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A Practical Method for the Reductive Cleavage of the Sulfide Bond in Xanthates.

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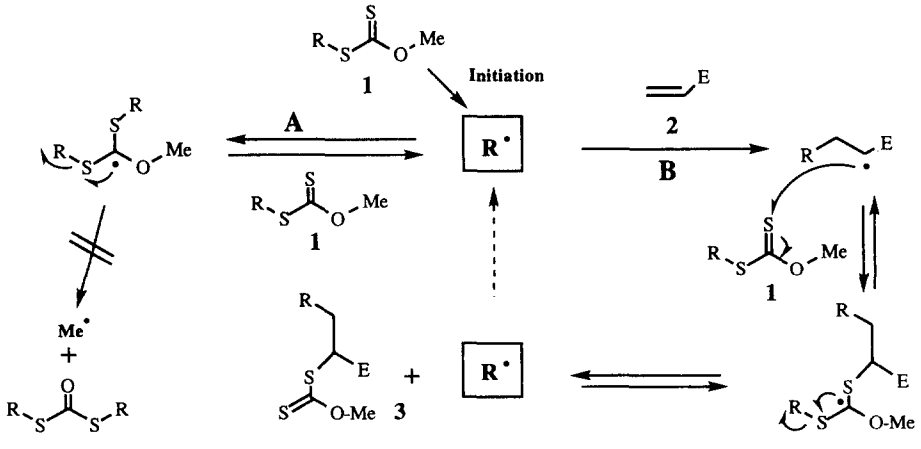
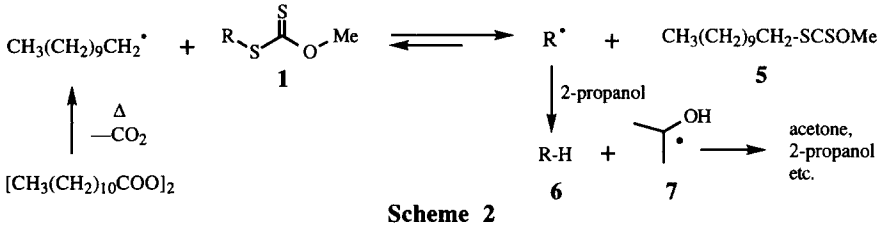
Abstract : Xanthates can be reduced to the corresponding alkane through cleavage of the sulfide bond by heating in 2-propanol in the presence of equimolar amounts of dilauroyl peroxide, added in small portions. Copyright © 1996 Published by Elsevier Science Ltd

We wish to report a simple yet efficient method for the reductive removal of a xanthate group by homolytic cleavage of the C-S sulfide bond. The need for such a process arose in the context of our work on xanthates as a general and synthetically useful source of radicals of various types such as alkyl, acyl, alkoxycarbonyl, alkoxythiocarbonyl, and even stannyl radicals.[1] The reaction manifold in Scheme 1 outlines the general case where the radicals thus produced are captured by an external olefin (an O-methyl xanthate **1** is shown for clarity even though other groups, such as ethyl or neopentyl, can be equally used in place of the methyl). Overall, the end product **3** consists of the two parts of the original xanthate added accross the double bond of the olefin trap. The most important property of this system is that the reaction of xanthate **1** with R• (path **A**) is degenerate and does not therefore compete with its capture via path **B**. This allows the use of relatively unreactive olefins as traps, or the execution of sluggish or difficult cyclisations or fragmentations without the need for high dilution or slow addition of the reagents, a problem commonly encountered with radical reactions based on the hugely popular stannane chemistry for example.[2]



