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Radical, One-Step Approach to *o*-Chlorophenyl Thioethers from Xanthates. A Rapid Access to Vinylsilanes

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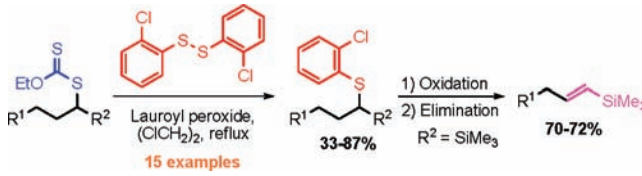
ABSTRACT



Xanthates have been readily converted into *o*-chlorophenyl thioethers using a one-step procedure conducted under radical conditions. In some selected cases, these aryl thioethers were successfully oxidized to the corresponding sulfoxides and sulfenic acid elimination afforded the corresponding vinylsilanes.

Xanthate (dithiocarbonate) transfer radical chemistry has proven over the years to be a useful tool in organic synthesis.[1] It enables the formation of carbon−carbon bonds in both inter- and intramolecular fashions and allows the expedient construction of a broad range of structures. Of particular interest is the modification of the xanthate group in the product using either radical or ionic chemistry.[2,3] Even though much has been done, there are certainly many interesting reactions still to be uncovered.

In this paper, we report a novel radical transformation of the dithiocarbonate group to aryl thioethers and more specifically to *o*-chlorophenyl thioethers. The ability to synthesize thioether functional groups is of special interest because of their importance in organic synthesis as a key entry point into the rich chemistry of sulfoxides and sulfones. Their preparation from the thiol is commonly achieved via standard nucleophilic substitutions or nucleophilic aromatic substitutions in basic media, but other methods are known, and recent examples include palladium- or copper-catalyzed cross-coupling reactions.[4]

If we consider xanthates as potential starting materials for the synthesis of thioethers, one could envision hydrolyzing the dithiocarbonate functional group to the corresponding thiol,[5] and further nucleophilic substitution would lead to the desired product. This classical two-step strategy is now well established in our laboratory (eq 1).[6] Some limitations exist when R^3 is an

(1) For general reviews, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672. (b) Quiclet-Sire, B.; Zard, S. Z. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *153*, 137. (c) Zard, S. Z. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, p 90. (d) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (e) Quiclet-Sire, B.; Zard, S. Z. *Chem. Eur. J.* **2006**, *12*, 6002. (f) Zard, S. Z. *Org. Biomol. Chem.* **2007**, *5*, 205.

(2) For examples utilizing radical chemistry, see: (a) Liard, A.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 5877. (b) Bertrand, F.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1999**, *38*, 1943. (c) Barbier, F.; Pautrat, F.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Synlett* **2002**, 811. (d) Boivin, J.; Jrad, R.; Juge, S.; Nguyen, V. T. *Org. Lett.* **2003**, *5*, 1645. (e) Ouvry, G.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 2907.

(3) For examples utilizing ionic chemistry, see: (a) Boivin, J.; Boutillier, P.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2529. (b) Lusinchi, M.; Stanbury, T. V.; Zard, S. Z. *Chem. Commun.* **2002**, 1532. (c) Quiclet-Sire, B.; Sanchez-Jimenez, G.; Zard, S. Z. *Chem. Commun.* **2003**, 1408. (d) Corbet, M.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 2861.

(4) For recent and representative examples, see: (a) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, *4*, 4309, and references cited therein. (b) Cai, L.; Cuevas, J.; Peng, Y.-Y.; Pike, V. W. *Tetrahedron Lett.* **2006**, *47*, 4449, and references cited therein.

(5) Mori, K.; Nakamura, Y. *J. Org. Chem.* **1969**, *34*, 4170.

(6) Boutillier, P.; Zard, S. Z. Unpublished results.

