Carbamate esters: a simple, mild method of formation

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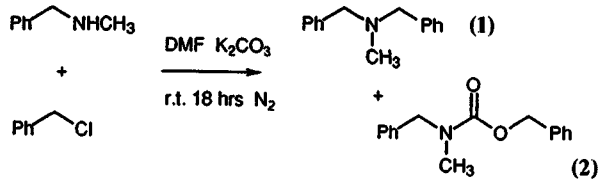
Received 9 August 1994

Abstract: Carbamate esters can be prepared in good yields from primary, secondary and aromatic amines, CO_2 and a variety of electrophiles. The reactions are straightforward and are performed at room temperature and atmospheric pressure, in the presence of an inorganic base.

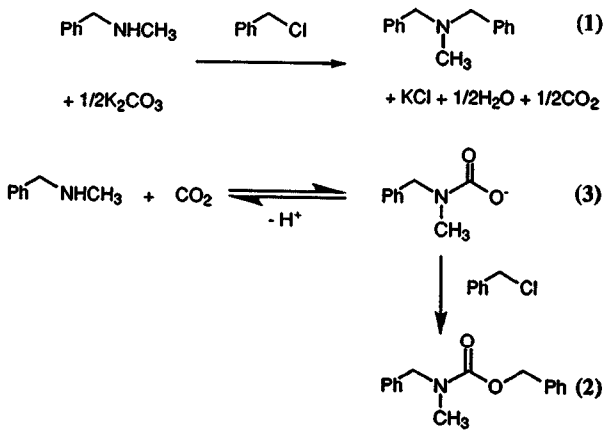
Carbamates have considerable importance, both in agriculture as herbicides, fungicides and pesticides, and in the chemical industry as intermediates for organic synthesis. The carbamate moiety also features in a variety of pharmaceuticals.

Carbamate esters have been prepared by the reactions of amines with alkyl chloroformates, alcohols with carbamoyl chlorides or isocyanates and, less commonly, reactions involving metal complexes[1] or acyl transfer reagents[2]. However, many alkyl chloroformates are unstable and the preparation of carbamoyl chlorides and isocyanates frequently involves the use of phosgene, which is both highly toxic and inconvenient to handle. The syntheses of carbamate esters by reactions using carbon dioxide as a direct starting component have been reported in recent years[3], but require elevated temperatures. Carbon dioxide is well known to react rapidly with amines to form carbamic acids but further reaction of these acids usually requires vigorous conditions (high temperature and pressure). Therefore there remains scope for improved procedures in the preparation of carbamate esters.

During the course of our work directed towards the preparation of a series of tertiary amines, we attempted to alkylate some secondary benzylamines with various electrophiles under standard conditions. To our surprise, in addition to the expected tertiary amine, the corresponding carbamate esters were also isolated[4] in yields up to 40%. Alkylation of N-methylbenzylamine with benzyl chloride, shown below, illustrates the general reaction.



We envisaged that the carbamate ester (2) was derived from the alkylation of a carbamate anion (3), generated by the reaction of the amine with CO_2. In turn, we hypothesised that the CO_2 was generated *in situ* from neutralisation of K_2CO_3, consequently limiting the yield of carbamate ester to a maximum 50%, as indicated in the following equations and equilibrium.



Following this initial observation, we decided to investigate whether selectivity in favour of carbamate ester formation was possible by varying the reaction conditions. To move the equilibrium in favour of the carbamate anion (3), the amount of available CO_2 was increased by bubbling CO_2 gas directly into the reaction mixture. To our delight, selectivity in favour of carbamate ester formation was seen, with the ratio of tertiary amine (1) to carbamate ester (2) changing from 60:40 to 40:60. The reaction was solvent dependent, as no carbamate ester formation was observed in either acetonitrile or tetrahydrofuran. We thought that further improvement in selectivity could be achieved if the

Table 1

Base	% Carbamate	% Tertiary Amine
Na_2CO_3	3	93
K_2CO_3	60	40
Cs_2CO_3	96	3

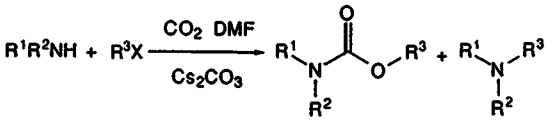
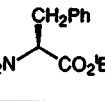
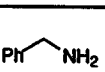
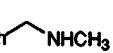
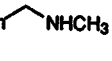
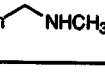


