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Triton-B Catalyzed, Efficient, One-Pot Synthesis of Carbamate Esters from Alcoholic Tosylates[+]

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

Keywords. Alcoholic tosylates; Triton-B; Carbon dioxide; *N*-Alkyl/aryl carbamates.

Introduction

Carbamation of amines has frequently been utilized in the synthesis of organic carbamates [1], which hold unique applications in the field of pharmaceuticals [2] and agriculture [3]. Organic carbamates have also played an important role in the area of synthetic organic chemistry, particularly as synthetic intermediates [4], protection of amino groups in peptide chemistry [5], and linkers in combinatorial chemistry [6]. Functionalization of amines as carbamates offers an attractive method for generating derivatives, which may display interesting medicinal and biological properties [7]. However, the scope of existing methodologies for carbamate formation is limited by the need of specialized reagents and operational complexity due to the use of either toxic or cumbersome reagents such as phosgene [8], its derivatives [9], and carbon monoxide [10]. Because of the toxicity of these chemicals, we have undertaken significant efforts for the development of more efficient and safer protocols using cheap and harmless reagents like CO_2. Preparation

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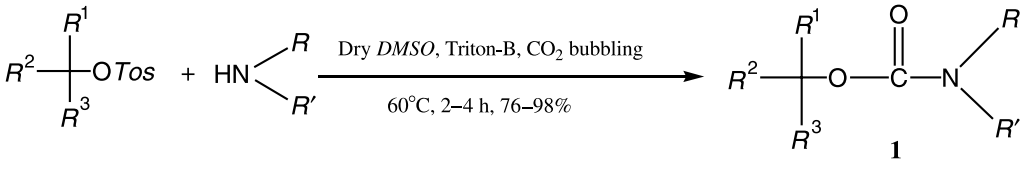
of carbamates using CO_2 electrochemically [11], supercritically [12], and in combination with metals and non-metals [13] has been reported. We have also reported [14] the synthesis of carbamates by use of *Mitsunobu*'s reagent, Triton-B, and *TBAI* using gaseous CO_2. Recently we found [14c, 15] that Triton-B is the best reagent for the chemoselective conversion of carbamates and dithiocarbamates from the corresponding alkyl halides. In this communication, we report a chemoselective, highly efficient, one-pot synthesis of *N*-alkyl/aryl carbamates from their corresponding amines and alcoholic tosylates using the Triton-B/CO_2 system.

Results and Discussion

We have recently assumed [14c] that two molar equivalents of amine reacted with CO_2 to form an ionic species, *i.e.* a monoalkylammonium alkyl carbamate (*MAAAC*) ion. It has been observed that the nucleophilicity of this *MAAAC* ion could be enhanced by a basic phase transfer catalyst like Triton-B.

This ionic species *MAAAC* gets stabilized in the presence of the phase transfer catalyst and would react with alkylating agents to afford carbamates in high yields. Based on the concept of formation of this *MAAAC* ion, we investigated the carbamate synthesis from alcoholic tosylates. The carbenium ion generated from the tosyl esters would undergo nucleophilic attack by O^- of *MAAAC* leading to the formation of carbamate esters. Alcoholic tosylates of primary, secondary, and tertiary alcohols were prepared from corresponding alcohols using *p*-toluenesulfonylchloride following the standard known procedure [16]. Thus, when alcoholic tosylates were reacted with amines in dry *DMSO* at 60°C it led to the isolation of carbamates in high yields (76–98%) (Scheme 1). Initially, the spectral charaterization of these carbamates from alcoholic tosylates was confirmed by the authentic carbamates prepared from their corresponding alkyl halides and alcohols as reported previously [14b, c]. Later on, a variety of carbamates were prepared from a variety of primary, secondary, and tertiary alcoholic tosylates using different aliphatic, aromatic, and cyclic amines as shown in Table 1. It was noticed that due to the higher reactivity of alcoholic tosylates as compared to alkyl halides the reaction was completed in less time with improved yields. Futhermore, the reaction was completed using alcoholic tosylates at 60°C rather than 90°C as in case of alkyl halides. We tried several solvents like *n*-pentane, *n*-hexane, *n*-heptane, *DMF*, *DMSO,* acetonitrile, *HMPA*, dichloromethane, chloroform, methanol, benzene, and toluene, and found dry *DMSO* most suitable for the carbamate esters obtained from aliphatic amines and *HMPA* for aromatic amines.

