

Ionic liquids as solvent for efficient esterification of carboxylic acids with alkyl halides

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The selective esterification of carboxylic acid derivatives with a variety of alkyl halides was carried out using ionic liquid as solvent in the presence of triethylamine. The reaction was found to proceed under relatively mild conditions with excellent conversions (up to 99%) and selectivities. The ionic liquid was recycled and reused.

Key Words: Ionic liquids, green solvent, esterification, imidazolidine, catalyst.

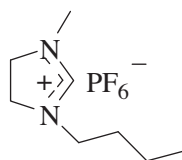
Introduction

Esterification of carboxylic acids is one of the most important reactions in organic synthesis, and more environmentally benign alternative approaches to those currently used by the chemical industry are in great demand.^{1,2} Conventional esterification is conducted with excess carboxylic acids (or alcohols) against a counterpart in the presence of an acid catalyst, or with stoichiometric dehydrating reagents or activated carboxylic acid derivatives. The use of excess substrates wastes these compounds, and the use of stoichiometric dehydrating reagents or activated carboxylic acid derivatives produces significant amounts of byproducts from the reagents. Salts of the carboxylic acids may also be converted into esters by heating them with alkyl halides. This reaction is most successful with primary halides, but secondary and tertiary halides given ester with olefin as a byproduct by loss of hydrogen halide from the alkyl halide. The contamination of crude products with excess substrates or byproducts requires substantial materials, energy, and time for the purification of ester. Recently, efforts

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have been made in order to replace the conventional methods and to develop clean catalytic methods such as supported sulfuric acid or solid superacid and by carrying out the reaction in ionic liquids for the syntheses of organic esters.^{3–16}

Ecological and economic problems impose more severe requirements on the application of alternative solvents in technology and large scale organic synthesis.¹⁷ An ideal solvent should be nonvolatile and low-toxic, highly resistant to chemical agents and temperature, and reusable. Ionic liquids have been described as one of the most promising new reaction media and meet the above requirements to a considerable extent. Unique properties, such as high thermal stability, negligible vapor pressure, easy handling, and the ability to dissolve both organic and inorganic compounds contribute to their increasing applications. On the other hand, immiscibility of ionic liquids with a number of organic solvents provides a solution for biphasic separation of the desired products. To date, ionic liquids have been successfully applied to effect a wide series of organic reactions, such as carbonylation, etherification, reduction of aldehydes and ketones, rearrangements, cycloaddition, and polymerization. Herein, we report our results about the use of the ionic liquid (**IL**, 1-butyl-3-methyl-4,5-dihydroimidazolium hexafluorophosphate) as reaction medium to carry out esterification of carboxylic acids by reacting with alkyl halides.^{18–23}



IL

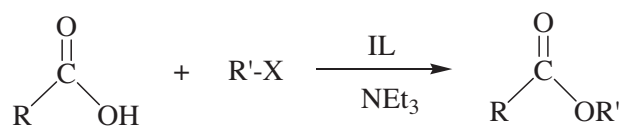
Experimental

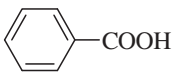
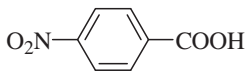
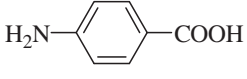
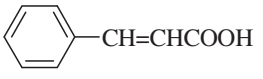
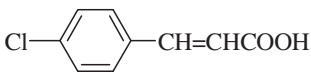
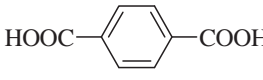
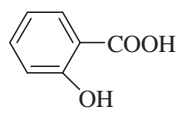
Manipulations were prepared with standard Schlenk techniques under an inert atmosphere of nitrogen with previously dried solvents. The **IL** was prepared with known methods.²⁴ Flash chromatography; Merck silica gel (230-400 mesh) eluent ethylacetate/hexane (1:5). ¹H-NMR (300 MHz) and ¹³C-NMR (75.5 MHz) spectra were recorded using a Bruker AM 300 WB FT spectrometer with chemical shifts referenced to residual solvent CDCl₃. Microanalyses were performed by the IBTAM-Malatya analysis center.

