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Baylis–Hillman reaction in [bdmim][PF_6] ionic liquid

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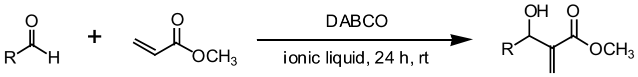
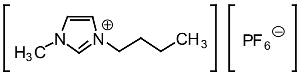
Abstract—A new use of ionic liquid [bdmim][PF_6] as solvent for the Baylis–Hillman reaction is presented. Unlike the commonly used [bmim][PF_6] that evidently reacts with electrophilic aldehydes under basic conditions, ionic liquid [bdmim][PF_6] is inert and the Baylis–Hillman reaction in [bdmim][PF_6] proceeds smoothly with better yield.

The Baylis–Hillman reaction has recently attracted much attention as a useful C–C bond-forming reaction, mainly because it readily undergoes the tandem Michael–aldol sequence reaction facilitated by a base to result in the formation of the β-hydroxy-α-methylene carbonyl compounds starting from simple acrylic compounds and aldehydes.[1] The adduct consists of rich functionalities, which can be employed for further transformations to lead to the preparation of, for example, the potent immunosuppressant (−)-mycestericin E and the plant cell wall biosynthesis inhibitor epopromycin B.[2,3] However, the Baylis–Hillman reaction often suffers from being inconveniently slow even for the most favorable systems. Acrylates with aldehydes in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) may require reaction times of days to weeks, and ketones are often unreactive.[1] Various efforts have been made to find effective catalysts and optimal experimental conditions to circumvent the sluggish nature of the reaction and to improve the overall efficiency of this α-substitution of acrylic compounds. Of nitrogen bases, DABCO,[4] 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[5] and most recently quinuclidine[6] are by far most effective. Physical methods such as high pressure[7] and microwaves[8] have also been recommended. Since polar solvents[6,9] such as methanol were known to accelerate the Baylis–Hillman reaction by stabilizing its polar reaction intermediate, room-temperature ionic liquids have recently been employed to facilitate the reaction (Scheme 1).[10]

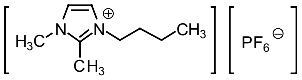


Scheme 1. DABCO-catalyzed Baylis–Hillman reaction of aldehydes.

Room-temperature ionic liquids are a new class of highly polar solvents that are entirely constituted of ions.[11] Ionic liquids have been considered as recyclable and environmentally friendly substitutes for volatile organic solvents, mainly owing to their attractive negligible vapor pressure, chemical and thermal stability, nonflammability, and high ionic conductivity. Because of these intriguing properties, ionic liquids have been found to be the solvents of choice for a large array of organic reactions.[11] Also, the high solubility of ionic liquids to many organic and inorganic compounds can in principle lead to enhanced rates and improved yields in reactions.[12] We report here that, in comparison with the popular 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]),[13] the Baylis–Hillman reaction proceeds smoothly and cleanly in a new ionic liquid, 1-*n*-butyl-2,3-dimethylimidazolium hexafluorophosphate ([bdmim][PF_6]),[14,15] with moderate to excellent yields.



[bmim][PF_6]



[bdmim][PF_6]

Keywords: Baylis–Hillman reaction; Ionic liquid.

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Recently, Afonso and Santos,[10c] and later Ko,[10a] reported that ionic liquids such as [bmim][PF_6] appeared to accelerate the rates of the Baylis–Hillman reactions studied. In addition, the reactions reported were, in general, low yielding. In those studies, gas chromatography was employed to quantitatively measure the conversion of the reaction and determine the rate acceleration by comparing the ratio of integration of the desired product and the starting aldehyde. Aggarwal et al.[10b] quickly and elegantly pointed out, however, that the ionic liquids used were all 1-*n*-butyl-3-methylimidazolium-based and, in the presence of bases such as DABCO or 3-hydroxyquinuclidine, the imidazolium moiety in ionic liquids could be deprotonated at its C-2 position and the resulting nucleophile directly reacted with and thereby consumed the aldehyde, leading to the misinterpretation of both the reaction rates and lower yields. Aggarwal, therefore, concluded that *the commonly used ionic liquids are not all inert to chemical reactions*. The apparent reactivity of [bmim][PF_6] under basic conditions prompted us to prepare [bdmim][PF_6] in which its C-2 carbon is methylated and to study its application to the Baylis–Hillman reaction and other organic reactions, with the ultimate goal to develop chemically inert ionic liquids. Our preliminary result of its use as solvent for the Baylis–Hillman reaction demonstrated that the [bdmim][PF_6] ionic liquid is indeed inert, while the [bmim][PF_6] ionic liquid was evidently reactive under our experimental conditions.

