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A New Protocol for the Formation of Carbamates and Thiocarbamates using Carbamoyl Imidazolium Salts

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Abstract: Carbamoyl imidazolium salts are demonstrated to act as useful carbamoylation reagents, in reactions with alcohols, phenols, thiols and thiophenols to form carbamates and thiocarbamates under relatively mild conditions. The salts are stable and easily prepared from the corresponding amines using CDI.

One of the most important ways of incorporating desirable properties into a molecule for pharmaceutical and agrochemical development, is through modification or elaboration of amine, hydroxyl or thiol groups. Introduction of carbamoyl functionality is accomplished by reaction of nucleophiles with various carbamoyl cation equivalents **1**. Isocyanates are used as *N*-monosubstituted carbamoyl cation equivalents, whereas carbamoyl chlorides **2** are the standard *N,N*-disubstituted carbamoyl cation equivalents. Several carbamoyl chlorides are commercially available, but they can be prone to decomposition, are unpleasant to work with, and are rapidly decomposed by water. Recently, we demonstrated the utility of carbamoyl imidazolium salts **3**, as *N,N*-disubstituted carbamoyl cation equivalents, for the formation of unsymmetrical tri- and tetrasubstituted ureas.[1] The salts **3** are stable, usually crystalline materials which can be stored for extended periods. They are not decomposed by water, and even though some salts are hygroscopic, this does not affect their reactivity. Unlike carbamoyl chlorides which are prepared from phosgene, the salts **3** are readily prepared from commercially available *N,N'*-carbonyldiimidazole (CDI).[2-4] Carbamoyl imidazolium salts **3** thus offer considerable advantages over carbamoyl chlorides, which have traditionally been used as carbamoyl cation equivalents. We now demonstrate their utility for the formation of carbamates and thiocarbamates.

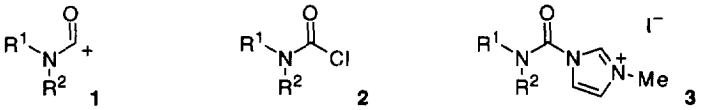

Figure 1: *N,N*-disubstituted carbamoyl cation **1** and synthetic equivalents **2** and **3**.

Carbamoylimidazoles, obtained from the reaction of a secondary amine and CDI are much less reactive toward nucleophilic attack than carbamoyl imidazolium salts **3**.[5] The salts **3** are readily obtained by methylation of carbamoylimidazoles (Scheme 1). Such activation of carbonylimidazole functionality as carbonylimidazolium ions has been demonstrated in a number of systems,[3,6-9] but was not applied to the activation of carbamoylimidazoles until recently.[1] Jencks established that acylimidazolium salts react with nucleophiles more rapidly than acylimidazoles.[6] Vilkas and co-workers first demonstrated that alkoxycarbonylimidazolium salts are similarly activated toward nucleophilic attack by amines (for the formation of BOC protected amino acids).[7] Rapoport was able to demonstrate this strategy for the selective protection of amino functionality in nucleosides, as amides, carbamates (Cbz protection) and thiocarbamates.[8] Dicationic 1,1'-carbonylbis(3-methylimidazolium)

