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# Efficient esterification of carboxylic acids with alkyl halides catalyzed by fluoride ions in ionic liquids

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**Abstract**—Ionic liquids based on 1,3-dialkylimidazolinium methanesulfonate have been used as efficient reusable reaction media in the esterification of several carboxylic acids with alkyl halides catalyzed by fluoride ions. The method has wide applicability, and it is mild and green; it is useful for the protection of acids, via ester formation, for alkali labile molecules.

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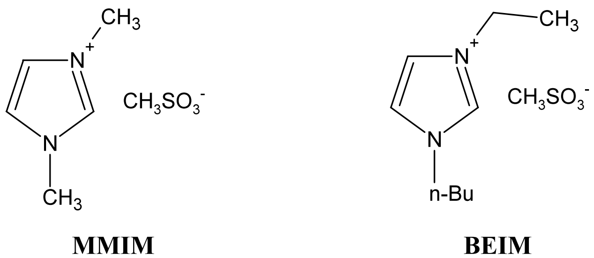
As part of a wide research program aimed at investigating structure–properties relationships for novel ionic liquids (IL), we have recently reported[1] our results about the preparation of new systems, as 1,3-dimethylimidazolinium (MMIM) and 1-butyl-3-ethylimidazolinium (BEIM) methanesulfonates (Scheme 1). The use of ionic liquids has recently received much attention for a series of advantages over organic solvents, such as low vapor pressure, recyclability, high thermal stability and ease of handling, other than the fact that ionic liquids often can act as catalysts and not only as reaction medium. All these properties make these systems very good candidates for application in developing environmentally benign chemical processes, and, nowadays, ILs are widely used as greener alternatives to classical volatile organic solvents in chemical transformations.[2] Our systems, BEIM and MMIM, have features quite useful for their use as reaction media. They have an inert anion, and are easy of handling; they are liquid at moderate temperature (ca. room temperature for BEIM and 82°C for MMIM); they are insoluble in a wide range of solvents useful for extraction such as *n*-hexane, diethyl ether, ethyl acetate, and this makes the work-up procedures quite easy. In fact, although by GC/MS analysis quantitative yields may be reported, actual isolated yields are often significantly lower, and mixtures of solvents have to be carefully searched for a satisfactory extraction of products.[3] Furthermore, these IL are prepared with a procedure that avoids several drawbacks often encountered in synthesis of ionic liquids, such as the use of large excess of toxic organic solvents, the separation of by-products, heat supply for several hours.[2] Our procedure, already published,[1] gives a high yield of IL in short time, without any by-product; it doesn't make use of energy supply because reaction itself, exothermic, provides the necessary heat; it is simple involving only one step. Moreover, the procedure has recently been improved with respect to that published, and now ethyl acetate is used as solvent, instead of toxic 1,1,1-trichloroethane.



**Scheme 1.** 1,3-Dimethylimidazolinium methanesulfonate (MMIM) and 1-butyl-3-ethylimidazolinium methanesulfonate (BEIM).

In our recent work, we used BEIM and MMIM as efficient systems for the esterification of carboxylates with alkyl halides, in mild conditions, with facile isolation of products and reuse of the reaction media.[1] Although this reaction has interesting uses, it has no applicability if the substrate has functional groups labile to alkaline conditions. Therefore, herein we report our results about the use of the same ionic

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*Keywords*: ionic liquids; esterification; carboxylic acid; nucleophilic substitution; fluoride ion.