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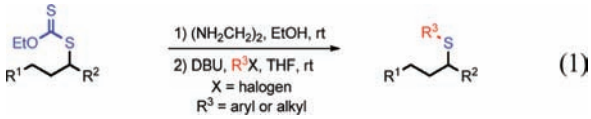
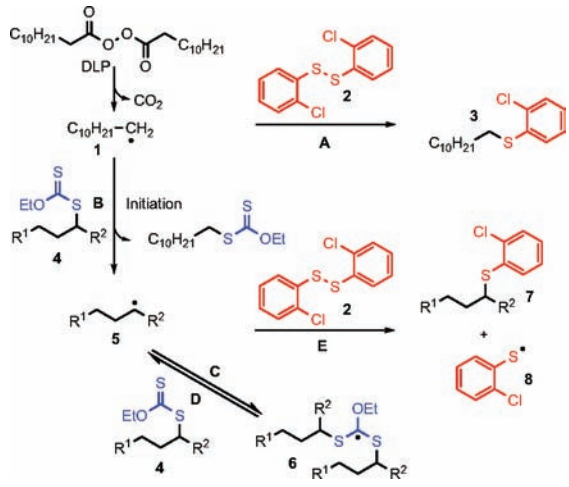
aryl group, since the latter needs to be rather activated for nucleophilic aromatic substitution to occur.



(1)

However, if one considers a possible one-step approach to aryl thioethers from xanthates, a radical-based strategy appears as a good alternative method to the ionic route. First attempts to obtain phenyl thioethers under radical conditions using lauroyl peroxide (DLP) as the initiator and phenyl disulfide as the thioether source in 1,2-dichloroethane (DCE) were disappointing. The reactions could not be readily driven to completion, and unacceptable amounts of sulfides derived from direct reaction of the radicals from the initiator were formed. However, the use of *o*-chloro-substituted disulfide **2** gave significantly better results. From a mechanistic point of view, it is clear that the chlorine atom of **2** offers its neighboring sulfur atom enough steric protection to limit unwanted direct attack by the undecyl radicals (**1**) from the initiator (DLP), leading to undesired thioether **3** (path A, Scheme 1).

Scheme 1. Reaction Manifold for the Synthesis of Aryl Thioethers (**7**)



The primary radical from DLP has no other choice than to attack the sulfur atom of the thiocarbonyl moiety of xanthate **4**, thus initiating the desired reaction (path B). The radical **5** produced can add to the thiocarbonyl group of the starting xanthate **4** (path C). The stabilized adduct radical **6** is too hindered to dimerize (or does so reversibly) and cannot disproportionate. It can therefore only undergo fragmentation by rupture of the C−S bonds (path D) leading simply to the starting xanthate **4** and the same radical **5**. Thus, the reaction of the initial radical (**5**) with its xanthate precursor is reversible and degenerate. As a consequence, the effective lifetime of **5** in the medium increases considerably, since it is continuously being regenerated. Now, addition to sterically hindered disulfide **2** becomes possible, and aryl thioethers (**7**) can be obtained (path E). Thiyl radical **8** can capture carbon radical **5** to also give the desired product or combine with another thiyl radical to return disulfide **2**; it cannot, however, propagate the chain process, and a stoichiometric amount of DLP is therefore needed.

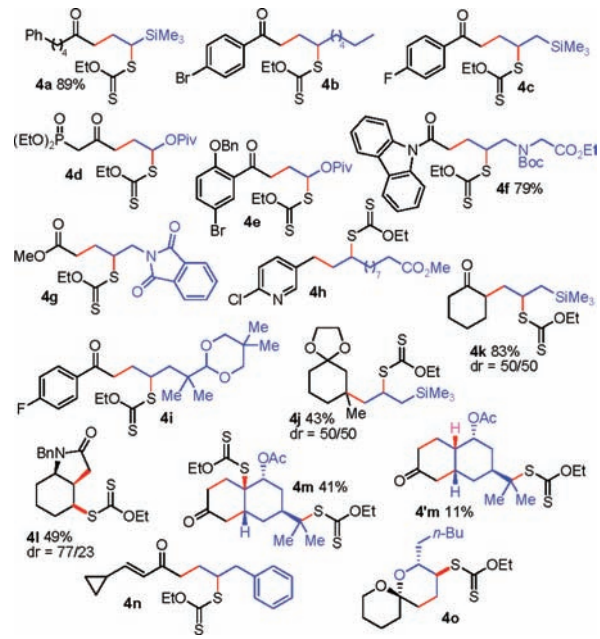
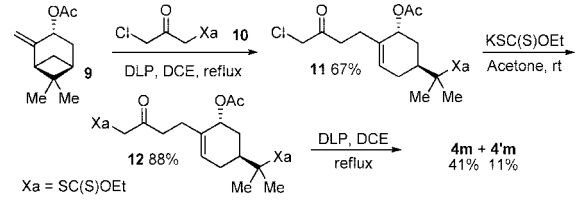


Figure 1. Xanthate adducts **4a**−**o**.

