Pergamon

Tetrahedron Letters 43 (2002) 4091–4093

TETRAHEDRON LETTERS

Efficient and clean synthesis of *N*-alkyl carbamates by transcarboxylation and *O*-alkylation coupled reactions using a DBU–CO_2 zwitterionic carbamic complex in aprotic polar media

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Received 31 January 2002; accepted 29 March 2002

Abstract—*N*-Alkyl carbamates were obtained with good to excellent yields by clean and mild transcarboxylation of several amines with the previously synthesized DBU–CO_2 complex and subsequent *O*-alkylation. Transcarboxylation was found to be selective, as only carbamate was formed from 1-hydroxy-2-aminobutanol. © 2002 Published by Elsevier Science Ltd.

N-Alkyl carbamates represent an important class of organic compounds, mainly employed in agriculture (pesticides, fungicides), pharmacology (medicinal drugs) and as valuable intermediates in synthesis.[1] Also, organic carbamates have been found useful as protective groups for the amine function in peptide synthesis.[2]

Classical procedures for the preparation of *N*-alkyl carbamates are based on the reaction of either amines with chloroformates,[3] or alcohols with isocyanates.[4] Chloroformates and isocyanates are toxic and polluting reagents and require careful handling. On the other hand, the uncatalyzed reaction of primary or secondary amines with carbon dioxide, and subsequent alkylation usually leads to mainly *N*-alkylation products.[5]

Recently, some attractive procedures for carbamates synthesis have been reported which proposed the use of carbon dioxide, as a clean and abundant raw material. Utilization of sterically hindered strong organic bases or cesium carbonate has been proposed to enhance the reactivity of the carbamate anion toward *O*-alkylation.[6] Use of amidines such as the diazabicycloundecene (DBU) for carbonylation with carbon dioxide was described in the synthesis of dihydroquinazolines.[7]

We report here the synthesis of *N*-alkyl ethyl carbamates, with good to excellent yields, by mild transcarboxylation of several amines (Table 1, entries 1–5) with a DBU–CO_2 complex followed by the *O*-alkylation of the *N*-alkyl carbamate intermediates with ethyl iodide.[8] An exploratory experiment was carried out using 1,6-dibromohexane for the *O*-alkylation of the model *N*-cyclohexyl carbamate intermediate to check the compatibility of our method with different alkyl halides. Hence, the corresponding *N*-cyclohexyl bromohexyl carbamate was obtained with 80% yield (GC).

In our experiments, DBU was found to be an efficient catalyst for the activation of the carbon dioxide molecule through nucleophilic attack on the weak electrophilic carbon center of the CO_2 molecule. The resulted DBU–CO_2 carbamic complex was able to transcarboxylate several amines (entries 1–5) to provide the *N*-alkyl carbamates intermediates as "naked anions" which, conjugated with protonated DBU, were converted to the corresponding *N*-alkyl carbamates esters by subsequent *O*-alkylation (Scheme 1).

About 75% (w/w) of the employed DBU was recovered as a free base, from the first catalytic cycle shown in Scheme 1, which has been reutilized once again for the synthesis of *N*-cyclohexyl ethyl carbamate (entry 1) with reproducible yield and purity. Carbamate intermediates, isolated from the reaction mixtures (entries 1 and 4), were unambiguously characterized (NMR, mass spectrometry) and subsequently transformed in the related *N*-alkyl ethyl carbamates.

Keywords: carbon dioxide; DBU–CO_2; transcarboxylation; *N*-alkyl carbamates.

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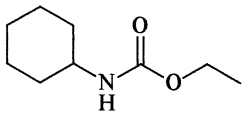
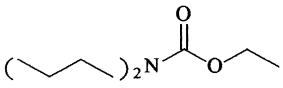
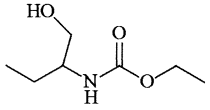
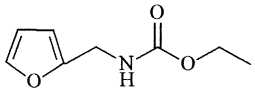
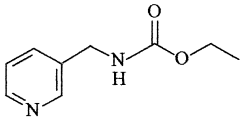
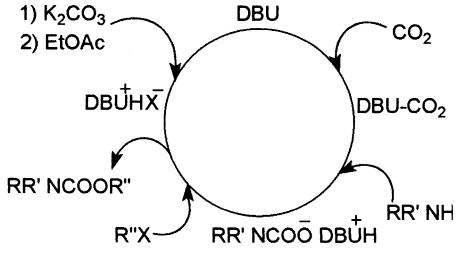
PII: S0040-4039(02)00697-4

Table 1.

Entry	RR' NH	*N*-alkylcarbamates[a]	Anal. Calcd (Found)	%Yield [b,c]
1	cyclohexylamine		$C_9H_{17}NO_2$: C 63.15 (62.86); H 9.94 (10.10), N 8.18 (8.25)	98 (96)
2	di-butylamine		$C_{11}H_{23}NO_2$: C 65.67 (65.28); H 11.44 (11.53); N 6.96 (7.02)	93 (89)
3	1-hydroxy-2-butylamine		$C_7H_{15}NO_3$: C 52.17 (51.84); H 9.31 (9.42); N 8.69 (8.77)	90[d] (85)
4	2-furfurylamine		$C_8H_{11}NO_3$: C 56.80 (56.48); H 6.50 (6.59); N 8.28 (8.32)	80 (77)
5	3-(aminomethyl) pyridine		$C_9H_{12}N_2O_2$: C 60.00 (59.73); H 6.66 (6.74); N 15.55 (15.68)	90 (84)

a) NMR, IR and Mass spectras were in accordance with the assigned structures for *N*-alkyl carbamates.
b) Determined by GC and GC-MS. Average yields of isolated products in parenthesis.
c) Complement to 100 % were mainly *N, N* – dialkyl carbamates (~3-7 %).
d) Reaction was found selective, since neither carbonate nor isoxazoline were formed.