Scheme 1

Another useful feature is that the end product **3** is also a xanthate that can be used as a starting point for another radical sequence, or as an entry into the exceptionally rich chemistry of sulfur. However it is often necessary to remove the xanthate group since many synthetic targets do not contain sulfur. This operation can usually be accomplished efficiently with tributylstannane,[3] Raney nickel,[4] or nickel boride;[4,5] but these reagents are not convenient for use on a large scale and sometimes lack in selectivity when certain other functional groups are present. We therefore considered taking advantage of the reversibility of the radical addition to a xanthate upon which the manifold in Scheme 1 is constructed in order to force hydrogen abstraction from a cheap hydrogen atom donor such as 2-propanol. This idea is summarised in scheme 2 for the case where an initial radical is generated from dilauroyl peroxide. The 2-hydroxyisopropyl radical **7** created in the hydrogen transfer step is too stabilised to propagate the chain and will simply undergo the usual radical termination reactions, mostly disproportionation in this case to give acetone and 2-propanol, both of which are innocuous. The overall process is hence not a radical chain any more: the peroxide "initiator" now becomes a stoichiometric reagent.[6]



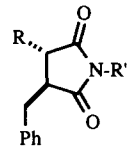
Scheme 2

The success of such an approach hinges on a central kinetic consideration implicit in scheme 2, namely that the radical from the "initiator" should react faster with the starting xanthate **1** than with the solvent and that the equilibrium in this reaction should as much as possible lie to the right (this is the case for instance when R• is secondary). This constraint does not encompass radical R•, which has no choice but to abstract a hydrogen from the solvent, since its reaction with xanthate **1** is degenerate (cf scheme 1, path **A**). Crystalline dilauroyl peroxide (DLP) was selected for this task because of its cheapness, safety, and, perhaps most importantly, because it produces cleanly primary undecyl radicals at a useful rate[7] (the half-life is of the order of two hours at 80°C —the boiling point of 2-propanol is 82-83°C). The S-undecyl xanthate **5** that is co-produced is a stable non polar entity and thus easily separated.

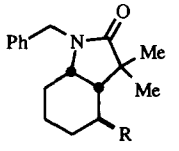
The effectiveness of this system for reducing xanthates was easily tested. Addition in small portions of DLP over several hours to a refluxing solution of xanthate **8a** in 2-propanol[8] resulted indeed in the clean formation of **9a** (92%). About 1.3 moles of DLP were needed. It is important to add the peroxide in small amounts at a time to avoid a build up in the radical concentration in the medium. The close analogue **8b** furnished **9b** in 95% yield on nearly a 4 mmole scale. In the same way, **10** gave the corresponding reduced lactam **11** also in high yield (84%). In the case of xanthate **12**, successive cyclisation and reduction took place in excellent overall yield (98%) to give **14** directly under the same reaction conditions. Intermediate **13**, which could be detected by thin layer chromatography, is the normal xanthate transfer product (cf Scheme 1) when only catalytic amounts of peroxide are used.

It is also possible to use mixtures of 2-propanol and another solvent such as diisopropyl ether or dichloroethane to improve the solubility of certain substrates.[8] This slight modification was applied to

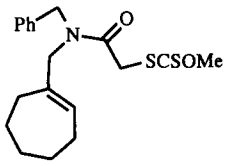
xanthates **15** (1:1, 2-propanol / diisopropyl ether) and **19** (1:1, 2-propanol / 1,2-dichloroethane) to afford reduced derivatives **16**, and **20** in 60 and 74% yield respectively. Diisopropyl ether can also be used as the hydrogen atom donor (but somewhat less effective than 2-propanol). Thus, under similar conditions (3:1, diisopropyl ether / 1,2-dichloroethane), xanthate **17** gave 3-deoxytigogenin **18** in 65% yield.



8a, R = -SCSOMe; R'= Me
9a, R = H; R'= Me (92%)
8b, R = -SCSOEt; R'= Bn
9b, R = H; R'= Bn (95%)



10, R = -SCSOCH$_2$CMe$_3$
11, R = H (84%)



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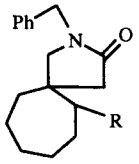
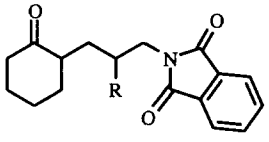
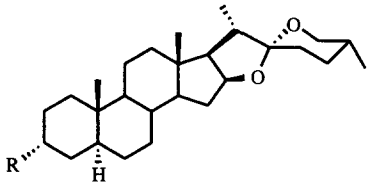


