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Lewis acidic ionic liquids for the synthesis of electrophilic alkenes via the Knoevenagel condensation

Jitendra R. Harjani, Susheel J. Nara and Manikrao M. Salunkhe*

Department of Chemistry, The Institute of Science, 15-Madam Cama Road, Mumbai 400 032, India

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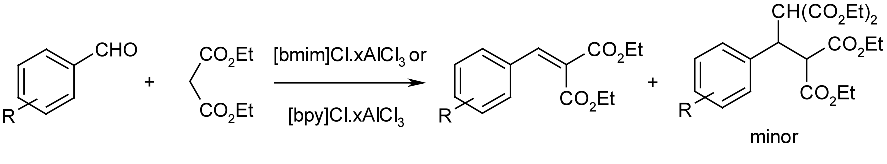
Abstract—1-Butyl-3-methylimidazolium chloroaluminate, [bmim]Cl·AlCl$_3$, $N=0.67$ and 1-butylpyridinium chloroaluminate, [bpy]Cl·AlCl$_3$, $N=0.67$ ionic liquids were found to work well as the Lewis acid catalyst and solvent in the Knoevenagel condensations of benzaldehyde and substituted benzaldehydes with diethyl malonate to give benzylidene malonates. The benzylidene malonates subsequently underwent Michael additions with diethyl malonate. The extent of Michael product formed during the reaction was found to vary with the Lewis acidity and the molar proportion of ionic liquid. The influence of Lewis acidity of the ionic liquid on the Knoevenagel and Michael products is demonstrated. In the case of 2-hydroxyarylaldehydes, the reactions led to the formation of 3-ethoxycarbonyl coumarins under ambient conditions. © 2002 Elsevier Science Ltd. All rights reserved.

Ever since the ionic liquids came into the spotlight during the last decade, rigorous and consistent efforts in this area have paved the way for alternative and new synthetic strategies in the realm of synthetic organic chemistry. The pioneering work of Seddon and others have unravelled several remarkable properties of ionic liquids that can be ably exploited in tackling problems encountered in synthetically useful reactions.[1] Their unprecedented ability to solvate a broad spectrum of substrates of organic and inorganic nature has widened the horizon of their applicability. Infinitesimally small vapour pressure, recyclability without any diminution in the desirable properties (except in the case of chloroaluminate ionic liquids), high thermal stability and ease of handling are the features possessed by these liquids. The hallmark of such liquids is our ability to alter their properties[2] as desired, by manipulating their structure with respect to the choice of organic cation, anion and side chain attached to the organic cation. All these properties have bestowed entirety to these liquids for their application in developing environmentally benign chemical technologies.

The Knoevenagel reaction is well known for its immense potential in the synthesis of electrophilic olefins from active methylene and carbonyl compounds.[3] More than a century old now, a wide array of catalysts have been employed to accomplish this reaction, each affording variable yields of olefins. The reaction is catalysed by weak bases under homogenous conditions.[3] However, the past decade has witnessed a rapid emergence of heterogeneous catalysts comprising of mainly inorganic materials such as clays, zeolites, etc. owing to their environmentally benign properties, which have been aptly employed in this reaction.[4] Apart from these properties, the feature which encouraged their application in Knoevenagel reaction is that most of them are ditopic in nature, containing both acidic and basic sites, while others are solely acidic or basic. Some Lewis acid catalysts have also been



Scheme 1. Reaction of benzaldehyde and substituted benzaldehydes with diethyl malonate in the Lewis acidic [bmim] Cl·xAlCl$_3$ and [bpy]Cl·xAlCl$_3$ ionic liquids.

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* Corresponding author. Tel.: 91-22-2816750; fax: 91-22-2816750; e-mail: mmsalunkhe@hotmail.com

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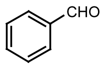
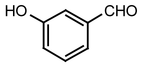
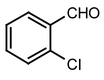
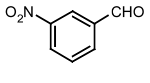
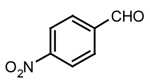
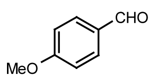
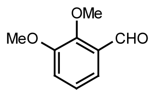
exploited for this reaction.[5] Chloroaluminate based ionic liquids have been the focal point of our investigations owing to their variable Lewis acidity. We have exploited the acidity of these liquids in Fries rearrangements[6a] and Friedel–Crafts sulphonylations.[6b] In continuation of our ongoing research program of exploration of newer reactions and their mechanistic investigations in these ionic liquids, we thought it would be worthwhile to investigate the Knoevenagel reaction in these liquids. We herein report for the first time Knoevenagel condensations of benzaldehyde and substituted benzaldehydes with diethyl malonate in Lewis acidic 1-butyl-3-methylimidazolium chloroaluminate, [bmim]Cl·xAlCl$_3$ and 1-butylpyridinium chloroaluminate, [bpy]Cl·xAlCl$_3$ ionic liquids (Scheme 1).