Table 1. Baylis–Hillman reaction of aliphatic, aromatic, and α,β-unsaturated aldehydes with methyl acrylate[a]

Entry	RCHO	Isolated yield (%)	
		[bmim][PF_6]	[bdmim][PF_6]
Aliphatic aldehyde			
1	Butyraldehyde	44	58
2	Propionaldehyde	29	59
3	Valeraldehyde	34	66
Aromatic aldehyde			
4	*o*-Anisaldehyde	50	61
5	*p*-Anisaldehyde	39	65
6	Benzaldehyde	63	79
7	*p*-Bromobenzaldehyde	52	74
8	*o*-Chlorobenzaldehyde	69	73
9	*p*-Chlorobenzaldehyde	66	99
10	*p*-Fluorobenzaldehyde	78	99
11	2-Furaldehyde	38	73
12	*o*-Nitrobenzaldehyde	45	79
13	2-Thiophenecarboxaldehyde	58	79
14	*p*-Tolualdehyde	57	80
15	3,4,5-Trimethoxybenzaldehyde	70	96
α,β-*Unsaturated aldehyde*			
16	*trans*-Cinnamaldehyde	23	57
17	Crotonaldehyde	18	27
18	3-Methylcrotonaldehyde	13	19

[a] The reaction condition: methyl acrylate, 190 μL (2.0 mmol); aldehyde, 1.0 mmol; DABCO, 2.0 mmol (224 mg); ionic liquid, 100 μL; ambient temperature, 24 h.

We investigated reactions of methyl acrylate and DABCO with a variety of aldehydes such as aliphatic, aromatic, and α,β-unsaturated aldehydes in both [bdmim][PF_6] and [bmim][PF_6] ionic liquids (Table 1).[16] All reactions were performed at ambient temperature for 24 h. Simple aliphatic and aromatic aldehydes worked well (entries 1–15). Our results shown in Table 1 clearly indicate that, regardless of the nature of aldehydes studied, the Baylis–Hillman reactions were all with higher yields in [bdmim][PF_6] than in [bmim][PF_6] ionic liquid. In cases of aromatic aldehydes in [bdmim][PF_6], good to excellent yields were obtained (61–99%, entries 4–15). Both electron-deficient and electron-rich aromatic aldehydes work equally well in this new ionic liquid. It is noted that *p*-anisaldehyde previously described as a slow reacting aldehyde in the Baylis–Hillman reaction was found to give satisfactory yield in [bdmim][PF_6] after only 24 h (65%, entry 5).[6] As expected, aliphatic aldehydes with enolizable protons tended to produce less Baylis–Hillman adducts, presumably due to possible competing aldol reactions under basic conditions (58–66%, entries 1–3). The fact of higher reaction yields obtained in [bmim][PF_6] than in [bdmim][PF_6] under our experimental conditions is in line with what Aggarwal previously suggested that [bmim][PF_6] ionic liquid is chemically reactive.[10b] To verify that the low-yielding reaction in [bmim][PF_6] was in part attributed to its apparent reactivity with the electrophilic aldehydes, we conducted the 2-furaldehyde reaction with methyl acrylate in the presence of DABCO as the representative example (Fig. 1). Results of the HPLC analysis of the reactions clearly demonstrated that, for the reaction performed in [bmim][PF_6], the Baylis–Hillman product was contaminated with the aldehyde-conjugated [bmim][PF_6] adduct (**1**) (Fig. 1c). As expected, the reaction carried out in [bdmim][PF_6] proceeded smoothly and was free of **1** (Fig. 1b). The chemical nature of the adduct **1** can be readily verified and unambiguously confirmed using proton NMR (Fig. 2). The disappearance of the C-2 proton signal at δ 9.07 ppm indicated the site of conjugation of [bmim][PF_6] with the aldehyde. For the results shown in Table 1, ionic liquid of only limited amount (100 μL, corresponding to 0.33 equiv) was used. If 1 equiv of ionic liquid (300 μL) was employed for 2-furaldehyde reaction with methyl acrylate and DABCO, a dramatic difference in the isolated yields from two ionic liquids was observed: 27% in [bmim][PF_6] and 88% in [bdmim][PF_6], respectively. This result confirmed again that [bmim][PF_6] ionic liquid is chemically reactive under basic conditions. Finally, the usefulness of this new ionic liquid in the Baylis–Hillman reaction is illustrated with α,β-unsaturated aldehydes, compounds that often are either poor substrates or unreactive. Low to moderate isolated yields were obtained after 24 h (19–57%, entries 16–18). Among α,β-unsaturated aldehydes tested, cinnamaldehyde reaction in [bdmim][PF_6] gave the best result.

