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

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Received (in Liverpool, UK) 19th January 2000, Accepted 14th February 2000

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 manipulations² and it would be convenient if appropriate ether derivatives of tertiary alcohols (generalised as RⁱOCHR₂) could be induced to undergo radical-chain deprotection and deoxygenation in a single step to yield the deoxy compound RⁱH, 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} is required to abstract hydrogen to give another nucleophilic radical R^tOCR₂), 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-tertbutylperoxybutane (DBPB, 2×3 mol%) as a thermal source of initiating alkoxyl radicals. We reasoned that step A should be subject to polarity-reversal catalysis⁴ 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 RtH and methyl formate.

R ^t •	+	XSH	 R ^t H	+	XS.	(1)
xs•	+	R ^t OCH ₂ OMe	 XSH	+	R ^t OĊHOMe	(2)
		R ^t OĊHOMe	 R ^t •	+	MeOCHO	(3)

When the previously-attempted reductive deprotection of **1a** was repeated in the presence of tri-*tert*-butoxysilanethiol⁵ (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



Scheme 2

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.[‡]

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 ($3 \times 3 \mod 8$), DBPB ($3 \times 3 \mod 8$) and 2,4,6-trimethylpyridine§ (collidine, $1 \times 3 \mod 8$)



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Fig. 1 EPR spectrum recorded during UV irradiation of a fluorobenzene solution containing Bu⁴OCH₂OMe 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 H_{α}) and 0.91 G (3 H_{γ}); for **9** (g = 2.0032) they are 18.0 G (2 H_{α}^{average}) and 0.87 G (2 H_{α}). The central multiplet in the spectrum of **9** is broadened because rotation about the C_{α}-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 Bu^oOCH₂OMe with *tert*-butoxyl radicals was investigated by EPR spectroscopy. UV irradiation of a fluorobenzene solution containing Bu^oOCH₂OMe (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 Bu^oOCHOMe **8**, Bu^oOCH₂OCH₂**9** and Buⁱ 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 ($2k_i$) 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.¶

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

The value of k_{β} extrapolated to 126 °C (the boiling point of octane) is $3.8 \times 10^7 \text{ s}^{-1}$. Even at +20 °C, there was no EPR evidence for the β -scission of **9** to give Bu'OCH₂ 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 MeOCH₂OCH₂ only the spectra of MeOCHOMe and MeOCH₂OCH₂ were observed up to +72 °C; in particular MeOCH₂ was not detected, supporting the conclusion that β -scission of **9** to give Bu'OCH₂ and formaldehyde must be *very* much slower than the cleavage of **8** to give Bu' and methyl formate. Although the selectivity of Bu'O in hydrogen-atom abstraction from Bu'OCH₂OMe will differ quantitatively from that of (Bu'O)₃SiS', 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 $R^{t}OCH_{2}OCH_{2}$ (or of radicals which might possibly be formed by abstraction of hydrogen from the R^{t} group)** must be 'repair' by hydrogen-atom transfer from the thiol to regenerate the starting MOM ether.

Financial support for this work was provided by the EPSRC. We thank Professors K. J. Hale and W. B. Motherwell for helpful discussions and we are grateful to Peroxid-Chemie GmbH for a gift of 2,2-di-*tert*-butylperoxybutane.

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 cm³) 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 $([Bu^t]/[8]){[Bu^t] + [8] + [9]}.^{11}$ The Arrhenius relation for the self-reaction of *tert*butyl radicals in fluorobenzene was taken¹² to be $\log_{10}(2k_t/M^{-1} s^{-1}) = 11.6 - 10.2/\theta$ and the rate constants for the diffusion-controlled reactions of Bu^t 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 Bu^O from Bu^OCH₂OMe 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 {[8] + [Bu^t]}/[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.

** Epimerisation⁸ at C-5 did not compete with the reductive deprotection reaction of 6 to give 4.

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Communication b000533i