DOI: 10.1002/ejoc.200600335

Ionic Liquid as Catalyst and Reaction Medium – A Simple, Efficient and Green Procedure for Knoevenagel Condensation of Aliphatic and Aromatic Carbonyl Compounds Using a Task-Specific Basic Ionic Liquid

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Keywords: Ionic liquid / Green chemistry / Catalysis / Knoevenagel condensation / Carbonyl compounds

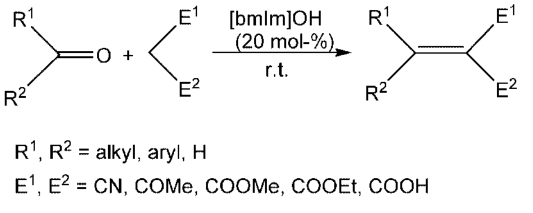
The basic ionic liquid 1-butyl-3-methylimidazolium hydroxide, [bmIm]OH, efficiently catalyzes Knoevenagel condensation without requirement of any organic solvent. A wide range of aliphatic and aromatic aldehydes and ketones easily undergo condensations with diethyl malonate, malononitrile, ethyl cyanoacetate, malonic acid and ethyl acetoacetate. The reactions proceed at room temperature and are very fast (10–30 min). However, the most significant feature of this methodology is the condensation of aliphatic aldehyde with diethyl malonate, which is not very easy to achieve by conventional reagents, and was not addressed adequately in literature providing a general and convenient procedure.

Introduction

During last decade ionic liquids have emerged as very potential green alternatives to volatile and hazardous organic solvents, and are being used as efficient and recyclable reaction media for a variety of important reactions.[1] However, we envisioned ionic liquids as far more potential than being employed as only reaction media, and thus initiated an investigation to explore their capability as effective catalysts[2] and reagents[3] for chemical transformations.

The Knoevenagel condensation is a very useful reaction and has been widely employed for carbon–carbon bond formation in organic synthesis.[4] This reaction is usually catalyzed by a base, an acid, or a heterogeneous neutral support. Among many other procedures a few using titanium tetrachloride,[5a] 1,5,7-triazabicyclo[4.4.0]dec-5-ene immobilized in MCM-41,[5b] modified Mg-Al hydrotalcite,[5c] MgO,[5d] rare-earth exchanged NaY zeolite,[5e] USY zeolite,[5f] aluminium oxide,[5g] water,[5h] high pressure,[5i] ethylenediammonium diacetate in ionic liquid,[5j] Lewis acidic ionic liquid, [bpy]Cl·$AlCl_3$,[5k] glycine in ionic acid,[5l] hydrotalcites in ionic liquid[5m] may be mentioned.

During the course of our investigations, on another project we need to make Knoevenagel condensation products of aliphatic aldehydes with malonic esters. We tried several conventional reagents like piperidine,[6] Al_2O_3,[5g] glycine in [bmIm]BF_4[5l] without any useful result within a reasonable time (24 h). Our literature search then revealed, that although reactions of aromatic aldehydes are very facile and were addressed in all the procedures, condensation of aliphatic aldehydes are difficult to achieve and were not adequately covered. Although there are isolated examples of condensation of aliphatic aldehydes with malonic esters as one of the steps in course of synthesis of target compounds,[5n] the reactions are not very fast and high yielding. A couple of reports[5a,5o,5p] also addressed a few reactions, however, these lack general applicability. In addition, the reactions are very slow (22–70 h),[5a] and the reaction conditions also vary with each substrate. This prompted us to develop a convenient method for this useful transformation utilizing our recent expertise on ionic liquids.[2,3] Recently, design of task specific ionic liquid has attracted much attention.[1m,1n] We also introduced the task-specific ionic liquid 1-butyl-3-methylimidazolium hydroxide, [bmIm]OH, with a remarkable effect on Michael addition[2h] and as a part of this program we report here an excellent catalytic efficiency of [bmIm]OH for Knoevenagel condensations, particularly for reactions of aliphatic aldehydes with diethyl malonate (Scheme 1).



Scheme 1.

