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## Convenient Esterification of Carboxylic Acids by S<sub>N</sub>2 Reaction Promoted by a Protic Ionic-Liquid System Formed in Situ in Solvent-Free Conditions

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# CONVENIENT ESTERIFICATION OF CARBOXYLIC ACIDS BY $S_{\rm N}2$ REACTION PROMOTED BY A PROTIC IONIC-LIQUID SYSTEM FORMED IN SITU IN SOLVENT-FREE CONDITIONS

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#### **GRAPHICAL ABSTRACT**

R-COO<sup>-</sup> HN<sup>+</sup>(Et)<sub>3</sub> + ArCH<sub>2</sub>Cl  $\xrightarrow{2h, 90^{\circ}C}$  R-COOCH<sub>2</sub>Ar + <sup>+</sup>NH(Et)<sub>3</sub> Cl<sup>-</sup> (PILs)

**Abstract** The reaction of esterification of benzoic acid with benzyl chloride was chosen as a model reaction to study the esterification by  $S_N 2$  promoted by tertiary amine as deprotonating agent. The use of ionic liquid (IL) 1,3-dimethylimidazolium methanesulfonate [MMIm][OMs] as reaction medium has proven to give quantitative yield of the ester, but interestingly the reaction does occur even in solvent-free conditions, where the acid + the amine form a liquid system (a protic IL) in situ. This last methodology was extended to several carboxylic acids in conditions of atom economy (i.e., without excess of any reagent), giving moderately good yields of esters (54–78%) recovered by weight in pure form.

**Keywords** Esterification; methanesulfonate anion; nucleophilic substitution; protic ionic liquids; solvent-free reaction; triethylamine

#### INTRODUCTION

Esterification is an important reaction widely used for the protection or manipulation of the carboxylic acid functional group. Esterification is also important in the industrial synthesis of various products, some of which are high production volume (HPV) chemicals.<sup>[1–3]</sup> Among the several synthetic procedures of esterification there is the nucleophilic substitution of carboxylate salts with alkylating agents, such as alkyl halides, sulfates, and phosphates.<sup>[4–6]</sup> This procedure is attractive especially because alkyl halides are cost-effective starting materials.

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However, so far, industrial application is limited due to drawbacks. In fact, this reaction is usually carried out in dipolar aprotic solvents (dimethylformamide [DMF], dimethylacetamide [DMA], hexamethylphosphoramide [HMPA]) where both the salts and the alkylating agent are soluble, and phase-transfer catalysis has also been used.<sup>[7]</sup> The main drawbacks of this method are the use of toxic volatile dipolar aprotic solvents and the difficulty of obtaining efficient carboxylate salts, especially in multifunctional molecules. The carboxylate anion can also be generated in situ by reaction of a base with the carboxylic group. The chosen base should have reduced nucleophilicity to avoid competition with the carboxylate anion towards the alkylating agent. As an example, nonquaternizable tertiary amines<sup>[8]</sup> or 1,8-diazabicy-clo[5.4.0]undecen-7-ene (DBU) in benzene<sup>[9]</sup> have been used. Also in this case organic volatile solvents have to be used, and furthermore base separation from the crude product is another major problem. Alternatively, the carboxylic group has been activated through the fluoride anion.<sup>[10,11]</sup>

Most of the recent research work dealing with esterification has been associated with the desire to advance benign and sustainable chemical technologies.<sup>[12]</sup> In fact, replacement of conventional organic solvents by new reaction media such as water or ionic liquids (ILs) has been extensively studied, as shown in the review of Otera and Nishikido.<sup>[1]</sup> In fact, ILs are organic nonvolatile salts, liquid at or near room temperature; nowadays they are considered good candidates in developing environmentally benign chemical processes and are widely used as "greener" alternative to classical volatile organic solvents.<sup>[13–17]</sup> Furthermore, their physical and chemical properties can be tailored to facilitate the reactivity of specific reactions. ILs have proven utility in improving various procedures of esterification,<sup>[1,18,19]</sup> including carboxylate alkylation.<sup>[1,20–23]</sup> In this regard, we have previously reported our results about the use of ILs 1,3-dimethylimidazolinium [MMIm][MsO] and 1-butyl-3-ethylimidazolinium [BEIm][MsO] methanesulfonates as efficient systems for the esterification of carboxylates with alkyl halides, in mild conditions, and also for esterification of carboxylic acids by reaction with alkyl halides activated by KF, with chemoselectivity in the cases of hydroxybenzoic acid and amino acids.<sup>[24–28]</sup>

