Monatshefte für Chemie 137, 201–206 (2006)
DOI 10.1007/s00706-005-0417-5

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

A High Yielding, One-Pot, Triton-B Catalyzed, Expeditious Synthesis of Carbamate Esters by Four Component Coupling Methodology[+]

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Received May 24, 2005; accepted (revised) June 23, 2005
Published online December 13, 2005

Summary. A novel process for the one-step chemoselective conversion of alkyl halides into carbamates as protected amines was developed using benzyltrimethylammonium hydroxide (Triton-B) in presence of gaseous carbon dioxide. Thus, carbamate esters of different amines were prepared in very good to excellent yields.

Keywords. Alkyl halides; Dimethylaminopyridine; Triton-B; Carbon dioxide; *N*-Alkyl/aryl carbamate.

Introduction

Organic carbamates are of considerable interest because of their interesting chemistry and wide utility. They have found extensive use as agrochemicals [1], pharmaceuticals [2], intermediates in organic synthesis [3], protection of amino functionality in peptide chemistry [4], linkers in combinatorial chemistry [5], *etc*. Functionalization of amines as carbamates offers an attractive method for generation of derivatives, which may constitute interesting medicinal and biological properties [6].

Classical synthesis of carbamates involves phosgene [7], its derivatives [8], or carbon monoxide [9], thus utilizing harmful chemicals directly or indirectly. Therefore, attention in the recent past has been payed to an alternative and efficient route to carbamates avoiding use of hazardous chemicals.

[+] CDRI Communication No.: 6297

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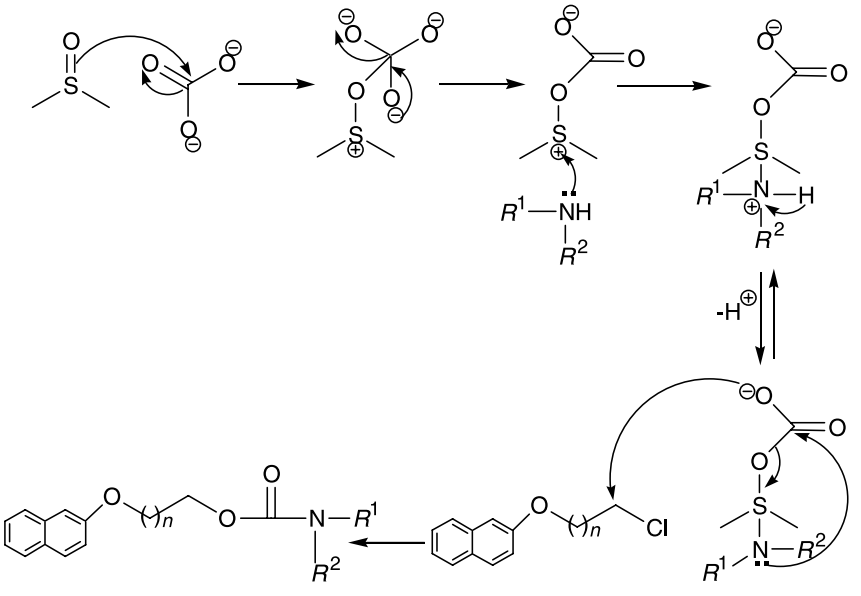
Result and Discussion

In context of ongoing research, we report herein a useful and safe methodology for a direct one-pot synthesis of *N*-alkyl/aryl carbamates beginning from primary, secondary, and aromatic amines. Our work [10] in this area started with the interesting findings that when alkyl halides were treated with amine derivatives in dry dimethylsulphoxide (*DMSO*) in the presence of K_2CO_3 and dimethylaminopyridine (*DMAP*) as a catalyst for the preparation of corresponding amines, it led to the isolation of carbamate esters, though in poor yields. A likely mechanism of carbamate formation is shown in Scheme 1. The formation of carbamate in poor yields might be explained on the basis of less possibility of O than N alkylation and K_2CO_3 alone as a poor source to provide carbonyl functionality. All our attempts to improve the yield of carbamates by changing reaction temperature, use of other metal carbonates and bicarbonates, such as lithium carbonate, calcium carbonate, sodium carbonate, cesium carbonate, potassium bicarbonate, sodium bicarbonate, *etc.*, solvent system, and reaction time had little effect. Furthermore, the high temperature and the longer reaction time did not favor the synthetic utility of the method. Also, this method failed to provide carbamate esters of aromatic amines.

