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ORIGINAL ARTICLE

CsF/[bmim][BF_4]: An efficient and reusable system for Henry reaction

Pravin S. Shinde [a], Sandip S. Shinde [a], Satish A. Dake [a], Vinayak S. Sonekar [a], Satish U. Deshmukh [b], Vinod V. Thorat [b], Narsing M. Andurkar [a], Rajendra P. Pawar [b,*]

[a] *Organic Synthesis Laboratory, Department of Chemistry, Dnyanopasak College, Parbhani 431 401, India*
[b] *Department of Chemistry, Deogiri College, Station Road, Aurangabad 431 005, India*

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Abstract Cesium fluorides in ionic liquid [bmim][BF_4] have been used to promote the Henry reaction effectively. These reactions proceed smoothly and afford an excellent yield of the products.

1. Introduction

Alkali metal fluorides are the important source of fluorides, found abundantly in nature. Metal fluorides are widely used as important catalysts in different organic synthesis. Various fluoride catalyzed reactions have been studied and reported (Clark, 1980). Fluorides-resins (Fringuelli et al., 2008), potassium fluoride-alumina (Clark et al., 1997; Bergbreiter and Lalonde, 1987; Clark, 2000; Gibbs, 1983; Kabashima et al., 2000; Blass, 2002), cesium fluoride-alumina (Clacens et al., 2004), potassium fluoride-crown-6 (Belsky, 1977) and double layered hydroxide fluoride (Choudary et al., 2001) systems have been also used in different organic transformations. The basicity of fluoride salts used usually depends on the dissolving solvents. Due to their limited solubility in organic solvents; they are used with phase transfer catalysts (PTCs) and facilitate the reaction between the organic substrate and the inorganic salt (Desikan and Doraiswamy, 1995; McMorn and Hutchings, 2004).

Room-temperature ionic liquid is one of the leading areas in green chemistry (Sheldon, 2001; Welton, 1999), used as solvent and catalysis in different organic transformations (Shinde et al., 2009; Bhosale et al., 2006). Due to the nonvolatile nature, high polarity and non-mixing properties of imidazolium-based ionic liquids; they are used more efficiently in several reactions (Gu et al., 2007; Hagiwara et al., 2004).

Building blocks nitroalkanes are synthesized by Henry reaction for the formation of new C-C single and double bonds (Luzzio, 2001; Khan et al., 2004; Ballini et al., 2003; Ballini et al., 2005; Ballini and Palmieri, 2006; Ballini et al., 2008; Ballini et al., 2004; Ballini et al., 1987; Danilenko et al., 2002). Recently, these reactions have been reported using ionic liquids, task-specific ionic liquids (Burguete et al., 2008; Jiang et al.,

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* Corresponding author. Tel.: +91 9421003806; fax: +91 240 2359940.
E-mail address: rppawar@yahoo.com (R.P. Pawar).

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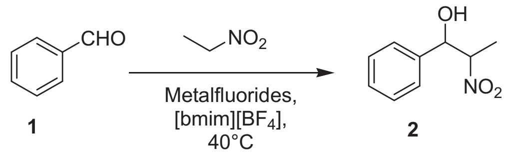


Scheme 1

2004; Wu et al., 2008) and water medium (Fan et al., 2008; Jyoti et al., 2008; Halimehjani and Saidi, 2008) extensively. However, ionic liquids and water mediated reactions create problems in product separation; especially when the product is polar and soluble in these solvents.

Herein, we investigated a new and simple protocol using alkali metal fluorides in the combination with [bmim][BF_4] ionic liquid as a catalyst for Henry reactions (Scheme 1).

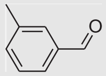
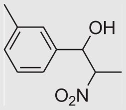
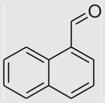
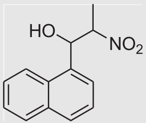
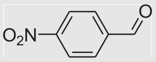
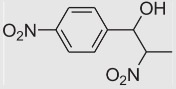
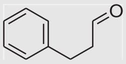
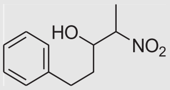
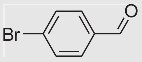
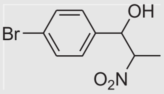
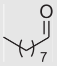
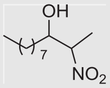
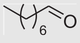
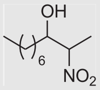
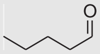
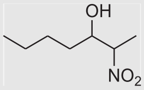
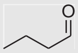
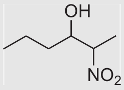
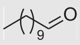
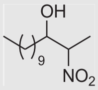
2. Experimental

All the chemicals were purchased from commercial sources and used without further purification. Flash chromatography was done using Merck silica gel 60 (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded on Varian Gemini-2000 (200 MHz) spectrometer.