Using the reaction of *p*-chlorobenzaldehyde with methyl acrylate and DABCO as the representative example, we also demonstrated that the ionic liquid [bdmim][PF_6] was a useful solvent substitute and could be recycled for the Baylis–Hillman reaction (Table 2).[17] As shown in Table 2, the Baylis–Hillman reaction was readily carried out at room temperature for 24 h and the ionic liquid

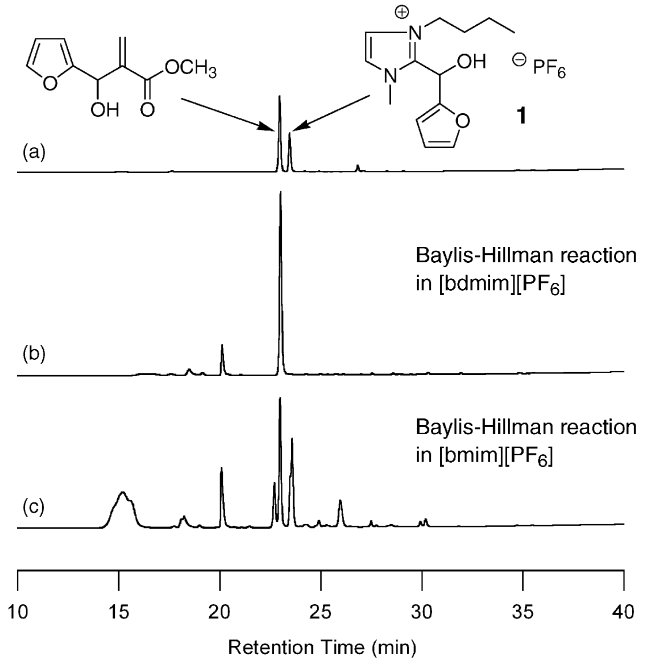

Figure 1. HPLC analysis of crude reaction mixtures from the Baylis–Hillman reaction of 2-furaldehyde with methyl acrylate and DABCO both in [bmim][PF$_6$] and in [bdmim][PF$_6$]. (a) Co-injection of purified Baylis–Hillman adduct and aldehyde-conjugated [bmim][PF$_6$] (**1**). (b) The crude mixture of the reaction carried out in [bdmim][PF$_6$]. (c) The crude mixture of the reaction carried out in [bmim][PF$_6$]. Each separation was carried out using a reversed phase column (Mightysil RP-C18 GP) under the same conditions. The analysis was monitored at 254 nm.

could be reused at least four times. In addition, no apparent loss of yield of the reaction was observed.

In summary, the use of ionic liquid [bdmim][PF$_6$] for base-mediated reactions such as the Baylis–Hillman reaction is recommended as a substitute for the commonly employed [bmim][PF$_6$], due to the fact that the deprotonated 1-butyl-3-methylimidazolium could readily react with electrophilic reactants, for example, aldehyde present in reaction mixtures. We are currently investigating the general applicability of this room-temperature ionic liquid for use in other important reactions, including multi-step combinatorial organic synthesis.

Table 2. Reuse of ionic liquid [bdmim][PF$_6$][a]

Cycle	Isolated yield (%)
1	94
2	95
3	95
4	98

[a] The experimental condition: *p*-chlorobenzaldehyde, 422 mg (3 mmol); methyl acrylate, 600 μL (6 mmol); DABCO, 672 mg (6 mmol); [bdmim][PF$_6$], 300 μL; room temperature, 24 h.

