18 (d, 1H, *J* = 7.6 Hz), 7.59 (m, 1H), 7.08 (m, 1H), 6.99 (d, 1H, *J* = 8.8 Hz), 3.93 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 158.9, 154.4, 136.5, 128.8, 121.1, 120.1, 114.3, 112.9, 111.4, 81.2, 55.9.

2-(Thiophen-2-ylmethylene)malononitrile (Entry 15, Table-2): (Solid, m.p. 96-97 °C), ¹H NMR (400 MHz, CDCl₃): δ 7.89 (d, 2H, *J* = 4.0 Hz), 7.81 (d, 1H, *J* = 3.2 Hz), 7.28 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): 151.0, 138.1, 136.8, 135.4, 129.0, 113.8, 112.9, 78.4.

Ethyl 2-cyano-3-(thiophen-2-yl)acrylate (Entry 16, Table-2): (Solid, m.p. 89-91 °C), ¹H NMR (400 MHz, CDCl₃): δ 8.34 (s, 1H), 7.80 (d, 2H, *J* = 7.6 Hz), 7.22 (m, 1H); 4.36 (m, 2H), 1.38 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 162.7, 146.2, 137.1, 136.0, 135.1, 128.6, 115.7, 99.4, 77.0, 62.5, 14.2.

2-(Benzo[d]thiazol-2-yl)-3-phenylacrylonitrile (Entry 1, Table-3): (Solid, m.p. 145-147 °C), ¹H NMR (400 MHz, CDCl₃): δ 8.26 (s, 1H), 8.09 (d, 1H, *J* = 6.4 Hz), 8.03 (d, 2H, *J* = 4.0 Hz), 7.91 (d, 1H, *J* = 6.4 Hz), 7.53 (m, 4H), 7.44 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 162.9, 153.8, 147.1,

135.2, 132.5, 130.6, 129.5, 127.2, 126.3, 123.8, 121.9, 116.7, 105.8.

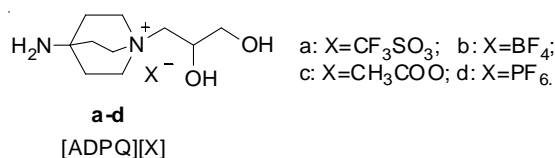
2-(Benzo[d]thiazol-2-yl)-3-(4-methoxyphenyl)acrylonitrile (Entry 2, Table-3): (Solid, m.p. 140-142 °C) ¹H NMR (400 MHz, CDCl₃): δ 8.18 (s, 1H), 8.04 (m, 3H), 7.89 (d, 1H, *J* = 6.4 Hz), 7.51 (t, 2H), 7.01 (d, 2H, *J* = 6.8 Hz), 3.90 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 163.6, 153.8, 146.7, 135.0, 132.9, 127.0, 125.9, 123.5, 121.8, 117.3, 114.9, 102.5, 55.8.

2-(1*H*-indol-2-yl)-3-phenylacrylonitrile (Entry 7, Table-3): (Solid, m.p. 173-174 °C); ¹H NMR (400 MHz, CDCl₃): δ 8.58 (s, 1H), 8.00 (d, 1H, *J* = 6.0 Hz), 7.88 (d, 2H, *J* = 5.6 Hz), 7.61 (t, 2H), 7.40-7.49 (m, 4H), 7.29-7.34 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 138.2, 137.3, 134.9, 129.8, 129.1, 129.0, 125.8, 124.4, 123.6, 121.5, 120.0, 118.9, 113.1, 112.4, 106.5.

2-(1*H*-indol-2-yl)-3-(*p*-tolyl)acrylonitrile (Entry 8, Table-3): (Solid, m.p. 192-194 °C); ¹H NMR (400 MHz, CDCl₃): δ 8.46 (s, 1H), 8.00 (d, 1H, *J* = 6.0 Hz), 7.79 (d, 2H, *J* = 6.4 Hz), 7.58 (t, 2H), 7.45 (d, 1H, *J* = 6.4 Hz), 7.27-7.33 (m, 3H), 2.42 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 140.2, 138.5, 137.2, 132.1, 129.8, 128.9, 125.4, 124.4, 123.5, 121.4, 120.0, 119.1, 113.3, 112.3, 105.3, 21.8.

