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n-Butylammonium carboxylates/Tf_2O: ionic liquid based systems for the synthesis of unsymmetrical imides via a Ritter-type reaction

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ABSTRACT

We have developed a new method for the preparation of unsymmetrical imides using liquid carboxylate salts via a Ritter-type process. The reactions were carried out with nitriles and *n*-butylammonium carboxylates as ionic liquids in the presence of triflic anhydride (Tf_2O) as the promoter. Mild reaction conditions, simplicity of the procedure, and proton-free conditions are the main advantages of this procedure.

The imide moiety represents an important substructure associated with natural products, such as fumaramidmycin,[1a,b] coniothyriomycin,[1c] and SB-253514.[1d] In addition, the imide group can act as a useful directing group in Michael addition and alkylation reactions.[2,3] Classically, imides are prepared by the reaction of amides with acyl chlorides, anhydrides, and carboxylic esters or acids.[4] In addition, other reported methods include the reaction of azlactones with O_2 and Pd/C,[5] aminocarbonylation of aryl bromides,[6] reaction of pentafluorophenyl (PFP) esters with deprotonated amides,[7] couplings of amides with thioesters using $FeCl_2$/NBS,[8] amidation of an aldehyde with CuBr/NBS,[9] and oxidation of *N*-alkylamides.[10]

Most of the above reported methods have one or more of the following drawbacks: high temperature, long reaction time, use of a solvent or two phase systems, toxic reagents, corrosive and hazardous oxidants, tedious work-up, and side reactions such as elimination to nitriles, formation of triacyl amides, or acyl group transfer.

The amidation of nitriles with alcohols in the presence of acid is known as the Ritter reaction.[11] Recently, Habibi et al.[12] extended this method and reported the synthesis of linear imides by reaction of nitriles with acid anhydrides in the presence of silica sulfuric acid. We believe that the extension of the Ritter reaction can be considered as an efficient procedure for the synthesis of imides because harsh reaction conditions are not required, and nitriles and acylating reagents (acid anhydrides) are easily available. However, the preparation of imides through Ritter-type reactions[13] has not been investigated extensively, and there is still considerable interest in developing this type of reaction.

Trifluoromethanesulfonic anhydride (triflic anhydride, Tf_2O) is commercially available and known for its utility for the conversion of an OH group into an OTf leaving group in organic transformations.[14] Although triflic anhydride is expensive, it has been widely used as a powerful promoter in different organic reactions.[15,16]

We were attracted toward the use of ionic liquids (ILs) in view of their benefits in organic transformations for sustainable development such as environmental compatibility, reusability, greater selectivity, operational simplicity, noncorrosiveness, and ease of isolation.[17] A survey of the literature indicated that there was no report on the synthesis of imides utilizing ionic liquids. Herein, we report liquid *n*-butylammonium carboxylates[18] as new nitrile acylating reagents for the synthesis of a range of imides through a Ritter-type route in the presence of triflic anhydride as the promoter.

The structures of the three *n*-butylammonium carboxylates utilized in this research are shown in Figure 1. Firstly, as a model system, the reaction of *n*-butylammonium acetate (**1**) (1 mmol) with 4-chlorobenzyl cyanide (1 mmol) was investigated in the presence of triflic anhydride (1 mmol) at 60 °C (Scheme 1). After 1 h, the corresponding imide was obtained in 83% yield, and a small amount of amide was also formed as a by-product (7%). When acetic acid was used instead of **1**, several by-products were produced in parallel with the formation of imide. This observation may be due to the presence of trifluoromethanesulfonic acid generated by the

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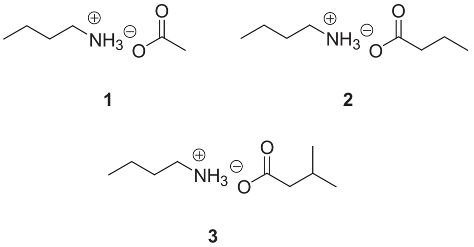
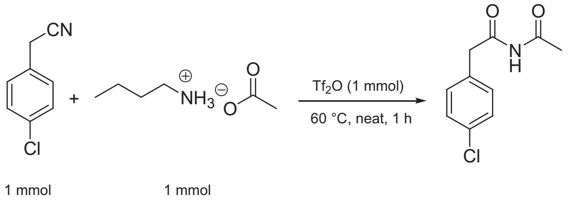


Figure 1. *n*-Butylammonium carboxylates.