Acknowledgements

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References and notes

1. (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891; (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001–8062.
2. Iwabuchi, Y.; Furukawa, M.; Esumi, T.; Hatakeyama, S. *Chem. Commun.* **2001**, 2030–2031.

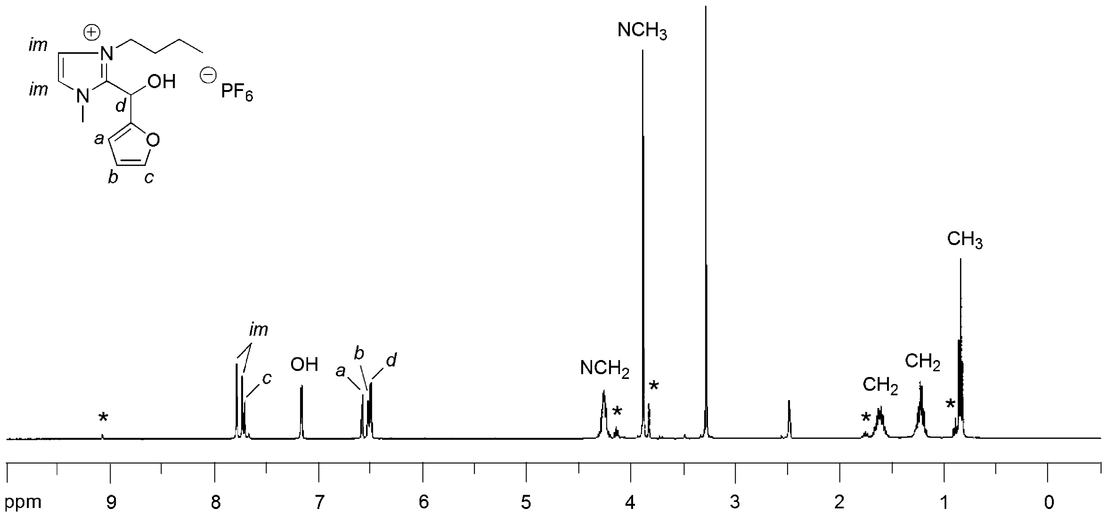

Figure 2. ^{1}H NMR spectrum of the 2-furaldehyde-conjugated [bmim][PF$_6$] adduct, **1**, in DMSO-d_6. In the spectrum, the adduct **1** was associated with a small amount of [bmim][PF$_6$] ionic liquid whose NMR signals were indicated as asterisks (*).

