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Preparation of carbamates from amines and alcohols under mild conditions

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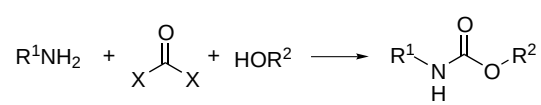
Abstract—The practical and mild preparation of carbamates in a two-component system is described. The smooth reaction of an alcohol with 1,1′-carbonyldiimidazole, followed by subsequent trapping with an amine represents a safe replacement for phosgene derivatives.

1. Introduction

Phosgene (**1**) is potentially a very versatile building block for organic synthesis.[1] It offers the possibility of binding two nucleophilic units to the same carbon atom, and such a two-component system is particularly well suited for the combinatorial synthesis of carbonates, ureas or carbamates (Scheme 1). Although phosgene is industrially produced and used, its gaseous nature and extreme toxicity often prevent its use in research laboratories. Safer substitutes have been proposed. 1,1,1-Trichloromethyl chloroformate (diphosgene, **2**)[2] and bis(1,1,1-trichloromethyl)carbonate (triphosgene, **3**)[3] are frequently used. A most interesting study by React-IR monitoring has recently shown that chloride ions could catalyze the depolymerization of **3** into **1**,[4] and it is now widely accepted that triphosgene can replace phosgene in most cases. A much safer substitute is 1,1′-carbonyldiimidazole, which cannot form phosgene under reasonable conditions.[5] On the other hand, the higher pK_a of imidazole makes this species significantly less reactive than phosgene, allowing clean successive reactions.[6,7]

As part of our program directed towards the development of new photolabile protecting groups for the amine function, we were faced with the issue of preparing numerous carbamates under especially mild conditions. To date, the two general procedures for preparing carbamates are either the reaction of amines with a chloroformate,[8] or of alcohols with an isocyanate.[9] The preparation of chloroformates or isocyanate frequently requires aggressive reagents and/or conditions, and the use of triphosgene **3** consistently failed in our hands. We describe here a convenient preparation of carbamates under mild conditions, with very high yields and no purification other than aqueous washing.

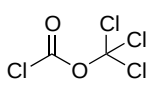


Scheme 1.

2. Results and discussion

The reaction of an alcohol with 1,1′-carbonyldiimidazole is well known to give an imidazolide with the release of one equivalent of imidazole, as has recently been demonstrated in the synthesis of mixed carbonates.[10] We anticipated that this moderately reactive intermediate would be easily trapped by an amine, without requiring an additional base. We tested this reaction with various benzylic alcohols and dodecylamine (Scheme 2). In all cases, the yields were higher than 85% (Table 1).

1



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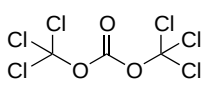

3

Keywords: carbamates; phosgene; two-component system; protecting groups.

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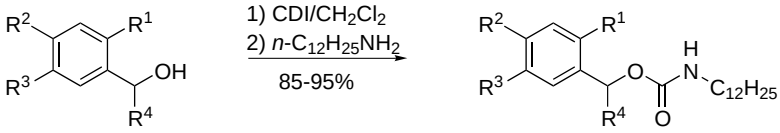
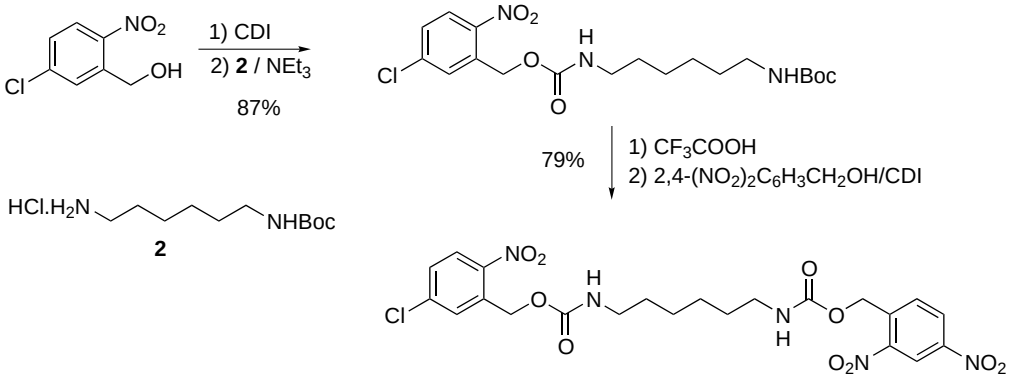


Scheme 2.