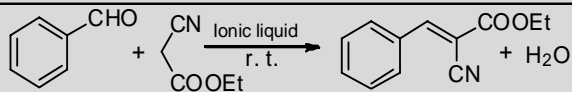
RESULTS AND DISCUSSION

For present investigations, four ionic liquids (ILs) were prepared.



The reaction of benzaldehyde with ethyl cyanoacetate at room temperature without any solvent was used as the model to optimize the reaction conditions (Table-1). The reaction did not proceed at all in absence of ionic liquid (**entry 1**, Table-1). To our pleasure, the model reaction proceeded smoothly in the presence of the novel ionic liquids **a-d**, leading to 76-89 % yields of product (Table-1, **entries 2-5**). Among the four ionic liquids tested, [ADPQ][CF₃SO₃] (**a**) was the most effective and an excellent yield of 89 % was obtained. Then we optimized the amount of **a**, the reaction was carried out in the presence of 5, 10, 20 and 30 mol % **a** under solvent-free conditions at room temperature (Table-1, **entries 5-8**). The best catalyst loading was found to be 20 mol %. Then we added some organic solvents, no significant change was found. Consequently, the reaction conditions of 20 mol % of ionic liquid **a** as the catalyst at room temperature without any organic solvent were subjected to further examination.

TABLE-1
OPTIMIZATION OF CATALYST/ORGANIC SOLVENT
IN KNOEVENAGEL CONDENSATION REACTION^a

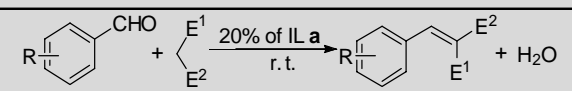


| Entry | IL (mol %) | Solvent | Time (min) | Yield (%) ^b |
|-------|------------|---------------------------------|------------|------------------------|
| 1 | blank | - | 60 | - |
| 2 | b (10) | - | 30 | 79 |
| 3 | c (10) | - | 30 | 76 |
| 4 | d (10) | - | 30 | 86 |
| 5 | a (10) | - | 30 | 89 |
| 6 | a (5) | - | 30 | 83 |
| 7 | a (20) | - | 30 | 91 |
| 8 | a (30) | - | 30 | 91 |
| 9 | a (20) | CH ₃ OH | 30 | 90 |
| 10 | a (20) | CH ₂ Cl ₂ | 30 | 91 |
| 11 | a (20) | Toluene | 30 | 92 |

^aReaction conditions: benzaldehyde (1 mmol) and ethyl cyanoacetate (1 eq), room temperature, reaction time = 0.5 h. ^bIsolated yields

With the optimal conditions in hand, we investigated the Knoevenagel reaction of various aromatic aldehydes with malononitrile and ethyl cyanoacetate and the results are presented in Table-2. The reaction proceeded smoothly to afford the corresponding products in good to excellent yields (83-98 %) within 2 h. Among these cases, the electron-withdrawing group substituted aromatic aldehydes with active methylene compounds converted smoothly to the corresponding products in high yields (**entries 3-8**, Table-2). Electron-donating group substituted aromatic aldehydes underwent Knoevenagel condensation with malononitrile smoothly and obtained good yield (**entries 9-14**, Table-2). In addition, Knoevenagel condensation of hetero aromatic aldehydes such as 2-thiophene-carboxaldehyde with active methylene compounds also

TABLE-2
KNOEVENAGEL CONDENSATION REACTION OF ACTIVE
METHYLENE COMPOUNDS WITH FUNCTIONALIZED
AROMATIC ALDEHYDES^a



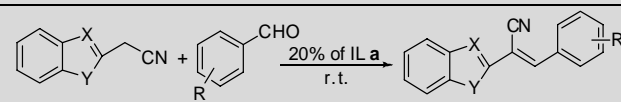
| Entry | R | E ¹ | E ² | Reaction time (min) | Yield (%) |
|-------|-------------------|----------------|----------------|---------------------|-----------|
| 1 | H | CN | CN | 5 | 96 |
| 2 | H | CN | COOEt | 30 | 91 |
| 3 | 3-NO ₂ | CN | CN | 3 | 97 |
| 4 | 3-NO ₂ | CN | COOEt | 20 | 96 |
| 5 | 2-Cl | CN | CN | 5 | 95 |
| 6 | 2-Cl | CN | COOEt | 30 | 93 |
| 7 | 4-Cl | CN | CN | 20 | 98 |
| 8 | 4-Cl | CN | COOEt | 30 | 94 |
| 9 | 4-OMe | CN | CN | 15 | 94 |
| 10 | 4-OMe | CN | COOEt | 60 | 86 |
| 11 | 2-OMe | CN | CN | 30 | 92 |
| 12 | 2-OMe | CN | COOEt | 60 | 87 |
| 13 | 3-OMe | CN | CN | 15 | 96 |
| 14 | 3-OMe | CN | COOEt | 60 | 83 |
| 15 | 2-Thienyl | CN | CN | 45 | 85 |
| 16 | 2-Thienyl | CN | COOEt | 120 | 79 |