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Results and Discussion

The experimental procedure is very simple. A mixture of aldehyde (5 mmol), diethyl malonate (or other active methylene compound) (5 mmol) and [bmIm]OH (20 mol-%) was stirred at room temperature for a certain period of time as required to complete the reaction (TLC). The product was isolated by direct distillation of the reaction mixture under reduced pressure. In case of small-scale reactions or any compound, which is not thermally stable, the product may be isolated by extraction with ethyl acetate followed by usual work-up and chromatography. The ionic liquid remaining in the reaction flask after being washed with ethyl acetate and dried at 80 °C under vacuum for 3–4 h was recycled in subsequent runs.

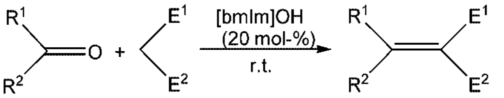
A wide range of aliphatic and aromatic aldehydes and ketones underwent condensations with a variety of active methylene compounds – such as diethyl malonate, ethyl cyanoacetate, malononitrile, malonic acid, ethyl acetoacetate – by this procedure to provide the corresponding Knoevenagel products. The results are summarized in Table 1. The ketones are found to be less reactive than aldehydes. Heteroaromatic aldehydes such as thiophenyl, pyridinyl and furfuryl aldehydes (Entries 28–31) also underwent smooth reactions. The condensations of aliphatic aldehydes with malonic acids were accomplished with moderate yields. The α,β-unsaturated aldehyde produced the corresponding product without any difficulty. It was also observed that the reaction of aliphatic aldehydes with diethyl malonate, which are easily achieved by [bmim]OH, did not proceed at all under the catalysis of [bmIm]BF_4 or [bmIm]Br. This shows the vital role of the hydroxy counterion of this task-specific ionic liquid in this transformation.

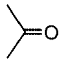
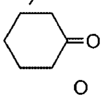
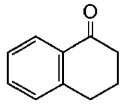
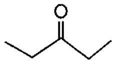
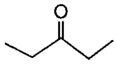
When an aromatic *o*-hydroxy aldehyde was condensed with diethyl malonate or ethyl acetoacetate by this procedure, the corresponding coumarin was obtained in one-pot in very high yields. Several aldehydes were found to undergo this reaction without any difficulty. The results are reported in Table 2.

All these reactions are, in general very fast and clean. The isolated yields of products are also quite high. The products are of high purity (^{1}H and ^{13}C NMR) irrespective of whether they are obtained by direct distillation or solvent extraction. The products, α,β-unsaturated esters are found to be *trans* (except a couple of reactions as in Entries 25 and 30, where *cis* isomers are also formed) as obtained in other procedures.[5c,5f,5j,5r] The products are easily identified by spectroscopic data (IR, ^{1}H NMR and ^{13}C NMR).

It has been found that the residual ionic liquid may be recycled for five runs without any loss of efficiency. After five runs 50% fresh ionic liquid was mixed with it to maintain equal efficiency. Although there are a few reports[18] of side reactions due to carbene formation of imidazolium-based ionic liquids under strong bases, we did not encounter such side reactions while using [bmIm]OH under the present procedure. This is possibly due to the faster reactions (10–30 min) of aldehydes with active methylene compounds.

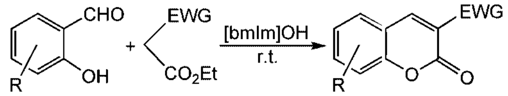
Table 1. Knoevenagel condensation catalyzed by [bmlm]OH.



