



A simple and efficient procedure for Knoevenagel condensation catalyzed by [C₄dabco]OH ionic liquid

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ABSTRACT

DABCO-based basic ionic liquid, 1-butyl-4-aza-1-azabicyclo [2.2.2]octane hydroxide, has been used as a catalyst for a simple, convenient and rapid method for Knoevenagel condensation of active methylene compounds and various carbonyl compounds affording very high yields. The catalyst can be recycled for several times without much loss of activity.

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KEYWORDS

Active methylene compounds;
Carbonyl compounds;
Dabco-base;
Ionic liquids;
Knoevenagel condensation;
Recyclable.

INTRODUCTION

Ionic liquids have emerged as environmentally benign solvents for many important organic reactions^[1]. During last two decades a number of ionic liquids have been synthesized and used as catalyst for different chemical reactions such as aldol reaction^[2], Diels-Alder reactions^[3], Henry reaction^[4], Knoevenagel condensation^[5], Mannich reaction^[6], and Michael reaction^[7]. The Knoevenagel condensation reaction is a useful reaction in organic synthesis that has been widely employed for carbon-carbon bond formation. It is usually performed in organic solvents in the presence of common bases such as ammonia, primary or secondary amines and their salts^[8]. In recent years, a number of catalysts have been used for the Knoevenagel condensation. A few of them includes Al₂O₃^[9], CdI₂^[10], Rare-earth exchanged NaY zeolite^[11], NH₄OAc^[12], ZnCl₂^[13], Lewis acidic ionic liquids [Bmim]Cl. xAlCl₃ and [Bpy]Cl.xAlCl₃^[14], ethylenediammonium diacetate

in ionic liquids^[15], K₂O-Al₂O₃^[16], CaO^[17], triphenylphosphane^[18], Ti(O-i-Pr)₄^[19], ethylammoniumnitrate^[20], triethylbenzyl ammonium chloride^[21], 1-aminoethyl-3-methylimidazolium hexafluorophosphate^[22], I₂-K₂CO₃^[23], 2-hydroxyethylammoniumacetate^[24], methoxy propylamine acetate^[25], Knoevenagel Condensation Catalyzed by 1,1,3,3 Tetramethylguanidium Lactate^[26]. However, these methods have some limitations, such as using hazardous solvents, high catalyst loading or non-recoverable catalysts that sometimes contain toxic metals. Therefore, there is a great need for new catalytic methods that do not have these problems. In continuation of our work, herein^[27], we report DABCO-based basic ionic liquids as simple, efficient and environmentally friendly catalysts for Knoevenagel condensation reaction of various carbonyl compounds with active methylene compounds at room temperature under solvent free conditions, providing excellent yields. The catalysts can be recycled many times

without much loss of activity.

EXPERIMENTAL

General experimental methods

All the reagents were commercial reagents of A.R. grade and were used without further purification. All the commercial solvents were used after distillation. Melting points were determined by using Veego melting point apparatus-I and were uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AV III 500 MHz or Varian 400 MHz or 300 MHz spectrometer in CDCl_3 or D_2O . ^1H NMR and ^{13}C NMR chemical shifts (δ) in ppm are downfield from tetramethylsilane. Elemental analyses were done in Perkin Elmer CHNS/O Analyzer 2400.

General procedure for synthesis of catalyst

The catalyst was prepared with modification according to the procedures reported previously^[28]. To a solution of 1-butyl-1,4-diazabicyclo [2.2.2]octan-1-ium chloride (5.4 g, 26.37 mmol) in dry acetonitrile, solid KOH (1.45 g, 26.37 mmol) was added and the mixture was stirred vigorously at room temperature for 15 hours. The precipitate, KCl was removed by filtration and the resulting filtrate was evaporated at reduced pressure. The viscous liquid so obtained was washed with diethyl ether (3X20 ml) and dried to give pure ionic liquid, $[\text{C}_4\text{dabco}]\text{OH}$ (4.56 g, 92.87%). ^1H NMR (500 MHz, D_2O): δ_{H} 3.3 (t, $J=7.0$ Hz, 6H), 3.1 (t, $J=9.0$ Hz, 2H), 3.0 (t, $J=8.0$ Hz, 6H), 1.6 (quintet, $J=8.5$ Hz, 2H), 1.3-1.2 (m, 2H), 0.8 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, D_2O): δ_{C} 64.4, 52.0, 44.2, 23.1, 19.1, 12.8. Anal. Calcd for: $\text{C}_{10}\text{H}_{22}\text{N}_2\text{O}$: C, 64.47; H, 11.90; N, 15.04%. Found: C, 64.37; H, 11.78; N, 14.91%.

