Radical-chain deoxygenation of tertiary alcohols, protected as their methoxymethyl (MOM) ethers, using thiols as polarity-reversal catalysts

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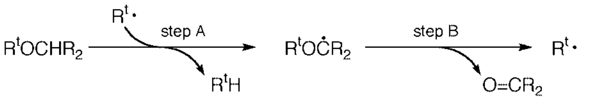
The deoxygenation of tertiary alcohols can be accomplished by heating their MOM ethers in the presence of a peroxide initiator and a thiol catalyst: the proposed radical-chain mechanism is supported by EPR spectroscopic studies.

Several free-radical based procedures are available for the deoxygenation of secondary alcohols (R^sOH). In particular, methods that involve radical-chain reactions of thiocarbonyl derivatives $R^sOC(=S)X$ with tributyltin hydride have found wide application in organic synthesis.[1] However, because of the thermal instability of many corresponding thiocarbonyl derivatives of tertiary alcohols, the number of methods available for the deoxygenation of the latter is more limited.[1] Conversion to an ether is commonly used to protect the alcohol functionality during chemical manipulations[2] and it would be convenient if appropriate ether derivatives of tertiary alcohols (generalised as R^tOCHR_2) could be induced to undergo radical-chain deprotection and deoxygenation in a single step to yield the deoxy compound R^tH, as shown in Scheme 1. Although the β-scission step B is expected to be rapid above room temperature,[3] the hydrogen transfer step A will be close to thermoneutral and also suffer from adverse polar effects in the transition state (a nucleophilic radical $R^{t\cdot}$ is required to abstract hydrogen to give another nucleophilic radical $R^tO\dot{C}R_2$), making it a relatively slow process at moderate temperatures.[4] Consonant with this analysis, no 2-methyladamantane **2a** was formed after heating the methoxymethyl (MOM) ether of 2-methyl-2-adamantanol **1a** in refluxing octane for 2 h in the presence of the 2,2-di-*tert*-butylperoxybutane (DBPB, 2 × 3 mol%) as a thermal source of initiating alkoxyl radicals. We reasoned that step A should be subject to polarity-reversal catalysis[4] by a protic catalyst such as a thiol when, in the case of a MOM ether, it would be replaced by the cycle of polarity-matched reactions (1) and (2). Coupled with the β-scission reaction (3), this sequence would then provide a pathway for the thiol-catalysed deprotection and deoxygenation of the MOM ethers of tertiary alcohols to give R^tH and methyl formate.



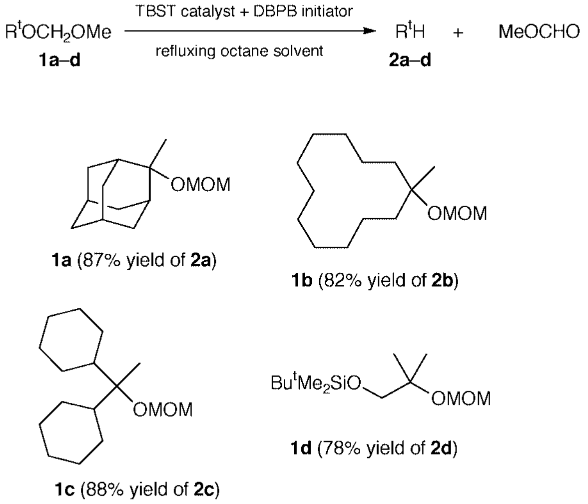
Scheme 1

$$R^{t}\cdot \;+\; XSH \longrightarrow R^tH \;+\; XS^{\cdot} \qquad (1)$$

$$XS^{\cdot} \;+\; R^tOCH_2OMe \longrightarrow XSH \;+\; R^tO\dot{C}HOMe \qquad (2)$$

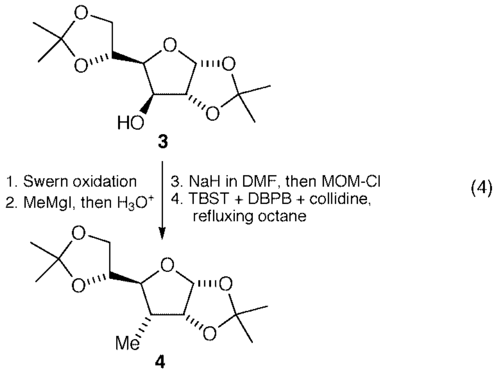
$$R^tO\dot{C}HOMe \longrightarrow R^{t}\cdot \;+\; MeOCHO \qquad (3)$$

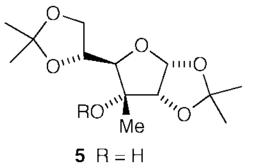
When the previously-attempted reductive deprotection of **1a** was repeated in the presence of tri-*tert*-butoxysilanethiol[5] (TBST; 2 × 3 mol%), the reaction now proceeded smoothly and 2-methyladamantane was isolated in 87% yield. Similar treatment of the tertiary alkyl MOM ethers **1b–d** gave the corresponding deoxy compounds **2b–d** in good yields (Scheme 2); only traces of R^tH were formed in the absence of the thiol catalyst and most of the MOM ether could be recovered unchanged.‡