In continuation of our research on the use of ILs in preparation of esters, we started a study about esterification of carboxylic acids with alkyl halides in the presence of tertiary amine as deprotonating agent. Deprotonating action of sterically hindered tertiary amines has already been used in the literature for this kind of reaction, using only one kind of ionic liquid (1-butyl-3-methyl-4,5-dihydroimidazolinium hexafluorophosphate) as reaction medium,<sup>[29]</sup> and for other reactions, for instance, to obtain phenyl ethers in solvent-free condition.<sup>[30]</sup> The initial aim of our investigation was a comparison of dipolar aprotic solvents generally used for such kinds of reactions, such as dimethylsulfoxide (DMSO), DMF, and CH<sub>3</sub>CN, and the use of IL of different structures, with variations in both the nature of the anion and the cation of the IL, as shown in Scheme 1. During the experimental work, we found out, with surprise, that the model reaction, esterification of benzoic acid with benzyl chloride in the presence of triethylamine, could be also carried out in solvent-free conditions, without molecular solvent or ionic liquid. As far as we know, there are not examples of this reaction carried out in solvent-free conditions in the literature.

Actually, esterification via  $S_N 2$  nucleofilic substitution reaction has been carried out in solvent-free conditions but the reaction between carboxylate-based



Scheme 1. Chemical structures and acronyms of ILs used in this work.

ionic liquids with alkyl halides has been used.<sup>[31]</sup> Therefore it was necessary to prepare the corresponding ionic liquids with the appropriate carboxylate as counterion, and globally two synthetic steps were involved: the quaternization of tertiary amine and the subsequent ion exchange reaction to introduce the carboxylate anion.

The solvent-free procedure developed by us is more convenient and immediate, relying on simple salification of the carboxylic acid with a tertiary amine. Therefore herein we report the procedure that was developed in solvent-free conditions.

#### **RESULTS AND DISCUSSION**

Herein, we report for the first time a fast reaction for esterification of carboxylic acid with benzyl chloride in the absence of any solvent and ionic liquid, with amine as base used to form the carboxylate salt in situ (Scheme 2).

Initially we used the reaction of benzyl chloride (widely used in protection routes) with solid benzoic acid, in the presence of triethylamine (TEA), as a model reaction to screen a series of reaction media (molecular solvents and ionic liquids). Table 1 summarizes the results of nonoptimized conditions. The use of different molecular solvents did not lead to good results, except DMF and DMSO, which have good performance (>75%, Table 1, entries 4 and 5) but are quite harmful. Various types of ionic liquids were tested, and results in Table 1 show that the nature of the anion varied with the widely used tetrafluoroborate [BF<sub>4</sub>], hexafluorophosphate [PF<sub>6</sub>], bis(trifluromethylsulfonyl)imide [NTf<sub>2</sub>], and methanesulfonate [MsO] playing important roles, and excellent yields (95%) are obtained only with methanesulfonate as counterion (Table 1, entry 10). Variations in the cation from [BMIm] to [MMIm] and to tetrabutylammonium, [TBMA] led to even better results, with quantitative yields in the last two cases (Table 1, entries 11 and 12). More interesting, we found out that the reaction occurred with excellent yield (Table 1, entry 13) in the absence of any molecular or IL solvent. The addition of the TEA to solid benzoic acid

R-COOH + ArCH<sub>2</sub>CI  $\xrightarrow{N(R)_3}$  R-COOCH<sub>2</sub>Ar + <sup>+</sup>NH(R)<sub>3</sub> CI

Scheme 2. General scheme for esterification reaction.