In view of the reasoning discussed above, we modified the method for a five component system using gaseous CO_2. Reports have appeared on the use of CO_2 electrochemically [11], supercritically [12], and in combination with metals and non metals [13]. We have also recently reported carbamate ester synthesis from alcoholic tosylates [14] and using *Mitsunobu*'s reagent [15].

CO_2 alone has low reactivity with nucleophiles, with amines it gives the unstable carbamic acid. However, with two equivalences of amine, the monoalkylammonium alkyl carbamate (*MAAAC*) ion is formed. The *MAAAC* ion thus formed reacts with alkylating agents to give rise to N- or O-alkylated (carbamate)



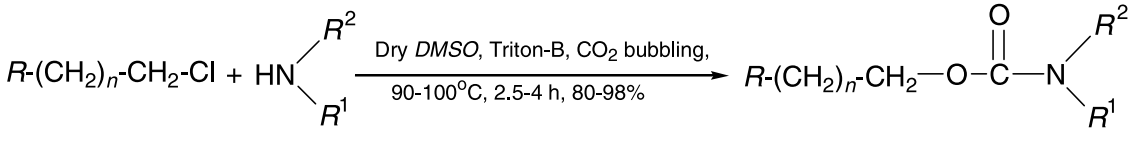
Scheme 1

products. Based on the concept of the ionic *MAAAC* species formed from CO_2 and amine, we used five component coupling methodology in which alkyl halide, amine, K_2CO_3, gaseous CO_2, and tetra *n*-butylammonium iodide (*TBAI*) were used. The reaction was carried out at 90–100°C for 5–6 h. This method gave better yields of carbamates from aliphatic amines but not for aromatic carbamates. To enhance yields of *N*-aryl carbamates, benzyltrimethylammonium hydroxide (Triton-B) was tried as a phase transfer catalyst to possibly help in increasing the basic nature of ionic *MAAAC* species. Thus, when the reaction was carried out using Triton-B, very good yields of carbamates were obtained within 3–4 h. Subsequently it was observed that K_2CO_3 could be eliminated from the reaction mixture without compromising with the yields of the carbamate formed. Accordingly, Triton-B was found to be a suitable catalyst for better yields in a four component carbamate synthesis. Carbamates thus prepared are shown in Table 1. The reaction is shown in Scheme 2. We have tried several solvents, like *n*-pentane, *n*-hexane, *n*-heptane, dimethylformamide, *DMSO*, acetonitrile, hexamethylphosphoric-triamide (*HMPA*), *etc*., and found dry *DMSO* most suitable for the carbamate esters obtained from aliphatic amines and *HMPA* for aromatic amines.

In conclusion, we have developed a simple and efficient one-pot four component synthesis of various carbamate esters starting with primary, secondary, and aromatic amines using the Triton-B/CO_2 system affording high yields.

