

The *Knoevenagel* reaction in water catalyzed by zwitterionic liquids

Dong Fang^{1,2}, Zheng-hao Fei¹, Zu-liang Liu^{1,2}

¹ Jiangsu Provincial Key Laboratory of Coast Wetland Bioresource and Environment Protection, Yancheng, P.R. China

² School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing, P.R. China

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Abstract Three hydroxyl functionalized zwitterionic liquids (ZILs) were found to be novel recyclable catalysts for the *Knoevenagel* condensation between aldehydes or ketones and active methylene compounds in aqueous medium. Both aldehydes and ketones gave satisfactory results. The products could simply be separated from the catalysts/water, and the catalysts could be recycled six times without noticeably decreasing the catalytic activity.

Keywords *Knoevenagel* condensation; Zwitterionic liquid; Catalyst; Aqueous medium.

Introduction

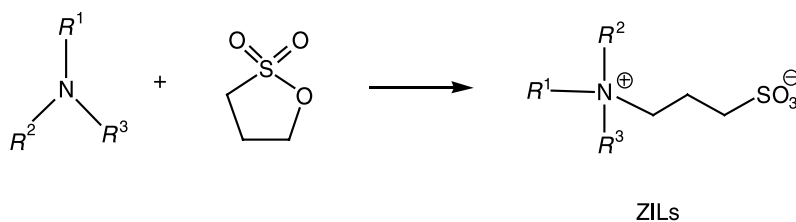
The *Knoevenagel* condensation is one of the most useful and widely employed methods for carbon–carbon bond formation in organic synthesis to produce important intermediates and end products for perfumes, pharmaceuticals, and polymers. It is accomplished by treating a carbonyl compound with an active methylene compound in the presence of a catalyst in organic solvents. Usually homogeneous base catalysts, such as ammonia or ammonium salts, primary and secondary amines, pyridine, and piperidine are used for this reaction [1].

The heterogeneous catalysts have also been used for the *Knoevenagel* reaction, including *Lewis* acids [2], $\text{HClO}_4\text{-SiO}_2$ and *PPA-SiO}_2* [3], solid base such as micelle template silica support primary, secondary, and tertiary amines, ammonium hydroxide [4], metal oxides [5], resins [6], ionic liquid [7], and other catalysts with more or less success [8–13]. In addition, electrochemically induced, microwave and ultrasound irradiation methods have also been reported [14].

With the increasing public concern over environmental degradation and future resources, one of the challenges for chemists is to come up with new approaches that are less hazardous to human health and environment. The solvents used in organic synthesis are high on the list of environmental pollutants, because they are employed in large amounts and are usually volatile liquids. For overcoming the problems, one approach is to use water as a green medium [15]. Another approach is using new processes involving solvent-free conditions. These methods have many advantages, such as reduced pollution, lower cost, and simplicity in processing which are beneficial to the industry as well as to the environment [16].

As a part of our research to develop a green chemistry by one-pot syntheses of target molecules in solvent-free systems or water alone as the reaction medium [17], we report here three zwitterionic liquids (ZILs), 3-trihydroxyethylammonium-*n*-propanesulfonate (*THEAPS*), 3-dihydroxyethylammo-

Correspondence: Dong Fang, Jiangsu Provincial Key Laboratory of Coast Wetland Bioresource and Environment Protection, Yancheng Teachers College, 50 Kai Fang Da Dao, Yancheng 224002, Jiangsu, P.R. China. E-mail: fang-njust@hotmail.com



HEAPS: $R^1 = \text{HOC}_2\text{H}_4$; $R^2 = R^3 = \text{H}$;
DHEAPS: $R^1 = R^2 = \text{HOC}_2\text{H}_4$; $R^3 = \text{H}$;
THEAPS: $R^1 = R^2 = R^3 = \text{HOC}_2\text{H}_4$

Scheme 1

nium-*n*-propanesulfonate (*DHEAPS*), and 3-hydroxyethylammonium-*n*-propanesulfonate (*HEAPS*) (Scheme 1), which have convenient physical properties (novolatillity, inflammability, large liquid range) like other ionic liquids, to catalyze the *Knoevenagel* condensation of aldehydes or ketones with active methylene compounds in water (Scheme 2). To the best of our knowledge in open literature, *Knoevenagel* condensation catalyzed by the zwitterionic liquid has not yet been reported.

