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Hydrotalcite catalysis in ionic liquid medium: a recyclable reaction system for heterogeneous Knoevenagel and nitroaldol condensation

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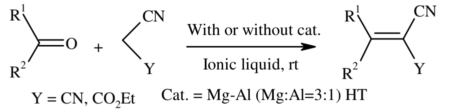
Abstract—Knoevenagel condensation proceeds efficiently in recyclable [bmim]PF_6 and [bmim]BF_4 without any catalyst, and hydrotalcites in ionic liquid serve as a safe and recyclable reaction system for both Knoevenagel as well as nitroaldol condensations.

Ionic liquids (ILs) are emerging as potential 'greener' alternatives to volatile organic solvents[1] and in recent years they have been used as environmentally benign media for several important reactions.[2] In continuation of our interest in using ionic liquids as a recyclable, eco-friendly alternative to organic solvents,[3] we report herein Knoevenagel reaction mediated by recyclable ILs and hydrotalcites in ILs as a heterogeneous, reusable catalyst system for Knoevenagel as well as nitroaldol reactions.

Heterogeneous catalysts are important not only from an economical viewpoint but also due to ease of handling, simple separation and reusability. Layered double hydroxides (LDH) or hydrotalcites (HT)[4] represent an efficient basic catalyst system, for epoxidation,[4a] Meerwein–Ponndorf–Verley reduction,[4b] cyanoethylation,[4c] aldol,[4d] nitroaldol[4e] and Knoevenagel[4e] condensations. The heterogeneous HT catalyst was recovered by simple filtration and activated for further use.[4b–e] We planned to devise a high-performance reusable reaction medium, with or without catalyst, that could be directly recycled for subsequent batches, without any activation.

Mg–Al (Mg:Al = 3:1) HT was prepared according to the original procedure of Miyata[5] and used without any pretreatment. Initially we carried out Knoevenagel condensations of aldehydes and ketones with active methylene compounds, a classical synthetic transformation to prepare electrophilic alkenes,[6] employing catalyic Mg–Al HT in ILs [bmim]PF_6 or [bmim]BF_4 (Scheme 1, Tables 1 and 2). The condensation of benzaldehyde with malononitrile in either of the ionic solvents [bmim][PF_6] or [bmim]BF_4 proceeded efficiently resulting in near quantitative yields of the product (Table 1, entries 1 and 3). A straightforward product isolation was achieved by the addition of ether or toluene, which generates a biphasic medium with a clear supernatant organic layer containing product and an ionic catalyst phase, ready for next use. Thus, the [bmim]BF_4–Mg–Al HT system was successfully recycled six times (entries 3–8) with no noticeable decrease in reactivity or yield of the reaction. The reaction system was equally efficient for the condensation of aldehydes with ethyl cyanoacetate (entries 9, 15–17). Ni–Al (Ni:Al = 3:1) HT was also efficiently used for the same purpose (Table 2, entry 6).

To our surprise, we observed that the condensation of aldehydes with malononitrile or ethyl cyanoacetate was taking place smoothly without any added catalyst, in either of the ionic solvents (Tables 1–3). In a typical experiment, 4-nitrobenzaldehyde was dissolved in [bmim]PF_6 or [bmim]BF_4 followed by the addition of malononitrile and the reaction mixture was stirred at rt



Scheme 1.

Keywords: Knoevenagel condensation; Nitroaldol condensation; Ionic liquid; Hydrotalcite; Catalysis.