Lewis acidity of such ionic liquids is a function of the apparent mole fraction of AlCl$_3$, N present in the liquid. We initially investigated the Knoevenagel condensation in [bmim]Cl·AlCl$_3$, $N=0.67$. Several experiments with substituted benzaldehydes gave us almost quantitative conversions[7] (Table 1) when the aldehyde, diethyl malonate and ionic liquid were taken in the molar ratio of 1.0:1.0:0.5, respectively. However, apart from the major product, i.e. the Knoevenagel product, some other products were also detected on GC in all the cases. The Knoevenagel product, benzylidene malonate, which happens to be an excellent Michael acceptor[8] underwent subsequent Michael addition with diethyl malonate and give the Michael adduct. Once benzylidene malonate is formed, the two reactions, Knoevenagel and Michael can become competitive to give different ratios of the two products. The ratio of Knoevenagel to Michael product (K/M) was found to be higher when the molar ratio of aldehyde, diethyl malonate and ionic liquid was 1.0:1.0:0.5, respectively, in most of the cases (Table 1) except in the case of 4-methoxybenzaldehyde. The presence of an electron-donating group at the 4-position decreases its reactivity towards the Knoevenagel reaction and consequently a significant amount of the Michael product was observed in this case. Hence, the influence of parameters such as the molar proportion and the Lewis acidity of the ionic liquid on conversion and K/M ratio of such a substrate is expected to be more pronounced. Obviously, 4-methoxybenzaldehyde was the substrate of choice for these studies. As the molar proportion of ionic liquid was increased progressively while, the molar ratio of aldehyde to diethyl malonate was maintained at 1.0:1.0, the extent of conversion and the K/M ratio increased, as illustrated in Table 2. Thus, a higher molar proportion of ionic liquid favours the Knoevenagel product.

The Lewis acidity of these liquids varies as an apparent mole fraction of AlCl$_3$. This feature of ionic liquids allowed us to monitor the influence of the Lewis acidity on the extent of conversion and on the K/M ratio. The expected trend of increase in conversion with increase in Lewis acidity was observed as illustrated in Table 3. However, the ratio K/M falls off as the Lewis acidity of the liquid increases.

Table 1. Reactions of benzaldehyde and substituted benzaldehydes with diethyl malonate in the Lewis acidic [bmim]Cl·AlCl$_3$, $N=0.67$ and [bpy]Cl·AlCl$_3$, $N=0.67$ ionic liquids

Entry	Substrate	% conversion		K:M	
		[bmim]Cl.AlCl$_3$, N=0.67	[bpy]Cl.AlCl$_3$, N=0.67	[bmim]Cl.AlCl$_3$, N=0.67	[bpy]Cl.AlCl$_3$, N=0.67
1		90	87	90:10 (9.0)	86:14 (6.1)
2		97	86	99:1 (99.0)	98:2 (49.0)
3		95	95	98:2 (49.0)	91:9 (10.1)
4		89	86	95:5 (19.0)	90:10 (9.0)
5		94	90	95:5 (19.0)	90:10 (9.0)
6		71	70	64:36 (1.8)	85:15 (5.7)
7		93	91	88:12 (7.3)	97:3 (32.3)

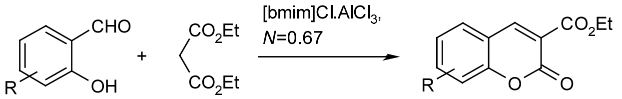
Values in parentheses indicate the K/M ratio

Table 2. Influence of the molar proportion of [bmim]Cl·$AlCl_3$, $N=0.67$ on the extent of conversion and K/M ratio in the reactions of 4-methoxybenzaldehyde with diethyl malonate

Molar proportion of [bmim]Cl·$AlCl_3$, $N=0.67$	Conversion (%)	K/M ratio
0.5	71	1.8
1.0	74	49.0
1.5	80	49.0

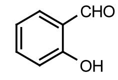
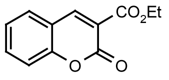
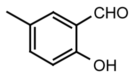
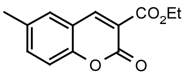
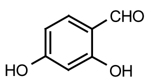
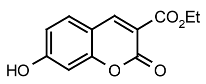
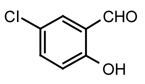
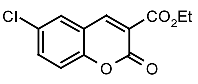
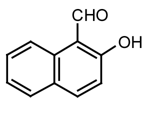
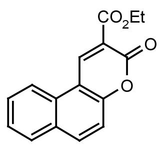
Table 3. Influence of Lewis acidity on the extent of conversion and K/M ratio in the reactions of 4-methoxybenzaldehyde with diethyl malonate in [bmim]Cl·$x$$AlCl_3$

N	x	Conversion (%)	K/M ratio
0.50	1.00	–	–
0.55	1.25	22	4.3
0.59	1.50	41	3.0
0.63	1.75	57	2.4
0.67	2.00	71	1.8



Scheme 2. Coumarin synthesis via Knoevenagel condensations of 2-hydroxybenzaldehydes with diethyl malonate in the Lewis acidic [bmim]Cl·$AlCl_3$, $N=0.67$.

