An Unusual Route to Deoxysugars by Hydrogen Atom Transfer from Cyclohexane. Possible Manifestation of Polar Effects in a Radical Process

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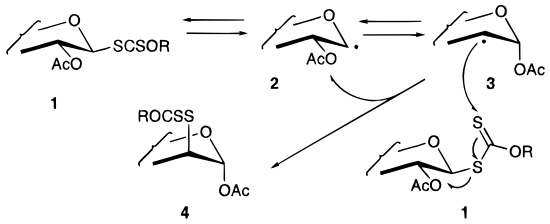
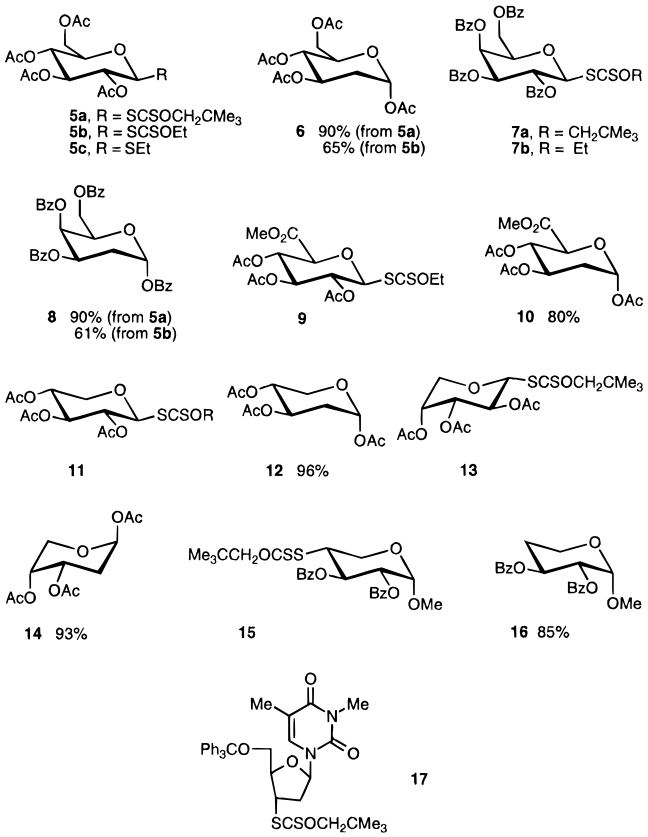
We have shown, over the past few years, that xanthates represent a synthetically useful source of a variety of radical species.[1] As part of this work, we considered the possibility of obtaining 2-thiosugars by generating an anomeric radical **2** from the corresponding xanthate **1**, allowing it, by analogy with the work of Giese and his collaborators,[2,3] to migrate to the 2-position as in **3**, and finally letting the transfer of the xanthate group occur to give the isomeric xanthate **4**, as outlined in Scheme 1. Carbohydrates containing a xanthate group in the anomeric position are known and readily accessible.[4] Compound **5a** was therefore prepared from 1-deoxy-1-bromo-2,3,4,6-tetra-*O*-acetylglucopyranose and sodium *O*-neopentylxanthate and subjected to our usual reaction conditions, which consisted in simply heating in cyclohexane in the presence of a suitable peroxide initiator. In much of our work in this area, we have successfully used cyclohexane alone or in mixtures with toluene as the solvent for these reactions since benzene, which is the most commonly used solvent for radical reactions,[5] is toxic and the trend is to replace it whenever possible. However, when a refluxing solution of **5a** in degassed cyclohexane was treated with a small amount of lauroyl peroxide (6%), a rapid and clean reaction ensued, but the product, isolated in 90% yield, turned out to be 2-deoxy-1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose (**6**) and not the expected rearranged xanthate **4**. The other coproduct was *S*-cyclohexyl-*O*-neopentylxanthate, produced in an equivalent amount. Clearly, we had stumbled accidentally upon an unusual radical chain reaction whereby cyclohexane is acting as a surprisingly effective hydrogen atom donor. Hydrogen abstraction from cyclohexane by highly reactive radicals (e.g., chlorine atoms or alkoxy radicals) has been known for a long time,[6] but as far as we know such a clean and effective hydrogen atom transfer from cyclohexane *to a saturated carbon radical* is unprecedented.

Scheme 1





In the same way, the benzoylated galactose xanthate **7a** furnished the corresponding 2-deoxy product **8** in 90% yield. This conversion could also be accomplished using the ethyl analogues **5b** and **7b**, but the yield (65 and 61%, respectively) was lower. In the former case, a small amount (17%) of ethylthio glycoside **5c**, probably of ionic origin,[4c] was isolated. A number of other carbohydrate neopentyl xanthate derivatives were successfully reduced under similar conditions. Thus, xanthate **9**, derived from peracetylated methyl glucuronate, and xanthates **11** and **13**, from D-xylose and D-arabinose (ring flip occurred in the latter case), respectively, produced compounds **10**, **12**, and **14** in high yield (80, 96, and 93%). The xanthate group need not be in the anomeric position as illustrated by example **15**, a derivative of arabinose, which showed the same reactivity and was easily converted into **16** (85%). No ben-