General procedure for Knoevenagel condensation

To a well stirred mixture of active methylene compound (2.0 mmol) and carbonyl compound (2.0 mmol), ionic liquid $[\text{C}_4\text{dabco}]\text{OH}$ (19.5 mg, 5 mol% of the substrate) was added and stirred at room temperature. The formation of the products was moni-

tored by TLC. After completion of the reaction, water (2 mL) was poured to the reaction mixture, filtered and dried to obtain the products. In general, no further purification was required for solid product. However, for liquid mixture, ethyl acetate (2.0 mL) was added to the water extract of the reaction mixture. The organic phase was dried with anhydrous MgSO_4 and evaporated. In some cases, the crude product was purified by column chromatography over silica gel to afford the pure product. All the products were previously reported and were characterized by melting point determination, ^1H NMR and ^{13}C NMR spectral data. The ionic liquid catalyst was recovered from water and reused for the subsequent reactions. Selected data for the product are given below.

2-(Phenylmethylene)malononitrile (3a)

White solid, m.p. 83-84 $^{\circ}\text{C}$ (lit 83-84 $^{\circ}\text{C}$)²⁰; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.5 (t, J 8.0, 2H), 7.6 (t, J 7.2, 2H), 7.7 (s, 1H), 7.9 (d, J 7.6, 2H).

Ethyl-(E)-2-Cyano-3-phenyl-2-propenoate (3b)

Colourless crystal, m.p. 49-50 $^{\circ}\text{C}$ (lit 49-50 $^{\circ}\text{C}$)¹⁸; ^1H NMR (400 MHz, CDCl_3) δ_{H} 1.4 (t, J 7.2, 3H), 4.4 (q, J 7.2, 2H), 7.6-7.5 (m, 3H), 8.0 (d, J 7.6, 2H), 8.3 (s, 1H).

Ethyl (E)-2-Cyano-3-(4-methoxyphenyl)-2-propenoate (3d)

Pale yellow crystalline solid, m.p. 81-82 $^{\circ}\text{C}$ (lit 79-81 $^{\circ}\text{C}$)¹⁸; ^1H NMR (300 MHz, CDCl_3) δ_{H} 1.4 (t, J 7.2, 3H), 3.9 (s, 3H), 4.4 (q, J 6.9, 2H), 7.0 (d, J 9, 2H), 8.0 (d, J 9.0, 2H), 8.2 (s, 1H); ^{13}C NMR (75MHz, CDCl_3) δ_{C} 14.1, 55.5, 62.3, 99.2, 114.7, 116.2, 124.2, 133.5, 154.3, 163.0, 163.7.

2-(4-Chlorophenylmethylene)malononitrile (3f)

Colourless solid, m.p. 159-160 $^{\circ}\text{C}$ (lit 161 $^{\circ}\text{C}$)²⁰; ^1H NMR (300 MHz, CDCl_3) δ_{H} 7.5 (d, J 8.4, 2H), 7.7 (s, 1H), 7.9 (d, J 8.4, 2H); ^{13}C NMR (75MHz, CDCl_3) δ_{C} 83.2, 112.3, 113.4, 129.2, 130.0, 131.8, 141.1, 158.3.

2-(3-Nitrophenylmethylene)malononitrile (3i)

Yellow crystalline solid, 99-100 $^{\circ}\text{C}$ (lit 100-101 $^{\circ}\text{C}$)²⁶; ^1H NMR (300 MHz, CDCl_3) δ_{H} 7.8 (t, J 7.8, 1H), 7.9 (s, 1H), 8.3 (d, J 7.8, 1H), 8.5 (d, J

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8.4, 1H), 8.7 (s, 1H); ^{13}C NMR (75MHz, CDCl_3) δ_{C} 86.7, 111.6, 112.6, 125.5, 128.2, 130.9, 131.9, 137.3, 148.6, 157.0.

3-(3-nitrobenzylidene)pentane-2,4-dione (3k)

White solid, m.p. 97-99 $^{\circ}\text{C}$ (lit 95-97 $^{\circ}\text{C}$); ^1H NMR (500 MHz, CDCl_3) δ_{H} 2.4 (s, 6H), 7.6-7.5 (m, 2H), 7.8 (d, J 7.8, 1H), 8.3 (d, J 7.0, 1H), 8.4 (s, 1H); ^{13}C NMR (125MHz, CDCl_3) δ_{C} 28.1, 122.6, 124.7, 129.4, 130.1, 133.7, 136.3, 140.2, 148.7, 197.5.

RESULTS AND DISCUSSION

The Knoevenagel condensation reaction of benzaldehyde (1a) and malonitrile (2a) was carried out under solvent free conditions, in the presence of $[\text{C}_4\text{dabco}]\text{OH}$ as the catalyst. The reaction was very fast and the reaction mixture solidified as soon as the catalyst was added (Entry 1, TABLE 1). The effect of the concentration of the catalyst was also studied (Entries 1-3, TABLE 1). When the amount of the catalyst used was changed, we found that 5 mol% of the catalyst gave quantitative yield of the product (Entry 3, TABLE 1). When the amount of the catalyst, $[\text{C}_4\text{dabco}]\text{OH}$ was further reduced to 1.0 mol% and 0.5 mol%, the reaction required more time to complete; however, the yields were still very high. Next, the Knoevenagel condensation reactions of 1a and 2a were studied by using various catalysts, such as, $[\text{C}_7\text{dabco}]\text{OH}$, $[\text{C}_9\text{dabco}]\text{OH}$ and $[\text{C}_4\text{dabco}]\text{Cl}$. It

was found that the reaction proceeded efficiently, resulting in near a quantitative yield of the product and a slight change in reaction time (Entries 4-6, TABLE 1). However in the absence of these catalysts, the Knoevenagel reaction was very slow and the yield also very low (Entry 7, TABLE I). Thus, $[\text{C}_4\text{dabco}]\text{OH}$ (5 mol%) was taken as the catalyst of choice for the Knoevenagel condensation reactions.