3. Iwabuchi, Y.; Sugihara, T.; Esumi, T.; Hatakeyama, S. *Tetrahedron Lett.* **2001**, *42*, 7867–7871.
4. Rafel, S.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 1521–1522.
5. Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311–2312.
6. Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 692–700.
7. (a) Hill, J. S.; Isaacs, N. S. *J. Chem. Res. (S)* **1988**, 330–331; (b) Hill, J. S.; Isaacs, N. S. *Tetrahedron Lett.* **1986**, *27*, 5007–5010.
8. Kundu, M. K.; Mukherjee, S. B.; Balu, N.; Padmakumar, R.; Bhat, S. V. *Synlett* **1994**, 444.
9. Aggarwal, V. K.; Dean, D. K.; Mereu, A.; Williams, R. *J. Org. Chem.* **2002**, *67*, 510–514.
10. (a) Kim, E. J.; Ko, S. Y.; Song, C. E. *Helv. Chim. Acta* **2003**, *86*, 894–899; (b) Aggarwal, V. K.; Emme, I.; Mereu, A. *Chem. Commun.* **2002**, 1612–1613; (c) Rosa, J. N.; Afonso, C. A. M.; Santos, A. *Tetrahedron* **2001**, *57*, 4189–4193.
11. (a) Zhao, H.; Malhotra, S. V. *Aldrichim. Acta* **2002**, *35*, 75–83; (b) Hagiwara, R.; Ito, Y. *J. Fluorine Chem.* **2000**, *105*, 221–227; (c) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083; (d) Holbrey, J. D.; Seddon, K. R. *Clean Products Process.* **1999**, *1*, 223–236.
12. Fraga-Dubreuil, J.; Bazureau, J. P. *Tetrahedron Lett.* **2000**, *41*, 7351–7355.
13. Huddleston, J. G.; Willauer, H. D.; Swatloski, R. P.; Visser, A. E.; Rogers, R. D. *Chem. Commun.* **1998**, 1765–1766.
14. The ionic liquid [bdmim][PF_6] was previously prepared and used solely to study its affinity with water: Cammarata, L.; Kazarian, S. G.; Salter, P. A.; Welton, T. *Phys. Chem. Chem. Phys.* **2001**, *3*, 5192–5200.
15. Synthesis and characterization of [bdmim][PF_6] ionic liquid: To a round-bottomed flask containing 1,2-dimethylimidazole (20 g, 0.21 mol) was added 1-bromobutane (31.4 g, 0.23 mol). The mixture was stirred and refluxed at 80 °C for 2 h. Using iodine for compound visualization, TLC could be employed to monitor the progress of the reaction. The resulting viscous reaction solution was allowed to cool to room temperature and mixed with water (104 mL), and then washed five times with ethyl acetate (300 mL). The residual ethyl acetate present in aqueous solution was removed by heating to 60 °C under reduced pressure. To the solution containing 1-*n*-butyl-2,3-dimethylimidazolium bromide ([bdmim][Br]), was added slowly the hexafluorophosphoric acid (39.8 mL, 0.27 mol). The reaction mixture was allowed to proceed the ion exchange for 12 h at ambient temperature. The upper acidic aqueous layer was decanted and the lower ionic liquid portion was then washed with water until the washings were no longer acidic. The resulting ionic liquid was further heated at 80 °C in vacuo to remove water. The desired product, 1-*n*-butyl-2,3-dimethylimidazolium hexafluorophosphate ([bdmim][PF_6]), was obtained in 61% overall yield (34.0 g). ^1H NMR (DMSO-d_6, 400 MHz) δ 0.90 (t, $J = 7.4$ Hz, CH_3, 3H), 1.28 (m, CH_2, 2H), 1.68 (m, CH_2, 2H), 2.56 (s, CH_3, 3H), 3.73 (s, NCH_3, 3H), 4.09 (t, $J = 7.3$ Hz, CH_2, 2H), 7.59 (d, $J = 2.0$ Hz, =CH, 1H), 7.62 (d, $J = 2.0$ Hz, =CH, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 9.21, 13.48, 18.99, 31.27, 34.77, 47.43, 120.98, 122.43, 144.
16. General procedure for the Baylis–Hillman reaction: To a stirred mixture of the substrate aldehyde (1.0 mmol) and methyl acrylate (2 mmol) were added DABCO (2 mmol) and ionic liquid (100 µL). The homogeneous reaction mixture was stirred at ambient temperature for 24 h and, if needed, the progress of the reaction could be monitored by TLC. The reaction mixture was first diluted with dichloromethane, extracted with 10% citric acid (3×), dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. The resulting crude oil was further purified by flash column chromatography on silica gel, using the mixed solvent of ethyl acetate and hexane (1:3 or 1:4, v/v), to give the desired product. All desired products were fully characterized by ^1H NMR, ^{13}C NMR, MS, and HRMS. Yields refer to spectroscopically and chromatographically homogeneous (>95%) materials.
17. Reuse of [bdmim][PF_6] ionic liquid: Methyl acrylate (600 µL, 6 mmol) was added to a stirred solution of *p*-chlorobenzaldehyde (422 mg, 3 mmol) and DABCO (672 mg, 6 mmol) in [bdmim][PF_6] (300 µL) at ambient temperature. The Baylis–Hillman reaction was allowed to proceed for 24 h at ambient temperature. The reaction mixture was first diluted with dichloromethane, washed with 10% citric acid three times, and then concentrated under reduced pressure. The product in the ionic liquid solution was extracted using diethyl ether (5×) and the combined ethereal mixture was reduced to dryness in vacuo. If necessary, flash chromatography was employed to purify the Baylis–Hillman adduct. A new portion of reactants and DABCO was added to the recycled ionic liquid and the cycle was repeated.