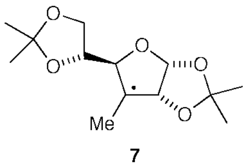
Scheme 2

In order to explore its applicability to more complex systems, we made use of the procedure in the conversion of diacetone D-glucose **3** to 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose **4** [eqn. (4)]. Swern oxidation followed by treatment of the derived ketone with methylmagnesium iodide afforded the tertiary alcohol **5**,[7] which was converted to the corresponding MOM ether **6**. The latter was heated under reflux in octane in the presence of TBST (3 × 3 mol%), DBPB (3 × 3 mol%) and 2,4,6-trimethylpyridine§ (collidine, 1 ×





5 R = H
6 R = MOM



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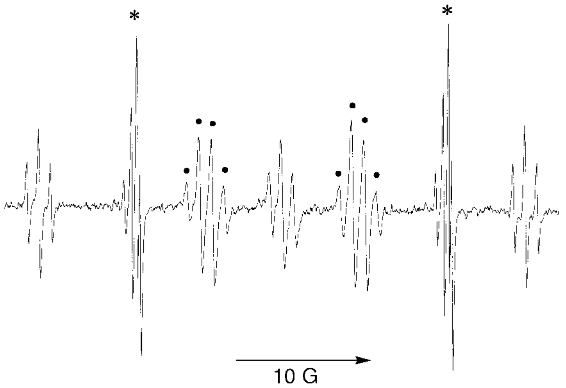

Fig. 1 EPR spectrum recorded during UV irradiation of a fluorobenzene solution containing $\mathrm{Bu^tOCH_2OMe}$ and di-*tert*-butyl peroxide at −61 °C. The two central 'lines' (showing second-order fine structure) from the *tert*-butyl radical are indicated by asterisks and the doublet of quartets from **8** by filled circles; the remaining lines arise from **9**. At −61 °C, the splitting constants for **8** (g = 2.0031) are 11.3 G (1 $\mathrm{H_\alpha}$) and 0.91 G (3 $\mathrm{H_\gamma}$); for **9** (g = 2.0032) they are 18.0 G (2 $\mathrm{H_\alpha}^{\mathrm{average}}$) and 0.87 G (2 $\mathrm{H_t}$). The central multiplet in the spectrum of **9** is broadened because rotation about the $\mathrm{C_\alpha}$–O bond is occurring at an intermediate rate on the EPR timescale.

10 mol%), to afford, after chromatography, a 91:9 mixture of **4**[9] and its C-3 epimer in a total isolated yield of 90%. The predominance of **4** in the epimeric product mixture is evidently a result of the preferential attack by TBST at the *exo*-face of the intermediate radical **7**.

In order to gain further insight into the mechanism of this redox process, the reaction of $\mathrm{Bu^tOCH_2OMe}$ with *tert*-butoxyl radicals was investigated by EPR spectroscopy. UV irradiation of a fluorobenzene solution containing $\mathrm{Bu^tOCH_2OMe}$ (1.4 M) and di-*tert*-butyl peroxide (*ca*. 20% v/v) at −61 °C, while the sample was in the microwave cavity of the spectrometer,[10] afforded the EPR spectrum shown in Fig. 1. The three radicals $\mathrm{Bu^tO\dot{C}HOMe}$ **8**, $\mathrm{Bu^tOCH_2O\dot{C}H_2}$ **9** and $\mathrm{Bu^{t\cdot}}$ are present at this temperature, while above *ca*. −35 °C only the spectra of the last two were detectable. The rate constant (k_β) for β-scission of **8** to give *tert*-butyl radicals was determined relative to the rate constant ($2k_t$) for self-reaction of the latter, using the established 'steady-state' EPR method,[11] and the Arrhenius relation obtained from measurements in the temperature range −70 to −40 °C is given in eqn. (5), where $\theta = 2.303RT$ kJ mol^{-1}.[¶]

$$\log_{10}(k_\beta/\mathrm{s}^{-1}) = (12.0 \pm 0.5) - (33.8 \pm 1.5)/\theta \qquad (5)$$

The value of k_β extrapolated to 126 °C (the boiling point of octane) is 3.8×10^7 s^{-1}. Even at +20 °C, there was no EPR evidence for the β-scission of **9** to give $\mathrm{Bu^tO\dot{C}H_2}$ although, because of line overlap, the latter radical could be difficult to detect in the presence of a higher concentration of the former. However, in similar experiments with $\mathrm{MeOCH_2OMe}$, only the spectra of $\mathrm{MeO\dot{C}HOMe}$ and $\mathrm{MeOCH_2O\dot{C}H_2}$ were observed up to +72 °C; in particular $\mathrm{MeO\dot{C}H_2}$ was not detected, supporting the conclusion that β-scission of **9** to give $\mathrm{Bu^tO\dot{C}H_2}$ and formaldehyde must be *very* much slower than the cleavage of **8** to give $\mathrm{Bu^{t\cdot}}$ and methyl formate. Although the selectivity of $\mathrm{Bu^tO^\cdot}$ in hydrogen-atom abstraction from $\mathrm{Bu^tOCH_2OMe}$ will differ quantitatively from that of $\mathrm{(Bu^tO)_3SiS^\cdot}$,[‖] both radicals are electrophilic and it is probable that the thiyl radical would also abstract hydrogen to some extent from the *O*-methyl group of the mixed acetal. However, for the tertiary alkyl MOM ethers examined in this work, the major fate of any radicals of the type $\mathrm{R^tOCH_2O\dot{C}H_2}$ (or of radicals which might possibly be formed by abstraction of hydrogen from the $\mathrm{R^t}$ group)[**] must be 'repair' by hydrogen-atom transfer from the thiol to regenerate the starting MOM ether.