To investigate the scope and limitations of this new radical exchange process, several xanthate adducts (**4a**−**o**, Figure 1) were first synthesized in good yield by treatment of various starting xanthates and excess olefins in degassed, refluxing solutions of DCE with substoichiometric amounts of DLP.[7]

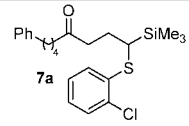
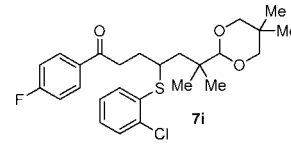
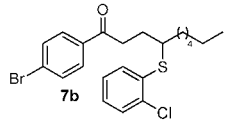
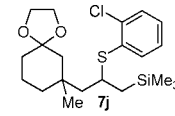
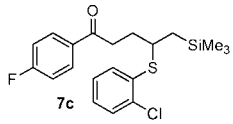
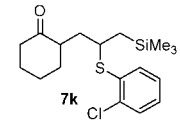
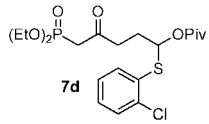
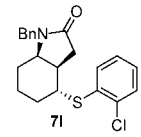
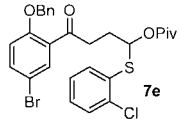
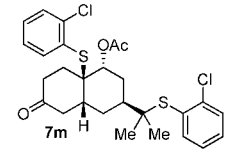
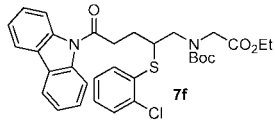
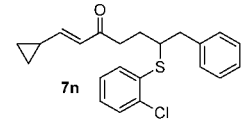
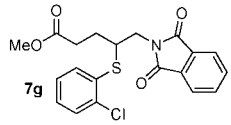
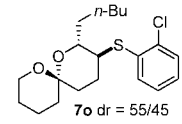
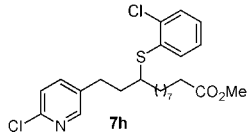
A noteworthy result is obtaining reduced compound **4′m** (11% isolated yield) along with the desired enantiopure *cis*-

Scheme 2. Synthesis of *cis*-Decalins **4m** and **4′m**



(7) (a) For the synthesis of **4b**, see ref 3b. (b) For the synthesis of **4c**, see: Briggs, M. E.; Zard, S. Z. *Synlett* **2005**, 334. (c) For the synthesis of **4d**,**n**, see: Corbet, M.; de Greef, M.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 253. (d) Compound **4e** was a gift from Dr. A. Cordero-Vargas (DCSO, Ecole Polytechnique). (e) For the synthesis of **4g**, see: Dublanchet, A.-C.; Lusinchi, M.; Zard, S. Z. *Tetrahedron* **2002**, *58*, 5715. (f) For the synthesis of **4h**, see: Ferjančić, Z.; Quiclet-Sire, B.; Zard, S. Z. *Synthesis* **2008**, in press. (g) Compound **4i** was a gift from Dr. T. V. Stanbury (DCSO, Ecole Polytechnique). (h) For the synthesis of **4o**, see: de Greef, M.; Zard, S. Z. *Org. Lett.* **2007**, *9*, 1773. (i) For the preparations of **4a**,**f**,**j**−**m** and their precursors in detail, see the Supporting Information.

