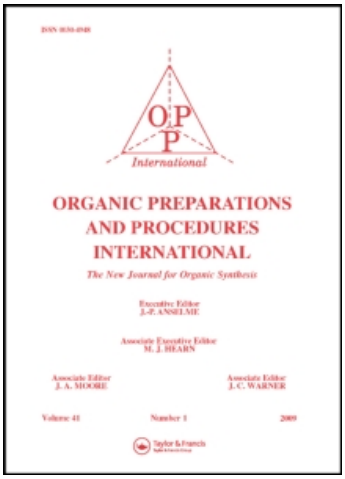

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AN IMPROVED PREPARATION OF 2,4-DINITROPHENYL THIOETHERS FROM THIOLCARBONIC ESTERS

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AN IMPROVED PREPARATION OF 2,4-DINITROPHENYL THIOETHERS FROM THIOLCARBONIC ESTERS

Submitted by (07/30/92)

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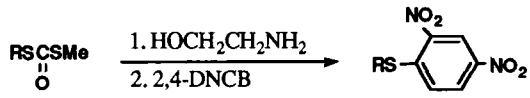
Thiolcarbonic esters are useful precursors of thiols. However, not only are these compounds often oils and have an unpleasant odor but they are also susceptible to nucleophiles. Therefore, milder conditions than refluxing with hydroxide ion are preferred for liberation of thiols. For this purpose, aminolysis reactions have been successfully used to give good yields of thiols. 2-Aminoethanol and ethylenediamine are mild reagents requiring only brief reaction times at low temperatures under neutral and non-aqueous conditions.[1] On the other hand, the most useful derivatives of alkyl- and arylthiols are the 2,4-dinitrophenyl sulfides and the corresponding sulfones.[2] The 2,4-dinitrophenyl sulfones are particularly valuable because they exhibit a wide range of melting points. However, in the method usually employed when only a small amount of thiol or its precursor is available, difficulty is sometimes encountered in the isolation of the sulfide. In the case of allylic thiols, excess of alkali causes a red coloration and a side reaction. We now report a one-pot synthetic method of the 2,4-dinitrophenyl sulfides from xanthates, dithiolcarbonates and trithiocarbonates without isolation of thiols.



The process can be carried out in a one vessel. A solution of thiolcarbonic ester and a large excess (3-5 eq.) of ethanolamine in a minimum volume of ethanol is heated at 70-80° for 10 min. After cooling, 2,4-dinitrochlorobenzene (2,4-DNCB) is added to the solution to give the 2,4-dinitrophenyl sulfide. In the case of S-alkyl S-methyl esters, alkanethiols were trapped exclusively and

gaseous methyl mercaptan could not be captured.

In the reaction, ethanolamine acts as not only as an aminolysis agent but also as a catalyst. As shown in Table, the present method is generally adopted to primary and secondary thiolcarbonic esters bearing allylic group and the smallscale reactions can be performed.

In the case of *S*-(1-phenylallyl) *S*-methyl dithiocarbonate (A), an interesting rearrangement was observed (Entries 9 and 10).

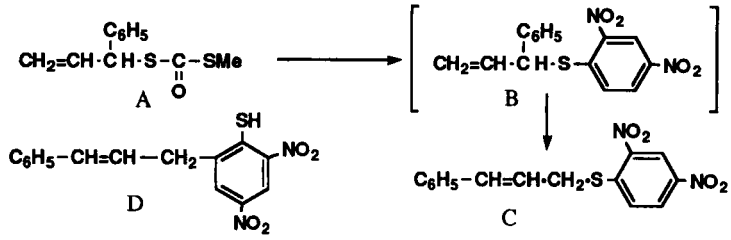
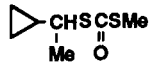
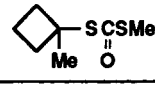


TABLE 2,4-Dinitrophenyl Sulfides from Thiolcarbonic Esters

Entry	Thiolcarbonic Ester	2,4-Dinitrophenyl Sulfide		
		Yield (%)	mp (°)	lit. mp (°)
1)	$Me(CH_2)_{13}SCSMe$ (O)	54	96-97	—
2)	$Me(CH_2)_{14}SCSMe$ (O)	63	98-99	—
3)	$Me(CH_2)_{15}SCSMe$ (O)	64	94-96	96 [a]
4)	$PhCH_2SCSMe$ (O)	82	129-130	128-129 [a]
5)	$(PhCH_2S)_2C{=}S$	82	129-130	128-129 [a]
6)	$CH_3OCSCH_2C_6H_5$ (S)	82	129-130	128-129 [a]
7)	$CH_2{=}CHCHSCSMe$ (Me, O)	71	69-71	—
8)	$C_6H_5CH_2{=}CHCH_2SCSMe$ (O)	90	126-128	—
9)	$CH_2{=}CH{-}CHSCSMe$ (Ph, O)	41	126-128 [b]	—
10)	$CH_2{=}CHCHSCSCH_2CH{=}CHPh$ (Ph, O)	40	126-128 [b]	—
11)		72	72-74	74.5-75 [c]
12)		44	107-110	—

a) Ref. 2b. b) The product was isolated as cinnamyl derivative. c) Ref. 3.