Table 2

Amine (R^1R^2NH)	Electrophile (R^3X)	% Carbamate[8]	% Tertiary Amine
		78	0
		58	19
		90	0
		96	3
		68	8
	$CH_3CH_2CH_2Br$	85	0
	CH_2Br_2	73[9]	0
	$(CH_3)_2CHBr$	44	0
	$(CH_3)_3CI$	0	0

rate of alkylation of the carbamate anion could be accelerated. Based on the observation[5] that the preferred counter-ion for rapid alkylation of carboxylic acids to carboxylic esters is caesium, the effect of this counter-ion was studied. As can be seen in **Table 1**, Cs_2CO_3 improved the selectivity dramatically in favour of the carbamate ester, which was readily separated from the tertiary amine in excellent yield.

Using the conditions described below, the reaction of a wide range of primary and secondary amines, of varying basicities, with a selection of electrophiles has been studied. As can be seen from **Table 2**, carbamate ester is the favoured product in all cases. Indeed, the only constraint to reaction appears to be steric in nature, as judged by the entries for secondary and tertiary electrophiles.

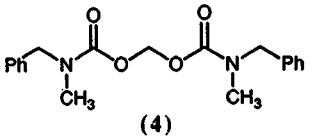
Typical experimental procedure:
(S)-N-(Phenylmethoxycarbonyl)phenylalanine,1,1-dimethylethyl ester. Carbon dioxide gas was bubbled into a stirred suspension of (S)-phenylalanine,1,1-dimethylethyl ester, hydrochloride (1.06 g, 0.0041 mol) and caesium carbonate[6] (4.00 g, 0.0123 mol) in N,N-dimethylformamide (30 ml) at room temperature for approximately 1 hour. Benzyl bromide (0.476 ml, 0.0041 mol) was added in one portion and carbon dioxide gas passed into the reaction for a further 30 minutes and the mixture stirred at room temperature overnight. After evaporation, the residue was suspended between ethyl acetate and water. The organic layer was separated, washed with brine (3 x 30 ml), dried (Na_2SO_4) and evaporated. Flash chromatography on silica, eluting with hexane to hexane/ethyl acetate 70:30, gave the product as a solid (1.13 g, 78%). $[\alpha]_D^{25}$= -7.8 (c = 1.0, EtOH). (Lit.[7] $[\alpha]_D^{20}$= -6.0 (c = 1.0, EtOH). IR 1700 cm^{-1}, 1740 cm^{-1}. Anal. calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94; Found: C, 70.79; H, 7.22; N, 3.91.

In conclusion, a method has been identified that allows the preparation of carbamate esters under simple, mild conditions with convenient reagents.

Acknowledgement. I thank Dr. P. T. Stephenson for his advice and support.

References and Notes

1) Sasaki, Y.; Dixneuf, P. *J. Org. Chem.* **1987**, *52*, 314.
2) Ohta, A.; Inagawa, Y.; Mitsugi, C. *J. Heterocyclic Chem.* **1985** , *22*, 1643.
3) Yoshida, Y.; Ishii, S.; Watanabe, M.; Yamashita, T. *Bull. Chem. Soc. Japan* **1989**, *62*, 1534. Aresta, M.; Quaranta, E. *Tetrahedron* **1991**, *47*, 9489.
4) Since the completion of this work, another group (Nussbaumer, P.; Leitner, I.; Stutz, A. *J. Med. Chem.* **1994**, *37*, 610) have independently reported a similar observation.
5) Wang, S.; Gisin, B.; Winter, D.; Makofske, R.; Kulesha, I.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1977**, *42*, 1286. Dijkstra, G.; Kruizinga, W.; Kellogg, R. *J. Org. Chem.* **1987**, *52*, 4230.
6) The amount of inorganic base has not been investigated. In most of the reactions 2 molar equivalents were used, whereas in reactions involving amine hydrochlorides 3 molar equivalents were used.
7) Miyoshi, M. *Bull. Chem. Soc. Japan* **1973**, *46*, 1489.
8) Yields refer to isolated products and have not been optimised. Satisfactory ^1H n.m.r., infra red, mass spectra and elemental analyses were obtained for all new compounds. All other compounds were purified further where necessary and compared to literature data.
9) Two equivalents of amine were used to give the biscarbamate ester (**4**), not readily prepared by conventional carbamate ester formation.



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