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A Practical Modification of the Barton-McCombie Reaction and Radical *O*- to *S*- Rearrangement of Xanthates

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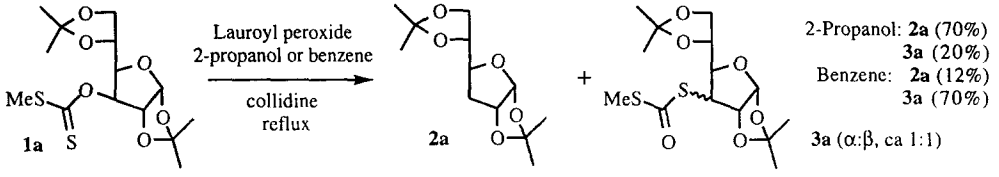
Abstract : The C-O bond in xanthates derived from carbohydrates can be reductively cleaved by heating in 2-propanol in the presence of equimolar amounts of dilauroyl peroxide, added in small portions; if benzene is used as the solvent, an *O*- to *S*- rearrangement of the xanthate occurs.

The Barton-McCombie reaction has found widespread use in organic synthesis, not only as a method for deoxygenation but also as a general process for producing radicals from alcohols.[1] Hundreds of applications have thus been reported, the most spectacular being no doubt in the carbohydrate field, where hydroxy groups are found in great abundance. One practical limitation of the original procedure is in the use of stannanes as the hydrogen atom transfer agents. The cost, toxicity, and the difficulties often encountered in separating tin residues[2] represent serious drawbacks in large scale work. Various alternative reagents, mostly based on silicon[3] or phosphorus[4] have been proposed to replace tin, but many are quite expensive and all do not exhibit the efficiency of stannanes. We now wish to report a simple yet efficient method for the reductive removal of a xanthate that is especially adapted for the deoxygenation of carbohydrates by using 2-propanol as the hydrogen atom donor.



Scheme 1

We recently described such a reductive cleavage of xanthates by *homolytic rupture of the C-S sulfide bond.*[5] This turns out to be quite efficient because radicals created in this manner have a relatively long lifetime in the medium, a consequence of the degeneracy of their reaction with the starting xanthate. There was nevertheless a possibility of extending this approach to the deoxygenation of secondary alcohols via their xanthates *through homolysis of the stronger C-O bond.* Indeed, when xanthate **1a** derived from diacetone glucose was dissolved in 2-propanol (0.2M) containing 2 equivalents of collidine and treated with 1.3 mole-equivalents of lauroyl peroxide, a smooth reaction occured to give the deoxygenated product **2a** (70%) as well as a small amount (20%) of the *O*- to *S*- rearranged material **3a**. The collidine is added to prevent cleavage of the isopropylidene groups by any lauric acid formed as a side product in the decomposition of the peroxide.

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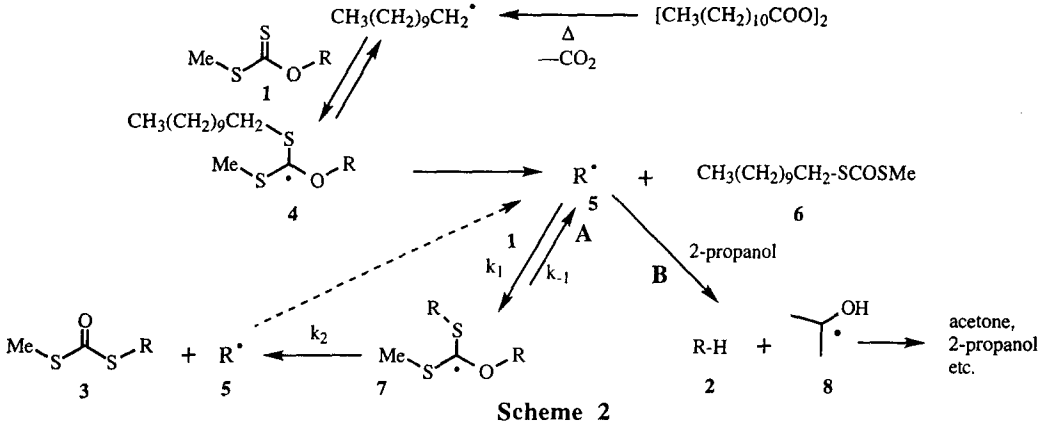
The mechanistic rationale underlying the formation of both of these products is outlined in Scheme 1. Undecyl radicals ultimately arising from the thermolysis of the peroxide add rapidly but reversibly to the thiocarbonyl group of the xanthate to give intermediate **4** which then undergoes β–scission to give a secondary carbon centered radical R• and lauroyl xanthate **6**. This radical has before it two alternatives: either it adds (reversibly) to the thiocarbonyl of another molecule of the starting xanthate (path **A**) or it abstracts, irreversibly, the tertiary hydrogen atom from the 2-propanol solvent to give the alkane **2** (pathway **B**). If the former route is followed by an irreversible β-scission, the rearranged product **3** is obtained, and radical **5** is regenerated in the process.