Table 1. Conversion of alkyl halides into carbamates

Product	*R*	R^1	R^2	*n*	Time/h	Yield/%
1a	2-Naphthyloxy	*n*-C_4H_9	H	3	3	93
1b	2-Naphthyloxy	*n*-C_6H_{13}	H	2	3	91
1c	2-Naphthyloxy	*n*-C_8H_{17}	H	1	3.5	89
1d	2-Naphthyloxy	*n*-$C_{12}H_{25}$	H	3	2.5	98
1e	2-Naphthyloxy	Cyclohexyl	H	2	3.5	90
1f	2-Naphthyloxy	*n*-C_3H_7	*n*-C_3H_7	2	3.5	85
1g	2-Naphthyloxy	$R^1 = R^2 =$ Morpholinyl		2	4	82
1h	2-Naphthyloxy	$R^1 = R^2 =$ Pyrrolidinyl		2	4	83
1i	2-Naphthyloxy	$C_6H_5CH_2$	H	1	3.5	87
1j	2-Naphthyloxy	3-Phenylpropyl	H	3	3	95
1k	2-Naphthyloxy	*p*-*Me*C_6H_4	H	2	3.5	80
1l	2-Naphthyloxy	*p*-*Me*OC_6H_4	H	2	3.5	83
1m	*Ph*	*n*-C_4H_9	H	1	3.5	86
1n	*Ph*CH_2	*n*-C_6H_{13}	H	2	3.5	88



Scheme 2

Experimental

Chemicals were obtained from Merck, Aldrich, and Fluka chemical companies. IR spectra were recorded on a Bomem MB-104 FTIR spectrometer and ^{1}H NMR data were scanned on a AC-300F NMR (300 MHz) instrument using $CDCl_3$ as solvent and *TMS* as internal standard. Elemental analysis were made by Carlo-Erba EA1110 CNNO-S analyzer and agreed favourably with calculated values.

Typical Experimental Procedure

Amine (5 mmol) was taken in 35 cm^3 dry *DMSO*. Purified (by passing through H_2SO_4 and $CaCl_2$ trap) CO_2 gas was rapidly bubbled into it at 90°C for 0.5 h and Triton-B (2 mmol) was added before the reaction was continued for 0.5 h. Then 2 mmol of the corresponding (chloroalkoxy) naphthalene were added. The reaction was further continued until completion of the reaction (Table 1) as checked by TLC. The reaction mixture was poured into 50 cm^3 distilled H_2O and extracted with ethyl acetate thrice. The organic layer was separated, dried (Na_2SO_4), and then concentrated to give the desired compound.

[4-(2-Naphthyloxy)but-1-yl] n-butyl carbamate (**1a**, $C_{19}H_{25}NO_3$)

Yield 93%; IR (KBr): $\bar{\nu} = 1689\,cm^{-1}$ (carbamate linkage); ^{1}H NMR ($CDCl_3$): $\delta = 0.92$–0.96 (t, CH_3), 1.30–1.34 (m, $\underline{CH_2}CH_3$), 1.53–1.56 (m, $\underline{CH_2}CH_2CH_3$), 1.56–1.59 (t, $\underline{CH_2}CH_2$–O–CO–NH), 1.69–1.72 (t, $\underline{CH_2}CH_2$–O–naphthyl), 2.92–2.96 (m, $\underline{CH_2}$NH), 4.01–4.05 (t, $\underline{CH_2}$–O–naphthyl), 4.07–4.11 (t, $\underline{CH_2}$–O–CO), 6.97–7.66 (m, Ar-H), 8.0 (br, NH) ppm; MS: $m/z = 315$.

[3-(2-Naphthyloxy)prop-1-yl] n-hexyl carbamate (**1b**, $C_{20}H_{27}NO_3$)

Yield 91%; IR (KBr): $\bar{\nu} = 1689\,cm^{-1}$ (carbamate linkage); ^{1}H NMR ($CDCl_3$): $\delta = 0.93$–0.99 (t, $J = 6.5$ Hz, CH_3), 1.25–1.29 (m, $\underline{CH_2}\underline{CH_2}$ of *n*-hexyl group), 1.30–1.34 (m, $\underline{CH_2}CH_3$), 1.52–1.56 (m, NH$\underline{CH_2}CH_2$), 1.98–2.10 (m, $CH_2\underline{CH_2}CH_2$), 2.92–2.96 (m, $\underline{CH_2}$NH), 4.01–4.04 (t, $J = 6.7$ Hz, $\underline{CH_2}$–O–naphthyl), 4.07–4.10 (t, $J = 7$ Hz, $\underline{CH_2}$–O–CO), 6.99–7.67 (m, Ar-H), 8.2 (br, NH) ppm; MS: $m/z = 329$.