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Table 1. Knoevenagel condensation of aromatic aldehydes (RCHO) in ionic liquids with or without Mg–Al HT

Entry	Substrate (R-CHO) R	Y	Ionic liquid	Time (h), Yield (%)[a]	
				With catalyst[b]	No catalyst[c]
1	Ph	CN	[bmim]PF_6	30 min, 98	1, 99
2				30 min, 96 (2. run)	
3			[bmim]BF_4	1, 99	2, 98
4				1.5, 96 (2. run)	
5				1, 97 (3. run)	
6				2, 94 (4. run)	
7				1, 94 (5. run)	
8				1, 92 (6. run)	
9	Ph	CO_2Et	[bmim]PF_6	30 min, 94	4, 98
10	4-$O_2NC_6H_4$	CN	[bmim]PF_6	20 min, 95	3, 100
					3, 96
					4, 98
11			[bmim]BF_4	3, 96	24, 98[d]
12					4, 98
13					3, 96
14					4, 94
15	4-$O_2NC_6H_4$	CO_2Et	[bmim]PF_6	30 min, 94	1, 96
16					1, 98
17			[bmim]BF_4	3, 95	

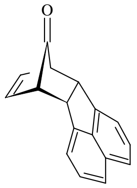
[a] Isolated yields of analytically pure products.

[b] All reactions were run using 0.5 mmol of aldehyde, 0.5 mmol of active methylene compound, 12 mg of Mg–Al HT in 1 mL of ionic liquid at rt.

[c] For [bmim]PF_6 at rt and for [bmim]BF_4 at 50 °C.

[d] At rt.

Table 2. Knoevenagel condensation of aldehydes and ketones with malononitrile in ionic liquids with or without Mg–Al HT

Entry	Substrate (R-CHO) R	Ionic liquid	Time (h), Yield (%)[a]	
			With catalyst[b]	No catalyst[c]
1	4-HOC_6H_4	[bmim]PF_6		2, 91
2		[bmim]BF_4	6, 91	4, 94
3	3-BrC_6H_4	[bmim]BF_4	2, 97	10, 95[d]
4			2, 98 (2. run)	3, 98
5	3,4,5-$(MeO)_3C_6H_2$	[bmim]PF_6		2, 97
6		[bmim]BF_4	3, 98[e]	5, 93
7			2, 98[e] (2. run)	4, 94
8	4-ClC_6H_4	[bmim]BF_4		3, 96
9	4-PhC_6H_4	[bmim]PF_6		2, 95
10				2, 96 (2. run)
11	C_6H_{13}	[bmim]BF_4	5, 93	
12	Me_2CH	[bmim]BF_4	5, 83	
13	Cyclohexanone	[bmim]BF_4	9, 91	
14		[bmim]BF_4	7, 93	

[a] Isolated yields of analytically pure products.

[b] All reactions were run using 0.5 mmol of aldehyde, 0.5 mmol of active methylene compound, 12 mg of Mg–Al HT in 1 mL of ionic liquid at rt.

[c] For [bmim]PF_6 at rt and for [bmim]BF_4 at 50 °C.

[d] At rt.

[e] Using 15 mg of Ni–Al HT.

to furnish the product in near quantitative yield. While the reaction was relatively slow at rt in [bmim]BF_4 (Table 1, entry 11) as compared to [bmim]PF_6, nonetheless an excellent yield of the product was obtained at 50 °C in a shorter reaction time (entries 12–14). To ensure that the traces of protic or acidic impurities that might be present in ILs are not responsible for the catalyst-free reaction, the ILs were passed through basic alumina, which gave essentially the same results. The ionic solvent was economically recycled several times,

Table 3. Knoevenagel condensation of different aldehydes with malononitrile in recycled ionic liquids without any catalyst

Entry	Substrate, RCHO	Cycle	[bmim]PF_6 rt, t/h, yield (%)[a]	[bmim]BF_4 50 °C, t/h, yield (%)[a]
1	4-$O_2NC_6H_4$	1	0.5, 99	3, 98
2	Ph	2	1, 96	7, 94
3	3,4,5-$(MeO)_3C_6H_2$	3	2, 93	4, 98
4	4-HOC_6H_4	4	2, 91	4, 95

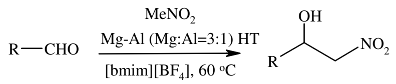
[a] Isolated yields of analytically pure products.

and Table 3 presents the efficient reprocessing of Knoevenagel condensations of different aldehydes in the same IL. To the best of our knowledge, this is the first report of a catalyst-free Knoevenagel reaction in ILs.[7]

The condensation of malononitrile with substituted benzaldehydes, aliphatic aldehydes and ketones, with or without the catalyst were investigated and the results are summarized in Table 2. The reactions using hydrotalcite catalyst were somewhat faster than the catalyst-free reactions.