Entry	Reaction medium	Yield (%)	
1	Water	15	
2	CH <sub>3</sub> CN	55	
3	Dioxane	16	
4	DMF	79	
5	DMSO	75	
6	Toluene	4	
7	[BMIm][BF <sub>4</sub> ]	77	
8	[BMIm][PF <sub>6</sub> ]	82	
9	[BMIm][NTf <sub>2</sub> ]	75	
10	[BMIm][MsO]	95	
11	[MMIm][MsO]	100	
12	[TBMA][MsO]	100	
13	None	96	

Table 1. Screening of different reaction media for the model reaction of benzyl chloride with benzoic acid in the presence of triethylamine<sup>a</sup>

<sup>*a*</sup>Temperature = 90 °C; reaction time = 2 h; amine/benzyl chloride/benzoic acid = 1.2:1.1:1.0; IL = 0.3 g; molecular solvent = 3 mL.

formed a liquid system at reaction temperature, which can be considered a protic IL formed in situ. This allowed us to carry out the reaction in a liquid system with magnetic stirring, with a simple procedure.

The procedure was thereafter tested with variation of the amine structure. Variations introduced were aimed at shifting the basicity/nucleophilicity ratio of the amine towards the basicity, and steric hindrance around nitrogen was the main factor considered. An increase in the alkyl chain length in aliphatic acyclic tertiary amines led to an unexpected decrease of the amine performance in IL: In fact, with  $N(n-Pr)_3$  the product yield was 90%. Introduction of oxygen atom was also tested and triethanolamine, which is very useful because of its lower toxicity,<sup>[32]</sup> but it led to product formation in only moderate yield, 53%.

This solvent-free procedure was finally tested with different acids to assess the scope of the reaction. With the aim of using the procedure for preparation of esters, yields by weight were evaluated and conditions of atom economy were used (i.e., without any reagent in excess). Results are shown in Table 2, where melting points of carboxylic acids are also reported. For all tested acids, at reaction temperature 90°C with molar ratio carboxylic acid/TEA 1:1, the reaction mixture was liquid, except with isonicotinic acid. In these conditions of atom economy the yield of the model reaction is less than in conditions used in the reaction reported in Table 1 (with an excess of the amine and a little excess of the benzyl chloride): In fact the model reaction gives a yield of only 64% in atom economy conditions (Table 2, entry 1), but it can be considered good because it is in terms of pure recovered ester. The procedure gives similar yields (ca. 65%) with the shortest of the aliphatic acids tested, and also with highly hindered acids such as pivalic acid (Table 2, entries 2 and 4). This last result is interesting because carboxylate alkylation is generally negatively affected by steric hindrance in the acid.<sup>[44]</sup> For the other acids tested, different kinds of structural variations were introduced, such as double bond, aromatic moiety, substituents in the aromatic ring, and others, mainly chosen to have a high melting point

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Table 2. Esterification of carboxylic acids with benzyl chloride in the presence of triethylamine in solvent-free conditions<sup>a</sup>

Entry	Carboxylic acid	Acid mp (°C)	Ester yield (%)	Ref.
1	Соон	121–125	64	[33]
2 3	НСООН СН <sub>3</sub> СООН СН <sub>3</sub>	8.2–8.4 16.2	66 68	[34] [35]
4	н₃с——соон	32–35	63	[36]
5	H <sub>3</sub> C H <sub>3</sub> C COOH	-34,5	56	[35]
6		-5	54 <sup>b</sup>	[37]
7	Соон	45–48	78	[38]
8	СООН	132–135	62	[39]
9	СООН	76–78	70	[40]
10	СООН	130	75	[41]
11	COOH	138–140	78	[39]
12	Соон	158–161	65	[42]
13	O <sub>2</sub> N COOH	237–240	74	[33]
14	Соон	>300	40	[43]

<sup>&</sup>quot;Isolated yields; all mixtures of these acids are liquid at temperature=90°C; reaction temperature = 90 °C; reaction time = 2 h; amine = benzyl chloride = benzoic acid = 1 mmol. The structures of esters were identified through the comparison of <sup>1</sup>H NMR spectra data with those reported in literature. <sup>b</sup>Yield after purification by chromatography column.

of the acid up to  $300 \,^{\circ}$ C. The systems carboxylic acid +triethylamine are always liquid at  $90 \,^{\circ}$ C. The reaction tolerates double bonds (Table 2, entry 6 and 8), the phenolic hydroxyl group in salicylic acid (Table 2, entry 12), and yields are generally moderately good (54–78% of recovered pure ester) in a short reaction time (2 h) a part from the isonicotin acid, but in this case the system was quite viscous.