^aReaction conditions: aldehyde (1 mmol) and active methylene compound (1 mmol), 20 mol % of ionic liquid a, room temperature

underwent favorable reaction at room temperature (**entries 15, 16**, Table-2).

Encouraged by the results, we continued to study the reaction of aromatic aldehydes with other active methylene compounds, such as benzimidazol-2-acetonitrile, benzothiazole-2-acetonitrile and indole-2-acetonitrile. The reaction smoothly proceeded to afford the corresponding products with moderate to good yield. It is found that the acidic proton of methylene group was the key factor influencing the reaction rate. For example, malononitrile, which the acidic proton of methylene was apparently stronger than those of others, results in comparatively rapid reaction rates.

TABLE-3
KNOEVENAGEL CONDENSATION REACTION OF OTHER
ACTIVE METHYLENE COMPOUNDS WITH FUNCTIONALIZED
AROMATIC ALDEHYDES^a



| Entry | R | X | Y | Reaction time (min) | Yield (%) |
|-------|-------|---|----|---------------------|-----------|
| 1 | H | N | S | 60 | 94 |
| 2 | 4-OMe | N | S | 90 | 92 |
| 3 | 2-Cl | N | S | 20 | 91 |
| 4 | H | N | NH | 30 | 93 |
| 5 | 2-Cl | N | NH | 60 | 90 |
| 6 | 4-OMe | N | NH | 10 | 92 |
| 7 | H | H | NH | 120 | 73 |
| 8 | Me | H | NH | 120 | 68 |

^aReaction conditions: aldehyde (1 mmol) and active methylene compound (1 mmol), 20 mol % a, room temperature

In order to demonstrate the industrial applicability of this methodology, the reaction of ethyl cyanoacetate and benzaldehyde was carried out on a larger scale (100 mmol). The reaction was completed in 0.5 h. A good yield of 91 % for the product was achieved. On the same scale, the recyclability of the catalytic system was investigated using the same reaction as the model reaction. The ionic liquid (**a**) was recovered by removing the aqueous layer using rotary evaporator. The recovered **a** was reused in subsequent reactions. As shown in Fig. 1, no significant decrease in yields was observed even after four runs.

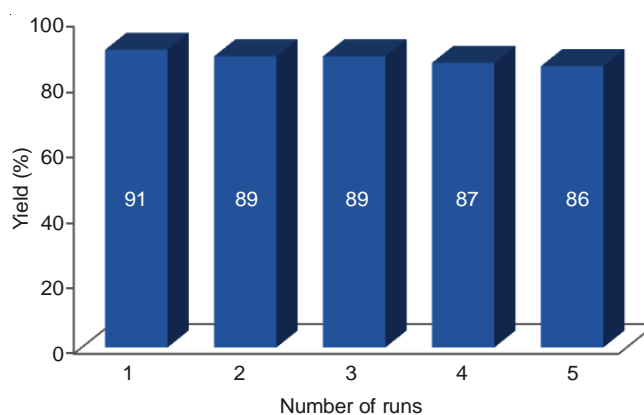


Fig. 1. Recyclability investigation of [ADPQ][CF₃SO₃] used as a catalyst for the Knoevenagel condensation of ethyl cyanoacetate and benzaldehyde

Conclusion

In conclusion, a series of novel ionic liquids, namely, [ADPQ][CF₃SO₃], [ADPQ][BF₄], [ADPQ][CH₃COO] and [ADPQ][PF₆] is developed. Among these functional ionic liquids, [ADPQ][CF₃SO₃] showed the best catalytic activity for Knoevenagel condensation of various aldehydes and different active methylene compounds to afford E-geometry products in good to excellent yields. The good catalytic effects and excellent recyclability of [ADPQ][CF₃SO₃] make this protocol more useful. Investigations of these novel ionic liquids in further application for other organic reactions are underway in our laboratory.

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