

A High Yielding, One-Pot Synthesis of *S,S*-Dialkyl Dithiocarbonates Through the Corresponding Thiols 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*

(Received 9 August 2009, Accepted 29 October 2009)

A novel Mitsunobu-based technique has been developed for the synthesis of a variety of symmetrical and unsymmetrical *S,S*-dialkyl dithiocarbonates from various corresponding primary, secondary and tertiary thiols using gaseous carbon dioxide, in good to excellent yields.

Keywords: Synthesis, Dialkyl dithiocarbonates, Thiols, Carbon dioxide, Mitsunobu's reagent

INTRODUCTION

Symmetrical and unsymmetrical *S,S*-dialkyl dithiocarbonates constitute an important and versatile class of compounds for a variety of industrial, synthetic and medicinal applications [1]. They have extensively been used as pharmaceuticals [2], agrochemicals [3], intermediates in organic synthesis [4] and in free radical polymerization reactions [5] as solvent for rechargeable lithium ion batteries [6] *etc.* Furthermore, their utility as a useful synthon for the synthesis of various kinds of compounds such as ketones [7], substituted ureas [8], alkane thiols [9], organic sulfides [10], thiocarboxylic acids [11], alkane-sulfonyl chlorides [12], thioleues [13] and as coupling agent for esterification of carboxylic acids [14] *etc.* all warrant their preparation through a convenient and safe methodology.

Classical synthesis of *S,S*-dialkyl dithiocarbonates involves the reaction of thiols with phosgene [15], or its derivatives [16], and carbon monoxide [17]. These reactions are

associated with several drawbacks such as use of the costly, toxic and corrosive reagents. Alternative routes for their synthesis involves thermal [18], acid [19] or base [20] catalyzed rearrangement of *O,S*-dialkyl dithiocarbonates to *S,S*-dialkyl dithiocarbonates. Furthermore, various kinds of Lewis acids [21] and phase transfer catalysts [22] were employed for the rearrangement of *O,S*-dialkyl dithiocarbonates to *S,S*-dialkyl dithiocarbonates. Most of these methods suffer from drawbacks such as long reaction times, use of expensive strongly basic reagents, tedious work-up and low yields. Consequently, there is continued interest in developing new and convenient methods for the synthesis of *S,S*-dialkyl dithiocarbonates using mild reaction conditions.

Our group [23] has been engaged for over several years on the development of new, efficient and safer methods for the synthesis of carbamates, dithiocarbamates, dithiocarbonates (xanthates) using cheap and abundantly available reagents like CO₂ and CS₂. Recently, we reported [24] the synthesis of carbamates, dithiocarbamates, carbonates, *O,S*-dialkyl dithiocarbonates (xanthates), *S*-alkyl thiocarbamates and trithiocarbonates from a variety of starting materials using

*Corresponding author. E-mail: ddchaturvedi002@yahoo.co.in

Mitsunobu's reagent. We report herein a chemoselective, highly efficient and mild synthesis of symmetrical and unsymmetrical *S,S*-dialkyl dithiocarbonates from a variety of primary secondary, and tertiary thiols using Mitsunobu's reagent. We carried out the synthesis of *S,S*-dialkyl dithiocarbonates by mild thiocarbonation of thiols with gaseous carbon dioxide using various primary, secondary and tertiary thiols mediated by Mitsunobu's reagent at room temperature. To the best of our knowledge, this is the first report for the efficient and mild synthesis of *S,S*-dialkyl dithiocarbonates starting from corresponding thiols using Mitsunobu's reagent.

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 analyses were conducted by means of a Carlo-Erba EA 1110-CNNO-S analyzer and agreed favorably with the calculated values.

General Experimental Procedure

Thiol (7.56 mmol) was taken in dry DMSO (25 ml) and gaseous CO_2 was bubbled through 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, the corresponding thiol (7.56 mmol) was added with constant stirring at rt. The reaction 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 *S,S*-dialkyl dithiocarbonate.

***S,S*-Dibenzyl dithiocarbonate** (Entry 1): Oil; IR (neat, cm^{-1}): $\nu = 1640, 880$; ^1H NMR (400 MHz, CDCl_3) $\delta = 4.21$ (s, 4H, SCH_2Ph), 7.06–7.24 (m, 10H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 36.2, 126.9, 127.9, 128.5, 142.3, 200.5$ (C=O) ppm; MS (m/z): 274; HRMS: calcd. for $\text{C}_{15}\text{H}_{14}\text{OS}_2$: 274.05; found: 274.15.