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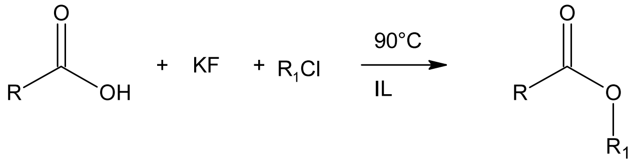
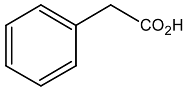
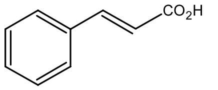
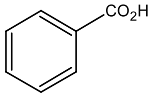
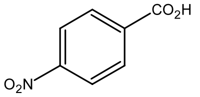
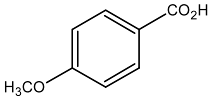
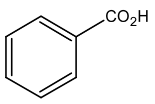
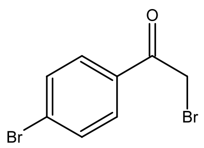


**Scheme 2.** Esterification of carboxylic acids with an alkyl halide.

liquids as reaction media to carry out esterification of carboxylic acids by reaction with alkyl halides. This reaction represents a fundamental transformation in organic synthesis, especially important when considering protection of the carboxylic acids,[4] and alternatives to the most common method which makes use of diazomethane are important, because the high toxicity of this reagent excludes large-scale operations. The main problem is the activation of the nucleophile. Clark et al. showed KF and also CsF to be effective in activate this reaction:[5] in fact they showed that in fluoride-carboxylic acid systems in a polar aprotic solvent such as DMF there is a very strong H-bond between the fluoride the anion and the acid hydroxy-proton.[6] This H-bond directs electrons from the electron-rich fluoride anion to the organic part of the complex, activating the nucleophile. These salts allowed the preparation of several kinds of esters, using DMF as solvent.[5,7] However, a solvent such as DMF has operational inconveniences and other systems are being looked for: for instance, more recently, activation by fluoride ions has been achieved under solid–liquid phase-transfer conditions in THF[8] and by the system CsF–Celite in $CH_3CN$.[9]

Herein we report the use of ionic liquids as reaction media for esterification of carboxylic acids with alkyl halides in presence of KF (Scheme 2). This reaction medium should allow solubilization of both fluoride salt and organic molecules, and has several advantages over the use of organic solvents such as THF, DMF and $CH_3CN$. The procedure we developed is operationally

**Table 1.** Esterification of carboxylic acids with alkyl halides in ionic liquid[a]

| Entry | Carboxylic acid | RX | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | $CH_3CO_2H$ | $PhCH_2Cl$ | 2 | >95[b] |
| 2 | $(CH_3)_3$-C-$CO_2H$ | ″ | ″ | >95[b] |
| 3 | $CH_3(CH_2)_2CO_2H$ | ″ | ″ | >95[b] |
| 4 | $CH_3(CH_2)_2CO_2H$ | ″ | ″ | 76[c] |
| 5 | $CH_3(CH_2)_{10}CO_2H$ | ″ | ″ | 83 |
| 6 | $CH_3(CH_2)_{10}CO_2H$ | ″ | 3 | >95[b] |
| 7 | COOH-$(CH_2)_4$-$CO_2H$[d] | ″ | ″ | >95[b] |
| 8 |  | ″ | 2 | >95[b] |
| 9 |  | ″ | ″ | >95[b] |
| 10 |  | ″ | ″ | >95[b] |
| 11 |  | ″ | ″ | >95[b] |
| 12 |  | ″ | ″ | >95 |
| 13 |  |  | ″ | >95[b] |

[a] at 90°C in MMIM; IL/acid = 5; Substrate/acid = 1.1; KF/acid = 2

[b] yields of isolated products

[c] KF/acid = 1.5

[d] IL/acid = 10; Substrate/acid = 2.1; KF/acid = 4

simple, fast safe, and allows reuse of the reaction medium.[†]

Table 1 summarizes the results of non-optimized conditions for reactions of alkyl halides with a variety of carboxylic acids and shows that the desired esters were generally obtained in excellent yields, usually bigger than 95%. Yields reported are based on GC analysis; but yields by weight were also evaluated (with complete extraction of the products) and were quantitative like the GC data. The structure of esters obtained was confirmed by NMR. The procedure gives similarly excellent results both in excess or in defect of the acid. The second case is useful for protection of the carboxylic group. Both ionic liquids (MMIM and BEIM) gave good yields and we therefore used extensively MMIM, which is cheaper, and easier to handle.