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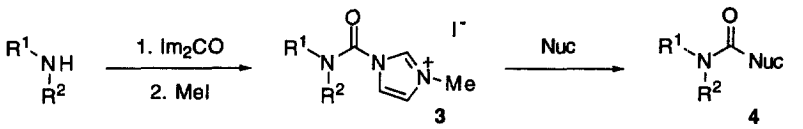
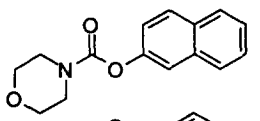
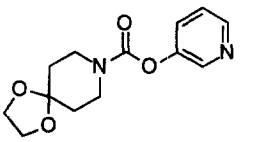
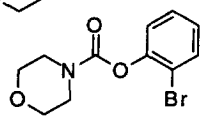
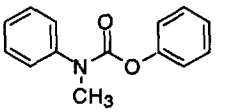
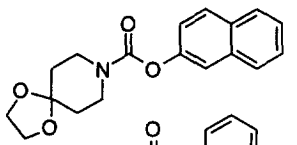
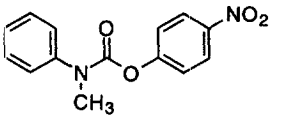
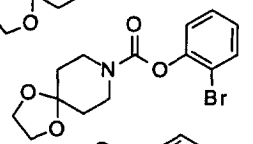
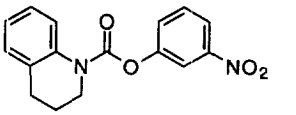
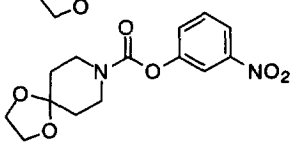
ions have also been used for alkoxycarbonylations,[9a] and peptide[9a,9b] and ester[9] bond forming reactions. In Carbamoyl imidazolium salts **3** react with nucleophiles under much milder conditions, such as for the formation of carbamates and thiocarbamates from alcohols and thiols respectively (Scheme 1). The byproduct, *N*-methylimidazole, is easily removed by washing the organic layer with dilute acid.



Scheme 1

Phenols produce the corresponding carbamates in excellent yields, by heating the sustrates overnight at reflux in acetonitrile, in the presence of one molar equivalent of triethylamine (Table 1).[10] This method often gives products of sufficiently high purity that chromatographic purification is not required. In the absence of triethylamine, no product was detected by NMR after refluxing overnight. Deprotonation of the phenol with sodium hydride and stirring with the imidazolium salt at room temperature in 1:1 THF/DMF for one day, yields the carbamates, but in lower yield (Table 1, Entry 1).

Table 1. Carbamates synthesized from Imidazolium Salts[a]

Entry	Carbamate	Isolated Yield	Entry	Carbamate	Isolated Yield
1		93% 57%[b]	6		88%
2		71%	7		86%
3		99%	8		89%
4		94%	9		94%
5		90%			

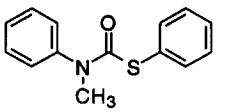
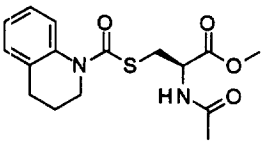
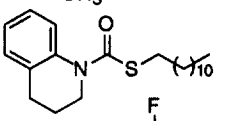
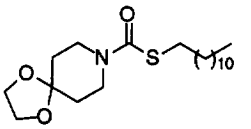
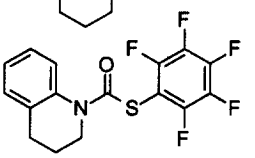
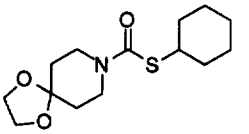
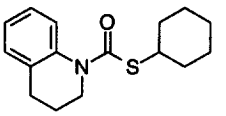
[a] Imidazolium salt **3**, phenol and triethylamine in acetonitrile were refluxed overnight. [b] 2-Naphthol in THF/DMF was treated with sodium hydride, and then stirred at room temperature with imidazolium salt **3** for one day.

Thiols and thiophenols also react cleanly and under mild conditions to yield thiocarbamates. Addition of one equivalent of the thiol to the carbamoyl imidazolium salt **3** at room temperature in chloroform or dichloromethane, in the presence of one equivalent of triethylamine, and stirring overnight yields the desired thiocarbamate (Table 2).[11] The yields are excellent, and again products often do not require chromatographic purification. The successful reaction of a protected cysteine (Table 2, Entry 5) suggests that this reaction may be useful for the functionalization of thiol residues in peptides.