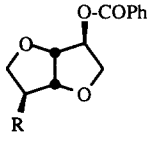
13, R = -SCSOMe
14, R = H (98%)



15, R = -SCSOEt
16, R = H (60%)

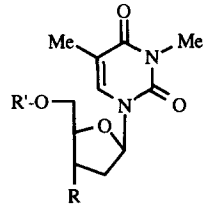


17, R = -SCSOEt
18, R = H (65%)

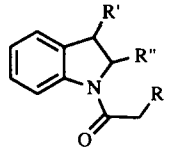


19, R = -SCSOEt
20, R = H (74%)

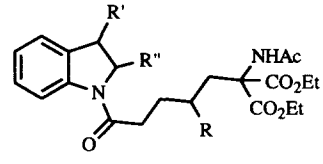
These various examples demonstrate the tolerance of this process to a variety of functional groups commonly encountered in organic synthesis. Some limitations appeared, however. Thus, in the case of the thymidine derivative **21**, partial detritylation of **22** was observed, presumably due to the presence of a small amount of lauric acid, a side product from the (slow) ionic decomposition of dilauroyl peroxide. Complete detritylation of the crude product with p-toluenesulfonic acid in a mixture of methanol and ethyl acetate neverthless gave a reasonable yield (60%) of the reduced alcohol **23**. This minor problem caused by lauric acid may in principle be overcome by adding an acid scavenger to the medium. Another side reaction was encountered in the case of indoline derivative **25**. In this instance, a significant amount (around 15%) of indole **27** was also formed in addition to the expected product **26** (50%). This compound seems to arise from intermolecular abstraction of a benzylic hydrogen followed by disproportionation (or reaction with a little oxygen that may have leaked into the system). When N-acetylindoline **28** was exposed to the same reaction conditions, N-acetyl indole **29** was formed to the extent of 16%.



21, R = -SCSOCH$_2$CMe$_3$;
R' = Ph$_3$C-
22, R = H; R' = Ph$_3$C-
23, R = R' = H (60%)



24, R = -SCSOEt;
R'= R"=H
28, R = R'= R"= H
29, R = H; R'= R"= Δ



25, R = -SCSOEt;
R'= R"=H
26, R = R'= R"= H (50%)
27, R = H; R'= R"= Δ (15%)

Finally, the reduction process appeared to be most efficient with secondary xanthates, which are synthetically the most useful class. Attempts to extend it to primary cases as were not very satisfactory. Large amounts of peroxide were needed and yields were poor.

Many of the substrates used in this study were prepared by application of the radical addition process displayed in Scheme 1. Compound **25** for instance results from the addition of xanthate **24** and allyl acetamidomalonate (73% yield, 90% based on recovered **24**). Xanthates are obviously accessible by many different routes. Xanthates **17** and **19** for example were made by displacement of the corresponding tosylates or mesylates, so that overall, this simple, practical approach can also be construed as an alternative way for deoxygenating secondary alcohols that is complementary to the Barton-McCombie reaction and its variants.[9]

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6. See for example: Coppa, F.; Fontana, F.; Minisci, F.; Pianese, G.; Tortoreto, P.; Zhao, L. *Tetrahedron Lett.* **1992**, *33*, 687-690.
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8. Typical experimental procedure: The xanthate (1 mmole) is dissolved in refluxing 2-propanol under an inert atmosphere. Di-lauroyl peroxide (0.8-1.3 mmoles) is added in 5% portions every hour or so until consumption of the starting material. When mixtures of solvents are used such as 2-propanol / diisopropyl ether (1:1) or 2-propanol / 1,2-dichloroethane (1:1), the boiling point is a little lower so that larger portions (15-20%) of the peroxide can be added every about 4 hours (the process can of course be interrupted at any time for convenience then continued again the next day). Upon completion, the solvent is evaporated under reduced pressure and the residue purified by chromatography in the usual way (for large scale work it is advisable to destroy any residual peroxide before concentration).
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