Pergamon

Tetrahedron Letters 43 (2002) 1217–1219

TETRAHEDRON
LETTERS

The synthesis of alkyl carbamates from primary aliphatic amines and dialkyl carbonates in supercritical carbon dioxide

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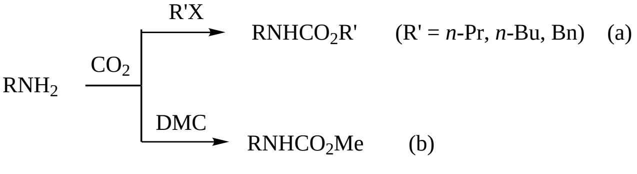
Received 17 October 2001; revised 17 December 2001; accepted 19 December 2001

Abstract—At 130°C and in the presence of compressed CO_2, primary aliphatic amines [RNH_2, $R=C_{10}H_{21}$, C_8H_{17}, cHex, 1-($C_{10}H_7$)CH_2] react with organic carbonates ($R'OCO_2R'$; R′ = Me, Et) to give alkyl carbamates ($RNHCO_2R'$, **1**). Although CO_2 promotes the reaction also at a low pressure, good yields (~80%) of **1** are achievable only with supercritical carbon dioxide ($scCO_2$) at 90 bar, which inhibits the formation of *N*-methylated by-products. © 2002 Elsevier Science Ltd. All rights reserved.

Organic carbamates ($RNHCO_2R'$, **1**) are compounds widely used for a number of scopes including pharmaceutical preparations, production of agrochemicals (pesticides and herbicides), and more generally, of intermediates for fine and commodity chemicals.[1]

By far, the most important reaction for the synthesis of these products, is the aminolysis of chloroformate esters obtained from phosgene and alcohols.[2] This method poses great concerns from both the environmental and safety standpoints because of the toxicity and corrosion properties of phosgene itself.[3]

To overcome this drawback, many alternative routes with low environmental impact have been conceived. Among them, the catalytic carbonylation of nitroaromatics and the oxidative carbonylation of amines should be noted,[4] as well as the even more eco-friendly procedures based upon the reaction of amines with carbon dioxide in the presence of alkyl halides[5] or dimethyl carbonate (DMC) (Scheme 1).[6]



Scheme 1.

In particular, very good results have been claimed with the use of alkyl halides and CO_2 [either in the gaseous or in the supercritical phase ($scCO_2$)], in the presence of onium salts and basic catalysts [(a) of Scheme 1].[5] While, moderate yields of **1** (~50%) were reported with dimethyl carbonate and gaseous CO_2 [(b) of Scheme 1].[6] This latter reaction attracted our attention for a two-fold reason: (i) DMC is a green reagent;[7] (ii) as a part of our research program on clean syntheses, the reactivity of DMC—both as a methylating and a methoxycarbonylating agent of amines—has been extensively investigated by us.[8] Moreover our group is involved in the study of $scCO_2$ as a solvent.[9]

We wish to report here that a convenient procedure for the carbamation of primary aliphatic amines with dialkyl carbonates can be performed in supercritical carbon dioxide (Table 1).

Caution: operation of high-pressure equipment requires proper safety precautions to minimise the risks of personal injury.[11]

In a typical procedure, a 150 mL stainless steel autoclave fitted with a thermostatic jacket was charged with *n*-decylamine (1.0 g, 6.3 mmol) and DMC (5.7 g, 6.4×10^{-2} mol). The autoclave was then pressurised with CO_2 (SFC/SFE grade) at approximately 40 bar, by using an automatic syringe pump (ISCO model 260 D), and it was heated to the desired temperature, through an oil-circulating thermostat. The final pressure of 90 bar was reached by slowly adding the remaining CO_2 to the reactor. The mixture was magnetically stirred

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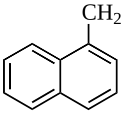
PII: S0040-4039(01)02390-5

Table 1. The carbamation of primary aliphatic amines with dialkyl carbonates in $scCO_2$[a]

Entry	Substrate RNH_2	Organic Carbonate	T (°C)	Reaction time (h)	Conv'n (%)	Product $RNHCO_2R'$,[10]	Isolated yield (%)
1	R: $C_{10}H_{21}$	DMC	130	17	95[b]	**1a**: R = Me	83
2	R: $C_{10}H_{21}$	DEC	130	20	80	**1b**: R = Et	65
3	R: 	DMC	130	20	91	**1c**: R = Me	80
4		DEC	140	18	65	**1d**: R = Et	48
5	R: C_8H_{17}	DMC	130	15	89	**1e**: R = Me	77
6	R: cHex	DMC	130	14	85	**1g**: R = Me	50

[a] All reactions were performed at 90 bar, using a dialkyl carbonate/substrate molar ratio of 10. DEC: diethyl carbonate.