The sulfide isolated was the allylically rearranged product (C) instead of the expected 2,4-dinitrophenyl sulfide (B). The ^{1}H-NMR spectral data supported the structure of C, ruling out a Claisen rearrangement product (D). However similar allylic shift could not be observed in *S*-(1-methylallyl) *S*-methyl dithiocarbonate (Entry 7). Further studies on the mechanism of the allylic rearrangement are in progress.

EXPERIMENTAL SECTION

Melting points were uncorrected. ^{1}H NMR spectra were obtained on a JEOL GX-400 spectrometer for *ca.* 10% (w/v) solutions in $CDCl_3$.

Preparation of Dithiol Esters.- The dithiol esters were prepared by catalytic thione-to-thiol rearrangement of the corresponding xanthates.[4-6] The allylic dithiol esters were prepared by [3,3]-sigmatropic rearrangement of the corresponding allylic xanthates.[7]

Preparation of 2,4-Dinitrophenyl Sulfide. General Procedure.- A solution of thiol ester (1 mmol) and 3-5 eq of 2-aminoethanol in ethanol (1-2 ml) was heated at 80° until evolution of methanethiol was ceased (*ca.* 10 min). After cooling, 2,4-dinitrochlorobenzene (1 mmol) in ethanol was added to the solution and allowed to stand overnight at room temperature. The precipitates were recrystallized from ethanol to give yellow crystals. If the product is an oil, the product should be purified by choromatography on silica gel.

The hexadecyl, benzyl and 1-cyclopropylethyl 2,4-dinitrophenyl sulfides were identified by comparison of the physical and spectral data with those reported in the literature. The physical data of the new compounds are as follows.

Tetradecyl 2,4-Dinitrophenyl Sulfide.- This compound was isolated as yellow prisms. mp 96-97°.
Anal. Calcd for $C_{20}H_{32}N_2O_4S$:C, 60.58; H, 8.13; N, 7.06. Found: C, 60.30; H, 7.80; N, 6.71

Pentadecyl 2,4-Dinitrophenyl Sulfide.- This compound was isolated as yellow prisms. mp 98-99°.
Anal. Calcd for $C_{21}H_{34}N_2O_4S$: C, 61.43; H, 8.35; N, 6.82. Found:C, 61.15; H, 8.11; N, 6.57

1-Methylallyl 2,4-Dinitrophenyl Sulfide - This compound was isolated as yellow prisms. mp 69-71°. ^{1}H NMR (60 MHz): δ 1.57 (d, 3H, CH_3), 4.13 (m, 1H CH), 5.13-6.20 (m, 3H, $CH=CH_2$), 7.62-9.02 (m, 3H, aromatic H).
Anal. Calcd for $C_{10}H_{10}N_2O_4S$: C, 47.24; H, 3.96; N, 11.02. Found; C, 47.24; H, 3.76; N, 11.03

Cinnamyl 2,4-Dinitrophenyl Sulfide.- This compound was isolated as yellow prisms. mp 126-128°. ^{1}H NMR (400 MHz): δ 3.92 (d, 2H, J = 6.96, CH_2), 6.25 (dt, 1H, J = 6.96, 15.75, CH=C**H**-CH_2), 6.75 (d, 2H, J = 15.75, CH_2), 7.24-7.37 (m, 5H, -Ph), 7.63-9.07 (m, 3H, aromatic H).
Anal. Calcd for $C_{15}H_{12}N_2O_4S$: C, 56.95; H, 3.87; N, 8.86. Found: C, 57.05; H, 3.78; N, 8.70

1-Methylcyclobutyl 2,4-Dinitrophenyl Sulfide.- This compound was isolated as yellow prisms. mp 107-110°.^{1}H NMR (60 MHz): δ 1.76 (s, 3H, SCH_3), 2.19-2.60 (m, 6H, three CH_2), 7.42-9.08 (m, 3H, aromatic H).
Anal. Calcd for $C_{11}H_{12}N_2O_4S$: C, 49.25; H, 4.51; N, 10.44. Found: C, 49.10; H, 4.29; N, 10.19

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A CONVENIENT PREPARATION OF N-DEMETHYLDILTIAZEM AND ITS CONVERSION TO A DILTIAZEM HOMOLOG

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Diltiazem (**1a**), (2*S*,3*S*)-3-acetoxy-5-(2-dimethylaminoethyl)-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one is a calcium channel blocker,[1] widely used for the treatment[2] of angina, hypertension and cardiac arrhythmias. It undergoes extensive metabolism *via* N- and O-demethylation, deacetylation, and N-oxidation, resulting in a variety of metabolites.[3] N-Desmethyldiltiazem (**1b**) accounts for approximately 50% of the unconjugated form excreted in 24 hrs human urine, about 45% being unchanged diltiazem.[4] In connection with the comparative performance evaluation of diltiazem tablets and extended release multiparticulate osmotic dosage forms,[5] and the subse-