General Procedure for the Esterification Reaction

Into a vial was loaded the carboxylic acid derivatives (1.00 mmol), the alkyl halides (1.00 mmol), ionic liquid (2 mL) and triethylamine (1.00 mmol). The mixture was stirred at 60 or 90 °C for 1 h. Formation of a white solid, presumably Et₃N.HX, is a useful indication of the reaction progress. After 1 h heating, the mixture was cooled to room temperature. The product was extracted with ethyl acetate (3 × 10 mL). The crude product was finally purified by flash chromatography on silica gel with EtOAc/hexane (1/5 v/v) as eluent.

The **IL** was easily recycled. After the reaction, with the mixture decanted, the rest of the viscous **IL** was thoroughly washed with EtOAc (2 × 10 mL) and reused after drying in a vacuum (0.01 Torr, 25 °C). The

Table. Esterification of carboxylic acids with alkyl halides in ionic liquid.^a


| Entry | RCO ₂ H | R'X | Yield(%) ^b |
|-------|---|--|--------------------------|
| 1 | | | no reaction ^c |
| 2 | | ButBr | no reaction ^c |
| 3 |  | | no reaction ^d |
| 4 | | | 98 |
| 5 | | C ₆ H ₅ CH ₂ Cl | 99 |
| 6 | | 2,4,6-(CH ₃) ₃ C ₆ H ₂ CH ₂ Cl | 99 |
| 7 | | (CH ₃) ₂ CHBr | 99 ^e |
| 8 | | BrCH ₂ CH ₂ CH ₂ Br | 98 |
| 9 | | BrCH ₂ CH ₂ CH ₂ CH ₂ Br | 99 |
| 10 |  | ButBr | 99 |
| 11 | | C ₆ H ₅ CH ₂ Cl | 99 |
| 12 | | 2,4,6-(CH ₃) ₃ C ₆ H ₂ CH ₂ Cl | 94 |
| 13 |  | (CH ₃) ₂ CHBr | 99 ^e |
| 14 | | H ₃ CCH ₂ CH ₂ CH ₂ Br | 88 |
| 15 | | (CH ₃) ₂ CHBr | 97 ^e |
| 16 |  | ButBr | 99 |
| 17 | | C ₆ H ₅ CH ₂ Cl | 99 |
| 18 | | 2,4,6-(CH ₃) ₃ C ₆ H ₂ CH ₂ Cl | 99 |
| 19 |  | (CH ₃) ₂ CHBr | 99 ^e |
| 20 | | ButBr | 99 |
| 21 | | C ₆ H ₅ CH ₂ Cl | 99 |
| 22 |  | (CH ₃) ₂ CHBr | 98 ^e |
| 26 | | ButBr | 92 |
| 27 | | C ₆ H ₅ CH ₂ Cl | 98 ^f |
| 28 | | (CH ₃) ₂ CHBr | 99 ^{e,f} |
| 29 | HO ₂ CCO ₂ H | ButBr | 98 ^f |
| 30 | HO ₂ C(CH ₂) ₂ CO ₂ H | ButBr | 99 ^f |
| 31 | HO ₂ C(CHOH) ₂ CO ₂ H | ButBr | 99 ^f |
| 32 | HOCH ₂ CO ₂ H | ButBr | 87 |
| 33 |  | ButBr | 99 |

^aAt 60 or 90 °C in **IL**; at 1 h; IL/acid = 5; RX/acid = 1; NEt₃/acid = 1. ^bIsolated yield. ^cIn the presence of THF or toluene instead of ionic liquid and NH₄F as catalyst. ^dIn the absence NEt₃. ^eAt 60 °C. ^fDi alkylation; 2 h.

IL was utilized repeatedly more than 3 times in the esterification of benzoic acids with alkyl halides with the conversions being unchanged.

Results and discussion

Esterification reactions of carboxylic acids with primary and secondary alkyl halides in the presence of triethylamine were carried out in **IL**. The results are listed in Table. Excellent yields and perfect selectivity were obtained in all cases. Olefins were not detected as elimination products from the secondary alkyl halides. Since the products were weakly soluble in the ionic liquid, they were easily separated by simple extraction with ether and purified by flash chromatography on silica gel with the eluent system of ethylacetate/hexane (1:5). The structure of the esters obtained was confirmed by NMR. As shown in Table, in the absence of the IL or NEt₃ as reaction medium or as base, respectively, reactions do not proceed (Entries 1-3). The ratio NEt₃/acid is 1.