Unlike phenols, simple alcohols (one molar equivalent) react slowly with carbamoyl imidazolium salts, even under reflux. However, 2,2,2-trifluoroethanol, *when used as solvent*, does react with **3** at room temperature overnight in the presence of triethylamine in excellent yield (Table 3). Reaction of the more

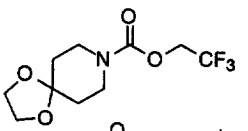
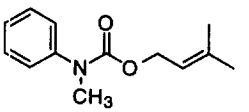
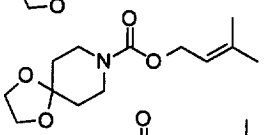
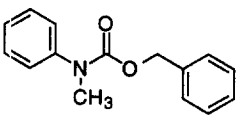
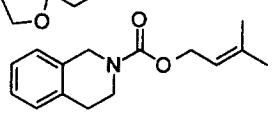
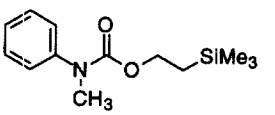
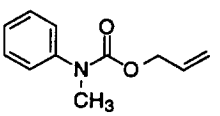
nucleophilic sodium alkoxides with the carbamoyl imidazolium salts does result in the formation of the desired carbamates after stirring at room temperature for one day.[12] The yields in these cases are moderate to good yields, perhaps because of competitive deprotonation of the imidazolium salts. Formation of Cbz, Alloc and Teoc carbamates from amines is thus possible via the corresponding carbamoyl imidazolium salts.

Table 2. Thiocarbamates synthesized from Imidazolium Salts[a]

Entry	Thiocarbamate	Isolated Yield	Entry	Thiocarbamate	Isolated Yield
1		86%	5		71%
2		84%	6		96%
3		92%	7		94%
4		91%			

[a] Imidazolium salt **3** (1.0 equiv.), thiol (1.0 equiv.) and triethylamine (1.0 equiv.) in CH_2Cl_2 or $CHCl_3$ were stirred at room temperature overnight.

Table 3. Carbamates synthesized from Imidazolium Salts[a]

Entry	Carbamate	Isolated Yield	Entry	Carbamate	Isolated Yield
1		95%[b]	5		63%
2		57%	6		83%
3		83%	7		55%
4		78%			

[a] Imidazolium salt **3** (1.0 equiv.), alcohol (1.0 equiv.) and NaH (1.1 equiv.) in THF/DMF (1:1) were stirred at room temperature for 1 day. [b] Imidazolium salt **3** (1.0 equiv.) and triethylamine (1.0 equiv.) in CF_3CH_2OH were stirred at room temperature overnight.

In conclusion, carbamoyl imidazolium salts are demonstrated as versatile reagents, for the formation of carbamates and thiocarbamates under relatively mild conditions. They are easily prepared from commercially available starting materials and offer significant advantages over carbamoyl chlorides in terms of their chemical behaviour and storage properties. Further studies on the utility of these reagents will be reported in due course.

Acknowledgements: This work was funded the Natural Sciences and Engineering Research Council of Canada (NSERC). R.A.B. thanks the University of Toronto, Astra Pharma Inc. and Astra Research Centre of Montreal for support.

References and Notes:

