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Synthesis and Application of Chlorodithiocarbonates, Thionothiocarbonates, and Thionoselenocarbonates in Radical Chain Reactions

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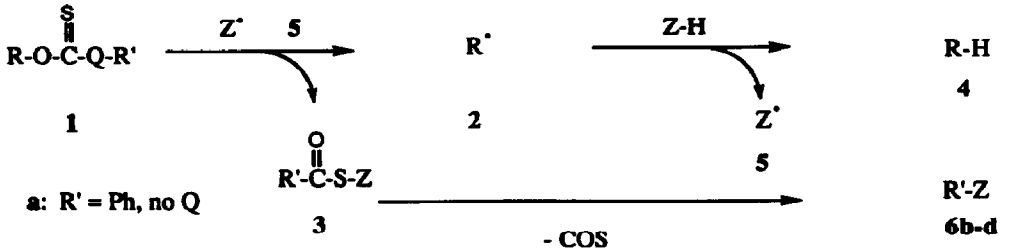
Abstract: Thionothiocarbonates as well as the corresponding selenium compounds are good radicophilic starting materials for the efficient radical chain reactions of alcohols.

There are many synthetic applications of the original Barton-McCombie reaction[1] for the radical chain deoxygenation of alcohols[2,3] (R-OH to **4** *via* the carbon-centered radical **2**). It has been demonstrated earlier, that thiobenzoates[1] **1a**, thionocarbonates[3] **1b** and xanthates[1,4] **1c** are useful precursors for this mild radical reaction, applicable to a wide range of sensitive natural products, including various carbohydrates and antibiotics. However, there are only a few published examples on the use of other dithiocarbonates[4] and, in particular, trithiocarbonates[5] as sources of carbon radicals (**Scheme 1**).

Scheme 1



a: R' = Ph, no Q

b: R' = Ar, Q = O

c: R' = Me, Q = S

d: R' = Ph, Q = S

e: R' = p-Tolyl, Q = S

f: R' = p-Fluorophenyl, Q = S

g: R' = p-Anisyl, Q = S

h: R' = p-Methylthiophenyl, Q = S

i: R' = Phenyl, Q = Se

j: R' = p-Chlorophenyl, Q = S

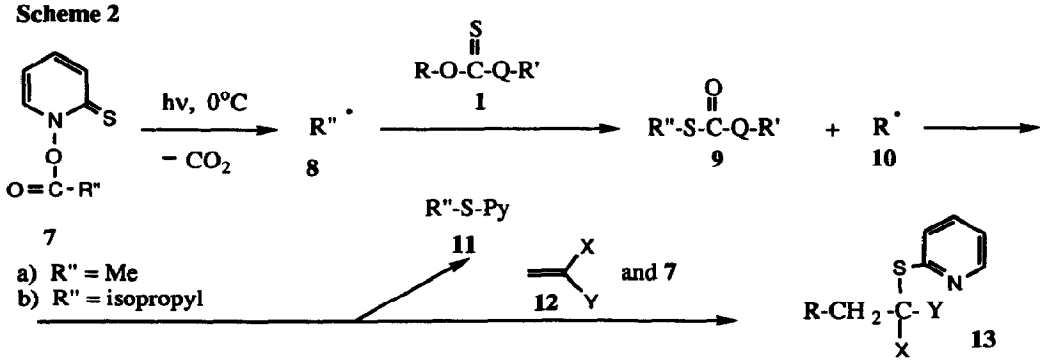
The application of (phenylthio)thiocarbonyl chloride in derivatization of carbohydrates of aminoglycoside antibiotics and the subsequent trialkyltin radical mediated radical chain deoxygenation of the (phenylthio)thiocarbonyloxy compounds **1d** has been described.[6] A systematic study, related to the potential role played by the substituents on the phenyl ring of these aryl dithiocarbonates in the radicophilicity of the

thiocarbonyl group, and, hence, in the outcome of the radical chain deoxygenation reactions has not yet been reported. Since we have demonstrated recently[7] that various substituents on the phenyl ring of aromatic thionocarbonates can enhance the radicophilicity of the thiocarbonyl group and improve the radical deoxygenation process,[7] it was of interest to study this effect in thionothiocarbonates and thionoselenocarbonates.

Thus, various reagents have been chosen from our potpourri in the hope that these could be suitable for syntheses of thionothiocarbonates and thionoselenocarbonates as potential substrates for the radical reaction outlined in **Scheme 1**. Thiophosgene can be utilized for the synthesis of these reagents and subsequently the desired substrates **1** in two independent ways. In version **A** the chlorothionocarbonate-type reagents could be made from the corresponding phenol, thiophenol or selenophenol and then reacted with an alcohol to form substrates of type-**1**. We have envisioned that likewise, depending on the structure and sensitivity of the alcohol that needs to be deoxygenated, in version **B**, a chlorothionocarbonate could also be prepared from the alcohol itself and subsequently transformed into thionothiocarbonates or thionoselenocarbonates upon reaction with the corresponding thiophenols or selenophenols, ArSH or ArSeH, respectively . This latter method is known to provide an easy access to thionocarbonates[8] with various phenols (especially pentafluorophenol).