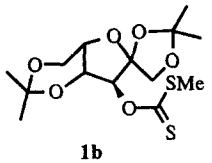
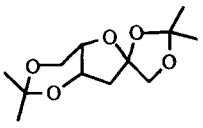
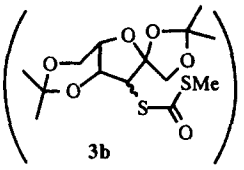
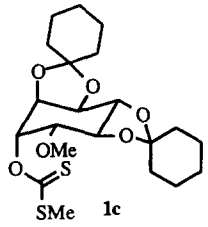
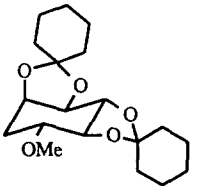
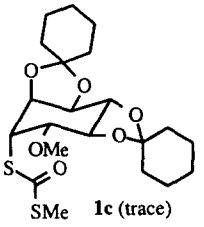
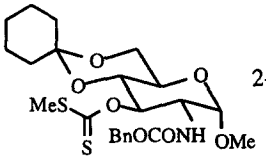
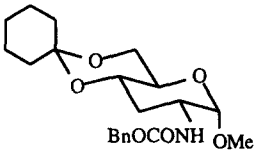
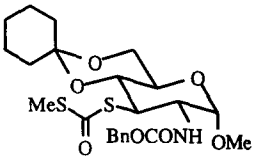
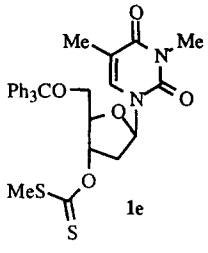
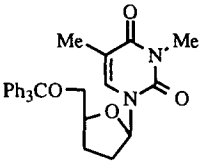
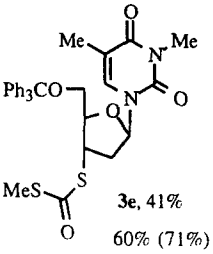
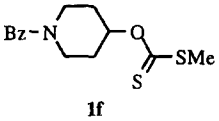
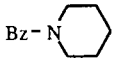
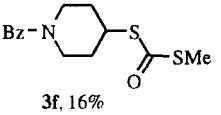
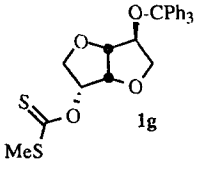
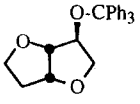
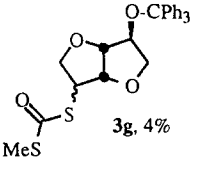


Scheme 2

Pathways **A** and **B** are thus in competition. Which will prevail depends on the experimental conditions, especially concentration and temperature, and the structure of the starting xanthate (which defines the nature (stability, electrophilicity, etc.) of radical **5**. For example, when the concentration was reduced to 0.1M in the above experiment, the yield of rearranged product **3a** decreased to 8%. Because 2-propanol is the solvent, path **B** is not affected by increasing the dilution, in contrast to route **A** which is disfavoured. On the other hand, if isopropanol is replaced by a solvent which is a poor hydrogen atom donor, then route **B** should be curtailed and the rearranged product should predominate. This is indeed the case for when a solution of xanthate **1a** in benzene (0.2M) was treated with lauroyl peroxide, **3a** was formed in 70% yield whereas the reduced product **2a** was isolated in only 12%.

