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BMIm HCO_3: an ionic liquid with carboxylating properties. Synthesis of carbamate esters from amines†

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1-Butyl-3-methylimidazolium hydrogen carbonate (BMIm HCO_3) was used as an ionic liquid with carboxylating properties able to convert, in the presence of an alkyl halide, amines into the corresponding carbamate esters. Moderate to good yields of carbamates were obtained according to the nature of the amine and the alkylating agent.

Organic carbamates[1] are a class of compounds of great interest in different fields of organic synthesis; they found wide use as synthetic intermediates and biologically active compounds (anticancer, antibacterial, antimalarial, antidiabetic, antioxidant, anti-inflammatory, antitubercular, antiprogestational, anti-HIV, anticoagulant, antiestrogenic compounds). They are also largely used as agrochemicals (herbicides, pesticides, insecticides, fungicides), pharmaceuticals and in synthetic chemistry. Their use as protective groups[2] for the amine function of amino acids or pesticides[3] is probably the most extensive application.

In recent years many synthetic routes have been proposed to replace the ''classical syntheses'' involving the use of toxic and harmful reagents such as phosgene and isocyanates.[4]

Our research group proposed, in the last few years, several syntheses of organic carbamates based on safe methodologies using carbon dioxide or a reagent derived from carbon dioxide itself. In particular, we proposed the synthesis of carbamate esters by reaction of aliphatic and aromatic amines with carboxylating reagents such as tetraethylammonium carbonate (TEAC)[5] or tetraethylammonium hydrogen carbonate (TEAHC)[6] or mediated by electrochemical methodologies.[7]

The growing demand for environment friendly technologies operating in accordance with the principles of green chemistry prompted us to develop new clean, safe and sustainable methodologies for the synthesis of organic carbamates. In recent years, room-temperature ionic liquids (RTILs), because of their low vapor pressure, chemical and thermal stability, solvating ability, non-flammability, and ability to act as catalysts, have been frequently used as ''green'' reaction media in clean organic synthetic processes as substitutes for conventional toxic and volatile solvents.[8] Recently we used ionic liquids as valuable substitutes of the classical solvent-supporting electrolyte systems (SSES) in carbon dioxide mediated electrochemical synthesis of carbamates.[9]

Starting from these considerations and making use of our previous experience, we decided to develop a new method for the synthesis of organic carbamates that made use of an ionic liquid that can act both as a solvent and as a carboxylating reagent. In order to achieve this target, we assumed to use an ionic liquid having a hydrogen carbonate ion as an anion.

Herein, we report a simple and safe methodology for the synthesis of alkyl and aryl carbamates by reaction of amines with butylmethylimidazolium hydrogen carbonate (BMIm HCO_3).

Imidazolium hydrogen carbonates were recently used as catalysts in the carbonylation reaction of amines to formamides,[10] in the conversion of CO_2 to cyclic carbonates from epoxides,[11] in the conversion of nitriles to amides,[12] as stable precursors of *N*-heterocyclic carbenes[13] or as intermediates in the synthesis of several halide-free ILs.[14]

At first, we synthesized BMIm HCO_3 through the classical anion metathesis reaction of BMIm halides with alkali metal hydrogen carbonates[14] or carbonates.[10,15] The unsatisfactory results obtained in terms of product purity led us to develop a new procedure for the synthesis of desired IL using ion-exchange resins.[16] The synthesis of BMIm HCO_3, based on the use of an ion-exchange resin, was set up. Dowex™ Monosphere™ 550A, a strong base anion exchange resin in the OH form, was chosen to perform a double anion substitution. First, the resin was treated with an aqueous solution of sodium hydrogen carbonate (1.0 mol L^{-1}) in order to switch hydroxide with hydrogen carbonate anions. Then, treatment of the resin in the HCO_3^- form with a methanol solution of butylmethylimidazolium chloride (BMIm Cl)

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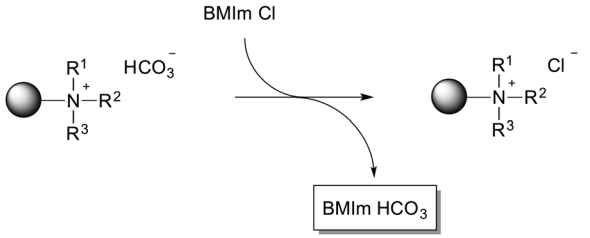
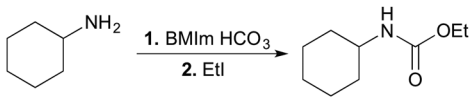


Fig. 1 Synthesis of BMim HCO_3 starting from Dowex™ Monosphere™ 550A.



Scheme 1 Reaction of cyclohexylamine with BMIm HCO_3.

allows the second anionic switch and the synthesis of the desired ionic liquid. BMIm HCO_3 was collected, dried and used, according to the scheme proposed in Fig. 1. The resin in the Cl form was then treated with NaOH 8%$_{w/w}$ and recycled.

