J. Iran. Chem. Soc., Vol. 8, No. 2, June 2011, pp. 396-400.

JOURNAL OF THE
Iranian
Chemical Society

An Efficient One-Pot Synthesis of Carbazates and Dithiocarbazates through the Corresponding Alcohols Using Mitsunobu's Reagent

A.K. Chaturvedi[a], D. Chaturvedi[b,†,*], N. Mishra[a] and V. Mishra[a]

[a]*Synthetic Research Laboratory, Department of Chemistry, B. S. A. P. G. College, Mathura-281004, U. P., India*

[b]*Bio-Organic Chemistry Division, Indian Institute of Integrative Medicine, Canal Road, Jammu-Tawi-180001, J. & K., India*

[†]*Present address for correspondence: Natural Products Chemistry Division, North-East Institute of Science and Technology (CSIR), Jorhat-785006, Assam, India*

(Received 16 November 2009, Accepted 29 January 2010)

A novel Mitsunobu-based protocol has been developed for the synthesis of carbazates and dithiocarbazates through the variety of corresponding primary, secondary and tertiary alcohols and various kinds of substituted hydrazines using Mitsunobu's reagent and CO_2/CS_2 system, in good to excellent yields.

Keywords: Alcohols, Carbon dioxide, Carbon Disulfide, Mitsunobu's reagent, Carbazates, Dithiocarbazates

INTRODUCTION

Organic carbazates and dithiocarbazates constitute an important and versatile class of compounds for a variety of industrial, synthetic and medicinal applications [1]. They have been extensively used as pharmaceuticals [2], agrochemicals [3], intermediates in organic synthesis [4], for the protection of amino groups in peptide synthesis [5] and linkers in solid phase organic synthesis [6] and as donor ligands in complexation reactions with transition metals [7]. These uses necessitate their preparation through a convenient and safe methodology.

To satisfy demand, their synthesis has been changed from the use of costly and toxic chemicals like phosgene/ thiophosgene [8] and its derivatives [9] directly or indirectly, to the abundantly available cheap and safe reagents such as CO_2/CS_2. Moreover, their formation using CO_2/CS_2 employed harsh reaction conditions such as use of strong bases, higher reaction temperatures and longer reaction times [10]. Thus, we were prompted to embark on developing the improved procedures. Our group [11] has been engaged over the past several years in the development of new methodologies for the preparation of carbamates, dithiocarbamates, and related compounds using cheap, abundantly available, and safe reagents like CO_2 and CS_2, respectively.

Recently, we reported [12] the synthesis of carbamates, dithiocarbamates, carbonates, *O,S*-dialkyl dithiocarbonates (xanthates), *S*-alkyl thiocarbamates, trithiocarbonates and *S,S*-dialkyl carbonates, through the variety of starting materials using Mitsunobu's reagent. We report herein a chemoselective, highly efficient and mild synthesis of carbazates and dithiocarbazates from the corresponding variety of primary, secondary and tertiary alcohols and substituted hydrazines using Mitsunobu's reagent/CO_2 and

*Corresponding author. E-mail: devduttchaturvedi@gmail.com

Mitsunobu's reagent/CS_2 system, respectively.

EXPERIMENTAL

Chemicals were procured from Merck, Aldrich and Fluka chemical companies. Reactions were carried out under Argon. IR spectra 4000-200 cm^{-1} were recorded on Bomem MB-104-FTIR spectrophotometer using neat technique, whereas NMRs were scanned on an AC-300F, NMR (300 MHz), instrument using $CDCl_3$ and *TMS* as internal standard. Elemental analysis were conducted by means of a Carlo-Erba EA 1110-CNNO-S analyzer and agreed favorably with calculated values.

Typical Experimental Procedure for the Synthesis of Carbazates

Substituted hydrazine (7.56 mmol) was taken in dry DMSO (25 ml) and purified gaseous CO_2 was bubbled in it for 30 min at room temperature. To this, a mixture of triphenylphosphine (7.56 mmol) and diethyl azodicarboxylate (7.56 mmol) was added slowly in 2-3 small portions. Next, corresponding alcohol (7.56 mmol) was added in it with constant stirring at room temperature. The reaction was continued until completion (*cf* Table 1) as confirmed by TLC. The reaction mixture was then poured into distilled water (50 ml) and extracted with ethyl acetate thrice. The organic layer was separated and dried over anhydrous sodium sulphate and then concentrated to afford the desired carbazate compound.

