Choline chloride and urea based eutectic solvents: effective catalytic systems for the Knoevenagel condensation reactions of substituted acetonitriles

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The Knoevenagel condensation of aromatic aldehydes with active methylene compounds such as malononitrile, ethyl cyanoacetate, benzimidazole-2-acetonitrile and benzothiazole-2-acetonitrile proceeded very smoothly, in a reusable and cheap choline chloride and urea based deep eutectic solvents. Both reaction time and yield are satisfactory. The advantages of this catalyst are that it is readily available, biodegradable, non-toxic, low cost and is recyclable.

Keywords: Knoevenagel condensation, deep eutectic solvents, choline chloride, urea

The Knoevenagel condensation reaction is an important reaction for the formation of carbon–carbon bonds.[1–3] It has been used for the synthesis of important intermediates or products for cosmetics, perfumes, pharmaceuticals, calcium antagonists and polymers.[4–8] Traditionally, the Knoevenagel condensation is performed in organic solvents in the presence of bases or acids.[9–12] Recently, heterogeneous catalysts have been used such as nitrogen-doped carbon materials,[13] Ni–SiO_2-supported catalysts[14] and modified polyacrylamide containing amino functional groups.[15] However, many of these procedures have drawbacks such as long reaction time, harsh reaction conditions, the use of hazardous organic solvent or catalysts, and, in some reactions, the catalysts are not efficient and cannot be reused.

With the introduction of the concept of green chemistry in the early 1990s, various ionic liquids have been used as solvents and catalysts for the Knoevenagel condensation[16–22] due to their unique chemical and physical properties of nonvolatility, nonflammability, thermal stability, and controlled miscibility.[23] Our group have used 2-hydroxyethylammonium formate[24] and several DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) based ionic liquids to catalyse the Knoevenagel condensation reaction with great success.[25–27] However, many ionic liquids have drawbacks such as high price, toxicity, and poor biodegradability.[28,29]

Deep eutectic solvents (DESs) emerged at the beginning of this century to overcome the high cost and toxicity of ionic liquids, DESs are generally composed of two or three cheap and safe components which are capable of associating with each other through hydrogen bond interaction, to form a eutectic mixture.[30–32] They have the advantage of low melting point and are not hazardous. We report a Knoevenagel condensation reaction of substituted acetonitriles and aromatic aldehydes using a DES prepared from choline chloride (ChCl) and urea.

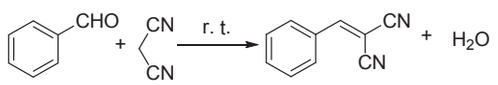
Results and discussion

The reaction of benzaldehyde with malononitrile was used as the model to optimise the reaction conditions (Table 1). The reaction did not proceed at all in absence of DES (entry 1, Table 1). However, reaction was observed soon after addition of DES. We used different DES prepared from different molar ratios of ChCl and urea to catalyse the reaction without any solvent (entry 2, Table 1). It was found that the best molar ratio was 1 : 2.

Then we studied the effect of the amount of the DES. We defined the molecular weight of the DES as the addition of the two components' molecular weight. Thus the molecular weight of the DES (ChCl : urea = 1 : 2) is 259.74. Through changing the amount of DES, it was found that 20% (molar) DES was the most effective (entry 3, Table 1). Attempts to combine DES with methanol as the solvent, led to no significant change of yield (entry 4, Table 1). Thus 20% DES is the most effective condition.

With the optimum catalytic system in hand, we investigated the Knoevenagel reaction of various aromatic aldehydes with malononitrile and ethyl cyanoacetate (Table 2). It can be seen that the two active methylene compounds reacted with various aromatic aldehydes. The effects of substituents on the aromatic ring in the Knoevenagel reaction were studied. Aromatic aldehydes substituted with electron-withdrawing groups reacted smoothly with active methylene compounds to give the corresponding products in high yields (entries 3–8, Table 2). Aromatic aldehydes substituted with electron-donating groups also underwent a Knoevenagel condensation with malononitrile smoothly and gave good yield (entries 11 and 13, Table 2). However, ethyl cyanacetate gave only low yields (entries 10, 12 and 14, Table 2). The Knoevenagel condensation of hetero-aromatic aldehydes such as 2-thiophenecarboxaldehyde with active methylene compounds also proceeded satisfactorily at

Table 1 Optimisation of catalyst/organic solvent in Knoevenagel condensation reaction[a]



Sample no.	Solvent	DES	Yield/%[b]
	Methanol	–	–
1	Toluene	–	–
	DMF	–	–
	–	ChCl : Urea=1 : 1[c]	54
2	–	ChCl : Urea=1 : 2[c]	86
	–	ChCl : Urea=1 : 3[c]	72
	–	10% DES[d]	84
	–	15% DES[d]	86
3	–	20% DES[d]	92
	–	25% DES[d]	91
4	Methanol	20% DES	88

[a]Reaction conditions: benzaldehyde (1.0 equiv.) and malononitrile (1.0 equiv.), 20% DES, room temperature, reaction time = 20 min.
[b]Isolated yields.
[c]Molar ratio.
[d]ChCl: Urea =1 : 2 (molar ratio).