Results and discussion

In case of the model *Knoevenagel* condensation reaction, the ZILs and the reaction substrates benzaldehyde and ethyl cyanoacetate were mixed in water, and the reaction mixture was stirred for a length of time at room temperature. TLC indicated that the

Table 1 The *Knoevenagel* condensation of benzaldehyde with ethyl cyanoacetate in catalyst/ H_2O ^a

Entry	Catalyst	Ratio (M/M%)	Time/min	Yield/%
1	0	0	120	no reaction
2	<i>HEAPS</i>	2	60	92
3	<i>HEAPS</i>	5	30	93
4	<i>HEAPS</i>	10	15	95
5	<i>HEAPS</i>	12	15	95
6	<i>HEAPS</i>	15	15	95
7	<i>HEAPS</i>	20	15	90
8	<i>DHEAPS</i>	5	30	91
9	<i>DHEAPS</i>	10	15	92
10	<i>DHEAPS</i>	15	15	94
11	<i>THEAPS</i>	5	60	91
12	<i>THEAPS</i>	10	60	95
13	<i>THEAPS</i>	15	45	95

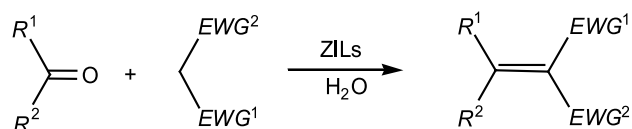
^a Reaction conditions: 10 mmol benzaldehyde, 10 mmol ethyl cyanoacetate and 6 cm³ H_2O , rt; ^b Isolated yield

starting materials had disappeared and the mixture was filtered or decanted and the product was purified by recrystallization or chromatography (silica gel, petroleum ether:ethyl acetate = 5:1). The filtrate containing the catalyst ZILs could be reused directly in the next run without further purification. The results are presented in (Table 1). They show that the *Knoevenagel* condensation reaction of benzaldehyde with ethyl cyanoacetate accomplished smoothly in water catalyzed by the ZILs. Nearly the same yields were obtained in the three zwitterionic liquids; however, *HEAPS* gave a higher rate enhancement than the others. Hence, *HEAPS* should be the best catalyst for the *Knoevenagel* condensation among the three ZILs and the optimized reaction conditions went to entry 4 in Table 1.

Table 2 The influence of the system of *HEAPS*/solvent on *Knoevenagel* condensation reaction of benzaldehyde and ethyl cyanoacetate to provide

Entry	Catalyst/solvent	Isolated yield/%
1	<i>HEAPS</i> / H_2O	95
2	<i>HEAPS</i> / CH_3CN	95
3	<i>HEAPS</i> / CH_3OH	90
4	<i>HEAPS</i> / $\text{C}_2\text{H}_5\text{OH}$	91
5	<i>HEAPS</i> / CH_2Cl_2	85
6	<i>HEAPS</i> / CHCl_3	84
7	<i>HEAPS</i> / $\text{C}_6\text{H}_5\text{CH}_3$	80

^a Reaction conditions: 10 mmol benzaldehyde, 10 mmol ethyl cyanoacetate, 6 cm³ H_2O , 1.0 mmol catalyst, rt, 15 min



Scheme 2

Table 3 Knoevenagel condensation in HEAPS/H₂O^a

Entry	R ¹	R ²	EWG ¹	EWG ²	Time/min	T/°C	Yield ^b /%	Ref. ^c
1	Ph	H	CN	CN	10	rt	95	[7b]
2	4-MeOC ₆ H ₄	H	CN	CN	10	rt	92	[7b]
3	2-MeC ₆ H ₄	H	CN	CN	10	rt	92	[7d]
4	4-MeC ₆ H ₄	H	CN	CN	10	rt	94	[7d]
5	2-ClC ₆ H ₄	H	CN	CN	10	rt	92	[7c]
6	4-ClC ₆ H ₄	H	CN	CN	10	rt	90	[7b]
7	4-NO ₂ C ₆ H ₄	H	CN	CN	10	rt	95	[7b]
8	2-Furyl	H	CN	CN	10	rt	93	[7c]
9	Ph	H	CN	CO ₂ Et	15	rt	95	[7d]
10	4-MeOC ₆ H ₄	H	CN	CO ₂ Et	15	rt	92	[7d]
11	2-MeC ₆ H ₄	H	CN	CO ₂ Et	15	rt	90	[7d]
12	4-MeC ₆ H ₄	H	CN	CO ₂ Et	15	rt	91	[7d]
13	4-ClC ₆ H ₄	H	CN	CO ₂ Et	15	rt	90	[7d]
14	Ph	H	CO ₂ Et	CO ₂ Et	15	70	83	[7a]
15	4-MeOC ₆ H ₄	H	CO ₂ Et	CO ₂ Et	15	70	80	[7a]
16	4-ClC ₆ H ₄	H	CO ₂ Et	CO ₂ Et	15	70	92	[7a]
17	Ph	H	COCH ₃	CO ₂ Et	15	70	81	[7a]
18	Ph	H	COCH ₃	COCH ₃	15	70	84	[7a]
19	n-C ₃ H ₇	H	CN	CO ₂ Et	15	70	85	[7a]
20	-(CH ₂) ₄ -	/	CN	CO ₂ Et	120	70	91	[7a]
21	Me	Me	CN	CO ₂ Et	120	70	90	[7a]

