

Zhang-Gao Le^{a,b,c} Zhen-Chu Chen^{a,b*} Yi Hu^b and Qin-Guo Zheng^d^a Department of Chemistry, Zhejiang University (xi xi campus), Hangzhou, 310028, P. R. China
E-mail: zhenchuc@mail.hz.zj.cn^b Ningbo Institute of Technology, Zhejiang University, Ningbo, 315100, P. R. China^c Department of Applied Chemistry, East China Institute of Technology, Fuzhou, 344000, P. R. China^d Pharmaceutical Science Research Institute, Aston University, Aston Triangle, Birmingham B4 TET, UK

Phthalic anhydride reacts rapidly with Aromatic and aliphatic amines in ionic liquid [Bmim][PF₆] or [Bmim][BF₄] at 130 °C to give *N*-aryl and *N*-alkylphthalimides in excellent yields.

J. Heterocyclic Chem., **42**, 735 (2005).

The development of simple, efficient and general synthetic methods for widely used organic compounds from readily available reagent is one of the major challenges in organic synthesis. Imide derivatives are among such types of organic compounds with numerous applications in biological properties [1] and synthetic [2] and polymer [3] chemistry. To date, most commonly *N*-substituted phthalimides are formed by direct dehydrative condensation of an amine with phthalic anhydride [1-5]. But those methods needed high temperature and long reaction times. For example, synthesis of *N*-phenylphthalimide [1e] needed at 160-180 °C for 2 h. Recently, improvement of classical methods has been obtained using Lewis-acid catalysis [4a], phthalic anhydride and azide with *in situ* reduction by condensation using chlorotrimethylsilane-sodium iodide [4b] and microwave irradiation [5]. Known literature methods have been limited due to harsh reaction conditions [4], lengthy reaction times or poor yields [5b]. Therefore the development of a simple, relatively mild, efficient and environmentally benign synthesis of *N*-alkyl and *N*-arylphthalimides is a major challenge. When writing this article, we found a literature reported by Li [6], in which *N*-arylphthalimides were synthesized in ionic liquid [Bmim][PF₆], however, this method required long reaction times.

In recent years, room temperature ionic liquids are attracting increasing interest as "green" recyclable alternatives to classical molecular solvents for synthetic organic chemistry [7]. To date, some of the more important reactions have been carried out and investigated in ionic liquids, and it has been demonstrated that, in some cases, reactions in ionic liquids show accelerated rates compared with those obtained using conventional solvents [8]. Our recent interest has been in the development of synthetic methods using ionic liquids as novel environmentally benign reaction media and promoters [9].

We report now the synthesis of *N*-alkyl and *N*-arylphthalimides by the direct dehydrative condensation reac-

tion of phthalic anhydride and the corresponding amine in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ([Bmim][PF₆]) at 130 °C (Scheme 1). We found that the reaction of phthalic anhydride and aniline proceeds very rapid in the ionic liquid [Bmim][PF₆] at 130 °C and is complete within 5 min to give *N*-phenylphthalimide in nearly quantitative yield. In similar fashion, the reaction of phthalic anhydride with a variety of amines proceeded rapidly under these reaction conditions and the products were obtained in excellent yields. These results are summarized in Table 1. All the products gave satisfactory mp, IR and ¹H NMR data, which were consistent with literature data.

As can be seen from Table 1, the reaction is general and applicable to aliphatic and aromatic amine bearing various different groups such as chloro, methyl, hydroxy, methoxy and nitro groups. This method is even effective on glycine and L-phenylalanine (entry 8,9). The related ionic liquid [Bmim][BF₄] showed the same effectiveness (Table 1, Entries 1,2,7). The experimental procedure is very simple and convenient. All of the tested reactions could be completed within 5 min. Since the products did not solve in the ionic liquid, they were easily separated by simple filtration. The rest of the viscous ionic liquid was thoroughly washed with a mixture of ether-ethyl acetate (1:1) followed by drying at vacuum. The recovered solvent can be reused with no appreciable decrease in yield. The representative results are summarized in Table 2.