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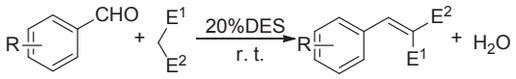
Table 2 Knoevenagel condensation reaction of active methylene compounds with functionalised aromatic aldehydes in DES[a]



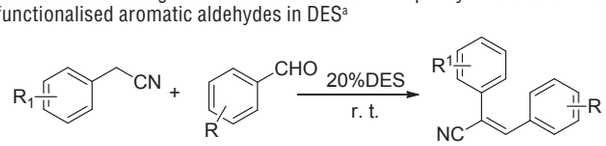
Entry	R	E^1	E^2	Reaction time /min	Yield/%
1	H	CN	CN	20	92
2	H	CN	COOEt	60	89
3	3-NO2	CN	CN	20	97
4	3-NO_2	CN	COOEt	30	96
5	2-Cl	CN	CN	20	95
6	2-Cl	CN	COOEt	120	85
7	4-Cl	CN	CN	20	94
8	4-Cl	CN	COOEt	90	90
9	4-Me	CN	CN	120	20
10[b]	4-Me	CN	COOEt	120	0
11	2-OMe	CN	CN	30	92
12	2-OMe	CN	COOEt	120	30
13	3-OMe	CN	CN	10	96
14[c]	3-OMe	CN	COOEt	120	Trace
15	2-thienyl	CN	CN	15	88
16	2-thienyl	CN	COOEt	150	79

[a]Reaction conditions: aldehyde (1.0 mmol) and active methylene compound (1.0 mmol), 20% DES, room temperature. If the aldehyde was solid, then 0.5 mL DES was added.
[b]Prolonged reaction time (12 h), no product appeared.
[c]Prolonged reaction time (12 h), only trace product appeared.

room temperature (entries 15 and 16, Table 2).

Encouraged by these results, we studied the reaction of aromatic aldehydes with other active methylene compounds, such as benzimidazole-2-acetonitrile, benzothiazole-2-acetonitrile, phenylacetonitrile, 3-chlorophenylacetonitrile and indole-2-acetonitrile. The reaction proceeded smoothly to afford the corresponding products in moderate to good yield except for the reaction of indole-2-acetonitrile with benzaldehyde (entry 9, Table 4). From these results we consider that the acidity of the proton of the methylene group was the key factor influencing the reaction rate (entries 1 and 2, Table 2; entry 3, Table 3; entries 1, 4 and 9, Table 4). Especially, noteworthy was malononitrile, for which the acidity of the proton of the methylene was greater than the other compounds leading to comparatively rapid reaction rates (entries 1, 3, 5, 7, 11, 13 and 15, Table 2).

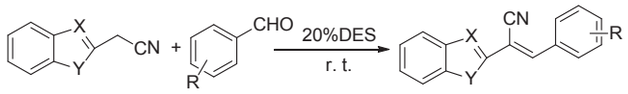
Table 3 Knoevenagel condensation reaction of phenylacetonitriles with functionalised aromatic aldehydes in DES[a]



Entry	R	R1	Reaction time /min	Yield/%
1	4-OMe	H	60	83
2	4-OH	H	60	85
3	H	3-Cl	45	90
4	4-OMe	3-Cl	45	92

[a]Reaction conditions: aldehyde (1.0 mmol) and active methylene compound (1.0 mmol), 0.5 mL DES, room temperature.

Table 4 Knoevenagel condensation reaction of other active methylene compounds with functionalised aromatic aldehydes in DES[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	120	90
6	4-OMe	N	NH	10	92
7	4-$N(Me)_2$	N	NH	60	82
8	2-thienyl	N	NH	180	84
9	H	H	NH	120	trace

[a]Reaction conditions: aldehyde (1.0 mmol) and active methylene compound (1.0 mmol), 0.5 mL DES, room temperature.

In order to demonstrate the industrial potential of this methodology, the reaction of ethyl cyanoacetate and benzaldehyde was scaled-up. The reaction was completed in 1 h. A good yield of 89% was achieved. On the same scale, the recyclability of the catalytic system was investigated using the same reaction as the model reaction. The DES was recovered by removing the aqueous layer using a rotary evaporator. The recovered DES was reused in subsequent reactions. As shown in Fig. 1, no significant decrease in yields was observed even after four runs.