^a Reaction conditions: 10 mmol aldehydes (ketones), 10 mmol active methylene compounds, 1.0 mmol HEAPS, 6 cm³ H₂O;

^b Isolated yield based on carbonyl compounds; ^c Their spectroscopic data used for identity proof have been described

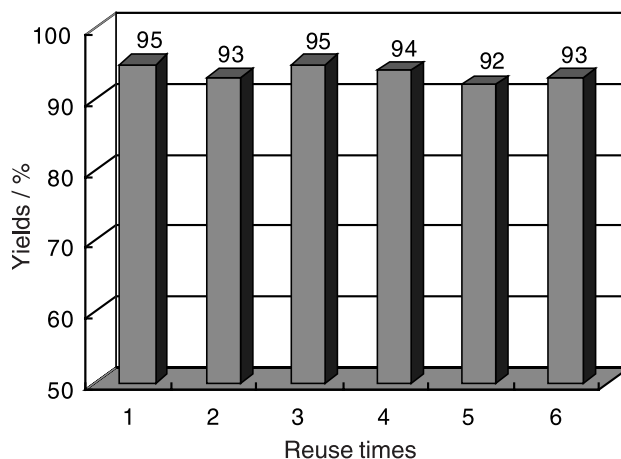
To optimize the reaction conditions, the same reaction of benzaldehyde with ethyl cyanoacetate was employed as the model reaction to screen the effect of solvents (Table 2). The results showed that the Knoevenagel reaction in HEAPS/H₂O gave an isolated yield of 95% (Table 2, entry 1), which was almost the same as that in HEAPS/CH₃CN, HEAPS/CH₃OH, and HEAPS/C₂H₅OH (Table 2, entries 2–4), but was higher than that in HEAPS/CH₂Cl₂, HEAPS/CHCl₃, and HEAPS/C₆H₅CH₃ (Table 2, entries 5–7). Water is a clean and cheap solvent, it is important to carry out organic reactions in water instead of volatile solvent for the environmental and economic reasons.

Subsequently, the scope of the Knoevenagel condensation of other aldehydes and ketones (**1**) with various active methylene compounds (**2**) in HEAPS/H₂O was investigated (Table 3).

As shown in Table 3, this reaction was found to be general. All aldehydes, both aliphatic and aromatic aldehydes with various substituents such as nitro, chloro, methyl, and methoxy gave good to excellent results (Table 3, entries 1–19), and all unsymmetric active methylene compounds gave (*E*)-isomers, the same as described in literature (Table 3, entries 9–13, 17, 19). In case of the ketones, perhaps for region

resistance, prolonged reaction times were needed (Table 3, entries 20 and 21) as compared with aldehydes. Several active methylene compounds containing different active groups such as cyano, carbonyl, and ethoxycarbonyl group could be successfully reacted with aldehydes or ketones.

The recycling performance of HEAPS in the same Knoevenagel condensation reaction was also investigated. After the reaction, the products were isolated from the catalytic system by filtration. The filtrate

**Fig. 1** Reuse performance of HEAPS

(aqueous medium containing catalyst) was reused in the next run without further purification. As shown in Fig. 1, the catalyst can be reused at least six times without appreciable decrease in yield and reaction rate.

In conclusion, it was demonstrated that the readily available zwitterionic liquids could behave as novel recyclable catalysts for the *Knoevenagel* condensation between aldehydes or ketones with active methylene compounds offering a procedure with generality, which is environmentally benign, and is of practical convenience in the product separation from the reaction system.