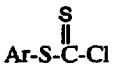
A special objective of our work was the synthesis of derivatives of **1** that would show an enhanced radicophilicity with respect to Barton esters of type **7**. In this way a new range of radical chain reactions might be inaugurated where the chain was not interrupted by reaction of the radical with the Barton ester (**Scheme 2**).

Scheme 2



The first formed radical **8** (from **7a** or **7b**), by reaction with **1** would furnish **9** and a second radical **10**. The latter would be trapped by a suitable olefin **12** to furnish **13** with reformation of the radical R" **8**. We have shown already[10] that the highly functionalised carbon atom in adducts of type **13** makes them versatile intermediates for the synthesis of a variety of compounds.

Two substituted (arylthio)thiocarbonyl chloride reagents **14a** and **14b** were prepared from thiophosgene in a water/methylene chloride two phase system in 90.7% and 90.17% yield, respectively.



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a) Ar = p-Tolyl
b) Ar = p-Fluorophenyl
c) Ar = Ph
d) Ar = p-Chlorophenyl

The corresponding unsubstituted phenyl compound **14c** is commercially available, but it can also be synthesized by this method in a higher than 90% yield. The 4-chloro analogue **14d** was prepared similarly to **14a** and **14b** in an 85% yield. These (arylthio)thiocarbonyl chlorides can then be used to functionalize alcohols via path **A** to furnish dithiocarbonates **1e** and **1f** (R = cyclododecyl), respectively. The alternative method (path **B**) involves the one-pot transformation of alcohols to the corresponding chlorothiocarbonyl derivatives in methylene chloride with thiophosgene[8] in the presence of *N,N*-dimethylamino pyridine, followed by the reaction with the corresponding thiophenol Ar-Q-H (Q = S). These compounds are suitable for deoxygenation by known methods. Thus, deoxygenation of the *p*-fluorophenyl-derivative **1f** (R = cyclododecyl) with tris(trimethylsilyl)silane[11] (1 equiv) and a catalytic amount of azobisisobutyronitrile at 110°C resulted in complete conversion of **1f** to cyclododecane. Analytically pure samples of cyclododecanol derivatives **1e**, **1g**, **1h** and **1f** can be obtained after recrystallization from methylene chloride/methanol in a 66-71% yield. Both methods give much higher yields than the reported arylation using carbon disulfide.[12] Attempts to synthesize the (phenylseleno)thiocarbonyl chloride resulted in a crude orange liquid that easily decomposed upon attempted purification. However, the alternative reaction (path **B**) gave the desired phenylselenothionocarbonate **1i** (R = cyclododecyl) in a 73% isolated yield after recrystallization from chloroform/methanol.

Competition experiments of selected dithiocarbonates (1-1 equivalents) with the corresponding methyl xanthate **1c** (R = cyclododecyl) with isopropyl radicals generated by the visible light photolysis[9] of the corresponding Barton ester **7b** revealed that the aryl dithiocarbonates were 5-6 times more reactive than the corresponding methyl xanthate (**Table 1**).

Table 1. Photolysis of thiohydroxamate **7b** in the presence of thiocarbonyl compounds.[a]

7b equivalents	1	2	3	4	5
Substrate(s)			Consumed (%)		
1e	40	74	100	-	-
1e/1c[b]	37/8	56/13	70/13	80/16	100/18
1d/1c[b]	25/2	53/5	-	83/11	100/17
1i/1c[b]	50/0	80/0	100/0	-	-
1j/1c[b]	38/0	59/12	69/16	100/18	100/20

[a]The reactions were carried out in C_6D_6 (see ref. 9) and the transformations were followed by ^1H NMR. [b]1 equivalent each, relative to the starting 1 equivalent of **7b**.

In order to achieve a 100% conversion of the aryl dithiocarbonates, however, the use of 3 to 5 equivalents of the thiohydroxamate **7b** was needed. This indicates that the thiocarbonyl group of **7b** is still more reactive than those of derivatives **1**, competing successfully for the carbon centered (isopropyl) reagent radical. The (phenylseleno)thionocarbonate **1i** was more reactive towards the isopropyl radical than the corresponding (4-fluorophenyl) dithiocarbonate of cyclododecanol **1f**.

We have already reported that methyl radicals generated from **7a** can induce at room temperature the fragmentation of the xanthate and sulfone residues in the Julia olefination reaction.[13] We have confirmed our original report (90% yield of olefin). The difference between this result and the data reported in **Table 1** must be explained by the concerted mechanism already proposed.[13] A similar phenomenon is seen in the fragmentation of trithiocarbonate and nitro groups in a related olefination reaction.[5, 14] In both olefination reactions the addition (1:1) of cyclododecyl methyl xanthate left this xanthate largely unchanged during the smooth olefination process.

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