To test the effectiveness of BMIm HCO_3 as a carboxylating agent, cyclohexylamine was used as a model compound, while ethyl iodide was used as the alkylating reagent according to the general scheme.

As reported in Scheme 1, the reaction was firstly carried out by mixing 1.0 mmol of cyclohexylamine with 0.5 mL of BMIm HCO_3. The reaction was conducted at different reaction times at room temperature, after that, an excess of ethyl iodide was added to the reaction mixture that was stirred for 2 hours and then worked up.

The results reported in Table 1 show that the best reaction yields are obtained when the reaction was carried out at 55 °C for 5 h (entry 6).

In order to verify the feasibility of the reaction, several experiments were carried out using different amines and alkylating reagents under the optimized reaction conditions. The results are reported in Table 2.

Reaction yields are very good when primary amines react with ethyl iodide (entries 1–7); cyclic primary amines (entries 1–3) afford carbamates in very good yields. Also benzylic amine (entry 4) affords very good yield of carbamate as amines **1e–f** do. Reaction with secondary amines **1g–h** (entries 7 and 8) gave very good reaction yields of carbamates too, but in the case of *N*-methylcyclohexylamine (**1h**), several difficulties in the extraction and purification of product **3h** were encountered and only 20% yields of an isolated product was obtained. Less basic substrates such as anilines gave, as expected, poor yields of carbamates (entries 9 and 10). Change of the alkylating reagent does not substantially affect the reaction yields; benzyl bromide **2b** reacts with cyclohexylamine only in moderate yields (48% entry 11) while reaction with 3-phenylpropyl bromide **2c** affords the corresponding carbamate in 70% yield (entry 12).

Table 1 Reaction of cyclohexylamine with BMIm HCO_3 under different reaction conditions[a]

Entry	T (°C)	t (h)	Yield[b] (%)
1	25	2	15
2	25	3	22
3	25	4	30
4	25	5	35
5	25	6	39
6	45	5	78
7	55	5	81

[a] 1.0 mmol of cyclohexylamine was added to 0.5 mL of BMIm HCO_3. The mixture was stirred at the desired temperature for the appropriate time, after that 3.0 mol of EtI were added. The reaction with EtI is usually completed in 2 h. Lower yields were obtained when the reaction is worked up in minor times. [b] Reaction yields refer to isolated products.

The reaction is supposed to proceed through the formation of the imidazolium carbamate by reaction of the amine with BMIm HCO_3. Then, the addition of the alkyl halide leads to the formation of the alkyl carbamate.

In order to investigate the effect of the ''onium'' cation structure on the carboxylation reaction, tetrabutyl phosphonium hydrogen carbonate (TBP HCO_3) was synthesized using the same procedure as that used for BMIm HCO_3. In a test reaction carried out using amine **1a** and ethyl iodide **2a** carbamate **3a** was obtained with reaction yields of 80% showing that the nature of the ''onium'' cation does not affect the outcome of the reaction.

In conclusion, we propose a new clean and safe methodology for the synthesis of organic carbamates starting from amines, BMIm HCO_3 and an alkylating reagent. The method avoids the use of any volatile and/or toxic solvent or catalyst. The synthesis was carried out under mild reaction conditions and carbamates were isolated in moderate to high yields. The reaction was carried out in a medium with the twofold function of the solvent and reagent. In addition, a new procedure for the synthesis of BMIm HCO_3 starting from an anionic resin was projected and set-up.

Experimental

General

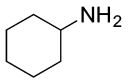
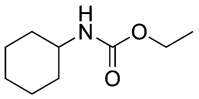
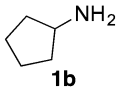
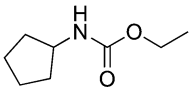
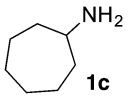
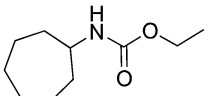
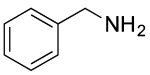
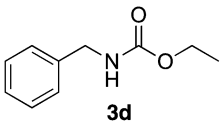
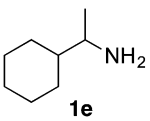
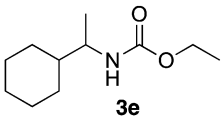
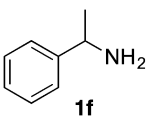
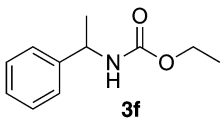
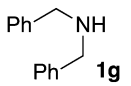
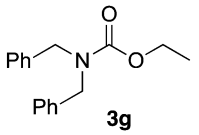
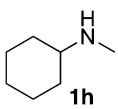
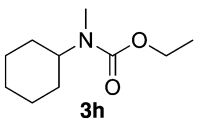
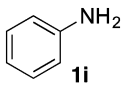
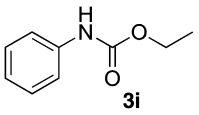
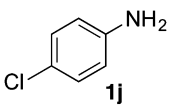
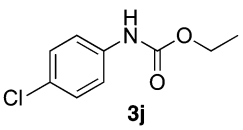
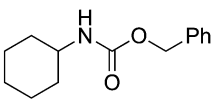
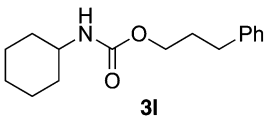
All commercially available reagents were used without further purification unless otherwise stated. Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F254 precoated glass plates (0.25 mm thickness) and visualized using UV light, iodide, and a molybdate reagent.