***S,S*-Di-4-Methoxybenzyl dithiocarbonate** (Entry 2): Oil; IR (neat, cm^{-1}): $\nu = 1638, 878$; ^1H NMR (400 MHz, CDCl_3) $\delta = 3.83$ (s, 6H, OMe) 4.22 (s, 4H, SCH_2Ph), 7.07–7.25 (m, 10H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 37.4, 56.2, 127.5, 128.5, 142.5, 202.2$ (C=O) ppm; MS (m/z): 334; HRMS: calcd. for $\text{C}_{17}\text{H}_{18}\text{O}_3\text{S}_2$: 334.07; found: 334.15.

RESULTS AND DISCUSSION

We assume that the unstable thiocarbonic acid **1**, generated from the reaction of thiol with carbon dioxide, reacts with Mitsunobu's zwitterion **2**, formed from the Ph_3P and diethyl azodicarboxylate, to furnish the unstable ionic species **3** which, in turn, would undergo a self-rearrangement to form a more stabilized ionic species **4**. The nucleophilic attack of sulfur atom of other thiols followed by intra-molecular electronic rearrangement leads to the formation of the *S,S*-dialkyl dithiocarbonate of the general formula **I** (see Schemes 1 and 2).

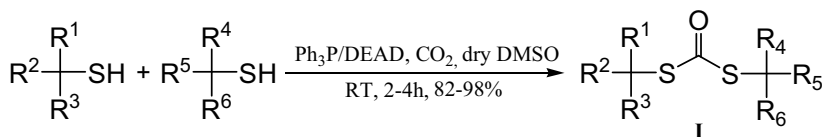
Thus, various primary, secondary and tertiary thiols were made to react with Mitsunobu's reagent/ CO_2 system to afford *S,S*-dialkyl thiocarbonates in very good to excellent yields (82–98%) at room temperature in 2–4 h. We tried many solvents like DMSO, DMF, benzene, acetonitrile, dichloromethane, hexane, heptane, methanol, chloroform and acetone, whereby dry DMSO was proved to be the most suitable solvent for carrying out this transformation.

In conclusion, we have developed a convenient and efficient technique for one-pot, three-component coupling of various thiols with a variety of primary, secondary and tertiary thiols *via* Mitsunobu's reagent/ CO_2 system. This reaction generates the corresponding *S,S*-dialkyl dithiocarbonates in excellent yields at room temperature. Furthermore, this method exhibits substrate versatility, mild reaction conditions and experimental convenience. This synthetic technique is believed to offer a more general method for the formation of C-S bonds essential for numerous organic syntheses.

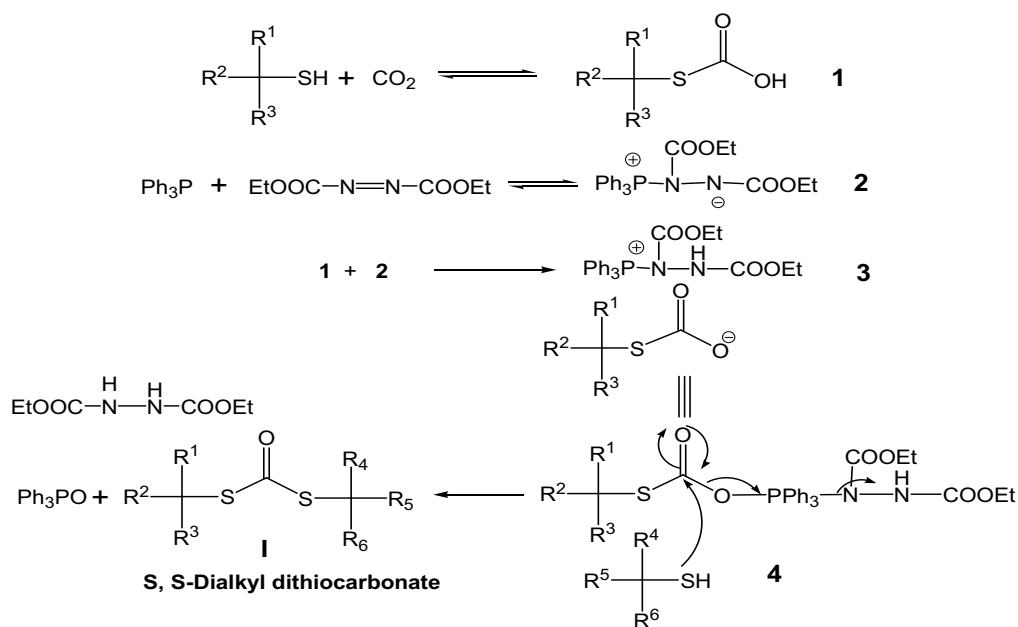
ACKNOWLEDGMENTS

The authors wish to thank SIAF division of the Indian Institute of Integrative Medicine for providing spectroscopic and analytical data.