Table 1. Synthesis of *o*-Chlorophenyl Thioethers **7a**−**o**[a]

entry	xanthate **4a-o**	product **7a-o**	yield[b] (%)	entry	xanthate **4a-o**	product **7a-o**	yield[b] (%)
1	**4a**	 **7a**	33 (38)[c]	9	**4i**	 **7i**	67
2	**4b**	 **7b**	74	10	**4j**	 **7j**	55
3	**4c**	 **7c**	53 (64)[c]	11	**4k**	 **7k**	78[d]
4	**4d**	 **7d**	56	12	**4l**	 **7l**	51 (61)[c,e]
5	**4e**	 **7e**	58	13	**4m**	 **7m**	45[f]
6	**4f**	 **7f**	42	14	**4n**	 **7n**	37 (40)[c]
7	**4g**	 **7g**	87	15	**4o**	 **7o** dr = 55/45	76
8	**4h**	 **7h**	75				

[a] General experimental procedure: a magnetically stirred solution of **4a**−**o** (1 equiv) and disulfide **2** (2 equiv) in DCE (1 mL/mmol of **2**) was refluxed for 15 min. DLP (20 mol %) was then added, and additional DLP (20 mol %) was added every hour until total consumption of **4a**−**o** or until no evolution was observed (TLC analysis). The mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to yield the desired compounds (**7a**−**o**). [b] Isolated yields. [c] Yields based on recovered starting material. [d] 8% of the corresponding vinylsilane **14** was detected by ^{1}H NMR. [e] This compound was obtained as a single diastereoisomer. [f] Yield based on the ^{1}H NMR of a mixture of compound **7m** with the corresponding monothioether.

decalin **4m** (41%) (Scheme 2). In this case, the reaction did not go to completion, and the more DLP was added, the more the proportion of reduced compound **4′m** increased (TLC analysis).

This surprising result is related to one we observed in our laboratory some years ago when carbohydrates containing a xanthate group were reduced under radical conditions with the help of cyclohexane (the solvent) acting as a hydrogen donor.[8] What is most likely happening in this case is that DCE (the solvent) acts as the hydrogen donor, and it is the acetate group that governs the polar effect needed for the reduction to occur. No reduction product was indeed observed when the same reaction was carried out in the absence of the acetate.[9]

With xanthate adducts **4a**−**o** in hand, we were able to proceed with our novel reaction, and several *o*-chlorophenyl thioethers (**7a**−**o**) were synthesized in moderate to good yields (Table 1).[10]

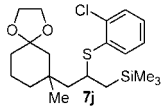
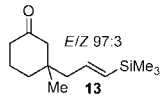
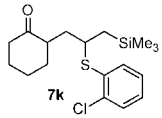
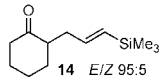
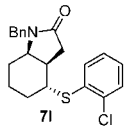
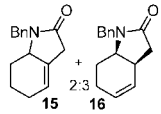
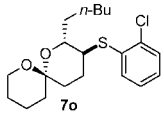
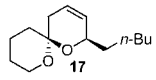
In most cases, the reaction did not go to completion (starting material was not always recovered), and in some cases 4 equiv of DLP were needed. Purification by flash chromatography was sometimes complicated because of the similar polarity of the starting materials (**4a**−**o**) and the products (**7a**−**o**). The low yield obtained with compound **7a** (33%, entry 1) can be explained by the steric hindrance caused by the trimethylsilyl group. In contrast, better yields were obtained when the latter was one carbon away from the thioether (entries 3, 10, and 11). For examples where

(8) Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **1996**, *118*, 9190.

(9) Bergeot, O.; Corsi, C.; El Qacemi, M.; Zard, S. Z. *Org. Biomol. Chem.* **2006**, *4*, 278.

(10) For the preparation of disulfide **2**, see: (a) McKillop, A.; Koyunçu, D.; Krief, A.; Dumont, W.; Renier, P.; Trabelsi, M. *Tetrahedron Lett.* **1990**, *31*, 5007.

Table 2. Oxidation and Elimination of Aryl Thioethers **7j**,**k**,**l**,**o**[a]

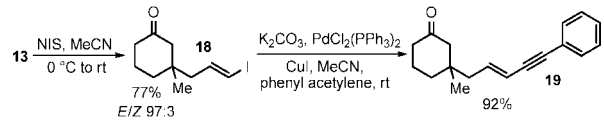
entry	substrate	product	yield[b] (%)
1	 **7j**	 **13** *E*/*Z* 97:3	70[c]
2	 **7k**	 **14** *E*/*Z* 95:5	72
3	 **7l**	 **15** + **16** 2:3	80[d]
4	 **7o**	 **17**	78