[2-(2-Naphthyloxy)eth-1yl] n-octyl carbamate (**1c**, $C_{21}H_{29}NO_3$)

Yield 89%; IR (KBr): $\bar{\nu} = 1685\,cm^{-1}$ (carbamate linkage); ^{1}H NMR ($CDCl_3$): $\delta = 0.92$–0.96 (t, CH_3), 1.23–1.29 (m, $\underline{CH_2}\underline{CH_2}\underline{CH_2}\underline{CH_2}$ of *n*-octyl group), 1.30–1.34 (m, $\underline{CH_2}CH_3$), 1.52–1.56 (m, NH$\underline{CH_2}CH_2$), 2.92–2.96 (m, $\underline{CH_2}$NH), 4.30–4.33 (t, $\underline{CH_2}$–O–naphthyl), 4.46–4.51 (t, $\underline{CH_2}$–O–CO), 6.95–7.66 (m, Ar-H), 8.0 (br, N$\underline{H}$) ppm; MS: $m/z = 343$.

[4-(2-Naphthyloxy)but-1-yl] n-dodecyl carbamate (**1d**, $C_{27}H_{41}NO_3$)

Yield 98%; IR (KBr): $\bar{\nu} = 1708\,cm^{-1}$ (carbamate linkage); ^{1}H NMR ($CDCl_3$): $\delta = 0.92$–0.96 (t, CH_3), 1.25–1.29 (m, $\underline{CH_2}\underline{CH_2}$ $\underline{(CH_2)_5}\underline{CH_2}$ of dodecyl group), 1.30–1.34 (m, $\underline{CH_2}CH_3$), 1.53–1.56 (m, NH$\underline{CH_2}CH_2$), 1.57–1.60 (m, naphthyl–O–$CH_2\underline{CH_2}$), 1.70–1.72 (m, naphthyl–O–$CH_2CH_2\underline{CH_2}CH_2$–O–CO), 2.93–2.97 (m, CH_2NH), 4.01–4.04 (t, $\underline{CH_2}$–O–naphthyl), 4.06–4.09 (t, $\underline{CH_2}$–O–CO), 6.97–7.64 (m, Ar-H), 8.4 (br, N$\underline{H}$) ppm; MS: $m/z = 427$.

[3-(2-Naphthyloxy)prop-1-yl] cyclohexyl carbamate (**1e**, $C_{20}H_{25}NO_3$)

Yield 90%; IR (KBr): $\bar{\nu} = 1688\,cm^{-1}$ (carbamate linkage); ^{1}H NMR ($CDCl_3$): $\delta = 1.42$–1.46 (m, $\underline{CH_2}\underline{CH_2}\underline{CH_2}$ of cyclohexyl ring), 1.63–1.66 (m, $\underline{CH_2}\underline{CH_2}$ of cyclohexane ring), 1.98–2.11 (m, naphthyl–O–$CH_2\underline{CH_2}CH_2$–O–CO–NH), 3.51–3.55 (m, tertiary C$\underline{H}$ of cyclohexane ring), 4.01–4.05 (t, $\underline{CH_2}$–O–naphthyl), 4.06–4.09 (t, $\underline{CH_2}$O–CO), 6.97–7.64 (m, Ar-H), 7.8 (bs, 1H, N$\underline{H}$) ppm; MS: $m/z = 327$.