In conclusion, we developed a convenient, safe, and efficient protocol for a one-pot, four components coupling of various primary, secondary aliphatic/aromatic



Scheme 1

Table 1. Conversion of alcoholic tosylates into carbamates of general formula **1**

Product	R^1	R^2	R^3	R	R'	Time/h	Yield/%	Ref.
1a	2-Naphthyloxypropyl	H	H	n-C_4H_9	H	2.5	94	[14c]
1b	2-Naphthyloxyethyl	H	H	c-C_6H_{13}	H	3	91	[14c]
1c	2-Naphthyloxyethyl	H	H	$R = R' =$ Morpholinyl		3.5	84	[14c]
1d	n-C_3H_7	H	H	n-C_8H_{17}	H	3	92	
1e	$(CH_3)_2CHCH_2$	H	H	n-C_8H_{17}	H	2.5	86	
1f	$CH_3(CH_2)_3$	H	H	n-C_4H_9	H	2.5	89	
1g	$CH_3(CH_2)_4$	H	H	c-C_6H_{11}	H	3	90	
1h	$CH_3(CH_2)_4$	H	H	n-C_3H_7	H	3	82	
1i	$CH_3(CH_2)_6$	H	H	3-*MeOPh*CH_2	H	3	81	
1j	$CH_3(CH_2)_8$	H	H	n-C_6H_{13}	H	2	98	
1k	*Ph*CH_2	H	H	n-C_4H_9	H	3	89	[14c]
1l	*Ph*$CH_2 \cdot CH_2$	H	H	n-C_6H_{13}	H	2.5	92	[14c]
1m	*Ph*CH_2	H	H	i-C_3H_7	i-C_3H_7	3.5	79	
1n	n-C_3H_7	H	H	i-amyl	H	2.5	84	[14b]
1o	2-Naphthyloxyethyl	H	H	3-*MeOPh*	H	2.5	85	[14c]
1p	n-C_4H_9	n-C_4H_9	H	n-C_8H_{17}	H	2.5	82	
1q	n-C_4H_9	n-C_4H_9	n-C_4H_9	n-$C_{12}H_{25}$	H	3	78	
1r	n-C_5H_{11}	H	H	*Ph*	H	4	76	

and cyclic amines with a variety of alcoholic tosylates of primary, secondary, and tertiary alcohols by means of a Triton-B/CO_2 system. This highly chemoselective reaction generates the corresponding carbamates in good to excellent yields. Furthermore, this method exihibits substrate versatility, mild reaction conditions, and experimental convenience. This synthesis protocol is believed to offer a more general method of the formation of C–N bonds, essential to numerous organic syntheses.

Experimental

Chemicals were obtained from Merck, Aldrich, and Fluka. IR spectra were run on a Bomem MB-104 FTIR spectrometer whereas ^{1}H NMRs were scanned on AC-300F NMR (300 MHz) instrument using $CDCl_3$ as solvent and *TMS* as internal standard. Elemental analyses were made by Carlo-Erba EA1110 CNNO-S analyzer and agreed favorably 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 $CaCl_2$ traps) CO_2 gas was rapidly bubbled into it at 60°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 alcoholic tosylates were added. The reaction was further continued until the completion of the reaction (*cf.* 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.

Butyl n-octylcarbamate (**1d**, $C_{13}H_{27}NO_2$)

Oil; IR (Neat): $\bar{\nu} = 1687\,cm^{-1}$ (O–CO–NH, carbamate linkage); ^{1}H NMR ($CDCl_3$): $\delta = 0.85$–0.88 (t, CH_3 of *n*-butyl and *n*-octyl group), 0.89–0.93 (m, CH_2 of *n*-butyl and *n*-octyl group), 1.18–1.21

(m, CH_2 CH_2 of *n*-butyl and *n*-octyl group), 1.29–1.33 (m, CH_2 of *n*-octyl group), 1.35–1.39 (m, CH_2 of *n*-octyl group), 1.52–1.54 (m, CH_2 of *n*-octyl group), 2.94–2.97 (t, NHCH_2 of *n*-octyl), 4.02–4.05 (t, CH_2–O– of *n*-butyl group), 7.5 (br, NH) ppm; MS: $m/z = 229$.

Isoamyl n-octylcarbamate (**1e**, $C_{14}H_{29}NO_2$)
Oil; IR (Neat): $\bar{\nu} = 1702\,cm^{-1}$ (O–CO–NH); ^1H NMR ($CDCl_3$): $\delta = 0.92$–0.96 (t, CH_3 of *n*-octyl group), 1.01–1.05 (d, CH_3 of *i*-amyl group), 1.29–1.33 (m, CH_2 of *n*-octyl group), 1.53–1.55 (m, CH_2 of *i*-amyl and *n*-octyl group), 1.83–1.85 (m, CH of *i*-amyl group), 2.93–2.96 (t, NHCH_2 of *n*-octyl), 4.03–4.06 (t, CH_2–O– of *i*-amyl group), 7.7 (br, NH) ppm; MS: $m/z = 243$.