1. Batey, R. A.; Santhakumar, V.; Yoshina-Ishii, C.; Taylor, S. D. *Tetrahedron Lett.* **1998**, *39*, 6267-6270.
2. (a) Staab, H. A.; Rohr, W. in *Newer Methods of Preparative Organic Chemistry*, Vol. V, Academic Press: New York, 1968, pp61-108.
3. For an excellent review of azolides, including the uses of CDI and substituted carbonylimidazolium ions as activated reagents, and the formation of carbamates and thiocarbamates, see: Staab, H. A.; Bauer, H.; Schneider, K. M. *Azolides in Organic Synthesis and Biochemistry*, Wiley-VCH: Weinheim, 1998.
4. Staab, H. A.; Benz, W. *Liebigs Ann. Chem.* **1961**, *648*, 72-82.
5. (a) Staab, H. A; Rohr, W. *Chem. Ber.* **1962**, *95*, 1298. (b) Staab, H. A.; Merdes, H. *Chem. Ber.*, **1965**, 98, 1134.
6. Oakenfull, D. G.; Salvesen, K.; Jencks, W. P. *J. Am. Chem. Soc.* **1971**, *93*, 188-194, and refs. cited.
7. Guibé-Jampel, E.; Bram, G.; Wakselman, M.; Vilkas M. *Synthetic Commun.*, **1973**, *3*, 111-114.
8. Watkins, B. E.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 4471-4477.
9. (a) Guibé-Jampel, E.; Bram, G.; Vilkas M. *Bull. Soc. Chim. Fr.* **1973**, 1021-1027. (b) Saha, A. K.; Schultz, P.; Rapoport, H. *J. Am. Chem. Soc.* **1989**, *111*, 4856-4859. (c) Kamijo, T.; Harada, H.; Iizuka, K. *Chem. Pharm. Bull.* **1984**, *32*, 5044-5047.
10. Representative procedure (Table 1, Entry 1): To a solution of **3** (323 mg, 1.0 mmol) in acetonitrile (6 ml) was added β-naphthol (144 mg, 1.0 mmol) and triethylamine (101 mg, 1.0 mmol) and heated to reflux overnight. Solvent was removed *in vacuo* and the residue dissolved in CH_2Cl_2 (15 ml), and aqueous HCl (15 ml, 0.1 M) added. The aqueous layer was extracted with three subsequent 15 ml portions of dichloromethane, and the combined organic layers washed with water (20 ml) and brine (20 ml), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum to yield an off-white solid (239 mg, 93%). IR (KBr disc) ν 2956, 2853, 1722, 1418, 1230, 1161, 1115, 1063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 - 7.78 (3H, m), 7.58 (1H, m), 7.49 - 7.42 (2H, m), 7.29 - 7.26 (1H, m), 3.77 - 3.74 (4H, m), 3.71 (2H, br s), 3.59 (2H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.53, 148.61, 133.51, 130.99, 129.01, 127.48, 127.30, 126.23, 125.27, 121.19, 118.22, 66.33, 66.21, 44.61, 43.86; HRMS (EI) m/e calcd (M+) 257.1052, found 257.1045.
11. Representative procedure (Table 2, Entry 4): To a suspension of **3** (369 mg, 1.0 mmol) in CH_2Cl_2 (6 ml) was added cyclohexyl mercaptan (116 mg, 1.0 mmol) and triethylamine (101 mg, 1.0 mmol) and stirred at room temperature overnight. CH_2Cl_2 (5ml) and aqueous HCl (10 ml, 0.1M) were then added. The aqueous layer was extracted with three subsequent 10 ml portions of CH_2Cl_2 and the combined organic layers washed once with water (10 ml) and brine (15 ml). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum to a straw-coloured oil. This material was purified by flash column chromatography (98:2 hexane:ethyl acetate) to yield a clear, colourless oil (250 mg, 91%). IR (thin film) ν 2930, 1646, 1580, 1488, 1446, 1362, 1295, 1197, 1162, 1089 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.72 (1H, d, J = 8 Hz), 7.20-7.02 (3H, m), 3.76 (2H, t, J = 6 Hz), 3.49 (1H, m), 2.75 (2H, t, J = 6.5 Hz), 2.07-1.15 (12H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.33, 138.06, 131.32, 128.55, 125.77, 124.86, 124.83, 44.96, 44.187, 33.52, 26.87, 26.17, 25.63, 23.64; HRMS (EI) m/e calcd (M+) 275.1344, found 275.1335.
12. Representative procedure (Table 3, Entry 5): To a solution of **3** (686 mg, 2.0 mmol) and alcohol (172 mg, 2.0 mmol) in THF/DMF (1:1, 12 ml) was added NaH (2.2 mmol, 66 mg, 80% in mineral oil). The solution was stirred at room temperature for 1 day, taken up in Et_2O (20 ml), washed with H_2O (3 x 10 ml), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The oil obtained was purified by flash column chromatography (CH_2Cl_2) to yield carbamate as clear, colourless oil (276 mg, 63%). IR (thin film) ν 2934, 1707, 1598, 1498, 1386, 1353, 1298, 1277, 1153 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.25 (5H, m), 5.33 (1H, m), 4.61 (2H, d, J = 7 Hz), 3.30 (3H, s), 1.71 (6H, d, J = 9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.56, 143.33, 137.79, 128.55, 125.60, 125.43, 119.29, 62.43, 37.43, 25.50, 17.84; HRMS (EI) m/e calcd (M+) 219.1259, found 219.1251.