[3-(2-Naphthyloxy)prop-1-yl] diisopropyl carbamate (**1f**, $C_{20}H_{27}NO_3$)

Yield 85%; IR (KBr): $\bar{\nu} = 1693\,cm^{-1}$ (carbamate linkage); ^{1}H NMR ($CDCl_3$): $\delta = 0.94$–0.99 (t, CH_3), 1.56–1.60 (m, $\underline{CH_2}CH_3$), 1.98–2.11 (m, naphthyl–O–$CH_2\underline{CH_2}CH_2$–O–CO–NH), 2.92–2.96 (d,

$\underline{CH_2}$NH), 4.01–4.05 (t, $\underline{CH_2}$–O–naphthyl), 4.06–4.09 (t, $\underline{CH_2}$–O–CO), 6.97–7.64 (m, Ar-H), 8.2 (br, N$\underline{H}$) ppm; MS: $m/z = 329$.

[3-(2-Naphthyloxy)prop-1-yl] morpholinyl carbamate (**1g**, $C_{18}H_{21}NO_4$)
Yield 82%; IR (KBr): $\bar{\nu} = 1688\,cm^{-1}$ (carbamate linkage); ^1H NMR ($CDCl_3$): $\delta = 1.98–2.11$ (m, naphthyl–O–$CH_2\underline{CH_2}CH_2$–O–CO–NH), 3.43.4.47 (t, –N–$\underline{CH_2}\underline{CH_2}$–N– of morpholine ring), 3.62–3.68 (t, $\underline{CH_2}$–O– of morpholine ring), 4.05–4.09 (t, $\underline{CH_2}$–O–naphthyl), 4.12–4.20 (t, $\underline{CH_2}$–O–CO–NH), 6.97–7.64 (m, Ar-H) ppm; MS: $m/z = 315$.

[3-(2-Naphthyloxy)prop-1-yl] pyrrodinyl carbamate (**1h**, $C_{18}H_{21}NO_3$)
Yield 83%; IR (KBr): $\bar{\nu} = 1689\,cm^{-1}$ (carbamate linkage); ^1H NMR ($CDCl_3$): $\delta = 1.57–1.59$ (m, $\underline{CH_2}\underline{CH_2}$ of pyrrolidine ring), 1.98–2.11 (m, naphthyl–O–$CH_2\underline{CH_2}CH_2$–O–CO–N), 3.34–3.38 (m, –N–$\underline{CH_2}\underline{CH_2}$–N– of pyrrolidine ring), 4.01–4.04 (t, $\underline{CH_2}$–O–naphthyl), 4.05–4.11 (t, $\underline{CH_2}$–O–CO–N), 6.97–7.64 (m, Ar-H) ppm; MS: $m/z = 299$.

[2-(2-Naphthyloxy)eth-1-yl] benzyl carbamate (**1i**, $C_{20}H_{19}NO_3$)
Yield 87%; IR (KBr): $\bar{\nu} = 1682\,cm^{-1}$ (carbamate linkage); ^1H NMR ($CDCl_3$): $\delta = 4.20–4.24$ (d, $\underline{CH_2}$ of naphthyloxy and phenyl ring of benzyl group), 4.30–4.34 (t, 2H, $\underline{CH_2}$–O–naphthyl), 4.48–4.53 (t, $\underline{CH_2}$–O–CO–NH), 6.97–7.64 (m, Ar-H), 7.6 (br, N$\underline{H}$) ppm; MS: $m/z = 321$.

[4-(2-Naphthyloxy)but-1-yl] 3-phenylpropyl carbamate (**1j**, $C_{24}H_{27}NO_3$)
Yield 95%; IR (KBr): $\bar{\nu} = 1699\,cm^{-1}$ (carbamate linkage); ^1H NMR ($CDCl_3$): $\delta = 1.54–1.57$ (m, $\underline{CH_2}CH_2$–O–CO), 1.70–1.72 (m, naphthyl–O–$CH_2\underline{CH_2}$), 1.86–1.89 (m, $CH_2\underline{CH_2}CH_2Ph$), 2.54–2.58 (t, $CH_2CH_2\underline{CH_2}Ph$), 2.93–2.97 (m, O–CO–N$H\underline{CH_2}$), 4.01–4.04 (t, CH_2–O–naphthyl), 4.05–4.08 (t, $\underline{CH_2}$–O–CO–NH), 6.97–7.64 (m, Ar-H), 8.0 (br, N$\underline{H}$) ppm; MS: $m/z = 377$.