Thus, depending on the way the reaction is performed, it is possible to direct the process towards reduction or towards rearrangement, the latter representing in fact a method to access thiols from alcohols. The thermal *O*- to *S*- transposition of xanthates is an old reaction, known as the Schönberg rearrangement,[6] and occurs upon pyrolysis in systems where a Chugaev elimination is not feasible (absence of a suitale β-hydrogen). More recently, Barton and Choi[7] have reported that in some cases this exchange can be triggered by trimethylaluminum at room temperature. A rearrangement product was also isolated in a low yield (10-19%) by Marco-Contelles and co-workers[8] when applying the Barton-McCombie reaction to a carbohydrate structure. This unexpected derivative arose by a radical chain mechanism identical to path **A**. Curiously, attempts to improve the yield were unsuccessful even when the xanthate was irradiated with hexabutylditin, in contrast to the ease with which we could accomplish the conversion of **1a** into **3a**. The reasons for this are not clear but may have to do with the higher dilution in their case (0.03M). Finally, a side-product, formed by an intramolecular radical shift of a xanthate group, has also recently appeared in the literature.[9] Unlike the deoxygenative reduction (path **B**), sub-stoichiometric amounts of peroxide are sufficient to trigger the *O*- to *S*- rearrangement, since this is a chain process — albeit not a very efficient one. The slow step is the rupture of the C-O bond in intermediate **7** (Scheme 2). Even if addition of R• to the xanthate is expected to be efficient (k_1 large), the reverse fragmentation involving cleavage of the weaker C-S bond is faster than the forward collapse (i. e. $k_{-1} > k_2$).

Table. Reduction and rearrangement of various xanthates (yield in parenthesis is based on recovered starting material).

Starting xanthate 1	Solvent	Reduced product 2	Rearranged product 3
 **1b**	2-propanol	 **2b**, 70% (81%)	+  **3b**
 **1c**	2-Propanol	 **1c**, 90%	+  **1c** (trace)
 **1d**	2-Propanol	 **2d**, 75%	+  **3c**, 15%
 **1e**	2-Propanol Benzene	 **2e**, 45% 11%	+  **3e**, 41% 60% (71%)
 **1f**	2-Propanol (no collidine)	 **2f**, 53%	+  **3f**, 16%
 **1g**	2-Propanol	 **2g**, 53% (77%)	+  **3g**, 4%

A number of xanthates were successfully reduced and / or rearranged. The results, compiled in the Table, require some comments. Xanthates derived from carbohydrates and related compounds which lead to secondary, electrophilic radicals are deoxygenated most efficiently in 2-propanol. The influence on the nature of the radical is subtle and reflects the role of polar effects in accelerating hydrogen abstraction.[10] Radicals derived from carbohydrates possess an enhanced electrophilic character because of the inductive

effect of the oxygen groups β-to the radical centre. We have recently shown that carbohydrate radicals (and other radicals with similar electrophilicity), produced under degenerative conditions where the radical has a relatively long lifetime, are capable of abstracting hydrogen even from cyclohexane; a clean chain reaction can thus be sustained wherein cyclohexane acts as the reducing agent.[11] These polar effects explain incidentally why xanthates of sugars are deoxygenated faster than less oxygenated substrates, as noted by Barton and his co-workers a few years ago.[12] In the present case, an electrophilic radical will react sufficiently rapidly with 2-propanol for reduction to occur, in preference to rearrangement. In the absence of electron withdrawing groups in the vicinity of the radical as in **1e** and **1f**, hydrogen abstraction is slower and the competition with the rearrangement and other side reactions becomes tougher.

In summary, this preliminary work shows that it is possible to induce a reasonably efficient radical *O*- to *S*- rearrangement of secondary xanthates and, if the ensuing radical is electrophilic as in carbohydrates and related derivatives, deoxygenation can be accomplished easily by changing the solvent to 2-propanol.[13] Even if the latter process requires stoichiometric amounts of lauroyl peroxide,[14] this reagent is cheap, safe, and easy to handle. Either mercapto-[15] or deoxy-sugars become thus readily available without the need to use organotin or organosilicon reagents. For derivatives which do not lead to electrophilic radicals, complete avoidance of the rearrangement and other pathways open to the intermediate carbon radical may be more difficult. Further studies aimed at exploring the scope of this reducing system are in progress.

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13. Typical experimental procedure: The xanthate (1 mmole) is dissolved in refluxing 2-propanol (10ml) or benzene (4ml) under an inert atmosphere (collidine 1-2eq. may be added for acid sensitive substrates). Lauroyl peroxide (1.3 mmoles in the former or 0.3-0.4 mmoles in the latter case) is added in 5-10% portions every hour or so until almost complete consumption of the starting material. 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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