Pentyl n-butylcarbamate (**1f**, $C_{10}H_{21}NO_2$)
Oil; IR (Neat): $\bar{\nu} = 1689\,cm^{-1}$ (O–CO–NH); ^1H NMR ($CDCl_3$): $\delta = 0.93$–0.97 (t, CH_3 of *n*-pentyl and *n*-butyl group), 1.29–1.33 (m, CH_2 of *n*-pentyl and *n*-butyl group), 1.55–1.58 (m, CH_2 of *n*-butyl and *n*-pentyl group), 2.93–2.96 (t, NHCH_2), 4.03–4.06 (t, CH_2–O–), 7.6 (br, NH) ppm; MS: $m/z = 187$.

n-Hexyl cyclohexylcarbamate (**1g**, $C_{13}H_{25}NO_2$)
Oil; IR (Neat): $\bar{\nu} = 1698\,cm^{-1}$ (O–CO–NH); ^1H NMR ($CDCl_3$): $\delta = 0.94$–0.98 (t, CH_3 of *n*-hexyl group), 1.29–1.33 (m, CH_2 of *n*-hexyl group), 1.43–1.45 (m, CH_2 of *c*-hexyl group), 1.58–1.66 (m, CH_2 of *n*-hexyl and *c*-hexyl group), 3.54–3.56 (m, NH*CH* of *c*-hexyl), 4.03–4.06 (t, CH_2–O– of *n*-hexyl group), 7.8 (br, NH) ppm; MS: $m/z = 227$.

n-Hexyl n-propylcarbamate (**1h**, $C_{10}H_{21}NO_2$)
Oil; IR (Neat): $\bar{\nu} = 1694\,cm^{-1}$ (O–CO–NH); ^1H NMR ($CDCl_3$): $\delta = 0.93$–0.96 (t, CH_3 of *n*-hexyl and *n*-propyl group), 1.29–1.33 (m, CH_2 of *n*-hexyl and *n*-propyl group), 1.56–1.59 (m, CH_2 of *n*-hexyl and *n*-propyl group), 2.94–2.97 (t, CH_2NH) 4.03–4.06 (t, CH_2–O– of *n*-hexyl group), 7.9 (br, NH) ppm; MS: $m/z = 187$.

n-Octyl m-methoxybenzylcarbamate (**1i**, $C_{17}H_{27}NO_3$)
Mp 119°C; IR (KBr): $\bar{\nu} = 1701\,cm^{-1}$ (O–CO–NH); ^1H NMR ($CDCl_3$): $\delta = 0.93$–0.96 (t, CH_3 of *n*-octyl group), 1.30–1.34 (m, CH_2 of *n*-octyl group), 1.57–1.60 (m, CH_2 of *n*-octyl group), 3.73 (s, OCH_3), 4.06–4.09 (t, CH_2–O– of *n*-octyl group), 4.21–4.23 (d, CH_2NH), 7.7 (br, NH) ppm; MS: $m/z = 293$.

n-Decyl n-hexylcarbamate (**1j**, $C_{17}H_{35}NO_2$)
Mp 105°C, IR (KBr): $\bar{\nu} = 1694\,cm^{-1}$ (O–CO–NH); ^1H NMR ($CDCl_3$): $\delta = 0.94$–0.97 (t, CH_3 of *n*-decyl and *n*-hexyl groups), 1.28–1.33 (m, CH_2 of *n*-decyl and *n*-hexyl group), 1.56–1.59 (m, CH_2 of *n*-decyl and *n*-hexyl group), 2.94–2.96 (m, CH_2NH), 4.07–4.10 (t, CH_2–O– of *n*-decyl group), 7.8 (br, NH) ppm; MS: $m/z = 285$.

2-Phenylethyl diisopropylcarbamate (**1m**, $C_{15}H_{23}NO_2$)
Oil; IR (Neat): $\bar{\nu} = 1697\,cm^{-1}$ (O–CO–NH); ^1H NMR ($CDCl_3$): $\delta = 1.24$–1.27 (d, CH_3 of *i*-propyl group), 2.81–2.84 (t, $PhCH_2$), 3.92–3.97 (m, CH of *i*-propyl group), 4.41–4.44 (t, CH_2–O– of phenyl group), 7.08–7.21 (m, Ph protons) ppm; MS: $m/z = 249$.

Isobutyl n-octylcarbamate (**1p**, $C_{18}H_{37}NO_2$)
Oil; IR (Neat): $\bar{\nu} = 1696\,cm^{-1}$ (O–CO–NH); ^1H NMR ($CDCl_3$): $\delta = 0.95$–0.98 (t, CH_3 of *i*-butyl and *n*-octyl group), 1.29–1.33 (m, CH_2 of *i*-butyl and *n*-octyl group), 1.55–1.58 (m, CH_2 of *i*-butyl and *n*-octyl group), 2.94–2.96 (m, CH_2NH), 3.95–3.97 (m, CH_2–O– of *i*-butyl group), 7.8 (br, NH) ppm; MS: $m/z = 299$.