2.1. General procedure for nitroaldol synthesis

To a mixture of aldehyde (2.0 mmol) and nitroalkane (2.2 mmol), [bmim][BF_4] (0.5 mmol) was added. The reaction mixture was stirred at 40 °C for 10 min and CsF (0.5 mmol) was added. The reaction mixture was further stirred for a specific time at 40 °C temperature (Table 1). Progress of the reaction was monitored on thin layer chromatography (TLC). On

Table 1 Henry reactions of nitroethane with various aldehydes at 40 °C.

Entries	Aldehydes	Products (2)	Time (h)	Yield (%)
1			6	82
2			6	68
3			4	77
4			6	83
5			4	82
6			6	70
7			8	82
8			3	80
9			3	92
10			12	55

[a] All reactions were carried out under the same condition as entry 4 in Table 3.

Table 2 Recovery of [bmim][BF_4] ionic liquid in the synthesis of nitroaldol.

Products (2) Entry No.	Percentage yield of [bmim][BF_4]		
	Recycle-1	Recycle-2	Recycle-3
1	82	81	81
4	83	81	81
9	92	91	90

completion of the reaction, the mixture was cooled, filtered, diluted with water (3 mL) and extracted with ethyl acetate (3 × 15 mL). Combined organic layer was dried over Na_2SO_4 and filtered. Solvent ethyl acetate was evaporated and the crude was purified by flash column chromatography. The water was evaporated from the aqueous layer to get an ionic liquid, which was further reused without change in its efficiency (Table 2). [Know compounds (3A, 5A),**[11b]** (4A, 6A, 8A, 9A)**[11c]**].

3. Results and discussion

In this protocol, the reactivity of various alkali metal fluorides like sodium fluoride, potassium fluoride, rubidium fluoride, and cesium fluorides were investigated in combination with ionic liquid [bmim][BF_4]. Table 3 illustrated the Henry reaction of benzaldehyde with nitroethane in the presence of alkali metal fluorides (0.5 equiv) and [bmim][BF_4] under various conditions. KF shows a significant conversion using this procedure, afforded 10% β-nitroalcohol after 12 h at 40 °C. Using NaF the same reaction did not proceed at all, after the same time period (entries 1 and 2). Fifth periodic alkali metal fluoride RbF made this reaction faster than KF; presumably due to loosely tightened ion pairs of RbF (compare entry 3 with 1, 2). Interesting results were obtained, when base CsF was used in the reaction as a catalyst. It afforded the desired product **2** (89%) without the formation of any side products. But the same reaction was not proceeding at all in the absence of CsF (entries 4, 5). The reaction conditions did not significantly influence the product formation, but the absence of [bmim][BF_4] significantly influenced the reaction rate after the same period of time (entries 6). The same reaction does not proceed at room temperature at all (entry 7). It should be noted that the use of [bmim][BF_4] as a solvent in the reaction affects the yield of the desired product **2**, even though starting benzaldehyde was consumed within a short time. A comparison study of entries 4 and 8 demonstrates that the catalytic amount 0.1 mL of [bmim][BF_4] is enough to proceed the reaction smoothly to offer a high yield of product **2**. To check the recycling activity of the catalyst, we carried out the same reaction by reusing the catalyst. The desired product formation takes place near about with the same yield (entry 8). Instead of nitroethane, the same reaction with nitromethane gave 60% yield of 2-nitro-1-phenylethanol (entry 9). These results show that RbF and CsF were more effective than KF; whereas, NaF was found to be ineffective. This dependence was attributed to increase solubility from NaF to CsF in combination with [bmim][BF_4] as a PTC.

We applied this protocol for the condensation of a variety of substituted aromatic and aliphatic aldehydes with nitroethane. The results are presented in Table 1. All the reactions were carried out under the same reaction conditions as for entry 4 in Table 3. Simple nitroethane gave fair to good results with both aromatic (entries 1–5) and aliphatic aldehydes (entries 6–10) using this method.

In summary, we developed an operationally simple and efficient methodology for nitro compound synthesis from several aldehydes and electrophilic alkenes, respectively using alkali metal fluorides with [bmim][BF_4] ionic liquid. All these reactions proceed smoothly to afford good yield of the desired products. Further studies to apply this protocol commercially and to derive some new methodologies are in progress.