We may say that alkylation of several carboxylic acid in the presence of TEA can be carried out in solvent-free conditions, with a protic ionic liquid system formed in situ. According to green chemistry principles, organic synthesis in the absence of solvent is of great value. The method in solvent-free conditions was used in atom economy conditions (none of reagents in excess) giving moderately good yields (54–78%) in short times, under mild and safe conditions, with most of the several carboxylic esters tested.

#### EXPERIMENTAL

Ionic liquids were prepared by procedures reported previously in the literature.<sup>[25,45]</sup> All other reagents, carboxylic acids, amines, benzyl chloride, *t*-butyl-benzene, and organic solvents were of analytical grade, purchased from commercial sources (Sigma-Aldrich). Melting points were determined with a Barloworld Scientific Stewart SMP3 apparatus and are uncorrected. Gas chromatography (GC) analyses were performed with an Agilent 6850 Series II Network GC instrument (column DB-35MS 1 30 m, d 0.32 mm, film 0.25  $\mu$ m). Thin-layer chromatography (TLC) was performed on silica gel on aluminum foil. <sup>1</sup>H NMR spectra were registered on a Bruker 200-MHz instrument using CDCl<sub>3</sub> as solvent. Chemical shifts are given in parts per million (ppm) relative to the signal of TMS.

#### Esterification in IL or in Molecular Solvents

The amount of 0.3 g of IL was weighed in a screw-capped 3-ml vial, equipped with a magnetic stirrer; thereafter, the carboxylic acid was added, and then the amine was introduced by a syringe (TEA/benzoic acid = 1.2:1.0). The mixture was magnetically stirred and heated to 90 °C until a clear colorless liquid phase was obtained. Finally, benzyl chloride (BnCl/benzoic acid 1.1:1 molar ratio) was added by means a syringe to the homogenous mixture. At the end of reaction, after cooling to rt, water and ethyl ether were added to the reaction mixture, and the mixture was transferred as quantitatively as possible (rinsing with both water and ethyl ether were carried out) to a separatory funnel, where also *t*-butylbenzene was added, as internal standard. The organic phase was washed twice with water (10 mL), twice with NaHCO<sub>3</sub> solution, and twice with 3 M HCl, and with water again until neutrality; it was thereafter dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and analyzed by GLC.

For reaction in traditional molecular solvents, the amount of 1 mmol of carboxylic acid was weighed in a screw-capped 5-ml vial, equipped with a magnetic stirrer, and then 3 mL of solvent were added. Thereafter, the amine, in the chosen molar ratio, was introduced by a syringe. The homogeneous mixture was magnetically stirred and heated to 90 °C. Finally, benzyl chloride (BnCl/carboxylic acid 1.1:1 molar ratio) was added by means a syringe to the homogenous mixture. Further elaboration was as described previously.

Identification of the products was carried out by comparison of the <sup>1</sup>H NMR spectra with those of authentic samples and with those reported in the literature (Table 2).

#### Esterification in Solvent-Free Conditions

The amount of 1 mmol of carboxylic acid was weighed in a screw-capped 3-ml vial, equipped with a magnetic stirrer; thereafter, the appropriate amount of TEA was introduced by a syringe (carboxylic acid/TEA 1:1). The mixture was magnetically stirred and heated to 90 °C until a clear colorless liquid phase was obtained (about 15 min). Finally, benzyl chloride (BnCl/carboxylic acid 1:1 molar ratio) was added by means a syringe to the homogenous mixture. At the end of reaction and at rt, the mixture had a semi-solid waxy appearance. Further elaboration was as described for the reaction in the presence of IL.

When yields by weight were determined, no internal standard was added at the end of reaction, and the organic solvent was eliminated by rotary evaporation. The product was thereafter dried and weighed; GC was performed to establish purity, which was always >97%.

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