Tert.butyl n-dodecylcarbamate (**1q**, $C_{26}H_{53}NO_2$)
Oil; IR (Neat): $\bar{\nu} = 1690\,cm^{-1}$ (O–CO–NH); ^1H NMR ($CDCl_3$): $\delta = 0.95$–0.98 (t, CH_3 of *t*-butyl and *n*-dodecyl group), 1.29–1.33 (m, CH_2 of *t*-butyl and *n*-dodecyl group), 1.55–1.58 (m, CH_2 of *n*-dodecyl group), 2.94–2.96 (m, CH_2NH), 7.5 (br, NH) ppm; MS: $m/z = 411$.

n-Hexyl phenylcarbamate (**1r**, $C_{13}H_{19}NO_2$)
Oil; IR (Neat): $\bar{\nu} = 1688\,cm^{-1}$ (O–CO–NH); ^1H NMR ($CDCl_3$): $\delta = 0.94$–0.97 (t, CH_3 of *n*-hexyl group), 1.29–1.33 (m, CH_2 of *n*-hexyl group), 1.56–1.59 (m, CH_2 of *n*-hexyl group), 4.10–4.13 (t, CH_2–O– of *n*-hexyl group), 7.08–7.65 (m, Ph protons), 7.9 (br, NH) ppm; MS: $m/z = 221$.

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References

[1] a) Adams P, Baron FA (1965) Chem Rev **65**: 567
[2] a) Ray S, Chaturvedi D (2004) Drugs of the Future **29**: 343; b) Ray S, Pathak SR, Chaturvedi D (2005) Drugs of the Future **30**: 161
[3] a) Mateen A, Chapalamadugu S, Kashar B, Bathi AR, Chaudhary GR (1994) Biol Degrad Biorem Toxic Chem 198; b) Wigfield YY(1996) Food Sci Technol (NY) **77**: 1501
[4] a) Snieckus V (1990) Chem Rev **90**: 879; b) Cleraland WW, Andrews TS, Gutteridge S, Hartman FC, Lorimer GH (1998) Chem Rev **98**: 549; c) Tanaka F (2002) Chem Rev **102**: 4885
[5] Greene TW, Wuts PGM (1999) Protecting Groups in Organic Synthesis 3rd ed. John Wiley and Sons, Inc; New York, 503
[6] a) Mayer JP, Lewis GS, Curtius MJ, Zhang J (1997) Tetrahedron Lett **38**: 8445; b) Buchstaller HP (1998) Tetrahedron **54**: 3465; c) Holte PT, Thijs L, Zwanenburg B (1998) Tetrahedron Lett **39**: 7404
[7] a) Matsui T, Kondo T, Nishita Y, Itadani S, Tsuruta H, Fujita S, Omawari N, Sakai M, Nakazawa S, Ogata A, Mori H, Ohno H, Obata T, Nakai H, Toda M (2002) Bioorg Med Chem Lett **12**: 907; b) Seko T, Kato M, Kohno H, Ono S, Hashimura K, Takimizu H, Nakai K, Maegawa H, Katsube N, Toda M (2002) Bioorg Med Chem Lett **12**: 915
[8] Satchell DPN, Satchell RS (1975) Chem Soc Rev **4**: 231
[9] Raucher S, Jones DS (1985) Synth Commun **15**: 1025
[10] a) Leung TW, Domblk BD (1992) Chem Commun **3**: 205; b) Mizuno T, Takahashi J, Ogawa A (2002) Tetrahedron **58**: 7805
[11] a) Casedei MA, Inesi A, Moracci FM, Rossi L (1996) Chem Commun 2575; b) Casadei MA, Moracci FM, Zappia G, Inesi A, Rossi L (1997) J Org Chem **62**: 6754; c) Feroci M, Inesi A, Rossi L (2000) Tetrahedron Lett **41**: 963
[12] Yoshida MA, Hara N, Okuyama S (2000) Chem Commun **2**: 151
[13] Mahe R, Sasaki Y, Bruneau C, Dixneuf PH (1989) J Org Chem **54**: 1518
[14] a) Chaturvedi D, Kumar A, Ray S (2002) Synth Commun **32**: 2651; b) Chaturvedi D, Kumar A, Ray S (2003) Tetrahedron Lett **44**: 7637; c) Chaturvedi D, Ray S (2006) Monatsh Chem **137**: 201
[15] Chaturvedi D, Ray S (2006) Monatsh Chem **137**: 311
[16] Kabalka GW, Varma M, Varma RS, Srivasava PC, Knapp FF (1986) J Org Chem **51**: 2386