4. Spectral data of selected compounds

4.1. 1-(3-Methylphenyl)-2-nitropropan-1-ol (entry 1, Table 2) as a yellow oil

^{1}H NMR ($CDCl_3$) δ 1.48 (d, J = 6.8 Hz, 3H), 2.34 (s, 3H), 2.60 (d, J = 3.4 Hz, 1H), 4.66 (qd, J = 3.7, 6.8 Hz, 1H), 5.34 (dd, J = 3.4, 3.7 Hz, 1H), 7.11–7.16 (m, 3H), 7.24 (d, J = 6.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 12.1, 21.4, 73.9, 87.5, 123.0, 126.6, 128.6, 129.3, 138.4, 138.5; Anal. Calculated for

Table 3 Nitroaldol reaction of benzaldehyde with nitroethane using various alkali metal fluorides.[a]

Entry	MF (0.5 equiv)	[bmim][BF_4] mL (0.5 equiv)	Time (h)	Yield 2 (%)[b]
1	NaF	0.1	12	–
2	KF	0.1	12	10[c]
3	RbF	0.1	06	80
4	CsF	0.1	06	89
5	CcF[c]	0.1	12	–
6	CsF[d]	–	06	trace
7	CsF[e]	0.1	06	62
8	CsF[f]	0.1	06	87
9	CsF[g]	0.1	06	73

[a] All reactions are carried out at 2.0 mmol of benzaldheyde, 2.2 mmol of nitroethane, [bmim][BF_4], using metal fluorides (MF).

[b] Isolated yield.

[c] Reaction was carried out in the absence of MF.

[d] Reaction was carried out in the absence of [bmim][BF_4].

[e] Reaction carried out at room temperature.

[f] Reaction was carried out with reused CsF/[bmim][BF_4] catalyst.

[g] Reaction was carried out in the presence of nitromethane in place of nitroethane.

$C_{10}H_{13}NO_3$; C, 61.53; H, 6.71; N, 7.18; found C, 61.88; H, 7.01; N, 6.89.

4.2. 1-(2-Nitro-1-propanol)-napthalene (entry 2, Table 2) colorless oil

^{1}H NMR ($CDCl_3$) δ 1.28 (d, J = 1.8 Hz, 3H), 2.68 (s, 1H), 5.14 (q, J = 3.4 Hz, 1H), 5.79–5.82 (m, 1H), 7.48–7.62 (m, 4H), 7.87–7.92 (m, 2H), 8.29 (d, J = 4.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) 16.8, 73.8, 88.4, 123.2, 125.3, 125.6, 126.1, 126.8, 129.1, 129.8, 130.8, 134.9, 134.0. Anal. Calculated for $C_{13}H_{13}NO_3$; C, 67.52; H, 5.67; N, 6.06; found C, 67.23; H, 6.01; N, 5.79.

4.3. 2-Nitrodecan-3-ol (entry 7, Table 2) as a colorless oil

^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 7.28 Hz, 3H), 1.15–1.21 (m, 10H), 1.35–1.38 (m, 2H), 1.45 (s, 3H), 3.1 (brs, 1H), 3.99–4.08 (m,1H), 4.42–4.46 (m, 1H). ^{13}C NMR (CDCl3) δ 12.1, 13.8, 15.8, 22.4, 25.5, 29.1, 31.5, 33.7, 72.8, 87.7. Anal. Calculated for $C_{10}H_{21}NO_3$; C, 59.08; H, 10.41; N, 6.89; found, C, 60.34; H, 10.09; N, 6.56.

4.4. 2-Nitrotridecan-3-ol (entry 10, Table 2) as a colorless oil;

^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.0 Hz, 3H), 1.22–126 (m, 16H), 1.43–1.51 (m, 2H), 1.54–1.57 (m, 3H), 2.48 (br. 1H), 3.91–4.17 (m, 1H), 4.52–4.54 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 12.4, 14.2, 16.3, 22.7, 25.2, 25.6, 29.3, 29.4, 29.5, 31.9, 33.0, 73.0, 87.7.; Anal. Calculated for $C_{13}H_{27}NO_3$; C, 63.64; H, 11.09; N, 5.71; found C, 64.02; H, 10.82; N, 5.42.

5. Conclusions

A simple and efficient protocol has been investigated to promote the Henry reactions effectively.

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