Experimental

Melting points were determined by X₆-Data microscope apparatus. ¹H NMR spectra were recorded on Bruker DRX300 (300 MHz). Mass spectra were obtained with automated FININIGAN TSQ QUANTUM ULTRA AM (Thermal) LC/MS spectrometer. Thermal analysis was determined by Mettler Toledo spectrometer (10°C/min heating rate under nitrogen). All chemicals (AR grade) were commercially available and used without further purification.

Synthesis of hydroxyl functionalized zwitterionic liquids (ZILs)

All used HO-functionalized zwitterionic liquids were synthesized according to our previous method [17d] with some changes.

3-Trihydroxyethylammonium-*n*-propanesulfonate (THEAPS, C₇H₂₁NO₆S)

To a solution of 13.3 cm³ triethanolamine (0.10 mol) in 20 cm³ 1,2-dichloroethane was added 12.2 g 1,3-propanesultone (0.10 mol) in portions within 30 min, and then the mixture was stirred under nitrogen for 2 h at 45–50°C. A biphasic mixture was then formed, the product (bottom phase) was obtained by decantation of the solvent (upper phase), and then washed repeatedly with a mixture of chloroform, petroleum ether, and ethanol to remove the unreacted material and dried in a vacuum at 60°C. A yield of 92% of a colorless liquid product was obtained, its melting point was not observed in the DSC curve when heated from –60°C to 50°C. The TGA analysis showed that THEAPS is thermally stable up to 240°C and this zwitterionic liquid was entirely miscible with water. ¹H NMR (300 MHz): δ = 2.13 (q, *J* = 3.9 Hz, 2H, –C–CH₂–C–SO₃), 2.88 (t, *J* = 14.1 Hz, 2H, –C–C–C–CH₂–SO₃), 3.34 (t, *J* = 5.1 Hz, 2H, –N–CH₂–C–C–SO₃), 3.54–3.64 (m, 2H + 4H, –N–CH₂–C–OH), 3.83–3.95 (m, 6H, –N–C–CH₂–OH) ppm; MS: *m/z* (%) = 274.19, 272.07 (M⁺+1), 194.11, 150.09 (100), 132.

3-Dihydroxyethylammonium-*n*-propanesulfonate (DHEAPS, C₇H₁₇NO₅S)

This compound was prepared in analogy to THEAPS, with 2 h reaction time at room temperature. The product was obtained

in 94% as a colorless liquid. ¹H NMR (300 MHz): δ = 2.01 (q, *J* = 7.2 Hz, 2H, –C–CH₂–C–SO₃), 2.40 (t, *J* = 7.5 Hz, 2H, –C–C–C–CH₂–SO₃), 3.04 (s, 3H, –CH₃), 3.35 (t, *J* = 7.1 Hz, 2H, –N–CH₂–C–C–SO₃), 3.44–3.51 (m, 4H, –N–CH₂–C–OH), 3.85–3.91 (m, 4H, –N–C–CH₂–OH) ppm; MS: *m/z* (%) = 225.98 (M⁺ – 1, 100), 453.00.

3-Hydroxyethylammonium-*n*-propanesulfonate (HEAPS, C₅H₁₃NO₄S)

This compound was prepared in analogy to THEAPS, with 1 h reaction time at room temperature. The product was obtained in 90% as a white solid. Mp 155–157°C; ¹H NMR (300 MHz): δ = 1.98 (q, *J* = 7.5 Hz, 2H, –C–CH₂–C–SO₃), 2.48 (t, *J* = 7.5 Hz, 2H, –C–C–C–CH₂–SO₃), 3.08 (s, 6H, –CH₃), 3.41 (t, *J* = 4.2 Hz, 2H, –N–CH₂–C–C–SO₃), 3.55 (t, *J* = 4.2 Hz, 2H, –N–CH₂–C–OH), 3.83 (s, 2H, –N–C–CH₂–OH) ppm; MS: *m/z* (%) = 183.89 (M⁺ + 1, 100), 366.90.

General procedure for the *Knoevenagel* condensation in the ZILs/H₂O system

To 1.06 g benzaldehyde (10 mmol) and 1.13 g ethyl cyanoacetate (10 mmol) in 6 cm³ H₂O was added 1.0 mmol ZILs under stirring. The mixture was typically allowed to proceed for a length of time at room temperature with the vigorous stirring. After TLC indicated that the starting materials has disappeared, the resulting mixture was filtered (solid product) or decanted (liquid product) and then the crude product was purified by recrystallization or chromatography (silica gel, petroleum ether:ethyl acetate = 5:1). The filtrate containing the ZILs could be reused directly in the next run without further purification. The products were identified by ¹H NMR, and physical data (mp or bp) with those reported in literature.