The results in Table show that the esterification of aromatic, aliphatic, and α,β -unsaturated acids with the halides was satisfactory. The hydroxy group of aromatic acid (Entry 33) and aliphatic acids (Entries 31-32) did not take part in the esterification. In the reaction of *p*-phthalic, oxalic, and succinic acid monoesterification products were detected (Entries 26-30). However, the monoester/diester ratio depends on the reaction time. It is worth noting that dibromides gave the desired diesters in high yields (Entries 8, 9).

Conclusion

We have demonstrated that the ionic liquid (**IL**) can be successfully used for esterification reactions involving carboxylic acids and a variety of alkyl halides in the presence of weak base NEt₃. The reaction was found to proceed with high conversions in relatively short reaction times and at lower temperatures. The process is also significant from the view point of pollution control since the ILs can be recycled.

Acknowledgments

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References

1. Grasa, G. S.; Singh, R.; Nolan, S. P. *Synthesis* **2004**, 971-985.
2. Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606-5655.
3. McNulty, J.; Cheekoori, S.; Nair, J. J.; Larichev, V.; Capretta, A.; Robertson, A. J. *Tetrahedron Lett.* **2005**, *46*, 3641-3644.
4. Duan, Z.; Gu, Y.; Deng, Y. *J. Mol. Cat. A* **2006**, *246*, 70-75.
5. Raab, T.; Bel-Rhlid, R.; Williamson, G.; Hansen, C. E.; Chaillot, D. *J. Mol. Cat. B* **2007**, *44*, 60-65.
6. Yoshion, T.; Imori, S.; Togo, H. *Tetrahedron* **2006**, *62*, 1306-1317.

7. Li, X.; Eli, W. *J. Mol. Catal. A Chem.* **2008**, *279*, 159-164.
8. Ishihara, K.; *Tetrahedron* **2009**, *65*, 1085-1109.
9. Villorbina, G.; Tomas, A.; Escriba, M.; Oromi-Farrus, M.; Eras, J.; Balcelles, M.; Canela, R. *Tetrahedron Lett.* **2009**, *50*, 2828-2830.
10. Nakamura, Y.; Maki, T.; Wang, X.; Ishihara, K.; Yamamoto, H. *Adv. Synth. Catal.*, **2006**, *348*, 1505-1510.
11. Handy, S.T. *Chem. Eur. J.* **2003**, *9*, 2938-2944.
12. Shaw, J. E.; Kunerth, D. C.; Sherry, J. J. *Tetrahedron Lett.* **1973**, *9*, 689-692.
13. Deng, Y.; Shi, F.; Beng, J.; Qiao, K. *J. Mol. Catal. A Chem.* **2001**, *165*, 33-36.
14. Cole, C. C.; Jensen, J. L.; Ntai, I.; Tram, K. L. T.; Weaver, K. J.; Forbes, D.C.; Davis, J. H. *J. Am. Chem. Soc.* **2002**, *124*, 5962-5963.
15. Zhu, H. P.; Tang, J.; He, M. Y. *Green Chem.* **2003**, *5*, 38-39.
16. Dubreuil, J. F.; Bourahla, K.; Rahmouni, M.; Bazureau, J. P.; Hamelin, J. *Catal. Commun.*, **2002**, *3*, 185-190.
17. Olivier-Bourbigou, H.; Magna, L. *J. Mol. Catal. A Chem.* **2002**, *182*, 419-437.
18. Borodkin, G. I.; Shubin, V. G. *Russ. J. Org. Chem.* **2006**, *42*, 1745-1770.
19. Welton, T. *Chem. Rev.* **1999**, *99*, 2071-2083.
20. Howarth, J.; Hanlon, K.; Fayne, D.; McCormac, P. *Tetrahedron Lett.* **1997**, *38*, 3097-3100.
21. Brinchi, L.; Savelli, G. G. *Tetrahedron Lett.* **2003**, *44*, 2027-2029.
22. Sheldon, R. *J. Chem. Soc.*, **2001**, 2399-2407.
23. Parvulescu, V. I.; Hardacre, C. *Chem. Rev.* **2007**, *107*, 2615-2665.
24. Ozdemir, İ.; Demir, S.; Gök, Y.; Çetinkaya, E.; Çetinkaya, B. *J. Mol. Catal. A* **2004**, *222*, 97-102.