Flash column chromatography was performed on a silica gel (230–400 mesh). ^{1}H NMR and ^{13}C NMR were recorded on a 400 MHz nuclear magnetic resonance spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR).

Synthesis of BMIm HCO_3

An 8%$_{w/w}$ solution of sodium hydroxide (200 ml) was percolated through a column filled in with DOWEX™ MONOSPHERE™ 550A (OH) (60 g; capacity 1.1 eq. per L). The resin was then washed with water until neutrality. Then a 1.0 M solution of sodium hydrogen carbonate (300 ml) was passed through the column, until the exchange of OH^- ions to HCO_3^- (pH was monitored during the switch). The column was then washed thoroughly

Table 2 Synthesis of carbamates by reaction of amines with BMIm HCO_3 and alkylating reagents[a]

Entry	Amine	Alkyl halide	Carbamate	Yield[b] (%)
1	 **1a**	CH_3CH_2I **2a**	 **3a**	81
2	 **1b**	**2a**	 **3b**	81
3	 **1c**	**2a**	 **3c**	83
4	 **1d**	**2a**	 **3d**	72
5	 **1e**	**2a**	 **3e**	73
6	 **1f**	**2a**	 **3f**	70
7	 **1g**	**2a**	 **3g**	82
8	 **1h**	**2a**	 **3h**	20
9	 **1i**	**2a**	 **3i**	17
10	 **1j**	**2a**	 **3j**	26
11	**1a**	$PhCH_2Br$ **2b**	 **3k**	48
12	**1a**	$Ph(CH_2)_3Br$ **2c**	 **3l**	70

[a] 1.0 mmol of amine was added to 0.5 mL of BMIm HCO_3. The reaction was maintained at 55 °C for 5 h, then 3.0 mmol of the desired alkyl halides were added. [b] Reaction yields refer to an isolated product.

with anhydrous methanol to remove any traces of water. An anhydrous methanol solution of 1-buthyl-3-methyl imidazolium chloride (5.0 g; 29 mmol) was passed through the column to exchange the chloride ions with hydrogen carbonate ions. The solvent was then evaporated under reduced pressure and the product was collected and dried *in vacuo* for 3 hours at room temperature.

Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3H); 1.34–1.41 (m, 2H); 1.83–1.90 (m, 2H); 4.12 (s, 3H); 4.29 (t, J = 7.4 Hz, 2H); 7.28 (s, 1H); 7.54 (s, 1H); 10.52 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 13.4; 19.4; 32.1; 36.4; 49.8; 121.5; 123.2; 137.3.[11]

General procedure for the synthesis of carbamates 3

A solution of amine **1** (1.0 mmol) and BMIm HCO_3 (0.5 ml) was stirred at 55 °C for 5 hours, then alkyl halide **2** was added (3.0 mmol) at room temperature for 2 hours. The crude reaction mixture was then extracted with diethyl ether (5 × 5 ml) and dried under reduced pressure. The residue was, in the case, purified by flash column chromatography.

3-Phenylpropyl cycloethylcarbamate (3l)

White solid (183 mg, 70%; mp 57–59 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11–1.25 (m, 4H); 1.33–1.42 (m, 2H); 1.60–1.76 (m, 4H); 1.90–2.00 (m, 2H, $OCH_2CH_2CH_2$); 2.71(t, J = 7.0 Hz, 2H, $OCH_2CH_2CH_2$); 3.50–3.53 (m, 1H, C*H*NH); 4.11 (t, J = 6.9 Hz, 2H, OCH_2CH_2); 4.72 (br, s, 1H, N*H*); 7.20–7.33 (m, 5H). ^{13}C (100 MHz, $CDCl_3$): δ 155.9; 141.5; 128.4; 128.3; 125.9; 64.0; 49.8; 33.5; 32.2; 30.8; 25.5; 24.9. MS m/z 41, 65, 91, 118, 261 (M+); IR (KBr): 3326, 2936, 2854, 1685, 1536 cm^{-1}.

Anal. calcd for $C_{16}H_{23}NO_2$: C, 75.53; H, 8.87; N, 5.36. Found: C, 75.35; H, 8.81; N, 5.35%.

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