Table 4. Synthesis of 3-ethoxycarbonyl coumarins via Knoevenagel condensations of 2-hydroxyarylaldehydes with diethyl malonate in the Lewis acidic [bmim]Cl·$AlCl_3$, $N=0.67$

Entry	Substrate	Product	Yield[a] (%)
1			86
2			82
3			80
4			92
5			78

[a]Isolated yields

In addition, [bpy]Cl·$AlCl_3$, $N=0.67$ was also employed for these reactions. The conversions in this ionic liquid were relatively less in comparison to [bmim]Cl·$AlCl_3$, $N=0.67$; consequently, the proportion of Michael product in this liquid is improved in most of the cases. This feature is in accordance with the results obtained in [bmim]Cl·$AlCl_3$, $N=0.67$ ionic liquid at lower molar proportions (Table 1). Thus, [bpy]Cl·$AlCl_3$, $N=0.67$ offers a relatively less reactive environment which fosters relatively low K/M product ratios in almost all the cases. However, the substrates (entries 6 and 7) which exhibited a lower K/M ratio in [bmim]Cl·$AlCl_3$, $N=0.67$, showed higher selectivities for the Knoevenagel product, i.e. a higher K/M ratio in [bpy]Cl·$AlCl_3$, $N=0.67$.

We also investigated Knoevenagel condensations of ketones with diethyl malonate. No reactions were observed in the cases of acyclic and cyclic ketones, under the conditions in which aldehydes gave almost quantitative conversions.[9] However, 2-cyclohexen-1-one spontaneously underwent the Michael reaction with diethyl malonate exclusively with no Knoevenagel condensation at all, yielding the Michael adduct characterised by ^1H NMR and MS m/z 256 (M^+) in almost quantitative yield. This observation prompted us to investigate the Michael addition of diethyl malonate with 1,3-diphenyl-2-propen-1-one, which at room temperature furnished the corresponding Michael adduct. Detailed investigations concerning Michael additions in these liquids are currently in progress.

In the case of 2-hydroxybenzaldehyde, the Knoevenagel condensation and transesterification led to the formation of 3-ethoxycarbonyl coumarin. To generalise the procedure and to demonstrate the ability of these liquids to catalyse the coumarin synthesis, various 2-hydroxyarylaldehydes were subjected to condensations with diethyl malonate[9] (Scheme 2), the results are summarised in Table 4. The substrates exhibited enhanced reactivity to such an extent that the reactions took barely a few minutes, furnishing 3-ethoxycarbonyl coumarins in good yields.

In conclusion, the two ionic liquids [bmim]Cl·$AlCl_3$, $N=0.67$ and [bpy]Cl·$AlCl_3$, $N=0.67$ served as an alternative media that catalysed Knoevenagel and Michael reactions, two synthetically useful reactions involving C–C bond formation. The synthesis of coumarins via Knoevenagel route is also demonstrated in these liquids. Considerable control over various products in these reactions can be exercised by variation of the parameters associated with the ionic liquid. The experimental procedure[9] is simple and timesaving, avoiding cumbersome water removal steps.

References

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4. Bigi, F.; Chesini, L.; Maggi, R.; Sartori, G. *J. Org. Chem.* **1999**, *64*, 1033 and references cited therein.
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7. Conversions in all cases were monitored with respect to the decay of an aldehyde on GC. Nucon 5700 chromatograph equipped with FID was employed for the analysis. The detector temperature was maintained at 270°C. The column was programmed with an initial temperature of 140°C and was increased thereafter to 270°C at the rate of 10°C min^{-1}. The column used was liquid phase ov-17 (length 6′).
8. Bergmann, E. D.; Ginsburg, D.; Pappo, R. *Organic Reactions*; Wiley: New York, 1959; Vol. X, p. 179.
9. Experimental procedure: In a typical experimental procedure, to the weighed quantity of ionic liquid, [bmim]Cl·$AlCl_3$, $N=0.50$–0.67 or [bpy]Cl·$AlCl_3$ $N=0.67$, an aldehyde and diethyl malonate were added in the molar ratio of 0.5:1.0:1.0 on a 5 mmol scale with respect to the aldehyde, unless otherwise stated in the text. All additions were carried out in an inert atmosphere glove box. The reaction commenced instantaneously making the reaction mixture highly viscous. The reaction was quenched after 5 min with 6N HCl in cold conditions. The product was extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried using anhydrous sodium sulphate, evaporated under reduced pressure and assayed on GC. The crude products were chromatographed using silica gel column chromatography to yield pure compounds that were characterised by IR, NMR, MS and physical constants.