[b] At 130 bar, conversion was 96%.

throughout the reaction which was allowed to proceed for the reported time (entry 1). After cooling, CO_2 was slowly vented by bubbling it into diethyl ether (5 mL). The content of the autoclave was washed with additional diethyl ether (5 mL), and the combined ethereal solutions were acidified (HCl 10%, 10 mL), extracted, and finally dried over Na_2SO_4. After filtration and rotary evaporation, compound **1a** was recovered as a yellow solid (1.15 g, 5.34 mmol; 83%) which was analysed by GC/MS (HP 5890, series II, fitted with a 30 m HP5MS column) and ^{1}HNMR (Bruker 300 MHz). The structure was also confirmed by comparison with an authentic sample obtained by reported procedures.[12]

Although the carbamation of amines with dialkyl carbonates is known,[13a] only catalysed reactions proceed with good yields and selectivities;[12] more recently, good results have been reported with Pb- and alumina-based catalysts.[13b,c] Instead, as mentioned above in Scheme 1, the uncatalysed process may take place in the presence of gaseous carbon dioxide through the formation of alkylammonium carbamates (**2**), (Eq. (1))[14] which appear as convenient nucleophilic precursors of alkyl carbamates.

$$2RNH_2 + CO_2 \rightleftharpoons \underset{\mathbf{2}}{RNHCO_2^- RNH_3^+} \xrightarrow{DMC} RNHCO_2Me \qquad (1)$$

However, in conventional solvents or in DMC as a reagent/solvent, results are modest: for instance, after 24 h at 90°C, cyclohexyl- and allyl-amines were reported to give the corresponding methyl urethanes in 35 and 55% yields.[6a]

As can be seen from Table 1, in the presence of supercritical carbon dioxide, the carbamation reactions with DMC proceed with good yields (77–83%: entries 1, 3, and 5; except for *c*Hex: 50%, entry 6), towards the formation of the corresponding methyl carbamates. Results also show that diethyl carbonate (DEC) is suitable for the preparation of ethyl carbamates (entries 2 and 4). However, lower conversions are due to the lower reactivity of DEC with respect to DMC,[15] and yields have not been optimised.

To investigate more in-depth the role of carbon dioxide, *n*-decylamine was made to react with DMC at 130°C and at different pressures of CO_2 (from 8 to 90 bar). Reactions were run also at different times (3, 6 and 14 h). Results are reported in Table 2.

Table 2. The reaction of $n\text{-}C_{10}H_{21}NH_2$ with DMC at different pressure of carbon dioxide[a]

Entry	Pressure of CO_2 (bar)	Reaction time (h)	Conv'n (%, GC)	Ratio of carbamate products (%)[b]		Isolated yield of **1a** (%)
				1a	**2a**[16]	
1	8	3	74	87	13	Nd[c]
2	8	6	100	76	24	54
3	8	14	100	74	26	51
4	19	6	100	82	18	57
5	19	14	100	83	17	58
6	40	6	100	87	13	68
7	90	6	100	96	4	77
8	90	14	100	90	10	76

1a: $n\text{-}C_{10}H_{21}NHCO_2Me$; **2a**: $n\text{-}C_{10}H_{21}N(Me)CO_2Me$.

[a] Reactions carried out with a DMC/$n\text{-}C_{10}H_{21}NH_2$ molar ratio of 10.

[b] Ratio determined by GC.

[c] Not determined.