Entry	R^1	R^2	E^1	E^2	Time [min]	Yield [%][a]	Ref.
1	*n*-C_2H_5	H	CO_2Et	CO_2Et	10	82	5a
2	*n*-C_2H_5	H	CN	CO_2Et	7	85	6
3	*n*-C_3H_7	H	CN	CN	10	90	
4	*n*-C_3H_7	H	CN	CO_2Et	12	89	6
5	*n*-C_3H_7	H	CO_2Et	CO_2Et	15	82	5a
6	n-C_3H_7	H	CO_2H	CO_2H	30	55	
7	*i*-C_3H_7	H	CN	CN	10	89	7
8	*i*-C_3H_7	H	CN	CO_2Et	10	93	6
9	*i*-C_3H_7	H	CO_2Et	CO_2Et	15	90	5a
10	*i*-C_3H_7	H	CO_2H	CO_2H	30	62	8
11	*n*-C_5H_{11}	H	CN	CN	10	92	9
12	*n*-C_5H_{11}	H	CO_2Et	CO_2Et	12	78	10
13	*n*-C_7H_{15}	H	CN	CN	13	87	
14	*n*-C_7H_{15}	H	CO_2Et	CO_2Et	15	75	5a
15	*n*-C_9H_9	H	CO_2Et	CO_2Et	16	85	11
16	*c*-C_6H_{11}	H	CO_2Et	CO_2Et	12	82	12
17			CN	CO_2Et	10	82	5j
18			CN	CN	30	87	5j
19			CN	CN	40	89	5i
20			CN	CN	30	89	5g
21			CN	CO_2Et	120	85	7
22	Ph	H	CN	CN	10	96	13
23	Ph	H	CN	CO_2Et	12	93	5l
24	Ph	H	CO_2Et	CO_2Et	30	89	5j
25	Ph	H	$COCH_3$	CO_2Et	20	87	5j
26	(*p*-OMe)C_6H_4	H	CN	CO_2Et	15	90	5j
27	(*p*-NO_2)C_6H_4	H	CN	CO_2Et	10	92	5j
28	2-thiophenyl	H	CN	CN	12	92	5g
29	2-furfuryl	H	CO_2Et	CO_2Et	30	82	5a
30	2-furfuryl	H	CO_2Et	$COCH_3$	25	87	
31	2-pyridinyl	H	CO_2Et	CO_2Et	15	85	11
32	cinnamyl	H	CN	CO_2Et	12	87	5c
33	cinnamyl	H	CO_2Et	CO_2Et	20	80	14

[a] Yields refer to those of pure isolated products characterized by IR and ^{1}H and ^{13}C NMR spectroscopic data.

Table 2. Synthesis of coumarins by Knoevenagel condensation.



Entry	R	EWG	Time [min]	Yield [%][a]	Ref.
1	H	CO_2Et	15	92	5a
2	H	$COCH_3$	15	88	5a
3	3-OMe	$COCH_3$	18	90	15
4	5-OMe	CO_2Et	20	87	16
5	5-OMe	$COCH_3$	25	82	17

[a] Yields refer to isolated pure products unless otherwise stated.

Conclusions

In conclusion, the present procedure using the task-specific basic ionic liquid [bmIm]OH provides a very efficient and convenient methodology for Knoevenagel condensation of aliphatic and aromatic carbonyl compounds with a variety of active methylene compounds. The significant advantages offered by this methodology are: (a) general applicability to a large number of substrates (33) with very facile reaction of aliphatic aldehydes with diethyl malonate, which is difficult to achieve by other methods, (b) mild reaction conditions (room temperature), (c) clean and fast (7–40 min) reaction, (d) high isolated yields of products, and (e) reusability of catalyst and cost-effectiveness. Another attractive feature of this methodology is the use of ionic liquid as catalyst as well as reaction medium primarily avoiding hazardous organic solvent in the whole procedure in contrast to the reported procedures using ionic liquids together with additional catalysts[5j,5i,5m] and organic solvents in the process. Thus, we believe that this simple and green procedure will be a practical alternative to the existing procedures to cater the need of academia as well as industries.

Experimental Section

General: NMR spectra were recorded with a Bruker DPX-300 instrument at 300 MHz for ^1H and 75 MHz for ^{13}C NMR in $CDCl_3$ solutions. IR spectra were measured with a FT-8300 Shimadzu spectrometer (neat for liquids and KBr pellet for solids). All liquid substrates were distilled before use. [bmIm]OH was prepared following our earlier procedure.[2h] This ionic liquid is considerably stable under ambient conditions and can be used in reactions without any difficulty as reported by us[2h] and another group recently.[19]

Knoevenagel Condensation of Isobutyraldehyde with Diethyl Malonate. Representative General Procedure: (Entry 9, Table 1) A mixture of isobutyraldehyde (360 mg, 5 mmol), diethyl malonate (800 mg, 5 mmol) and [bmIm]OH (156 mg, 20 mol-%) was stirred at room temperature (25–30 °C) for 15 min until completion of reaction as indicated by TLC. The product was then directly distilled out from the reaction vessel under reduced pressure to furnish diethyl 2-isobutylidenemalonate as a colourless liquid; yield: 963 mg (90%); R_f = 0.75. IR: $\tilde{\nu}$ = 1720, 1625, 1211 cm^{-1}. ^1H NMR: δ = 6.77 (d, J = 10.5 Hz, 1 H), 4.19–4.33 (m, 4 H), 2.65–2.73 (m, 1 H), 1.25–1.36 (m, 6 H), 1.07 (d, J = 6.5 Hz, 6 H) ppm. ^{13}C NMR: δ = 165.5, 164.0, 154.6, 126.5, 61.1, 61.0, 29.2, 21.6 (2 C), 14.0, 13.9 ppm. These values are in good agreement with the reported ones.[5a]