[a] The thioethers were oxidized to the corresponding sulfoxides with *m*-CPBA (1 equiv), and sulfenic acid elimination was realized in refluxing toluene with PPh_3 (1 equiv). [b] Isolated yields. [c] Deprotection was achieved with 1 N HCl in acetonitrile. [d] No PPh_3 was added; regioisomers were separated but compound **16** was contaminated with an unidentified impurity; ratio based on the ^{1}H NMR of the mixture of both regioisomers.

the formation of tetralones was expected to be a serious competing side reaction (entries 2, 3, 5, and 9), no significant amounts were detected. To our surprise, in the course of the reaction leading to thioether **7k** (entry 11), 8% of eliminated product corresponding to the *E*-vinylsilane **14** (see Table 2) was formed. The origin of this side product is unclear and remains to be determined. Interestingly, compound **7l** (entry 12) was obtained as a single diastereoisomer from a starting mixture of distereoisomeric xanthates **4l**. In the case of the reaction of **4m** (entry 13), it was mistakenly stopped prematurely and furnished a mixture of desired compound **7m** (45%) and monothioether (16%). However, we were unable to determine the regiochemistry of the latter; i.e., we do not know if the remaining xanthate function is at the cyclic junction or α to the *gem*-dimethyls. But, if we take into account the previous observation of reduced compound **4′m** (vide supra), one can deduce that the thioether is most likely at the cyclic junction. If it was the other way round, some reduced compound should have been detected. This would also indicate that the reaction leading to the thioether is faster than the hydrogen abstraction from the solvent. Although the yield of **7n** was rather moderate (37%, entry 14), it was remarkable that no product resulting from a potential 5-*exo* cyclization/cyclopropane ring-opening was observed. The synthesis of compound **7o** enabled us to compare the ionic method (i.e., aminolysis of the xanthate group followed by arylation of the resulting thiol with *p*-fluoronitrobenzene)[7h] with our radical-based approach, and we were glad to see that the yields were relatively close (76% for the one-step radical method against 80% for the two-step ionic route).[7h]

Some of these aryl thioethers were oxidized and the resulting sulfoxides eliminated (Table 2).[11] A couple of

Scheme 3. Example of the Utilization of Vinylsilane **13**



vinylsilanes were successfully obtained this way (entries 1 and 2). Remarkably, the regioselectivity of the elimination was complete, furnishing only the vinylsilane.[12] In the case of **7j**, partial deprotection of the dioxolane moiety was observed during the elimination process, but acidic treatment of the crude reaction mixture gave compound **13** in 70% yield along with a good *E*/*Z* selectivity (97:3, entry 1).[12]

Compound **7k** was treated under the same reaction conditions as **7j**, and vinylsilane **14** was obtained in 72% yield over two steps (entry 2). It is worth noting that in the absence of PPh_3 this reaction gave several byproducts and the desired compound (**14**) was isolated in low yield (22%). Under similar conditions, aryl thioether **7l** gave regioisomers **15** and **16** in good yield (80%) but poor regioselectivity (2:3, entry 3). A sulfenic acid trap was not compulsory in this case. Alkene **17** could also be obtained in a yield comparable to the one previously reported (78% against 81%).[7h]

Finally, as an illustration of the importance and versatility of vinylsilanes in organic synthesis,[13] compound **13** was converted into vinyl iodide **18** using *N*-iodosuccinimide (NIS) in acetonitrile (77%),[14] with retention of olefin geometry (Scheme 3). The latter successfully underwent Sonogashira coupling with phenyl acetylene in acetonitrile using a Pd(II) catalyst to afford enyne **19** in excellent yield (92%).[15]

In summary, we have developed a novel one-step, radical approach to aryl thioethers. A number of xanthates were successfully transformed into the corresponding aryl thioethers. The easy access to valuable vinylsilanes in only three steps from simple xanthate adducts is worthy of note and underscores the synthetic potential of this functional group exchange process.

Supporting Information Available: Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For a general review, see: (a) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363.

(12) A similar observation was made some time ago, but no satisfactory explanation has been given, nor has this led to any synthetic applications, presumably because of the difficulty encountered in accessing the required precursors. See: (a) Ochiai, M.; Tada, S.-I.; Sumi, K.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1982**, 281.

(13) For general reviews, see: (a) Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761. (b) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857. (c) Fleming, I.; Barbero, I. A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063. (d) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61.

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