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Notes and references

[‡] *Representative procedure*: a solution containing the MOM ether **1a** (210 mg, 1.0 mmol), TBST (9 mg, 3 mol%) and DBPB (18 μl of a 50% w/w solution in mineral oil, 3 mol%) in dry octane (1.2 cm^3) was stirred and heated under gentle reflux (bath temperature 130 °C, pre-heated) under an atmosphere of argon. After 40 min, more initiator and thiol (3 mol% of each) were added and heating was continued for a further 2 h. The solvent was removed by evaporation under reduced pressure and the residue was subjected to flash chromatography on silica gel (hexane eluent) to give 2-methyladamantane **2a** (131 mg, 87%), mp 146–147 °C (lit.[6] mp 146–148 °C).

[§] The yield was improved in the presence of collidine, probably because this acts as a scavenger of acid resulting from reactions between the initiator and the thiol.[8] Collidine was also present during the reductive deprotection of **1d** (Scheme 2).

[¶] The value of $(k_\beta/2k_t)$ at a given temperature is equal to $([\mathrm{Bu^{t\cdot}}]/[\mathbf{8}])\{[\mathrm{Bu^{t\cdot}}] + [\mathbf{8}] + [\mathbf{9}]\}$.[11] The Arrhenius relation for the self-reaction of *tert*-butyl radicals in fluorobenzene was taken[12] to be $\log_{10}(2k_t/\mathrm{M^{-1}\,s^{-1}}) = 11.6 - 10.2/\theta$ and the rate constants for the diffusion-controlled reactions of $\mathrm{Bu^{t\cdot}}$ with **8** and with **9** are assumed to be equal to $2k_t$.

[‖] The relative molar rate constants (k_8/k_9) for hydrogen abstraction by $\mathrm{Bu^tO^\cdot}$ from $\mathrm{Bu^tOCH_2OMe}$ to give **8** and **9** were determined by measuring relative radical concentrations in the temperature range −70 to −20 °C.[13] The value of k_8/k_9 is given by $\{[\mathbf{8}] + [\mathrm{Bu^{t\cdot}}]\}/[\mathbf{9}]$ and was shown to conform to the Arrhenius relation $\log_{10}(k_8/k_9) = -0.59 + 4.4/\theta$; the extrapolated value of k_8/k_9 at 126 °C is 0.97.

[**] Epimerisation[8] at C-5 did not compete with the reductive deprotection reaction of **6** to give **4**.

1 W. B. Motherwell and D. Crich, *Free Radical Chain Reactions in Organic Synthesis*, Academic Press, London, 1992, pp. 47–50, 54-58.
2 T. W. Green and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, 3rd edn, 1999,
3 M. J. Perkins and B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 1975, 77.
4 B. P. Roberts, *Chem. Soc. Rev.*, 1999, **28**, 25.
5 A. Herman, B. Becker and W. Wojnowski, *Z. Anorg. Allg. Chem.*, 1979, **450**, 178.
6 S. F. Nelsen, G. R. Weisman, E. L. Clennan and V. E. Peacock, *J. Am. Chem. Soc.*, 1976, **98**, 6893.
7 Z. Ali, S. Qureshi and G. Shaw, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2627.
8 H.-S. Dang and B. P. Roberts, *Tetrahedron Lett.*, 1999, **40**, 4271.
9 O. R. Martin, R. C. Nabinger, Y. Ali, D. M. Vyas and W. A. Szarek, *Carbohydr. Res.*, 1983, **121**, 302.
10 J. A. Baban and B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 1981, 161; V. Diart and B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 1992, 1761.
11 D. Griller and B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 1972, 747; D. Griller and K. U. Ingold, *Acc. Chem. Res.*, 1980, **13**, 317.
12 H.-H. Schuh and H. Fischer, *Helv. Chim. Acta.*, 1978, **61**, 2130; J. C. Walton, *J. Chem. Soc., Perkin Trans. 2*, 1987, 231.
13 A. G. Davies, D. Griller and B. P. Roberts, *J. Chem. Soc. B*, 1971, 1823; D. Griller and K. U. Ingold, *Acc. Chem. Res.*, 1980, **13**, 193; H. Fischer and H. Paul, *Acc. Chem. Res.*, 1987, **20**, 200.

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