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Short Communication

An Efficient, One-Pot Synthesis of Carbamates from the Corresponding Alcohols Using *Mitsunobu*'s Reagent

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Summary. A novel *Mitsunobu*-based protocol was developed for the synthesis of carbamates from the corresponding alcohols using carbon dioxide and amines in good to excellent yields. This protocol is mild, chemoselective, and efficient compared to other reported methods.

Keywords. *Mitsunobu*'s reagent; Carbon dioxide; Alcohols; Carbamates; Carbamation.

Introduction

Carbamation of amines has frequently been utilized in the synthesis of organic carbamates, which holds unique applications in the field of pharmaceuticals [1] and agriculture [2]. Organic carbamates have also played an important role in the area of synthetic organic chemistry, particularly as synthetic intermediates [3], for the protection of amino groups in peptide chemistry [4], and as linkers in combinatorial chemistry [5]. Functionalization of amines as carbamates offers an attractive method for the generation of derivatives, which may display interesting medicinal and biological properties [6]. During recent years their synthesis has changed from the use of harmful chemicals like phosgene or its derivatives [7] and carbon monoxide [8] directly or indirectly to abundantly available cheap and safe reagents like CO_2. The preparation of carbamates using CO_2 has been reported to proceed electrochemically, supercritically, in combination with metal and non-metal species and macrocyclic polyethers [9]. However, most of these methods suffer from limitations, such as long reaction times, use of expensive strongly basic reagents, tedious work-up, and low yields specifically for the carbamates obtained from aromatic

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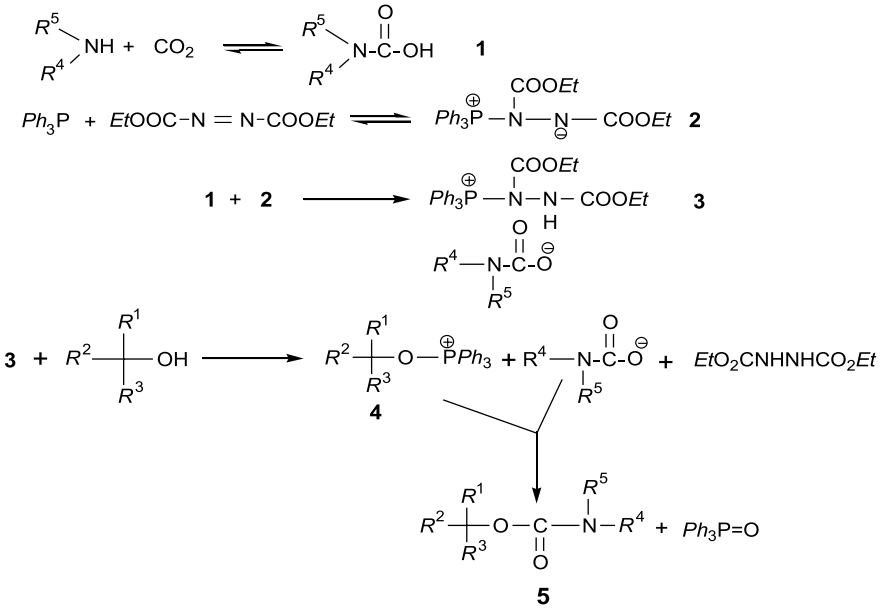
amines. Consequently, there is continued interest in developing new and convenient methods for the synthesis of carbamates using mild reaction conditions. Our group [10] has been engaged during the past several years in the development of new methodologies for the synthesis of carbamates and dithiocarbamates using gaseous CO_2 and CS_2. Recently, we have reported [11] an efficient and mild synthesis of dithiocarbamates and dithiocarbonates (xanthates) from a variety of primary, secondary, and *tert.* alcohols using *Mitsunobu*'s reagent. Taking the lead from these last reports as a guide, we report herein a convenient and safe methodology for the synthesis of *N*-alkyl/arylcarbamates from a variety of alcohols (primary, secondary, and tertiary) and amines (primary and secondary) using *Mitsunobu*'s reagent.

Results and Discussion

In our previous synthesis [11] of dithiocarbamates and xanthates, CS_2 has been used at room temperature. But due to the lesser reactivity of CO_2 as compared to CS_2, a reaction temperature of 90–100°C was required. Thus, we carried out the synthesis of carbamates by mild carbamation of amines with carbon dioxide and an alcohol in the presence of *Mitsunobu*'s reagent. We assume that the unstable carbamic acid **1** generated from the amine and CO_2 reacts with the *Mitsunobu* zwitterion **2** formed from Ph_3P and diethyl azodicarboxylate, to furnish the stabilized zwitterionic species **3**, which in turn undergoes O-alkylation giving rise to the formation of the carbamate ester **5** as shown in Scheme 1. The spectroscopic confirmation of product structures was achieved using authentic carbamates prepared according to the references given in Table 1.