The procedure was successfully tested with several carboxylic acids. Aliphatic acids give good yields, be they liquid (acetic, trimethylacetic, butyric, entries 1–4), or even solid ones, with quite a long chain (entries 5, 6), but in this case a slightly longer reaction time is required to obtain a high yield. Also, dicarboxylic acids are successfully used (adipic acid, entry 7), provided that a factor of 2 was considered in the ratios of the reagents and of the IL: the reaction time used was 3 h. Acids containing aromatic moiety such as phenylacetic (entry 8), *trans* cinnamic (entry 9), benzoic and some of their derivatives (entries 10–12) give also excellent yields.

The amount of ionic liquid used, as reaction media is generally small, the ratio of IL/acid is 5. The ratio KF/acid is also small, 2: attempts to lower it to values smaller than 2 reduced the yield (entries 3, 4). As the alkyl halide, we generally used benzyl chloride, but we also tried *p*-bromo-phenacyl bromide (entry 13); both are useful and widely used in protection routes. In all cases, the halogen exchange reaction (Cl–F) is limited to <2%, as shown by results from GC analysis. However, it has recently been shown that this reaction is also activated using KF in ionic liquids, but conditions are quite different from ours, because the ionic liquid was not the reaction medium, but was used with a large excess of acetonitrile and water.[10]

In the absence of the ionic liquid as reaction medium, reactions do not proceed. We tried reactions in the presence of KF and without ionic liquid, and also in ionic liquid but without KF. In the first case, reactions of liquid $PhCH_2Cl$ with both liquid acetic acid (the mixture is heterogeneous, but can be magnetically stirred), and solid benzoic acid (the mixture is quite heterogeneous, and cannot be magnetically stirred) were tried, and no reaction occurred in either case in the experimental conditions that give quantitative yields in the presence of ionic liquid. In the second case, we also tried both kinds of acids (acetic and benzoic), and in this case, no reaction occurred in the experimental conditions that give quantitative yields in the presence of KF.

Furthermore, after reaction, it was possible to reuse the IL in a further run: after extraction with diethyl ether, the ionic liquid is dried under vacuum (to eliminate traces of the solvent) and simply reused.

We think that this new approach for the synthesis of esters and protection of carboxylic acids offers many advantages over classical procedures. Our method does not require the use of alkali at any stage, provides high yield in short times, can be accomplished under mild and safe conditions, without volatile solvents and the reaction medium can be recycled. The method has proven to have validity in defect of the acid, and is useful for protection purposes, even in multifunctional molecules eventually alkali-labile. We are currently investigating the extension of this method to multifunctional molecules, including the objective of regio- chemo- and stereoselectivity.

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[†] Procedure for esterification in an ionic liquid. In a dried (in oven at 120°C) 4-ml vial, a mixture of ionic liquid and the carboxylic acid was magnetically stirred for ca. 15 min until the acid was dissolved. Potassium fluoride, dried at 200°C and thereafter kept in the presence of $P_2O_5$, was then added under nitrogen. The mixture was then heated to 90°C (the mixture is not perfectly homogeneous, but fluid) and magnetically stirred for 10–15 min and the alkyl halide was added. The mixture was stirred for the required time. After ca. 1 h the mixture became quite viscous and heterogeneous. At the end of reaction, after cooling to room temperature, $^t$Bu–benzene was added, as internal standard; water was then added, and the mixture was extracted with diethyl ether (3×10 ml). The combined organic extracts were washed with sodium bicarbonate, dried over $Na_2SO_4$, and analyzed by GC. When yields by weight were determined, no internal standard was added at the end of reaction, and the organic solvent was eliminated from combined extracts by rotatory evaporation. After reaction, it was possible to reuse IL in a further run: after extraction with diethylether, the ionic liquid was dried under vacuum (to eliminate traces of the solvent), and benzoic acid and benzyl chloride reloaded, but no KF was reloaded. This reuse gave 60% yield by weight of benzyl benzoate. This process has to be optimized, as regards reaction time, and because of problems arising from heterogeneity of the reaction mixture during the second run.

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