Scheme 1

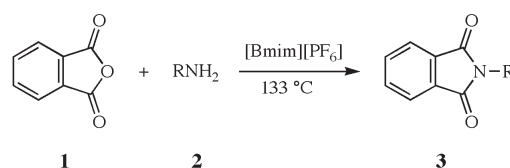


Table 1

The Reaction of Phthalic Anhydride with Amine in Ionic Liquid [Bmim][PF₆] [a]

Entry	Amine (RNH ₂)	M.p.(°C)	Lit. mp(°C)	Yield (%)
1	C ₆ H ₅ NH ₂	207.9-208.9	206-208 [6]	98 (97 [b])
2	<i>p</i> -ClC ₆ H ₅ NH ₂	196.8-197.9	192-194 [6]	97 (98 [b])
3	<i>p</i> -CH ₃ C ₆ H ₅ NH ₂	204.6-205.2	203-204 [6]	95
4	<i>p</i> -NO ₂ C ₆ H ₅ NH ₂	269.8-271.4	264-266 [6]	98
5	<i>m</i> -HOC ₆ H ₅ NH ₂	173.7-173.9	173-174 [6]	96
6	4,5-dimethoxyaniline	243.0-243.9	242-243.5 [10]	90
7	C ₆ H ₅ CH ₂ NH ₂	115.9-116.0	114-115 [9a]	96 (94 [b])
8	NH ₂ CH ₂ COOH	194.7-195.6	194-197 [2a]	94
9	L-phenylalanine	177.4-178.1	175-177 [11]	91
10	n-C ₄ H ₉ NH ₂	31.8-32.5	32 [9a]	95
11	NH ₂ CH ₂ CH ₂ OH	126.1-126.7	126 [12]	94

[a] All reactions were run with phthalic anhydride (2 mmol), amine (2 mmol) in ionic liquid [Bmim][PF₆] (2 mL) at 130 °C for 5 min; [b] In ionic liquid [Bmim][BF₄]

Table 2

Recycling of [Bmim][PF₆] in *N*-Benzyl Phthalimide [a]

Entry	Cycle	Yield (%)
1	1	96
2	2	97
3	3	95

[a] All reactions were run with phthalic anhydride (2 mmol), benzylamine (2 mmol) in ionic liquid [Bmim][PF₆] (2 mL) at 130 °C for 5 min.

In conclusion, we have demonstrated that the reaction of phthalic anhydride with amine can be performed rapidly in the ionic liquids [Bmim][PF₆] or [Bmim][BF₄] at 130 °C to give the corresponding imide derivatives in excellent yields. The ionic liquid plays the dual role of solvent and promoter. The substrates show significant increase in reactivity thus improving the yield substantially. The present method has many obvious advantages compared to that of classical methods reported in literature, including its high efficiency, operational simplicity, environmentally benign character and its ability to be recycled. Further studies to expand this methodology for the preparation of other cyclic imide derivatives is now under way in our laboratory.

EXPERIMENTAL

Melting points were determined on digital melting point apparatus and were not corrected. Infrared spectra were recorded on a VECTOR22 (Bruker) infrared spectrometer, nuclear magnetic resonance spectra were recorded on AVANCE DMX 400 (Bruker) spectrometer. The ionic liquids [bmim][BF₄] and [bmim][PF₆] were synthesized according to reported procedures [13]. All other materials are commercially available and were used without further purification.

General Procedure for the *N*-Alkylation of Heterocyclic Compounds.

Phthalic anhydride (2 mmol) and the corresponding amine (2 mmol) were added to the ionic liquids [Bmim][PF₆] or [Bmim][BF₄] (2 mL) as appropriate, the mixture was stirred at 130 °C for 5 min and cooled to room temperature. The solid was collected by filtration and washed with AcOEt to give the corresponding pure *N*-alkyl or *N*-arylphthalimide. In some case, the product was further purified by recrystallization from a mixture of EtOH-AcOEt. After collecting the product by filtration, the remaining viscous ionic liquid was further washed with a mixture of ether-ethyl acetate (1:1) and dried at 80 °C under reduced pressure and reused in subsequent runs.