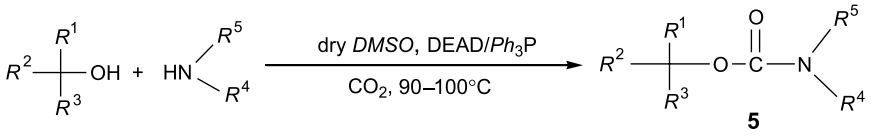
Accordingly, aliphatic/aromatic amines (primary and secondary) were reacted with various alcohols (primary, secondary, and tertiary) using *Mitsunobu*'s reagent and carbon dioxide in dry *DMSO* at 90–100°C for 2–5 h affording carbamates in



Scheme 1

Table 1. Conversion of alcohols into carbamates **5**

Product	R^1	R^2	R^3	R^4	R^5	t/h	Yield/%	Ref.
1a	*Ph*CH_2	H	H	*n*-C_4H_9	H	2.5	90	[10e]
1b	*Ph*CH_2CH_2	H	H	*n*-C_6H_{13}	H	2	95	[10e]
1c	*Ph*CH_2CH_2	H	H	*n*-C_3H_7	*n*-C_3H_7	3	82	[10c]
1d	*n*-C_3H_7	H	H	*n*-C_8H_{17}	H	2	96	[10c]
1e	$(CH_3)_2CHCH_2$	H	H	*c*-C_6H_{11}	H	3	84	[10c]
1f	*n*-C_4H_9	H	H	*n*-C_4H_9	H	2.5	88	[10c]
1g	*n*-C_4H_9	*n*-C_4H_9	H	*n*-C_8H_{17}	H	3.5	93	
1h	*n*-C_4H_9	*n*-C_4H_9	*n*-C_4H_9	*n*-$C_{12}H_{25}$	H	4	79	
1i	*n*-C_6H_{13}	H	H	*Ph*	H	5	76	[10c]
1j	*n*-C_7H_{15}	H	H	*Ph*CH_2	H	3.5	81	[10c]
1k	*n*-C_8H_{17}	H	H	3-*Me*O*Ph*CH_2	H	3	87	[10c]
1l	*n*-C_7H_{15}	H	H	*n*-$C_{12}H_{25}$	H	2	98	[10c]
1m	*n*-C_5H_{11}	CH_3	H	*c*-C_6H_{11}	H	3.5	88	[10c]
1n	2-Naphthyl-oxyethyl	H	H	*n*-C_4H_9	H	3	85	[10e]
1o	2-Naphthyl-oxyethyl	H	H	R^4 & R^5 = morpholinyl		3	82	[10e]
1p	2-Naphthyl-oxyethyl	H	H	R^4 & R^5 = pyrrolidinyl		3	81	[10e]



Scheme 2

good to excellent yields (76–98%) as shown in Table 1. We tried several solvents such as *n*-heptane, *n*-hexane, *DMSO*, *DMF*, and *HMPA* of which dry *DMSO* proved to be the most suitable one. The overall reaction is shown in Scheme 2.

In conclusion, we have developed a convenient and efficient protocol for the one-pot, four component coupling of various aliphatic/aromatic amines with a variety of primary, secondary, and tertiary alcohols via a *Mitsunobu* zwitterion. This highly chemoselective reaction generates the corresponding carbamates in high yields without direct N-alkylation. Furthermore, this method exhibits substrate versatility, mild reaction conditions, and experimental convenience. This synthesis protocol developed is believed to offer a more general method for the formation of C–N bonds, essential in numerous organic syntheses.

Experimental

Chemicals were obtained from Merck, Aldrich, and Fluka. IR spectra were run on a Bomem MB-104 FTIR spectrometer. ^{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.

Procedure

Amine (5 mmol) was taken up in 35 cm^3 dry *DMSO* and purified (by passing through H_2SO_4 and $CaCl_2$ traps) CO_2 gas was rapidly bubbled into it at 90–100°C for 0.5 h. To the reaction mixture, triphenylphosphine (5 mmol) and then diethyl azodicarboxylate was added slowly in 2–3 small portions. Then

5 mmol of the corresponding alcohol were added. The reaction was further continued until the completion of the reaction (*cf.* Table 1) was 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 afford the desired compound.

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

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

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References

[1] 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
[2] a) Adams P, Baron FA (1965) Chem Rev **65**: 567; b) Mateen A, Chapalamadugu S, Kashar B, Bathi AR, Chaudhary GR (1994) Biol Degrad Biorem Toxic Chem 198; c) Wigfield YY (1996) Food Sc. Technol. (NY) **77**: 1501
[3] 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
[4] Greene TW, Wuts PGM (1999) Protecting Groups in Organic Synthesis 3rd edn. John Wiley and Sons Inc., NY, p 503
[5] 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
[6] a) Matsui T, Kondo T, Nishita Y, Itadani S, Itadani 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
[7] a) Satchell DPN, Satchell RS (1975) Chem Soc Rev **4**: 231; b) Raucher S, Jones DS (1985) Synth Commun **15**: 1025
[8] a) Leung TW, Domblk BD (1992) Chem Commun 205; b) Mizuno T, Takahashi J (2002) Tetrahedron **58**: 7805
[9] For review article on carbon dioxide in carbamates synthesis, see: Chaturvedi D, Ray S (2006) Monatsh Chem **137**: 127
[10] a) Chaturvedi D, Kumar A, Ray S, Synth Commun **32**: 2651; b) Chaturvedi D, Kumar A, Ray S, Tetrahedron Lett **44**: 7637; c) Chaturvedi D, Ray S (2005) Lett Org Chem **2**: 742; d) Chaturvedi D, Ray S (2005) J Sulfur Chem **26**: 365; e) Chaturvedi D, Ray S (2006) Monatsh Chem **137**: 201; f) Chaturvedi D, Ray S (2006) Monatsh Chem **137**: 311; g) Chaturvedi D, Ray S Monatsh Chem **137**: 459; h) Chaturvedi D, Ray S (2006) Monatsh Chem **137**: 465; i) Chaturvedi D, Ray S (2006) J Sulfur Chem **27**: 265
[11] a) Chaturvedi D, Ray S (2006) Tetrahedron Lett **47**: 1307; b) Chaturvedi D, Ray S (2006) Tetrahedron Lett (in press)