A High Yielding, One-Pot Synthesis of *S,S*-Dialkyl Dithiocarbonates



Scheme 1



Scheme 2. Proposed mechanism of formation of *S,S*-dialkyl dithiocarbonates

Table 1. Conversion of Various Thiols into *S,S*-Dialkyl dithiocarbonates of General Formula **I**^a

Entry	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Time (h)	Yield (%) ^b
1	Phenyl	H	H	Phenyl	H	H	2.5	91
2	4-Methoxyphenyl	H	4-Methoxyphenyl	H	H	H	2.5	93
3	4-Chlorophenyl	H	H	4-Chlorophenyl	H	H	3	86
4	<i>n</i> -Butyl	H	H	<i>n</i> -Butyl	H	H	2.5	94
5	<i>n</i> -Heptyl	H	H	<i>n</i> -Propyl	H	H	2	95
6	<i>n</i> -Octyl	H	H	<i>n</i> -Octyl	H	H	2	96

Table 1. Continued

7	Phenyl	Methyl	H	<i>n</i> -Hexyl	H	H	2.5	91
9	<i>n</i> -Butyl	<i>n</i> -Butyl	H	4-Methoxyphenyl	H	H	3	86
10	<i>n</i> -Butyl	<i>n</i> -Butyl	<i>n</i> -Butyl	<i>n</i> -Octyl	H	H	3.5	83
11	<i>n</i> -Hexyl	H	H	Benzyl	H	H	2.5	94
12	<i>n</i> -Heptyl	Me	H	<i>n</i> -Heptyl	H	H	2	94
13	<i>n</i> -Octyl	H	H	Phenethyl	H	H	2.5	90
14	<i>n</i> -Heptyl	H	H	<i>n</i> -Butyl	<i>n</i> -Butyl	H	2.5	91
15	<i>n</i> -Pentyl	Methyl	<i>n</i> -Butyl	<i>n</i> -Butyl	<i>n</i> -Butyl	<i>n</i> -Butyl	4	82
16	2-Naphthyloxyethyl	H	H	<i>n</i> -Octyl	H	H	2.5	86
17	3-(2-Naphthyloxy)prop-1-yl	H	H	<i>n</i> -Dodecyl	H	H	2	95
18	<i>n</i> -Hexyl	Me	Me	Benzyl	H	H	3	88
19	<i>n</i> -Decyl	H	H	<i>n</i> -Heptyl	H	H	2	98

^aAll the products were characterized by IR, NMR and mass spectral data. ^bIsolated yields.

REFERENCES

- [1] a) K. Yoshida, K. Kosegaki, *Makromol. Chem.* 161 (1972) 267; b) E. Reid, *Organic Chemistry of Bivalent Sulfur*, Vol. 4, Chemical Publishing Co. New York, 1962, p. 170 and references cited therein.
- [2] a) H. Foks, J. Mieczkowska, M. Janowiec, Z. Zwolska, Z. Andrzejczyk, *Chemistry of Heterocyclic Compounds* 38 (2002) 810; b) F. Dehmel, T. Ciossek, T. Maier, S. Weinbrenner, B. Schmidt, M. Zoche, T. Beckers, *Bio-Org. Med. Chem. Lett.* 17 (2007) 4746.
- [3] H. Elster, W. Hahn, K. Goliasch, W. Behrenz, German Patent (DOS) a) 1207140, 1965; b) H. Jindal, A. Fischer, German Patent (DOS) 1950433, 1971.
- [4] a) J. Crosby, K.J. Grant, D.J. Greig, R.M. Paton, R.G. Rankin, J.F. Ross, *ARKIVOC* (2002) 121; b) M. Barbero, S. Cadamuro, I. Degani, R. Fochi, V. Regondi, *Synthesis* (1989) 957; c) D. Witt, R. Klajn, P. Barski, B.A. Grzybowski, *Curr. Org. Chem.* 8 (2004) 1763.
- [5] a) L. Benati, R. Learndini, M. Minozzi, D. Nanni, R. Scialpi, P. Spagnolo, S. Strazzari, G. Zanardi, *Angew. Chem. Int. Ed.* 116 (2004) 3682; b) B. Quiclet-Sire, S.Z. Zard, *Top. Current Chem.* (2006) 201.
- [6] a) Y. Ein-Eli, S.F. McDevitt, J. Solid State Electrochem. 1 (1997) 227; b) S.J. Santner, K.C. Moller, M.G. Ramsey, F.P. Netzer, S. Yamaguchi, J.O. Besenhard, W. Winter, *J. Power Sources* 119-121 (2003) 368.