The carbamation reaction may take place also at a low pressure (8 bar, entries 1–3), though under such conditions, a competitive methylation process occurs and a mixture of n-$C_{10}H_{21}NHCO_2Me$ (**1a**) and its *N*-methyl derivative [n-$C_{10}H_{21}N(Me)CO_2Me$, **2a**] is recovered. After 6 h, the ratio **1a**:**2a** is 76:24 (entry 2), and even at a lower conversion (74%, 3 h), it does not exceed 87:13 (entry 1). Prolonged reaction times do not alter significantly the product distribution, suggesting that **2a** comes mainly from the *N*-methylated amine rather than **1a** (entries 3 and 5). However, as the CO_2 pressure is increased, the carbamation selectivity is enhanced as well, up to 96% at 90 bar (entry 7). The effect of the solvent pressure results in the inhibition of the methylation reaction,[17] which is advantageous for the formation of pure carbamates **1**.

In conclusion, the reported procedure is an example of a genuinely clean synthesis of alkyl carbamates using eco-friendly reagents without any catalysts or additional co-solvents. The efficiency of the method lies in the use of compressed CO_2 whose pressure must be high enough ($\sim$90 bar) to favour the formation of alkylammonium carbamates **2** (Eq. (1)), thus leading to a substantial inhibition of *N*-methylated by-products. However, solvation effects may also have a role: in fact, at a higher CO_2 pressure [130 bar, footnote (b) in the Table 1], the conversion does not vary, meaning that a higher concentration of the reactant CO_2 does not accelerate the reaction.

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10. Compound **1a**: ^1H NMR ($CDCl_3$) δ: 0.89 (t, 3H, CH_3, $J=6.5$ Hz), 1.27 (m, 14H, $7CH_2$), 1.49 (m, 2H, CH_2), 3.16 (q, 2H, CH_2N, $J=6.4$ Hz), 3.67 (s, 3H, OCH_3), 4.66 (brs, 1H, NH); GC/MS (70 eV) m/z (relative intensity): 215 (M^+, 4), 200 (3), 88 (100), 76 (17), 44 (13).

    Compound **1b**: ^1H NMR ($CDCl_3$) δ: 0.89 (t, 3H, CH_3, $J=6.7$ Hz), 1.27 (m, 17H, $7CH_2$ and $1CH_3$), 1.49 (m, 2H, CH_2), 3.17 (q, 2H, CH_2N, $J=6.7$ Hz), 4.11 (q, 2H, OCH_2, $J=6.8$ Hz), 4.62 (brs, 1H, NH); GC/MS (70 eV) m/z (relative intensity): 229 (M^+, 6), 200 (20), 102 (100), 90 (17), 41 (15).

    Compound **1c**: ^1H NMR ($CDCl_3$) δ: 1.67 (brs, 1H, NH), 3.73 (s, 3H, OCH_3), 4.83 (d, 2H, CH_2, $J=5.5$ Hz), 7.4-8.05 (m, 7H, Ar); GC/MS (70 eV) m/z (relative intensity): 216 (12), 215 (M^+, 81), 201 (12) 200 (87), 156 (60), 155 (21), 154 (51), 141 (60), 129 (100), 128 (48), 127 (48), 115 (48).

    Compound **1d**: ^1H NMR ($CDCl_3$) δ: 1.25 (t, 3H, CH_3, $J=6.9$ hz), 1.61 (brs, 1H, NH), 4.16 (q, 2H, OCH_2, $J=6.9$ Hz), 4.83 (d, 2H, CH_2, $J=5.6$ Hz), 7.40-7.90 (m, 7H, Ar); GC/MS (70 eV) m/z (relative intensity): 230 (8), 229 (M+, 49), 201 (15), 200 (100), 183 (12), 156 (62), 155 (12), 154 (32), 141 (48), 129 (93), 128 (34), 127 (33), 115 (32).

    Compounds **1e** and **1f**: full characterisation data are in Refs. 13c and 6a, respectively.
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16. Compound **2a**: GC/MS (70 eV) m/z (relative intensity): 229 (M^+, 8), 102 (100), 88 (19), 58 (18), 42 (18), 41 (29). The structure of **2a** was confirmed by reacting n-$C_{10}H_{21}NHMe$ with $ClCO_2Me$ according to known procedures (Bortnick, N.; Luskin, L. S.; Hurwitz, M. D.; Rytina, A. W. *J. Am. Chem. Soc.* **1956**, *78*, 4358).
17. DMC is an excellent *N*-methylating agent at temperatures over 130°C (Ref. 8).