N'-(4-Methoxyphenyl) hydrazinecarboxylic acid n-butyl ester (Table 1, entry 1, $C_{12}H_{18}N_2O_3$). Yield: 94%; m.p.: yellow oil; IR (neat) $\ddot{v}$ = 1690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.96 (t, 3H, CH_3), 1.35 (m, 2H, CH_2CH_3), 1.60 (m, 2H, CH_2), 3.73 (s, 3H, OCH_3), 4.12 (t, 2H, J = 6.5 Hz, OCH_2), 5.20 (br, s, NH), 6.75-7.66 (m, 4H, Ar-H), 8.05(s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.8, 21.8, 32.4, 33.9, 55.6, 112.5, 114.9, 134.5, 153.4, 160.5 (C=O) ppm; MS (EI): *m/z* = 238; Analysis: $C_{12}H_{18}N_2O_3$, calcd.: C, 60.49; H, 7.61; N, 11.76%; found: C, 60.67; H, 7.44; N, 11.56%.

Typical Experimental Procedure for the Synthesis of Dithiocarbazates

Substituted hydrazine (7.56 mmol) was taken in dry DMSO (25 ml) and CS_2 (11.34 mmol) was added dropwise in it for 30 min at room temperature. To this, a mixture of triphenylphosphine (7.56 mmol) and diethyl azodicarboxylate (7.56 mmol) was added slowly in 2-3 small portions. Next, corresponding alcohol (7.56 mmol) was added in it with constant stirring at rt. The reaction was continued until completion (*cf* Table 2) as confirmed by TLC. The reaction mixture was then poured into distilled water (50 ml) and extracted with ethyl acetate thrice. The organic layer was separated and dried over anhydrous sodium sulphate and then concentrated to afford the desired dithiocarbazate compound**.**

N'-(4-Methoxyphenyl) hydrazine carbodithioc acid butyl ester (Table 2, entry 1, $C_{12}H_{18}N_2OS_2$). IR υ (neat) = 675, 1210 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.85 (t, 3H, J = 7.2 Hz, CH_3), 1.33 (m, 2H, CH_2CH_3), 1.85 (m, 2H, $CH_3CH_2CH_2$), 2.0 (s, NH), 2.95 (t, 2H, J = 6.5 Hz), 3.73 (s, 3H, OCH_3), 4.05 (m, NH), 6.76-7.64 (m, 4H); ^{13}C NMR ($CDCl_3$) δ = 13.5, 21.8, 32.4, 33.9, 43.7, 55.6, 112.5, 114.9, 134.5, 152.4, 222.5 (C=S) ppm; MS (EI): *m/z* = 270; Analysis: $C_{12}H_{18}N_2OS_2$, calcd.: C, 53.30; H, 6.71; N, 10.36; S, 23.72%; found: C, 53.24; H, 6.65; N, 10.33; S, 23.58%.

RESULTS AND DISCUSSION

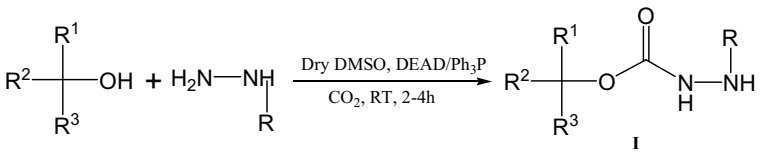
Synthesis of a carbazate compound was achieved through the reaction of the corresponding alcohol with a suitable substituted hydrazine using Mitsunobu's reagent/CO_2 system at room temperature. The product was observed and confirmed by the various spectroscopic and analytical techniques. Thus, a variety of primary, secondary and tertiary alcohols underwent through the Mitsunobu coupling reaction with a variety of substituted aliphatic/aromatic hydrazines using gaseous carbon dioxide to afford the corresponding carbazates in high yields (80-98%) as mentioned in Table 1. To the best of our knowledge this is the first report for the direct synthesis of carbazates from the corresponding alcohols using Mitsunobu's reagent/CO_2 system at room temperature. The reaction-conditions have been depicted in Scheme 1.

