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An efficient, one-pot synthesis of trithiocarbonates from the corresponding thiols using the Mitsunobu reagent

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ABSTRACT

A novel Mitsunobu-based protocol has been developed for the synthesis of a variety of symmetrical and unsymmetrical trithiocarbonates from primary, secondary and tertiary thiols using carbon disulfide, in good to excellent yields. This protocol is mild and efficient compared to other reported methods.

Organic trithiocarbonates have received much attention due to their numerous industrial, synthetic and medicinal applications.[1] They have been used extensively as pharmaceuticals,[2] agrochemicals,[3] intermediates in organic synthesis,[4] for protection of thiol functionality,[5] in free radical polymerization reactions,[6] as lubricating additives,[7] in material science,[8] in froth flotation[9] for the recovery of minerals from their ores and for their absorption properties of the metals.[10] Moreover, they are useful synthons for the preparation of various compounds such as sulfines,[11] ketenes,[12] trithiocarbonate-*S*-oxides,[13] thiols,[14] dithiocarboxylate derivatives,[15] thioacetates,[16] olefins,[17] nitro 1,3-benzodithiole-2-thiones,[18] phosphite ylides[19] and in various C–C bond forming reactions[20] which necessitates their preparation through convenient and safe methods.

The classical synthesis of trithiocarbonates involves reaction of thiols with thiophosgene[21] or its derivatives.[22] These methods have several drawbacks such as the use of costly, toxic and corrosive reagents. Alternative routes for their synthesis involve reaction of metal xanthates with epoxides,[23] or episulfides,[24] the reaction of sodium trithiocarbonates with organic dihalides,[25] or epoxides,[26] reaction of CS_2 with alkyl halides using KOH,[27] reaction of alkyl halides with the hydroxide form of an anion exchange resin,[28] and by S-arylation of potassium carbonotrithiolates with diaryliodonium salts.[29] The application of a phase transfer catalyst has had an enormous impact on the synthesis of this class of compounds[30] but the method requires strongly basic conditions. Recently, a method for the synthesis of trithiocarbonates was reported using a Cs_2CO_3/CS_2 system.[31] Most of these methods suffer from limitations 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 trithiocarbonates under mild reaction conditions.

Our group[32] has been engaged over several years on the development of new, efficient and safer protocols for the synthesis of carbamates, dithiocarbamates and dithiocarbonates (xanthates) using cheap and readily available reagents such as CO_2 and CS_2. Recently, we reported[33] the synthesis of carbamates, dithiocarbamates, carbonates, *O,S*-dialkyl dithiocarbonates (xanthates) and *S*-alkyl carbamates from a variety of starting materials using the Mitsunobu reagent. We report herein a chemoselective, highly efficient and mild synthesis of symmetrical and unsymmetrical trithiocarbonates from various primary, secondary and tertiary thiols using the Mitsunobu reagent. Thus, we carried out[34] the synthesis of trithiocarbonates by mild thiocarbonation of thiols with carbon disulfide using the Mitsunobu reagent at room temperature. To the best of our knowledge, this is the first report on an efficient and mild synthesis of symmetrical and unsymmetrical trithiocarbonates from the corresponding thiols using Mitsunobu's reagent (Table 1).

We assume that the unstable thiocarbonic acid **1** generated from the reaction of a thiol with carbon disulfide, reacts with the Mitsunobu zwitterion **2** formed from reaction of Ph_3P and diethyl azadicarboxylate, to furnish the unstable ionic species **3** which in turn undergoes rearrangement to form a more stabilized ionic

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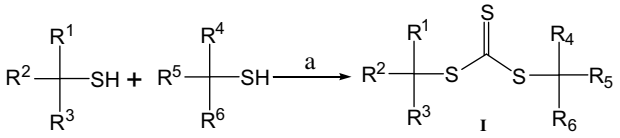
Table 1
Conversion of various thiols into trithiocarbonates of general formula **I**[a]

Entry	R^1	R^2	R^3	R^4	R^5	R^6	Time (h)	Isolated yield (%)
1	Phenyl	H	H	Phenyl	H	H	3	82
2	2-Phenethyl	H	H	*n*-Hexyl	H	H	3	93
3	2-Phenethyl	H	H	*n*-Propyl	*n*-Propyl	H	4	85
4	*n*-Propyl	H	H	*n*-Octyl	H	H	2	91
5	*i*-Amyl	H	H	Cyclohexyl	H	H	3	84
6	*n*-Butyl	H	H	*n*-Butyl	H	H	3	82
7	2-Naphthyloxyethyl	H	H	Phenyl	H	H	3	80
8	2-Naphthyloxyethyl	H	H	4-Methoxyphenyl	H	H	3	83
9	*n*-Butyl	*n*-Butyl	H	*n*-Octyl	H	H	2	81
10	*n*-Butyl	*n*-Butyl	*n*-Butyl	*n*-Dodecyl	H	H	3	83
11	*n*-Hexyl	H	H	Phenyl	H	H	3	78
12	*n*-Heptyl	H	H	Benzyl	H	H	2	82
13	*n*-Octyl	H	H	3-Methoxybenzyl	H	H	2	88
14	*n*-Heptyl	H	H	*n*-Dodecyl	H	H	2	98
15	*n*-Pentyl	Methyl	H	Cyclohexyl	H	H	3	90
16	2-Naphthyloxyethyl	H	H	*n*-Butyl	*n*-Butyl	*n*-Butyl	3	80
17	3-(2-Naphthyloxy)prop-1-yl	H	H	*n*-Octyl	H	H	2	90

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



Scheme 1. Reagents and conditions: (a) dry DMSO, DEAD/Ph_3P, CS_2, rt, 2–4 h.

species **4**. Nucleophilic attack of the sulfur atom of the other thiol followed by intramolecular electronic rearrangement leads to the formation of the trithiocarbonate of general formula **I**.

Thus, various primary, secondary and tertiary thiols were reacted with the Mitsunobu reagent/CS_2 system to affords trithiocarbonates in very good to excellent yields (78–98%) at room temperature in 2–4 h. We have used solvents including DMSO, DMF, benzene, acetonitrile, dichloromethane, hexane, heptane, methanol, chloroform and acetone with dry DMSO proving to be the most suitable for carrying out this transformation. The overall reaction is shown in Scheme 1.

In conclusion, we have developed a convenient and efficient protocol for the one-pot, three-component coupling of various thiols with primary, secondary and tertiary thiols using the Mitsunobu reagent/CS_2 system. This reaction generates the corresponding, trithiocarbonates in good to excellent yields at room temperature. Furthermore, this method exhibits substrate versatility, mild reaction conditions and experimental convenience.

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34. *General experimental procedure:*
Thiol (7.56 mmol) was taken in dry DMSO (25 ml) and CS_2 (11.5 mmol) was added and the reaction mixture was stirred at room temperature for 30 min. 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 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 combined organic layer dried over anhydrous sodium sulfate and then concentrated to afford the desired trithiocarbonate.
*Trithiocarbonic ester dibenzyl ester (entry 1)*IR (neat): 1205 (C=S) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.62 (s, 4H, J = 7.2 Hz, PhCH_2S), 7.24–7.35 (m, 10H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.52 (Ph.CH_2S), 127.51, 128.53, 129.62, 131.50, 140.10, 142.20 (aromatic region), 222.72 (C=S) ppm; Mass (EI): *m/e* (%) 290 (89); Anal. Calcd for $C_{15}H_{14}S_3$: C, 62.02; H, 4.86; S, 33.12. Found: C, 62.34; H, 5.02; S, 32.89.