- [7] a) C.D. Chen, J.W. Huang, M.K. Leung, H.S. Li, *Tetrahedron* 54 (1998) 9067; b) C. Cardilliccio, V. Fiandanese, G. Marchese, L. Ronzini, *Tetrahedron Lett.* 26 (1988) 3595; c) B.F. Bonini, C.M. Capperuci, A. DeglInnocent, G. Mazzanti, A. Ricci, P. Zani, *Synlett* (1993) 937.
- [8] M.K. Leung, J.L. Lai, K.H. Lan, Y.H. Yu, H.J. Hsiao, *J. Org. Chem.* 61 (1996) 4179.
- [9] a) I. Degani, R. Fochi, V. Regondi, *Synthesis* (1983) 630; b) I. Degani, R. Fochi, V. Regondi, *Chem. Ind.* (1986) 671; c) S. Cacamura, I. Degani, R. Fochi, V. Regondi, *Synthesis* (1986) 1073.
- [10] I. Degani, R. Fochi, V. Regondi, *Synthesis* (1979) 178.
- [11] S. Cadzurao, I. Degani, R. Fochi, V. Regondi, *Synthesis* (1986) 1070.
- [12] M. Barbero, S. Cadamura, I. Degani, R. Fochi, V. Regondi, *Synthesis* (1989) 957.
- [13] a) X. Yang, G.K.W. Freeman, T.B. Rauchfuss, S.R. Wilson, *Inorg. Chem.* 30 (1991) 3034; b) S.B. Wilkes, I.R. Butler, A.E. Underhill, A. Kobayashi, H. Kobayashi, *J. Chem. Soc. Chem. Commun.* (1994) 53.
- [14] S. Kim, S. S. Kim, *Synthesis* (1986) 1017.
- [15] I. Degani, R. Fochi, V. Regondi, *Synthesis* (1975) 375.
- [16] H. Ester, E. Muhlauer, German Patent (DBP) 1181205, (1965).
- [17] T. Mizuno, T. Yamaguchi, I. Nishiguchi, T. Okushi, T. Hirashima, *Chem. Lett.* (1990) 811.
- [18] K. Harano, T. Taguchi, *Chem. Pharm. Bull.* 20 (1972) 2357.
- [19] T. Kirata, K. Harano, *Yakugaku Zasshi.* 76 (1976) 832.
- [20] Y. Yoshida, *Bull. Chem. Soc. Jpn.* 42 (1969) 1948.
- [21] a) K. Komaki, T. Kowata, K. Harano, T. Taguchi, *Chem. Pharm. Bull.* 26 (1978) 3807; b) T. Kowata, K. Harano, T. Taguchi, *Chem. Pharm. Bull.* 21 (1973) 604; c) K. Harano, I. Shinohara, S.I. Sugumoto, T. Matsuoka, T. Hisano, *Chem. Pharm. Bull.* 37 (1989) 576.
- [22] I. Degani, R. Fochi, V. Regondi, *Synthesis* (1980) 375; b) I. Degani, R. Fochi, V. Regondi, *Synthesis* (1981) 149.
- [23] For reviews see: a) D. Chaturvedi, S. Ray, *Curr. Org. Chem.* 11 (2007) 987; b) D. Chaturvedi, N. Mishra, V. Mishra, *Curr. Org. Synthesis* 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, S. Ray, *Monatsh. Chem.* 137 (2006) 201; h) D. Chaturvedi, S. Ray, *Monatsh. Chem.* 137 (2006) 311; i) D. Chaturvedi, S. Ray, *Monatsh. Chem.* 137 (2006) 459; j) D. Chaturvedi, S. Ray, *Monatsh. Chem.* 137 (2006) 465; k) D. Chaturvedi, S. Ray, *Monatsh. Chem.* 137 (2006) 1219; l) D. Chaturvedi, N. Mishra, V. Mishra, *J. Sulfur Chem.* 28 (2007) 39; m) D. Chaturvedi, N. Mishra, V. Mishra, *J. Sulfur Chem.* 28 (2007) 607; n) D. Chaturvedi, N. Mishra, V. Mishra, *Monatsh. Chem.* 139 (2008) 267; 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, *Synth. Commun.* 39 (2009) 1273; q) D. Chaturvedi, A.K. Chaturvedi, N. Mishra, V. Mishra, *J. Iran. Chem. Soc.* 6 (2009) 510.
- [24] 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.