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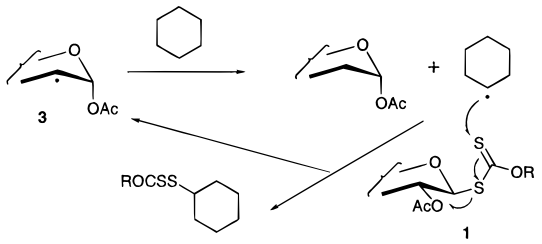
Scheme 2

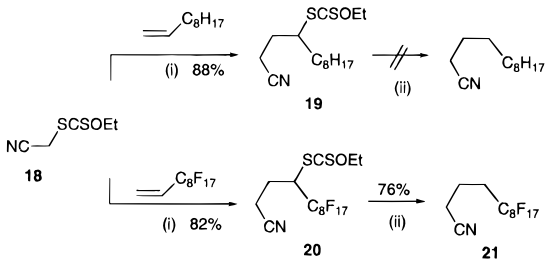


zoyloxy group migration occurs in this case. We also found that it was possible to use the 1-bromo precursors as substrates but the reaction was relatively inefficient and a much greater amount of peroxide was needed to drive the reaction to completion. Bromine atom abstraction by the cyclohexyl radical to give the same anomeric radical **2** is apparently slower than the equivalent, two-step transfer of the xanthate group (addition to the thiocarbonyl then fragmentation).

A plausible mechanism for these transformations is portrayed in Scheme 2. The success of the process hinges on at least two considerations. The first is the fact that the reaction of radical **3** with its xanthate precursor **1** is redundant,[1a] and consequently this radical has a sufficiently long lifetime to be able to react with cyclohexane. The second is of course the hydrogen abstraction step which in this case must be especially favored, since ordinary secondary radicals do not react with cyclohexane to any significant extent under similar conditions. This is further shown by the sluggish, relatively unclean, and clearly non chain reaction of nucleoside derivative **17**[1f] when it was subjected to the same conditions. The special behavior in the present situation appears thus to be due to the electron-attracting acetate or benzoate groups flanking the radical center, which are absent in compound **17**.

Barton and co-workers had noted the effect of an alkoxy or acyloxy group in the β-position in lowering the temperature required for deoxygenating certain thiocarbonyl ester type derivatives and termed this the "β-oxygen effect".[7] Later studies by Beckwith did not indicate a significant stabilization of the ensuing radical by such substituents,[8] and some uncertainty remains as to whether this phenomenon is due essentially to steric[9] or polar[10,11] effects. Our present work is strongly in favor of the latter as the dominating factor. Further evidence was

Scheme 3[a]



[a] Conditions: (i) 1,2-dichloroethane, di-lauroyl peroxide (5 mol %) (ii) cyclohexane, di-lauroyl peroxide (4 mol %).

obtained by comparing the behavior of xanthates **19** and **20** under the usual reaction conditions. These substrates were easily prepared in high yield (88 and 82%, respectively) by reacting xanthate **18** with 1-decene and heptadecafluorodecene in 1,2-dichloroethane in the presence of a small amount (4%) of lauroyl peroxide (Scheme 3). In the event, when an equimolar mixture of **19** and **20** in refluxing cyclohexane was treated with lauroyl peroxide (4%), only the latter underwent reduction to **21** in 76% yield. It is difficult to invoke steric effects in this instance, whereas enhancement of the electrophilic character of the radical arising from cleavage of the xanthate group by the powerful electron-withdrawing perfluorinated chain must be quite significant. This results in a considerable acceleration in the rate-determining hydrogen abstraction step.[11] Notice also that precursor **20** was prepared in 1,2-dichloroethane which, because of the presence of the electronegative chlorine atoms, does not act as a hydrogen atom donor in this case, even though from a thermodynamic stance, the stability of the ensuing radical would have been easily comparable to that of a cyclohexyl radical.

This new reduction process illustrates what appears to be a manifestation of polar effects in a hydrogen abstraction process that is clearly not limited to carbohydrates. The preliminary results presented here open the way to a number of synthetic possibilities for exploiting the subtle factors that control the rates and hence the selectivity of such radical reactions. But beyond the more enduring fundamental aspects uncovered by this work, it is perhaps worth underlining the extreme simplicity (and cheapness) of the method from a preparative point of view.[12]

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Supporting Information Available: Experimental procedures for the preparation and reduction of the xanthates, as well as a compilation of spectral and analytical data of all new compounds (5 pages). See any current masthead page for ordering and Internet access instructions.

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(12) Typical experimental procedure: A solution of the xanthate (1 mmol) in degassed cyclohexane (7 mL) or a 9:1 mixture of cyclohexane and 1,2-dichloroethane was heated under reflux and lauroyl peroxide was added portionwise (2% every 2 h) until the starting material was consumed (6−15% was needed depending on the substrate). The solvents were evaporated under reduced pressure, and the residue purified by chromatography on a silica gel column to afford the deoxygenated derivative.