(*E*)-Ethyl 2-cyano-3-phenylacrylate (3a, C₁₂H₁₁NO₂)

White crystals; mp 51°C; ¹H NMR (300 MHz, CDCl₃): δ = 1.40 (t, *J* = 6.9 Hz, 3H, CH₃), 4.39 (q, *J* = 6.9 Hz, 2H, CH₂), 7.48–7.60 (m, 3H, *Ar*-H), 8.01 (d, *J* = 7.2 Hz, 2H, *Ar*-H), 8.25 (s, 1H, CH=) ppm; MS: *m/z* (%) = 201.00 (M⁺, 100).

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References

1. a) Trost BM (1991) In: Comprehensive Organic Synthesis, vol. 2. Pergamon Press, Oxford, p 341; b) Balalaie S, Sheikh-Ahmadi M, Bararjanian M (2007) Catal Commun 8:1724
2. Khan AT, Parvin T, Choudhury LH (2007) Tetrahedron 63:5593
3. Kantevari S, Bantu R, Nagarapu L (2007) J Mol Catal A: Chemical 269:53

4. Climent MJ, Corma A, Dominguez I, Iborra S, Sabater MJ, Sastre G (2007) *J Catal* 246:136
5. Reddy BM, Patil MK, Rao KN, Reddy GK (2006) *J Mol Catal A: Chemical* 258:302
6. Saito T, Goto H, Honda K, Fujii T (1992) *Tetrahedron Lett* 33:7535
7. a) Su C, Chen Z, Zheng Q (2003) *Synthesis* 4:555; b) Xu XM, Li YQ, Zhou MY (2004) *Chin J Org Chem* 24:1253; c) Gao G, Lu L, Zou T, Gao J, Liu Y, He MY (2007) *Chem Res in Chin Univ* 23:169; d) Yue CB, Wei YY (2007) *Fine Chem* 24:166; e) Xu X, Guo X, Duan H, Lin Y, Sun H (2007) *Catal Commun* 8:115; f) Lai GH, Peng JJ, Li J, Qiu H, Jiang J, Jiang K, Shen Y (2006) *Tetrahedron Lett* 47:6951; g) Hangarge RV, Jarikote DV, Shingare MS (2002) *Green Chem* 3:266; h) Cai YQ, Peng YQ, Song GH (2006) *Catal Lett* 109:61; i) Paun C, Barklie J, Goodrich P, Gunaratne HQN, McKeown A, Parvulescu VI, Hardacre C (2007) *J Mol Catal A: Chem* 269:64
8. Reddy TI, Varma RS (1997) *Tetrahedron Lett* 38:1721
9. Tamami B, Fadavi A (2005) *Catal Commun* 6:747
10. Wang Y, Shang Z, Wu T, Fan J, Chen X (2006) *J Mol Catal A: Chemical* 253:212
11. Martins L, Bonagamba TJ, de Azevedo ER, Bargiela P, Cardoso D (2006) *Appl Catal A: General* 312:77
12. Bigi F, Chesini L, Maggi R, Sartori G (1999) *J Org Chem* 64:1033
13. Reddy KR, Rajgopal K, Maheswari CU, Kantam ML (2006) *New J Chem* 11:1549
14. a) Peng YQ, Song GH (2003) *Green Chem* 6:704; b) Feroci M, Orsini M, Palombi L, Inesi A (2007) *Green Chem* 4:323
15. Li CJ (1993) *Chem Rev* 93:2023
16. Tanaka K, Toda F (2000) *Chem Rev* 100:1025
17. a) Fang D, Luo J, Zhou XL, Liu ZL (2007) *Catal Lett* 116:76; b) Fang D, Luo J, Zhou XL, Ye ZW, Liu ZL (2007) *J Mol Catal A: Chemical* 274:208; c) Gong K, Fang D, Wang HL, Liu ZL (2007) *Monatsh Chem*, doi: 10.1007/S00706-007-0767-2; d) Fang D, Zhou XL, Ye ZW, Liu ZL (2006) *Ind Eng Chem Res* 45:7982; e) Fang D, Gong K, Shi QR, Liu ZL (2007) *Catal Commun* 8:1463