Unusual generation of methoxy groups in Barton deoxygenations of alcohols

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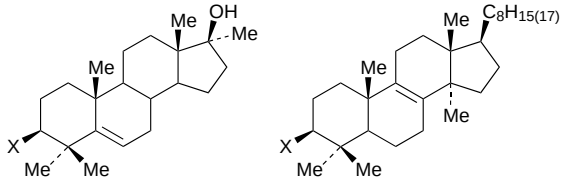
Reaction of the *S*-methyl dithiocarbonate of lanosterol with excess of tributyltin deuteride and azoisobutyronitrile in benzene afforded lanosteryl methyl ether in which all hydrogen in the methoxy group originated from the organotin reagent.

In mid-1996 C. S. B. prepared 4,4,17-trimethylandrost-5-en-17β-ol **1** from the *S*-methyl dithiocarbonate **2** in refluxing benzene with tributyltin hydride and the initiator AIBN, an unexpected product, methyl ether **3**, was formed in 28% yield. The ether was thought at the time to be a contaminant, inadvertently formed by a Williamson synthesis, of xanthate **2** which had been prepared by the usual treatment of alcohol **4** with sodium hydride, carbon disulfide and then iodomethane. However, spectra of **2** showed only slight contamination with **3**. Some months later, M. H. D. informed J. C. that an unrelated xanthate had yielded principally the analogous methoxy compound on attempted Barton deoxygenation, and that the corresponding imidazolylthiocarbamate (prepared without use of a methylating agent) gave the same methoxy compound. J. C. mentioned his view of this result to J. R. H., who recalled C. S. B.'s expermiment. We decided to investigate the matter by an experiment with lanosterol.



1 X = H
2 X = OC(=S)SMe
3 X = OMe
4 X = OH

5 X = OC(=S)SMe
6 X = OMe
7 X = H

The lanosterol available was a commercial preparation containing the 24,25-dihydro compound. The *S*-methyl dithiocarbonate **5**, prepared by Barton and McCombie's[1] procedure, contained *ca*. 40% dihydro compound and only traces of methyl ether **6** (by ^{1}H NMR spectroscopy). On reduction with tributyltin hydride (5 equiv.; initial concentration 0.17 mol dm^{-3}) and AIBN (0.36 equiv.) in boiling benzene for 6 h, a 42% yield of methyl ether **6**, along with deoxygenated product **7**, was formed. With tributyltin deuteride (95 atom%) the yield of **6** was 14%. The ^{1}H NMR spectrum of the labelled compound at 500 MHz showed, instead of the sharp 3H singlet of **6** at δ 3.37, three signals (total 0.75H) at δ 3.33, 3.35 and 3.37. The ^{2}H NMR spectrum showed that all excess deuterium was in the methoxy group and that the CHD_2 and CD_3 concentrations were about equal, as required by statistical distribution of H and D in a 1 : 3 ratio. This agrees with the total H content and corresponds to an average isotope effect (k_H/k_D) of *ca*. 5 for the three hydrogen transfers. The molecular ions in the EI mass spectrum were grouped in eight peaks showing minor amounts of the OMe species **6** with larger proportions of OCH_2D, $OCHD_2$ and OCD_3 species along with 24,25-dihydro analogues and ^{13}C companions. The peak pattern was accurately matched (Fig. 1) by the distribution calculated for random substitution of 75% of the methoxy protium by deuterium (as observed by NMR spectroscopy) combined with a 70 : 30 ratio of methoxylanostadienyl ions to methoxylanostenyl ions.‡ The major peak, principally lanostadienyl trideuteromethyl ether ion, had an exact mass of 443.4210 (Calc. for $^{12}C_{31}{}^1H_{49}{}^2H_3{}^{16}O$: 443.4206). The excess of deuterium-free species indicates slight (*ca*. 0.2%) contamination of **5** with pre-existing **6**. These results demonstrate that all three hydrogen atoms in the methoxy group of the reduction product **6** originated from the tin hydride. It follows that the carbon source of this methoxy group was the –OC(=S)S– group.

Barton and co-workers[1–3] have shown that octadecyloxythiocarbonylimidazole with 2 equiv. of tributyltin hydride in boiling toluene gave the hemithioformal $C_{18}H_{37}OCH_2SSnBu_3$, and analogous by-products were also formed from various dithiocarbonates (including *S*-methyl) of cholestanol. Formation of methoxy groups has not been reported until now, although it might well have been observed and misinterpreted as we initially did. As applied to an *S*-methyl dithiocarbonate **8** the mechanism for Barton deoxygenation preferred at first by its originator[3] postulates reversible addition of tributylstannyl radical to the C=S bond (Scheme 1). The ensuing radical **9** can either undergo thermal cleavage to dithiocarbonate **10** and alkyl radical **11** leading to deoxygenated product **12** (route a), or accept a hydrogen from Bu_3SnH to form **13** which is then cleaved (thermally?) to thioformate *O*-ester **14** which finally adds Bu_3SnH yielding hemithioformal **15** (route b). The last step was supported by a separate experiment with *O*-ethyl thioformate which gave the hemithioformal $EtOCH_2SSnBu_3$. When later experiments[4] indicated that radicals of type **9** are thermally very unstable, a non-radical mechanism of hydride transfer was preferred for generation of **13** from **8** and presumably of **15** from **14**.