The synthesis of dithiocarbazate compound was achieved through the direct reaction of an alcohol with a substitiuted hydrazine using Mitsunobu's reagent/CS_2 system at room temperature. The structure was further confimed through various spectroscopic and analytical techniques. It was further reallized that the reaction of dithiocarbazate formation is faster as compared to carbazate, perhaps may be due to the greater

Table 1. Conversion of Various Alcohols into Carbazates of General Formula **I**[a] of Scheme 1

Entry	R^1	R^2	R^3	R	Time (h)	Isolated yield (%)
1	*n*-C_3H_7	H	H	4-MeOPh	2.5	94
2	$PhCH_2CH_2$	H	H	Ph	2.5	90
3	$PhCH_2$	H	H	Ph	3.0	86
4	Ph	H	H	*n*-C_4H_9	2.5	92
5	C_2H_5	Me	H	*n*-C_4H_9	2.0	87
6	4-MeOPh	H	H	3-NO_2Ph	3.5	83
7	*n*-C_3H_7	H	H	4-NO_2Ph	3.5	82
8	*n*-C_3H_7	H	H	2,4-NO_2Ph	4.0	80
9	*n*-C_3H_7	H	H	Naphthyl	3.5	83
10	*n*-C_4H_9	H	H	Ph	2.5	88
11	*n*-C_4H_9	*n*-C_4H_9	*n*-C_4H_9	Ph	4.0	82
12	*n*-C_5H_{11}	H	H	*n*-C_4H_9	2.5	90
13	*n*-C_7H_{15}	H	H	Ph	2.5	92
14	*n*-C_9H_{19}	H	H	*n*-C_4H_9	2.0	98
15	*n*-C_3H_7	*n*-C_3H_7	H	Ph	2.5	86
16	Ph	CH_3	H	Ph	2.5	85

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



Scheme 1

reactivity of CS_2 as compared to CO_2. Thus, various kinds of dithiocarbazates were prepared through the reaction of various kinds of structurally diverse primary, secondary and tertiary alcohols with variety of substituted hydrazines using Mitsunobu's reagent/CS_2 system, to afford the corresponding dithiocarbazates in high yields (82-98%) as mentioned in Table 2. To the best of our knowledge this is the first report for the direct synthesis of dithiocarbazates from the corresponding alcohols using Mitsunobu's reagent/CS_2 system. The whole reaction conditions are depicted in Scheme 2.

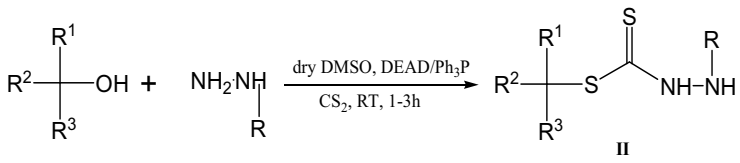
We tried many solvents like, *n*-heptane, *n*-hexane, acetonitrile, benzene, toluene, methanol, dichloromethane, chloroform, DMSO, dimethylformamide, hexamethyl-phosphoric triamide of which dry DMSO proved to be most suitable at room temperature for caring out the synthesis of carbazates and dithiocarbazates.

In conclusion, we have developed a convenient and efficient protocol for one-pot, three components coupling of various alcohols with variety of substituted hydrazines *via* Mitsunobu's reagent/CO_2 and Mitsunobu's reagent/CS_2 system. This reaction generates the corresponding, carbazates/dithiocarbazates in excellent yields at room temperature. Furthermore, this method exhibits substrate versatility, mild reaction conditions and experimental convenience. This synthetic protocol is believed to offer a

Table 2. Conversion of Various Alcohols to Dithiocarbazates of General Formula **II**[a] of Scheme 2