[3-(2-Naphthyloxy)prop-1-yl]-p-toluendinyl carbamate (**1k**, $C_{21}H_{21}NO_3$)
Yield 80%; IR (KBr): $\bar{\nu} = 1680\,cm^{-1}$ (carbamate linkage); ^1H NMR ($CDCl_3$): $\delta = 1.97–2.11$ (m, naphthyl–O–$CH_2\underline{CH_2}CH_2$–O–CO), 2.33–2.37 (s, CH_3), 4.01–4.04 (t, $\underline{CH_2}$–O–naphthyl), 4.05–4.08 (t, $\underline{CH_2}$–O–CO–NH), 6.97–7.64 (m, Ar-H), 7.8 (br, NH) ppm; MS: $m/z = 335$.

[3-(2-Naphthyloxy)prop-1-yl] p-anisidinyl carbamate (**1l**, $C_{21}H_{21}NO_4$)
Yield 83%; IR (KBr): $\bar{\nu} = 1683\,cm^{-1}$ (carbamate linkage); ^1H NMR ($CDCl_3$): $\delta = 1.98–2.15$ (m, naphthyl–O–$CH_2\underline{CH_2}CH_2$–O–CO), 3.73 (s, OCH_3), 4.01–4.04 (t, $\underline{CH_2}$–O–naphthyl), 4.05–4.08 (t, $\underline{CH_2}$–O–CO–NH), 6.97–7.64 (m, Ar-H), 7.9 (br, NH) ppm; MS: $m/z = 351$.

2-Phenylethyl n-butyl carbamate (**1m**, $C_{13}H_{19}NO_2$)
Yield 86%; IR (neat): $\bar{\nu} = 1684\,cm^{-1}$ (carbamate linkage); ^1H NMR ($CDCl_3$): $\delta = 0.89–0.96$ (t, CH_3), 1.28–1.34 (m, CH_2CH_3), 1.54–1.59 (m, $CH_2CH_2CH_3$), 2.83–2.88 (t, Ph$\underline{CH_2}$), 2.94–2.96 (m, O–CONH$\underline{CH_2}$), 4.40–4.45 (t, $\underline{CH_2}$–O–CO–NH), 7.08–7.21 (m, Ar-H), 7.7 (br, N$\underline{H}$) ppm; MS: $m/z = 221$.

3-Phenylpropyl n-hexyl carbamate (**1n**, $C_{16}H_{25}NO_2$)
Yield 88%; IR (neat): $\bar{\nu} = 1687\,cm^{-1}$ (carbamate linkage); ^1H NMR ($CDCl_3$): $\delta = 0.89–0.96$ (t, CH_3), 1.28–1.30 (m, CH_2CH_2 of *n*-hexyl group), 1.32–1.36 (m, $\underline{CH_2}CH_3$), 1.54–1.57 (m, O–CO–NH$CH_2\underline{CH_2}$), 1.88–1.93 (m, $PhCH_2\underline{CH_2}CH_2$), 2.54–2.58 (t, Ph$\underline{CH_2}$), 2.95–2.99 (m, O–CO–NH$\underline{CH_2}$), 4.07–4.10 (t, $\underline{CH_2}$–O–CO–NH), 7.08–7.21 (m, Ar-H), 7.9 (br, NH) ppm; MS: $m/z = 263$.

Acknowledgements

Authors are grateful to Dr. *N. Anand* for fruitful discussions and to SIAF Division of CDRI for providing spectroscopic and analytical data.

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