In these mechanisms both methylene hydrogens are supplied from Bu_3SnH by additions, radical or non-radical, to thiocarbonyl groups. For addition of the third hydrogen no thiocarbonyl intermediate is possible. It seems necessary to postulate that

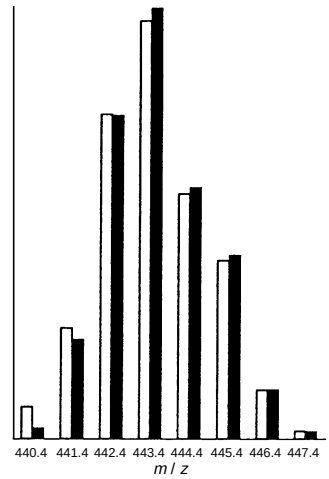
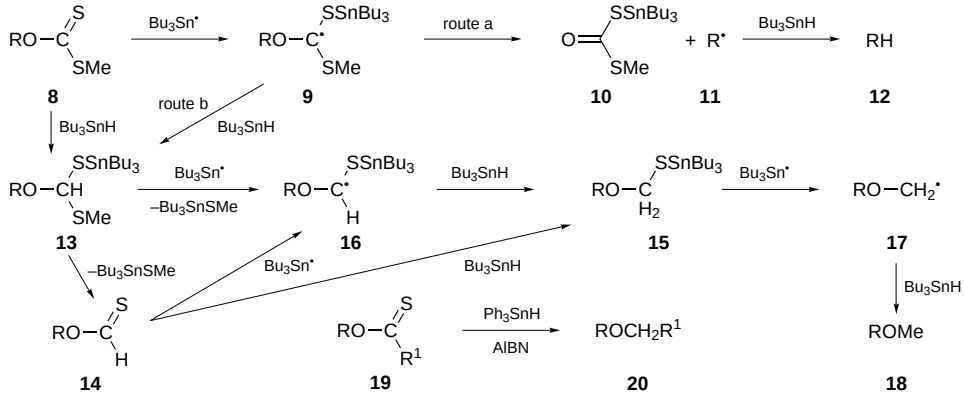


Fig. 1 Molecular ions from deuteriated **6**: (□) measured and (■) calculated. See text for basis of calculation.



Scheme 1

hemithioformals **15** can generate radicals **17** either by thermolysis or (more probably, we think) by attack of $Bu_3Sn^{\cdot}$ on the sulfur atom leading to elimination of $(Bu_3Sn)_2S$. The radical product **17** then accepts its third hydrogen from Bu_3SnH, forming **18**. Nicolaou *et al.*§ showed[5] that thioesters **19** with triphenyltin hydride–AIBN (and in one example, less efficiently, with tributyltin hydride–AIBN) yielded ethers **20**; thioformate *O*-esters were not tried but there seems little doubt that these could yield methyl ethers. The reaction, as we also prefer, was represented as addition of $Bu_3Sn^{\cdot}$ and elimination of $(Bu_3Sn)_2S$. A similar mechanism might apply also to addition of the *second* hydrogen, attack of $Bu_3Sn^{\cdot}$ on the SMe sulfur atom of the earlier intermediate **13** leading to elimination of Bu_3SnSMe and formation of the oxygen-stabilized radical **16**, which then accepts hydrogen from Bu_3SnH. Such a mechanism could apply to addition of the *first* hydrogen only if the initial attack of $Bu_3Sn^{\cdot}$ on **8** is at SMe instead of S=C, as Barker and Beckwith[6] suggested on the basis of experiments with $Bu_3Sn^{\cdot}$ in the absence of Bu_3SnH. Barton's later work[4] controverts this mechanism.

Deoxygenation to RH species by (unpromoted) Bu_3SnH is favoured[1] by higher dilutions and higher temperatures: the branching to give routes a and b, whatever the mechanisms, is due to competition between a unimolecular thermolysis and a bimolecular hydrogen-transfer. Conversely, higher concentrations of Bu_3SnH should favour the pathways leading to hydrogen additions. In fact an excess of Bu_3SnH over the 3 equiv. theoretically required was used in all experiments where formation of ROMe was observed, and **5** with only 1.5 equiv. of Bu_3SnD formed no measurable **6**. The step preceding addition of the third hydrogen is therefore the slowest.

Footnotes and References

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‡ In the molecular ions the dienyl species appears to be enriched. The two heaviest fragment ions ($M-15$ containing methoxy, and methoxy-free $M-47$) show the opposite effect and their peak patterns are both matched by assuming a 55 : 45 ratio. The base peak in the spectrum is at *m*/*z* 69, indicating favoured cleavage of the dienyl species to $Me_2C{=}CHCH_2^{+\cdot}$. The observed patterns are consistent with the dienyl species being preferentially ionized, but also preferentially cleaved so as to be under-represented in the heavier fragments.

§ We are indebted to a referee for drawing attention to this work.

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