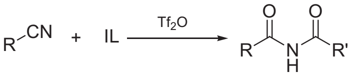
Scheme 1. Model reaction.

reaction of acetic acid and triflic anhydride. It seems that the use of *n*-butylammonium acetate (**1**) creates proton-free conditions.

In order to study the generality of this procedure, other types of nitriles were reacted with ILs **1**, **2,** and **3** according to the reaction conditions shown in Scheme 1, and the results are presented in Table 1. The reaction of 4-chlorobenzyl cyanide with ILs **2** and **3** afforded the desired products in good yields (Table 1, entries 2 and 3). In comparison with IL **1**, the results of the reactions of **2** and **3** did not show any noticeable differences with respect to yield and reaction time. The reactions of benzyl cyanide were investigated under similar reaction conditions, and a remarkable decrease in yield was observed (Table 1, entries 4 and 5). In these reactions, Friedel–Crafts acylation[19] on the aromatic ring occurred as a competitive side reaction. When benzyl cyanides with electron-donor groups such as an *o*-methoxy group and *p*-methyl group were used, no imides were produced since the aromatic rings were activated. However, the reaction of 4-nitrobenzyl cyanide with ILs **1** and **2** in the presence of triflic anhydride afforded the desired products in 46% and 45% yields, respectively (Table 1, entries 6 and 7). In these cases, the electron-withdrawing NO_2 group decreased the nucleophilicity of the nitrogen of the CN group, and therefore these reactions did not go to completion.

The reactions of several other aryl nitriles were investigated under the present reaction conditions. As shown in Table 1, benzonitrile produced the corresponding imide in 81% yield (Table 1, entry 8). The introduction of halides such as Cl and Br also afforded the corresponding imides (Table 1, entries 10 and 11). Finally, the

Table 1
Synthesis of imides using ILs **1**–**3** and various nitriles in the presence of triflic anhydride



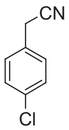
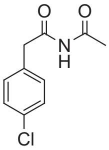
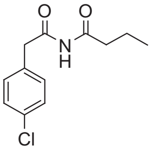
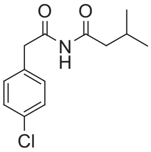
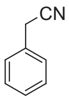
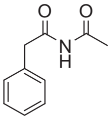
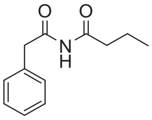
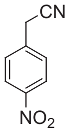
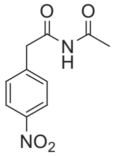
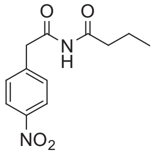
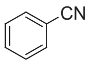
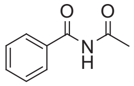
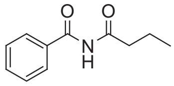
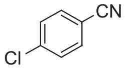
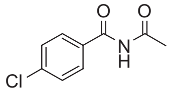
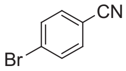
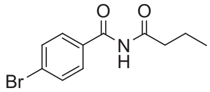
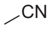
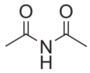
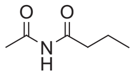
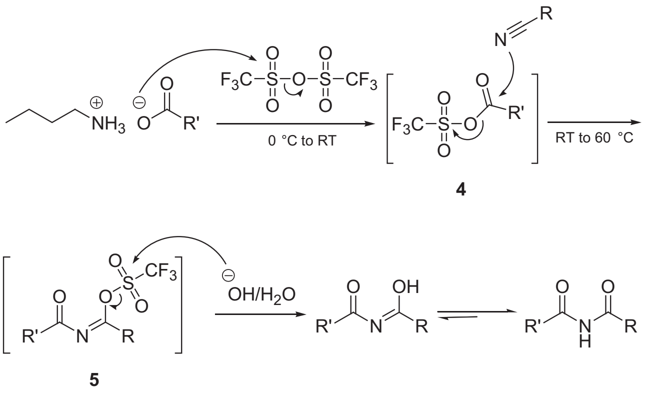
Entry	Nitrile	IL	Product	Yield^{a} (%)$^{Ref.}$
1		**1**		83[20]
2		**2**		85
3		**3**		85
4		**1**		42[5]
5		**2**		44[8]