Conclusions

The use of DES (choline chloride/urea) as a solvent without any additional catalyst permits an efficient Knoevenagel condensation of aromatic aldehydes with active methylene compounds. Compared to the reported methods, this method offers marked improvements in terms of simplicity, decreased reaction time, chemoselectivity, general applicability, low cost and no need for a hazardous organic solvents and toxic catalysts. Thus it provides a better and practical alternative to existing procedures.

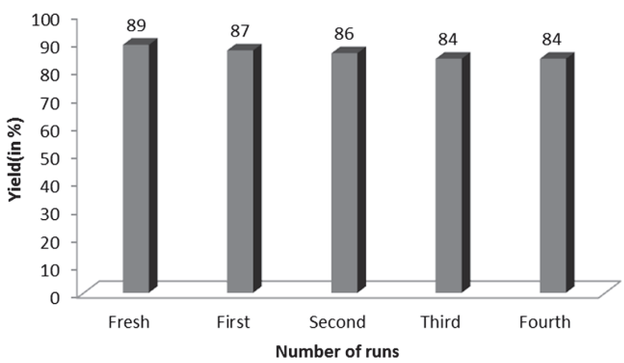


Fig. 1 Reuse of catalyst for Knoevenagel condensation between benzaldehyde (100 mmol) and ethyl cyanoacetate (100 mmol) in 20 mmol DES at room temperature for 2 h.

Experimental

All chemicals were used as supplied without further purification unless otherwise specified. Melting points were taken on a Gallenkamp melting point apparatus and were uncorrected. ^{1}H and ^{13}C 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 DES; general procedure

Choline chloride (10 g, 71.4 mmol) and urea (8.6 g, 142.8 mmol) were heated with stirring at 80 °C until a clear solution was obtained. After cooling to room temperature, the DES could be used for the Knoevenagel condensation reactions without any purification.

Knoevenagel condensation; typical procedure

Benzaldehyde (1 mmol) and ethyl cyanoacetate (1 mmol) were mixed together in the presence of 20 mol% DES 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 deep eutectic solvent 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.

2-(3-Chlorophenyl)-3-phenylacrylonitrile (entry 3, Table 3): White solid; m.p. 94–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (m, 2H), 7.67 (s, 1H), 7.57 (m, 2H), 7.50 (m, 3H), 7.40 (d, 2H, J = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 136.5, 135.4, 133.5, 131.2, 130.5, 129.7, 129.5, 129.3, 126.2, 124.5, 117.8, 110.5; MS m/z = 239.1. Anal. calcd for $C_{15}H_{12}ClN$: C, 74.53; H, 5.00; Cl, 14.67; N, 5.79; found: C, 74.35; H, 5.12; Cl, 14.93; N, 5.50%.

2-(3-Chlorophenyl)-3-(4-methoxyphenyl)acrylonitrile (entry 4, Table 3): White solid; m.p. 97–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88(s, 3H), 6.99(d, 2H, J = 6.8 Hz), 7.33–7.36(m, 2H), 7.47(s, 1H), 7.54(s, 1H), 7.56(s, 1H), 7.90(d, 2H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6, 113.8, 117.8, 123.5, 126.4, 128.4, 129.6, 132.6, 133.5, 134.7, 146.8, 160.5; MS m/z = 269.1. Anal. calcd for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.48; Cl, 13.14; N, 5.19; O, 5.94; found: C, 71.21; H, 4.51; Cl, 13.13; N, 5.18; O, 5.97%.

2-(Benzo[d]thiazol-2-yl)-3-(2-chlorophenyl)acrylonitrile (entry 3, Table 4): Yellow solid; m.p. 241–242 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (s, 1H), 8.28 (m, 1H), 8.14 (d, 1H, J = 6.4 Hz), 7.93 (d, 1H, J = 6.4 Hz), 7.50 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 154.3, 153.8, 132.2, 131.6, 128.8, 128.6, 127.5, 126.5, 124.6, 124.3, 122.5, 116.8, 108.4; MS m/z = 296.1. Anal. calcd for $C_{16}H_9ClN_2S$: C, 64.75; H, 3.06; Cl, 11.95; N, 9.44; S, 10.80; found: C, 65.28; H, 3.25; Cl, 11.83; N, 9.13; S, 10.51%.

2-(1H-Benzo[d]imidazol-2-yl)-3-(thiophen-2-yl)acrylonitrile (entry 8, Table 4): Yellow solid; m.p. 203–205 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.65(s, 1H), 7.88(s, 1H), 7.77(s, 1H), 7.68(m, 2H), 7.51(m, 1H), 7.32(m, 2H), 7.18(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6, 141.9, 139.6, 138.9, 136.6, 132.5, 130.6, 126.5, 117.8, 114.6, 112.5; MS m/z = 251.1. Anal. calcd for $C_{14}H_9N_3S$: C, 66.91; H, 3.61; N, 16.72; S, 12.76; found: C, 66.83; H, 3.65; N, 16.74; S, 12.78%.

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