Entry	R^1	R^2	R^3	R	Time (h)	Isolated yield (%)
1	*n*-C_3H_7	H	H	4-MeOPh	1.5	95
2	$PhCH_2CH_2$	H	H	Ph	1.5	91
3	$PhCH_2$	H	H	Ph	2.0	87
4	Ph	H	H	*n*-C_4H_9	1.5	91
5	C_2H_5	Me	H	*n*-C_4H_9	1.0	88
6	4-MeOPh	H	H	3-NO_2Ph	2.5	84
7	*n*-C_3H_7	H	H	4-NO_2Ph	2.5	83
8	*n*-C_3H_7	H	H	2,4-NO_2Ph	3.0	82
9	*n*-C_3H_7	H	H	Naphthyl	2.5	84
10	*n*-C_4H_9	H	H	Ph	1.5	89
11	*n*-C_4H_9	*n*-C_4H_9	*n*-C_4H_9	Ph	2.0	83
12	*n*-C_5H_{11}	H	H	*n*-C_4H_9	1.5	92
13	*n*-C_7H_{15}	H	H	Ph	1.5	94
14	*n*-C_9H_{19}	H	H	*n*-C_4H_9	1.0	98
15	*n*-C_3H_7	*n*-C_3H_7	H	Ph	1.5	87
16	Ph	CH_3	H	Ph	1.5	86

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



Scheme 2

more general method for the formation of *C-O, C-S* and *C-N* bonds essential to numerous organic syntheses.

REFERENCES

[1] U. Ragnarsson, Chem. Soc. Rev. 30 (2001) 205.

[2] E.U. Schmidt, Hydrazine and its Derivatives Preparation, Properties, Applications, 2nd ed., Wiley-interscience, New York, 2001.

[3] a) M.S.C. Pedras, M. Jha, Bioorg. Med. Chem. 14 (2006) 4958; b) Shailendra, N. Bharti, F. Naqvi, A. Azam, Helv. Chim. Acta 85 (2002) 2713; c) N. Bharti, M.R. Maurya, F. Naqvi, A. Azam, Bioorg. Med. Chem. Lett. 10 (2000) 2243; d) N. Bharti, M.R. Mannar, N. Fehmida, A. Bhattacharya, S. Bhattacharya, A. Azam, Eur. J. Med. Chem. 35 (2000) 481.

[4] a) S.K. Sengupta, O.P. Pandey, P.G. Rao, Sugarcane Pathology 1 (1999) 279; b) H.S. Chen, Z.H. Li, Y.H. Han, Z.W. Wang, Chin. Chem. Lett. 10 (1999) 365; c) K. Chaturvedi, A.K. Jaiswal, K.N. Mishra, O.P. Pandey, S.K. Sengupta, ACH-Models in Chemistry 135 (1998) 93; d) G.C. Briggs, C.L. Cornell, D.J. Mansfield, R.M. Turner, PCT Int Appl. 1999, WO9923066, CAN:130:337920 (1999).

[5] a) T.J. Connolly, A.J. Crittal, A.S. Ebrahim, G. Ji, Org. Process. Res. Dev. 4 (2000) 526; b) M.S. Gordan, J.G.

Krause, M.A. Linneman-Mohr, R.R. Parchue, Synthesis 3 (1998) 244; c) M.J. Hauser, J. Org. Chem. 31 (1966) 968.

[6] a) S. Sakakibara, I. Honda, M. Naruse, M. Kanaoka, Experimentia 25 (1969) 576; b) S. Sakakibara, I. Honda, K. Takada, M. Miyoshi, T. Ohnishi, K. Okumura Bull. Chem. Soc. Jpn. 42 (1969) 809; c) M. Quibell, W.G. Turnell, T. Johnson, J. Chem. Soc. Perkin. Trans. I 22 (1993) 2843; d) C.J. Gray, M. Quibell, N. Baggett, T. Hammerle, Int. J. Pept. Protien Res. 40 (1992) 351.

[7] a) J.Y. Huang, H.S. Choi, D.H. Lee, S.E. Yoo, Y.D. Gong, J. Comb. Chem. 7 (2005) 136; b) J.Y. Hwang, H.S. Choi, D.H. Lee, Y.D. Gong, J. Comb. Chem. 7 (2005) 816.

