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A high yielding one-pot, novel synthesis of carbamate esters from alcohols using Mitsunobu's reagent☆

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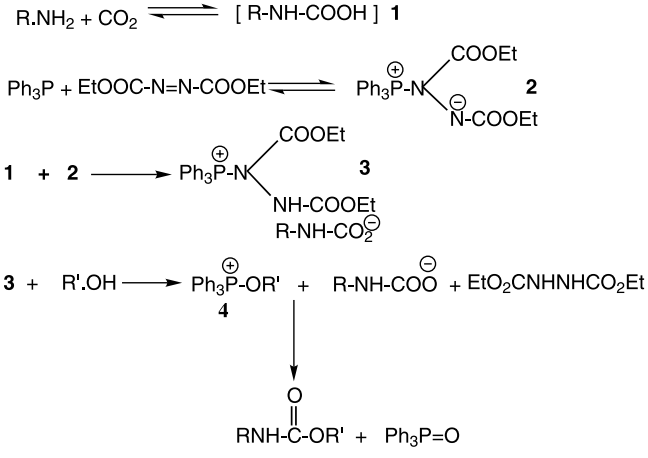
Abstract—A novel process for the one-step conversion of primary alcohols into carbamates as protected amines has been developed using Mitsunobu's reagent in the presence of gaseous carbon dioxide. Thus, carbamate esters of the different amines were prepared in very good to excellent yields.

Organic carbamates, initially encountered largely as agrochemicals[1] and in peptide chemistry as protecting groups[2] or linkers in combinatorial synthesis[3] are rapidly emerging as pharmaceuticals[4] mainly in the form of prodrugs. To satisfy the demand, their synthesis has changed from the use of harmful chemicals like phosgene and its derivatives directly or indirectly, to the use of chloroformates[5] or isocyanates,[6] to abundantly available cheap and safe reagents like CO_2. The preparation of carbamates using CO_2 has been reported electrochemically,[7] supercritically,[8] in combination with metals and non metal species,[9] macrocyclic polyethers,[10] and various phase transfer catalysts.[11] Utilization of sterically hindered strong bases or cesium carbonate has been proposed to enhance the reactivity of carbamate anions towards *O*-alkylation.[12] Recently we have reported[13] an efficient, high yielding, one-pot carbamate ester synthesis from alcoholic tosylates using carbon dioxide and tetra-*n*-butylammonium iodide.

We report here the synthesis of *N*-alkyl carbamates in good to excellent yields, by mild carboxylation of alkylamines with CO_2 followed by *O*-alkylation with an alcohol in the presence of Mitsunobu's reagent (i.e. diethyl azodicarboxylate and triphenylphosphine). The use of Mitsunobu's reagent in ether formation is well known.[14] Its use for the synthesis of carbonate esters has also been reported by Hoffmann.[15] Taking this last report as a guide, we attempted[16] the synthesis of carbamates by mild carboxylation of alkyl amines with CO_2 and an alcohol in the presence of Mitsunobu's reagent.

We assumed that the unstable carbamic acid generated from alkylamine and CO_2 would react with the Mitsunobu complex formed from Ph_3P and diethyl azodicarboxylate, to furnish the stabilized ionic species which in turn would undergo *O*-alkylation giving rise to the formation of carbamate esters as shown in Scheme 1.

Thus, the alkylamine was taken in a suitable solvent and a stream of CO_2 was rapidly passed through it for its conversion to substituted carbamic acid. The Mit-



Scheme 1. Proposed mechanism of formation of carbamate ester.

Keywords: diethyl azodicarboxylate (DEAD); triphenylphosphine; Mitsunobu's reagent; carbon dioxide; *N*-alkylcarbamates.

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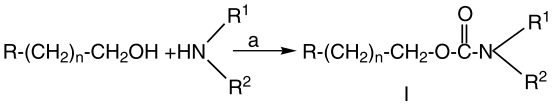
Table 1. Conversion of the primary alcohols into carbamates of general formula I

Entry no.	R	R^1	R^2	*n*	Time (h)	Yields (%)
1	Phenyl	*n*-C_4H_9	H	1	2.5	90
2	Phenyl	*n*-C_6H_{13}	H	2	2	95
3	Phenyl	*n*-C_3H_7	*n*-C_3H_7	1	3	81
4	Phenyl	*n*-C_3H_7	*n*-C_3H_7	2	3	85
5	*n*-Octyl	*n*-C_6H_{13}	H	3	2	98
6	*n*-Hexyl	3-Methoxybenzyl	H	1	2.5	92
7	*n*-Butyl	*n*-Butyl	H	1	2.5	89
8	*n*-Propyl	Cyclohexyl	H	2	3	90
9	*i*-Propyl	*n*-Hexyl	H	2.5	1	92
10	*n*-Propyl	*i*-Amyl	H	2.5	1	90
11	Ethyl	*n*-Hexyl	H	3	1	86
12	2-Naphthyloxy	Cyclohexyl	H	3	1	96

All the products were characterized by IR, NMR, and mass spectral data.



Scheme 2. *Reagents and conditions*: (a) dry DMSO, DEAD/Ph_3P, CO_2 bubbling, 90–100°C.

sunobu's reagent generated from triphenylphosphine and diethyl azodicarboxylate in dry dimethylsulfoxide (DMSO) was then added to it followed by addition of the alcohol.

The carbamate esters thus prepared from aliphatic amines are given in Table 1. We tried several solvents like *n*-heptane, *n*-hexane, DMSO, dimethylformamide and hexamethylphosphoric triamide of which dry DMSO proved to be the most suitable, in a temperature range of 90–100°C. The overall reaction is shown in Scheme 2.

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16. **Typical experimental procedure**: 2-phenylethyl *n*-butyl carbamate.
n-Butylamine (0.83 ml, 9 mmol) in dry DMSO (60 ml) was reacted with dried CO_2 gas rapidly bubbled into it at 90°C for 0.5 h. To the reaction mixture triphenylphosphine (2.2 g, 9 mmol) was added and then diethyl azodicarboxylate (1.33 ml, 9 mmol) was added slowly in 2–3 small portions. Next, 2-phenylethyl alcohol (1 ml, 9 mmol) was added. The reaction was continued till completion (3.5 h). The reaction mixture was poured into distilled water (80 ml) and extracted with ethyl acetate thrice. The organic layer was separated and dried over

anhydrous sodium sulfate, and then concentrated to give 2-phenylethyl *n*-butyl carbamate. (1.68 g, 91%), as an oil. IR (neat, cm^{-1}): 1684 (O-CO-NH, carbamate linkage), ^1H NMR ($CDCl_3$): $\delta = 0.89$–0.96 (t, 3H, $J =$ 6.5 Hz, CH_3), 1.28–1.34 (m, 2H, CH_2CH_3), 1.54–1.59 (m, 2H, $CH_2CH_2CH_3$), 2.83–2.88 (t, 2H, $J = 6.7$ Hz, $PhCH_2$), 2.94–2.96 (m, 2H, O-CONHCH_2), 4.40–4.45 (t, 2H, $J = 7$ Hz, CH_2-O-CO-NH), 7.08–7.21 (m, 5H, Ar-H of phenyl ring), 7.7 (bs, 1H, NH). Mass: m/z 221 (91%). Analysis: $C_{13}H_{19}NO_2$, calcd: C, 70.56%; H, 8.65%; N, 6.33%; obsd: C, 70.89%; H, 8.18%; N, 6.14%.