We next examined the Henry reaction (nitroaldol) in IL over solid base hydrotalcite catalysts. The Henry reaction is a fundamental carbon–carbon bond forming reaction providing convenient entry to important building blocks such as nitro alkenes, β-amino alcohols and α-hydroxy carbonyl compounds.[8] To our knowledge, there is no literature report on nitroaldol reactions in ionic liquids, whereas aldol and asymmetric aldol condensations have been well studied in this medium.[9] Our results, summarized in Table 4, demonstrate that both aromatic and aliphatic aldehydes give excellent yields of products. Ni–Al (Ni:Al = 3:1) HT was also efficiently used and recycled to furnish the nitroaldol products. The reaction system was efficiently recycled for four cycles (Table 4, entries 4–7). Isobutyraldehyde furnished a 27:83 mixture of the corresponding nitroalkene and nitro aldol product upon direct distillation under reduced pressure from the reaction mixture. It is interesting to note the significant alteration in the diastereoselectivity, giving 48:52 of *syn anti* as compared to 0:100 reported[4e] for 4-nitrobenzaldehyde and nitroethane (Scheme 2). The reaction medium was efficiently recycled for four subsequent reactions without substantial change in diastereoselection.

Table 4. Nitroaldol reaction using Mg–Al HT in [bmim][BF_4][a]



Entry	Substrate, R	Time (h)	Yield[b] (%)
1	Ph	10	64
2	4-$O_2NC_6H_4$	7	81
3		(2. run), 9	83
4	4-$O_2NC_6H_4$[c]	6	93
5		(2. run), 9	91
6		(3. run), 9	87
7		(4. run), 11	85
8	4-IC_6H_4	10	81
9	3,4,5-$(MeO)_3C_6H_2$	20	43, 95[d]
10	$PhCH_2$	9	74
11	$CH_3(CH_2)_2$	5	81
12	Me_2CH	13	76[e]
13	$CH_3(CH_2)_5$–	6	73

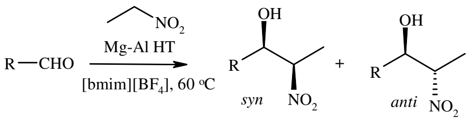
[a] All reactions were run using 0.5 mmol of aldehyde, 0.75 mmol of nitromethane, 19–30 mg Mg–Al HT in 1 mL of ionic liquid.

[b] Isolated yields of analytically pure products.

[c] Using Ni–Al HT.

[d] Based on starting material recovery.

[e] 27:83 mixture of 3-methyl-1-nitro-1-butene and nitroaldol product.



R	time (h)	cycle	yield (%)[a,b]	ratio
4-$O_2NC_6H_4$	5	1	73 (92)	48:52
	8	2	85 (94)	46:54
	10	3	84 (90)	45:55
	10	4	82 (91)	45:55
3-BrC_6H_4	8	1	81 (90)	41:59
	15	2	71 (81)	42:58

[a] isolated yields, [b] yields in parentheses is based on starting aldehyde recovered.

Scheme 2.

In summary, we have developed an eco-friendly catalyst-free reaction system for the Knoevenagel condensation. The efficiency of hydrotalcites as solid base catalysts in ILs as a safe and reusable media was demonstrated for the Knoevenagel and Henry reactions. Significant alteration in the diastereoselectivity was observed in the case of the nitroaldol reaction with nitroethane. The advantages include easy product isolation and catalyst as well as ionic solvent recycling.

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