Table 1 (*continued*)

Entry	Nitrile	IL	Product	Yield[a] (%)[Ref.]
6		**1**		46[12]
7		**2**		45[12]
8		**1**		81[9]
9		**2**		83[9]
10		**1**		88[9]
11		**2**		91[8]
12		**1**		93[12]
13		**2**		92[12]

[a] Isolated yield.



Scheme 2. A proposed reaction mechanism.

reaction of acetonitrile as a representative alkyl nitrile was investigated with ILs **1** and **2**, and excellent yields of the corresponding imides were observed (Table 1, entries 12 and 13).

It should be noted that in all cases, except for acetonitrile, a small amount of the corresponding amide by-product was generated. Also, the attempted synthesis of ILs containing aromatic carboxylate anions was not successful because the solid state of the corresponding carboxylic acids prevented formation of the desired ILs.

A proposed reaction mechanism is outlined in Scheme 2. Nucleophilic attack of the carboxylate on triflic anhydride leads to mixed anhydride **4** in which the triflate leaving group is ready to be replaced by a nucleophile. Subsequent replacement of triflate with nitrile produces intermediate **5** which was hydrolyzed by dilute $NaHCO_3$ solution to yield the corresponding imide.

In conclusion, the present procedure involving mild reaction conditions, the use of inexpensive ionic liquids, and the avoidance of volatile organic and toxic solvents, is very simple and convenient.[21] Other advantages of this procedure are proton-free conditions and relatively short reaction times.

Acknowledgment

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18. *Preparation of n-butylammonium carboxylates*: 1 mmol of liquid carboxylic acid was added to 1 mmol of *n*-butylamine at 0 °C, and the mixture was stirred for 10 min at room temperature to give the desired ionic liquid.
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21. *General Procedure for the synthesis of imides*: 1 mmol of Tf_2O (0.16 mL) was added to 1 mmol of ionic liquid at 0 °C, and the mixture was stirred for 5 min at room temperature. Then, 1 mmol of the nitrile was added and the mixture was heated at 60 °C. After 1 h, $NaHCO_3$ (2%, 5 mL) was added and the mixture was extracted with EtOAc (2×5 mL). The organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography using EtOAc/*n*-hexane (2:8) as eluent to afford the desired imide. Spectral and analytical data for new compounds:

    (Table 1, entry 2): White solid; Mp 142–143 °C. IR (KBr): 1732, 3172, 3265 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, J = 3.4 Hz, 3H), 1.57–1.72 (m, 2H), 2.57 (t, J = 7.4 Hz, 2H), 3.89 (s, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 8.71 (br s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): 13.5, 17.4, 42.3, 128.1, 131.4, 131.5, 133.8, 171.4, 173.8. Anal. Calcd for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.84. Found: C, 60.07; H, 5.92; N, 5.77.

    (Table 1, entry 3): White solid; Mp 121–122 °C. IR (KBr): 1684, 1732, 3151, 3201 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (d, J = 6.6, 6H), 2.06–2.19 (m, 1H), 2.46 (d, J = 7.0 Hz, 2H), 3.91 (s, 2H), 7.20 (d, J = 8.4 Hz, 2H), (7.30, J = 8.4 Hz, 2H), 9.37 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): 22.4, 25.2, 43.2, 46.3, 128.8, 130.9, 132.0, 133.3, 172.1, 174.3. Anal. Calcd for $C_{13}H_{16}ClNO_2$: C, 61.54; H, 6.36; N, 5.52. Found: C, 61.47; H, 6.43; N, 5.49.