Scheme 1.

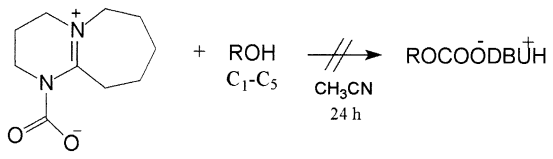
The reactivity of the DBU–CO_2 complex has been investigated towards aliphatic primary (C_1–C_5) alcohols. Consequently, with the selective amine transcarboxylation observed for aminoalcohols (entry 3), carbonate formation was unsuccessful even with DBU–CO_2 excess (5 equiv.) for 24 h (Scheme 2). In all the cases, starting alcohols and DBU–CO_2 complex were almost quantitatively recovered. Similar results were obtained when the reactions were carried out using DBU (5 equiv.) as base under pressurized CO_2 (10 atm) even with heating (60°C) for reaction times up to 48 h.

Under the above conditions, the formation of the DBU–CO_2 adduct occurs rather than thermodynamic proton transfer, despite the reported[9] pK_a (23.9) value for DBU in acetonitrile being greater than those for investigated alcohols (e.g. pK_a of ethanol is 17.0). On the other hand, alcohols used in our experiments were not strong enough as nucleophiles to displace the CO_2 molecule from the DBU–CO_2 complex.

The most important features of the protocol described here are the following:

i. The suitability of DBU as a trap for fixation and storage of CO_2 in the form of a reactive DBU–CO_2 adduct, which is useful for transcarboxylation of several amines.

ii. The cleanness and mildness of the procedure that employs CO_2 as a trouble-free starting material for the preparation of important synthetic intermediates



Scheme 2.

and biologically interesting compounds (e.g. pyridine and furfuryl derivatives).

In summary, we propose the utilization of the DBU–CO_2 carbamic complex as an efficient, clean and selective transcarboxylating reagent for preparation of *N*-alkyl carbamates. Furthermore, this procedure could be used as a combinatorial chemistry approach for simultaneous synthesis of several *N*-alkyl carbamates from a diverse range of amines and alkyl halides.

Experimental and theoretical studies concerning the capability of several hindered bases for CO_2 coordination and transfer towards various nucleophiles are currently in progress at our Laboratory. Results from these studies will be communicated elsewhere.

Acknowledgements

We gratefully acknowledge financial support from FAPESP. One of us, Eduardo R. Pérez is thankful for a CAPES fellowship.

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8. **Representative experimental procedures:** (a) DBU–CO_2: DBU (1.52 g, 10 mmol) was stirred in anhydrous acetonitrile (10 mL) under a continuous stream of carbon dioxide (30 mL/min) for 1 h at 5°C. Then, deposited solid was filtered off and washed with cold acetonitrile (3×5 mL) to give DBU–CO_2 as a white powder (1.57 g, 80%) with high purity; mp 38–39°C dec. with a loss of 23% of mass (CO_2) on TGA analysis; ^{1}H NMR (200 MHz, D_2O) δ 1.75–2.01 (m, $3CH_2$, C-5+C-6+C-8), 2.65 (t, CH_2, C-4), 3.15–3.25 (m, $2CH_2$, C-7+C-11), 3.51 (t, CH_2, C-12), 4.60 (t, CH_2, C-10); ^{13}C NMR (50.32 MHz, D_2O) δ 19.5 (C-6), 23.9 (C-5), 26.4 (C-7), 29.0 (C-11), 33.2 (C-12), 38.5 (C-4), 48.7 (C-8), 54.6 (C-10), 160.7 (C-1), 166.4 (C-3); (b) *N*-alkyl carbamates: In a typical procedure, 2 mmol of amine (entry 4), were slowly added to the suspension of DBU–CO_2 (0.47 g, 2.4 mmol) in 10 mL of anhydrous acetonitrile, with stirring for 1.5 h at 5°C. Then, ethyl iodide (0.47 g, 3 mmol) was poured into the solution and the reaction mixture was stirred at ambient temperature for an additional 6 h. Evaporation of the solvent and extraction with ethyl ether (3×10 mL) or alternative column chromatography (6:1 hexanes/EtOAc) gave the *N*-(2-furfuryl) ethyl carbamate as a yellow oil. ^{1}H NMR (200.13 MHz, $CDCl_3$) δ 1.24 (t, 3H, methyl), 4.11 (q, 2H, methylene), 4.29 (d, 2H, methylene), 5.05 (t, 1H, amino), 6.20 (d, 1H, 3-furyl), 6.29 (dd, 1H, 4-furyl), 7.32 (d, 1H, 5-furyl). ^{13}C NMR (50.32 MHz, D_2O) δ 15.3, 37.9, 61.0, 107.0, 109.5, 142.1, 151.6, 156.3. MS (70 eV) m/z 69, 81, 96 (100%), 140, 169 (M^+). IR (thin film on silicon wafer) cm^{-1} 3336, 1679, 1312.
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