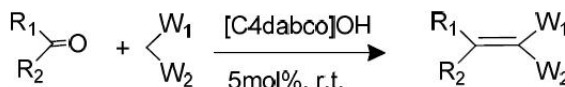
The Knoevenagel condensation reactions of various carbonyl compounds with active methylene compounds were examined in presence of $[\text{C}_4\text{dabco}]\text{OH}$ (5 mol %) under solvent free condition and the products were isolated with excellent yields (TABLE 2). In general, Knoevenagel condensation reaction of various carbonyl compounds with malononitrile were Faster than ethylcyanoacetate and acetylacetone. This may be because of strong electron withdrawing nature of cyanide group compare to ester and ketonic group.

The recyclability of the catalyst was also examined. Once product 3a had been filtered from the reaction mixture after addition of water (2.0 mL), excess water from the ionic liquid was evaporated under reduced pressure, and the catalyst was reused for the same reaction. The catalyst did not show much reduction of activity even after the sixth run. All reactions were completed in 1-2 min affording 94-100% yields.

TABLE 1 : Effect of concentration of dabco-base ionic liquids in the Knoevenagel condensation of benzaldehyde and malonitrile(3a)^a

Entry	Catalyst	Time(min)	3a(%) ^c
1	$[\text{C}_4\text{dabco}]\text{OH}^{\text{b}}$	3s	82
2	$[\text{C}_4\text{dabco}]\text{OH}^{\text{c}}$	10s	89
3	$[\text{C}_4\text{dabco}]\text{OH}^{\text{d}}$	1	100
4	$[\text{C}_7\text{dabco}]\text{OH}^{\text{b}}$	17s	92
5	$[\text{C}_9\text{dabco}]\text{OH}^{\text{b}}$	33s	92
6	$[\text{C}_4\text{dabco}]\text{Cl}^{\text{b}}$	20	85
7	Neat	24h	20

^a Reaction conditions: 1a (2 mmol), 2a (2 mmol), catalyst $[\text{C}_4\text{dabco}]\text{OH}$, room temperature; ^b catalyst 15 mol%; ^c catalyst 10 mol%; ^d catalyst 5 mol%; ^e isolated yield of the product.

TABLE 2 : Knoevenagel condensation catalyzed by [C₄dabco]OH^a

Entry	1	W ₁	W ₂	Product	Time(min)	Yield(%) ^b
1	PhCHO	CN	CN	3a	1	100
2	PhCHO	CN	CO ₂ Et	3b	4	98
3	4-MeOPhCHO	CN	CN	3c	1	99
4	4-MeOPhCHO	CN	CO ₂ Et	3d	3	98
5	4-MeOPhCHO	COMe	COMe	3e	20	97
6	4-ClPhCHO	CN	CN	3f	1	100
7	4-ClPhCHO	CN	CO ₂ Et	3g	3	100
8	4-ClPhCHO	COMe	COMe	3h	20	98
9	3-NO ₂ PhCHO	CN	CN	3i	1	100
10	3-NO ₂ PhCHO	CN	CO ₂ Et	3j	2	99
11	3-NO ₂ PhCHO	COMe	COMe	3k	20	97
12	C ₂ H ₅ CHO	CN	CN	3l	2	98
13	CH ₃ COC ₃ H ₇	CN	CN	3m	10	94
14	2-furfural	CN	CN	3n	2	98
15	Cyclohexanone	CN	CN	3o	2	98

^aReaction conditions: 1(2 mmol), 2(2 mmol), catalyst [C₄dabco]OH (5 mol%), room temperature; ^bIsolated yield of the product.

CONCLUSION

In conclusion, we have demonstrated that readily available basic ionic liquid [C₄dabco]OH behave as recyclable catalysts for the Knoevenagel condensation of varieties of carbonyl compounds with active methylene compounds affording excellent yields in short durations. This method exhibits a simple, clean, and green manner, mild conditions and avoids hazardous organic solvents. Most of the products required no further purification. In this process, after stirring for a few minutes, the product was isolated in pure form for both solid and liquid products. The catalyst was easily recovered and could be reused more than six times without much loss of activity. The procedure can be applied for large-scale syntheses also. Thus, we have developed an improved process which offers several advantages over other processes and would contribute to environmentally friendly and safer processes.

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