When the reaction was carried out with 1 mmol or smaller amounts the product was isolated by extraction with ethyl acetate followed by column chromatography over silica gel. In a few cases where the products were prone to decomposition under distillation condition, solvent extraction process was followed. The residual ionic liquid was washed with small amount of ethyl acetate, dried under vacuum at 80 °C for 4 h and recycled.

This procedure is followed for condensations of all substrates listed in Table 1 and synthesis of coumarins is listed in Table 2. All the products except four (entries 3,6,13,30 in Table 1) are known compounds (references in Table 1, Table 2) and were identified by comparison of their spectroscopic data with those reported. The new compounds were properly characterized by their spectroscopic data (IR, ^1H and ^{13}C NMR) and elemental analysis. These values are reported below.

2-Butylidenemalononitrile: (Entry 3, Table 1). Yellowish liquid. IR: $\tilde{\nu}$ = 2237, 1604 cm^{-1}. ^1H NMR: δ = 7.35 (t, J = 7.9 Hz, 1 H), 2.54–2.61 (m, 2 H), 1.54–1.71 (m, 2 H), 1.01 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR: δ = 169.5, 111.9, 110.3, 89.7, 34.4, 20.8, 13.3 ppm. $C_7H_8N_2$ (120.15): calcd. C 69.97, H 6.71, N 23.32; found C 69.72, H 6.75, N 23.25.

2-Butylidenemalonic Acid: (Entry 6, Table 1). Low-melting solid. IR: $\tilde{\nu}$ = 3071 (broad), 1690, 1643 cm^{-1}. ^1H NMR: δ = 9.8 (broad, 2 H), 7.85 (t, J = 7.5 Hz, 1 H), 2.72–2.84 (m, 2 H), 1.51–1.66 (m, 2 H), 0.99 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR: δ = 169.4, 168.0, 165.7, 121.3, 33.0, 21.7, 13.8 ppm. $C_7H_{10}O_4$ (158.15): calcd. C 53.16, H 6.37; found C 53.02, H 6.24.

2-Octylidenemalononitrile: (Entry 13, Table 1). Viscous liquid. IR: $\tilde{\nu}$ = 2237, 1647, 1608, 1465 cm^{-1}. ^1H NMR: δ = 7.34 (t, J = 7.8 Hz, 1 H), 2.55–2.62 (m, 2 H), 1.47–1.54 (m, 2 H), 1.18–1.33 (m, 8 H), 0.87–0.91 (m, 3 H) ppm. ^{13}C NMR: δ = 169.7, 111.9, 111.2, 89.5, 32.6, 31.3, 29.0, 28.5, 27.3, 22.4, 13.8 ppm. $C_{11}H_{16}N_2$ (176.26): calcd. C 74.96, H 9.15, N 15.89; found C 74.72, H 9.21, N 15.68.

Ethyl 2-Acetyl-3-(furan-2-yl)acrylate: (Entry 30, Table 1). Yellowish liquid. IR: $\tilde{\nu}$ = 1720, 1660, 1625, 1211 cm^{-1}. ^1H NMR: δ = 7.47 (s, 1 H), 7.31 (s, 1 H), 6.71 (d, J = 3.5 Hz, 1 H), 6.43–6.44 (m, 1 H), 4.23 (q, J = 7.0 Hz, 2 H), 2.43 (s, 3 H), 1.27 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR: δ = 201.9, 164.3, 149.0, 146.2, 129.5, 125.8, 117.6, 112.5, 61.5, 26.3, 13.9 ppm. $C_{11}H_{12}O_4$ (208.21): calcd. C 63.45, H 5.81; found C 63.28, H 5.75.

Acknowledgments

This work has enjoyed the support from CSIR, New Delhi [Grant No. 01(1936)/04]. R.J. is also thankful to CSIR for his fellowship.

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Received: April 15, 2006