REFERENCES AND NOTES

- [1a] J. M. Chapman, P. J. Vorstad, G. H. Cocolas and I. H. Hall, *J. Med. Chem.*, **26**, 237 (1983); [b] M. K. Hargreaves, J. G. Pritchard and R. Dave, *Chem. Rev.*, **70**, 439 (1970); [c] Y. Shibata, K. Sasaki, Y. Hashimoto and S. Iwasaki, *Chem. Pharm. Bull.*, **44**, 156 (1996); [d] H. Miyachi, A. Azuma, A. Ogasawara, E. Uchimura, N. Watanabe, Y. Kobayashi, F. Kato, M. Kato and Y. Hashimoto, *J. Med. Chem.*, **40**, 2858 (1997).
- [2a] T. Vidal, A. Petit, A. Loupy, and R. N. Gedye, *Tetrahedron*, **56**, 5473 (2000); [b] L. M. Lima, P. Castro, A. L. Machado, C. A. M. Fraga, C. Lugnier, V. L. G. Moreas and E. Barreiro, *J. Bioorg. Med. Chem.*, **10**, 3067 (2002).
- [3] R. Jayakumar, R. Balaji and S. Nanjundan, *Eur. Polym. J.*, **36**, 1659 (2000).
- [4a] P. Y. Reddy, S. Kondo, T. Toru and Y. Ueno, *J. Org. Chem.*, **62**, 2652 (1997); [b] A. Kamal, E. Laxman, N. Laxman, N. V. Rao, *Tetrahedron Lett.*, **39**, 8733 (1998).
- [5a] B. M. Barchin, A. M. Cuadro and A. B. Julio, *Synlett*, 343 (2002); [b] S. Chandrasekhar, N. B. Padmaja and A. Raza, *Synlett*, 1597 (1999).
- [6] M. Y. Zhou, Y. Q. Li and X. M. Xu, *Synth. Commun.*, **33**, 3777 (2003) and references therein.
- [7a] Welten, T. *Chem. Rev.*, **99**, 2071 (1999); [b] P. Wassercheid and W. Keim, *Angew. Chem. Int. Ed.*, **39**, 3772 (2000); [c] R. Sheldon, *Chem. Commun.*, 2399 (2001); [d] C. M. Gordon, *Appl. Catal.*, **A**, 101 (2001); [e] H. Olivier-Bourbigou and I. Magna, *J. Mol. Catal.*, **A**, 419

(2002); [f] D. Zhao, M. Wu, Y. Kou and E. Min, *Catal Today*, **74**, 157 (2002).

[8a] Ionic liquids in Synthesis, P. Wassercheid and T. Welton, Eds: VCH Wiley: Weinheim, Germany, 2002; [b] h. Ohara, H. Kiyokane, and T. Itoh, *Tetrahedron Lett.*, **43**, 3041 (2002).

[9a] Z. G. Le, Z. C. Chen, Y. Hu and Q. G. Zheng, *Synthesis*, 208 (2004); [b] Z. Liu, Z. C. Chen and Zheng, Q. G. *Org. Lett.*, **5**, 3321 (2003); [c] Y. Y. Xie, Z. C. Chen and Q. G. Zheng, *Synthesis*,

1505 (2002); [d] C. Su, Z. C. Chen and Q. G. Zheng, *Synthesis*, 555 (2003).

[10] R. J. Perry and S. R. Turer, *J. Org. Chem.*, **56**, 6573 (1991).

[11] J. Kehler and E. Breuer, *Synthesis*, 1419 (1998).

[12] R. Jayakumar, R. Balaji and S. Naniundan, *Eur. Polym. J.*, **36**, 1659 (2000).

[13] G. S. Owens and M. M. Abu-Omer, *J. Mol. Cata. A: Chem.*, **187**, 215 (2002).