[8] a) C. Bolzati, E. Benini, M. Cavazza-Ceccato, E. Cozzala, E. Malago, S. Agostini, F. Tisato, F. Rofosco, G. Bandoli, Bioconjugate Chemi. 17 (2006) 419; b) M.A. Ali, A.H. Mirza, R.J. Butcher, K.A. Krause, Transit. Metal Chem. 31 (2006) 79; c) R. Singh, N.K. Kaushik, Main Group Met. Chem. 27 (2004) 327.

[9] H. Dyker, J. Scherkenbeck, D. Gondol, A. Goehrt, A. Harder, J. Org. Chem. 66 (2001) 3760; a) A.S. Dutta, J.S. Morley, J. Chem. Soc. Perkin Trans. I 1712 (1975); b) S. Nara, T. Sakamoto, E. Miyazawa, Y. Kikugawa, Synth. Commun. 33 (2003) 87.

[10] a) A. Saxena, J.P. Tandon, Polyhedron 2 (1983) 443; b) D.L. Fox, J.T. Ruxer, R.M. Liver, K.L. Alford, R.N. Salvatore, Tetrahedron Lett. 45(2004) 401.

[11] For Reviews see: a) D. Chaturvedi, S. Ray, Curr. Org. Chem. 11 (2007) 987; b) D. Chaturvedi, N. Mishra, V. Mishra, Curr. Org. Synth. 3 (2007) 308; For Our Research Work See; c) D. Chaturvedi, A. Kumar, S. Ray, Synth. Commun. 32 (2002) 2651; d) D. Chaturvedi, S. Ray, Lett. Org. Chem. 2 (2005) 742; e) D. Chaturvedi, S. Ray, J. Sulfur Chem. 26 (2005) 365; f) D. Chaturvedi, S. Ray, J. Sulfur Chem. 27 (2006) 265; g) D. Chaturvedi, N. Mishra, V. Mishra, Chinese Chem. Lett. 17 (2006) 1309; h) D. Chaturvedi, S. Ray, Monatsh. Chem. 137 (2006) 201; i) D. Chaturvedi, S. Ray, Monatsh. Chem. 137 (2006) 311; j) D. Chaturvedi, S. Ray, Monatsh. Chem. 137 (2006) 459; k) D. Chaturvedi, S. Ray, Monatsh. Chem. 137 (2006) 465; l) D. Chaturvedi, S. Ray, Monatsh. Chem. 137 (2006) 1219; m) D. Chaturvedi, N. Mishra, V. Mishra, J. Sulfur Chem. 28 (2007) 39; n) D. Chaturvedi, N. Mishra, V. Mishra, J. Sulfur Chem. 28 (2007) 607; o) D. Chaturvedi, A.K. Chaturvedi, N. Mishra, V. Mishra, Synth. Commun. 38 (2008) 4013; p) D. Chaturvedi, N. Mishra, A.K. Chaturvedi, V. Mishra, Monatsh Chem. 139 (2008) 1467; q) D. Chaturvedi, N. Mishra, A.K. Chaturvedi, V. Mishra, Synth. Commun. 39 (2009) 1273; r) D. Chaturvedi, A.K. Chaturvedi, N. Mishra, V. Mishra, J. Iran. Chem. Soc. 6 (2009) 510.

[12] a) D. Chaturvedi, A. Kumar, S. Ray, Tetrahedron Lett. 44 (2003) 7637; b) D. Chaturvedi, S. Ray, Tetrahedron Lett. 47 (2006) 1307; c) D. Chaturvedi, S. Ray, Tetrahedron Lett. 48 (2007) 149; d) D. Chaturvedi, N. Mishra, V. Mishra, Tetrahedron Lett. 48 (2007) 5043; e) D. Chaturvedi, N. Mishra, V. Mishra, Synthesis (2008) 355; f) D. Chaturvedi, A.K. Chaturvedi, N. Mishra, V. Mishra, Tetrahedron Lett. 49 (2008) 4886; g) D. Chaturvedi, N. Mishra, V. Mishra, Monatsh. Chem. 139 (2008) 267; h) A.K. Chaturvedi, D. Chaturvedi, N. Mishra, V. Mishra, J. Iran. Chem. Soc. 7 (2010) 702.