Scheme 3.

Table 1.

Entry	R^1	R^2	R^3	R^4	Yield (%)
1	SO_2Ph	H	MeO	H	100
2	SO_2Ph	MeO	MeO	H	88
3	NO_2	MeO	MeO	H	94
4	H	NO_2	H	H	95
5	NO_2	NO_2	H	H	94
6	NO_2	H	Cl	H	91
7	NO_2	MeO	MeO	Me	89
8	NO_2	Cl	H	H	89
9	NO_2	Br	H	H	83

In a typical procedure (Table 1, entry 1), carbonyldiimidazole (30 mg, 0.18 mmol) was suspended in anhydrous dichloromethane (0.5 ml) and the mixture was cooled to 0°C. 5-Methoxy-2-phenylsulfonylbenzyl alcohol (50 mg, 0.18 mmol) was slowly added as a solution in dichloromethane (0.5 ml). The mixture was stirred at room temperature for 1 h. The amine was added (33 mg, 0.18 mmol) and the mixture was stirred at room temperature for 6 h. Ethyl acetate was added, and the mixture was washed four times with HCl 10%, and once with brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to give the pure carbamate as a white solid (90 mg, 100%).

This coupling is not limited to primary benzylic alcohols or primary amines, as shown by the entry 7, and by the virtually quantitative reaction between *n*-pentanol, CDI and piperidine. On the other hand, more hindered alcohols such as menthol or *tert*-butanol gave complex mixtures of products. The two-component nature of this procedure is clearly well suited for parallel synthesis; some of the reactions were also checked on small-scale experiments, in a 4×4 array of 8 mm test tubes. Micro-workups and direct analysis by GC-MS gave similar results as those obtained by separate syntheses.

The same procedure was also applied for the protection of diamines, as shown in Scheme 3. The commercially available hydrochloride **2** was condensed (as its free base upon treatment with triethylamine) with the imidazolide derived from 5-chloro-2-nitrobenzyl alcohol in excellent yield. Liberation of the Boc group under acidic conditions was followed by the condensation with the 2,4-dinitrobenzyl alcohol and carbonyldiimidazole to give the desired *bis* carbamate. The overall yield of the process was around 70%.

In conclusion, we could prepare a series of carbamates by the simple successive mixing of an alcohol and 1,1′-carbonyldiimidazole, and an amine. Using our standard protocol, only primary or benzylic alcohols were found satisfactory, whereas the amine could be primary or secondary. This method is well suited for parallel or combinatorial synthesis. To illustrate this feature, we prepared a small library of carbamates using standard laboratory equipment.

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References

1. Eckert, H.; Foster, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 894.

2. (a) Kurita, K.; Matsumura, T.; Iwakura, Y. *J. Org. Chem.* **1976**, *41*, 2070; (b) Kurita, K.; Iwakura, Y. *Org. Synth.* **1980**, *59*, 195; (c) Katakzi, R.; Iizuka, Y. *J. Org. Chem.* **1985**, *50*, 715–716.
3. Cotarca, L.; Delogu, P.; Nardelli, A.; Sunjic, V. *Synthesis* **1996**, 553.
4. Pasquato, L.; Modena, G.; Cotarca, L.; Delogu, P.; Mantovani, S. *J. Org. Chem.* **2000**, *65*, 8224–8228.
5. Staab, H. A. *Angew. Chem.* **1962**, *74*, 407–423.
6. Staab, H. A. *Liebig's Ann. Chem.* **1957**, *609*, 83–88.
7. (a) The reactivity can be increased by *N*-methylation: Saha, A. K.; Schultz, P.; Rapoport, H. *J. Am. Chem. Soc.* **1989**, *111*, 4856–4859; (b) For a recent application: Batey, R. A.; Yoshina-Ishii, C.; Taylor, S. D.; Santhakumar, V. *Tetrahedron Lett.* **1999**, *40*, 2669–2672.
8. Bergmann, M.; Zervas, L. *Chem. Ber.* **1932**, *65*, 1192.
9. Osaki, S. *Chem. Rev.* **1972**, *72*, 475–496.
10. Bertolini, G.; Pavich, G.; Vergani, B. *J. Org. Chem.* **1998**, *63*, 6031–6034.