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Radical-chain redox rearrangement of cyclic benzylidene acetals to benzoate esters in the presence of thiols

Brian P. Roberts* and Teika M. Smits

Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK

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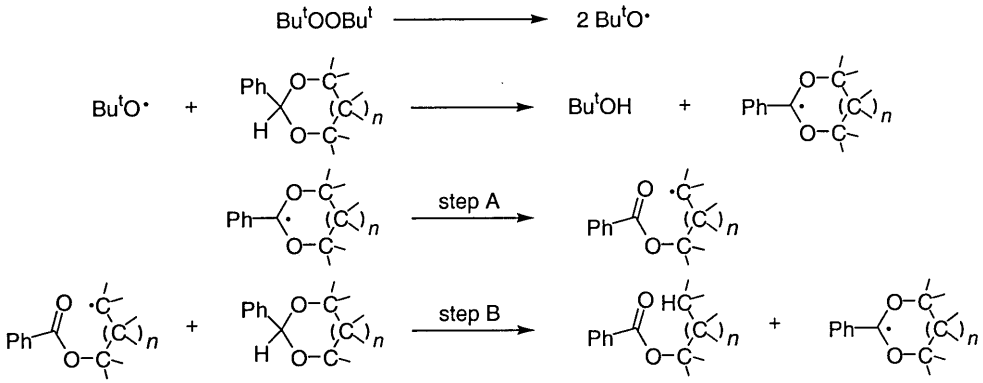
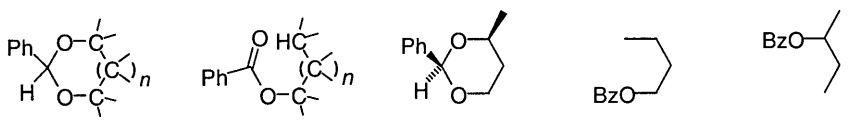
Abstract—Cyclic benzylidene acetals derived from 1,2- and 1,3-diols undergo an efficient ring-opening redox rearrangement to give benzoate esters in the presence of a peroxide initiator and a thiol, which acts as a polarity-reversal catalyst to promote the radical-chain reaction.

1,2- and 1,3-Diols are commonly protected as cyclic benzylidene acetals **1** ($n = 0$ or 1) during organic synthesis.[1] In 1962, Huyser and Garcia[2] reported that some simple benzylidene acetals underwent an intramolecular redox rearrangement to give alkyl benzoates **2** when heated with di-*tert*-butyl peroxide (DTBP) at ca. 135°C for 18 h. For example, 2-phenyl-4-methyl-1,3-dioxane **3** gave a mixture of the benzoates **4** and **5**, together with by-products including benzaldehyde. When the starting ratio **3**:DTBP was 5:1, 47% of **3** was converted to products and the ester ratio **4**:**5** was 5.4:1, but when **3**:DTBP was increased to 36.8:1 conversion was only 9.8% and the ratio **4**:**5** was 4.5:1.

The reaction was thought to follow the radical-chain mechanism shown in Scheme 1, although the kinetic chain length was very short (1.3–1.9), probably because step B of the propagation cycle is relatively slow even



Scheme 1.



1 **2** **3** **4** **5**

Keywords: radicals and radical reactions; catalysis; thiols; diols; rearrangements; carbohydrates.

* Corresponding author.

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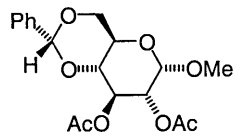
though the acetal was present as the solvent. The benzaldehyde was believed to arise from ring-opening rearrangement and subsequent fragmentation of the radical produced by abstraction of hydrogen from C-4 of **3** by the reactive and relatively unselective *tert*-butoxyl radical.[2] The same methodology was applied by Jeppesen et al.[3] to bring about intramolecular redox rearrangement of cyclic benzylidene acetals derived from carbohydrates; DTBP was usually used as solvent, but no improvements in yields were found when chlorobenzene was present as co-solvent, despite the low solubility of some of the acetals in neat DTBP. For example, the 4-benzoate **7** was isolated in 41% yield after heating the 4,6-*O*-benzylidene acetal **6** in DTBP at 140°C for 7 h; none of the primary benzoate **8** was detected in this reaction.[3]



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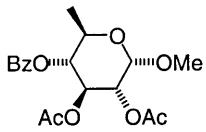

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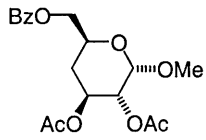

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Although step B of Scheme 1 should be appreciably exothermic, because of the benzylic stabilisation of the product radical, the reaction still suffers from adverse polar effects in the transition state and should, therefore, be subject to polarity-reversal catalysis[4] by a thiol. Indeed, we have recently reported[5] that radical-chain redox reactions of the type shown in Eq. (1) are promoted by thiols, which act as protic polarity-reversal catalysts for hydrogen-atom transfer from the methylene group of the acyclic acetal to the tertiary alkyl radical $R^{t\bullet}$.

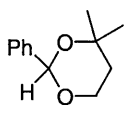
$$R^tOCH_2OMe \rightarrow R^tH + MeOCHO \qquad (1)$$

We reasoned that thiols should also function as polarity-reversal catalysts for step B of Scheme 1 and should thus promote the redox rearrangement of benzylidene acetals to give benzoate esters. In the present paper we report the experimental verification of this proposal.

A solution in dry octane (2 ml) containing the benzylidene acetal **9** (1 mmol), 2,2-di-*tert*-butylperoxybutane[6] (DBPB, 5 mol%) as a thermal source of initiating *tert*-butoxyl radicals, *tert*-dodecanethiol[7] (TDT, 5 mol%) and collidine[8] (10 mol%) was heated under reflux (bath temp. 140–145°C) for a total of 3 h. A second addition of DBPB and TDT (5 mol% of each) was made after 40 min. Removal of the solvent and examination of the residual oil by NMR spectroscopy showed complete ($\geq 99\%$) conversion of **9** to 3-methylbutyl benzoate **10**; *tert*-pentyl benzoate (which would arise from cleavage of the primary C–O bond) was not detected. Similar results were obtained when tri-*tert*-butoxysilanethiol [$(Bu^tO)_3SiSH$, TBST] was used as catalyst. However, in the absence of any thiol catalyst, under otherwise identical conditions, only ca. 2% conversion of **9** to **10** was observed.

Analogous thiol-catalysed redox rearrangements take place with the benzylidene acetals **3** and **11**. Essentially complete conversion of **11** to the secondary alkyl benzoate **12** was observed in the presence of TDT or TBST and only a trace of the isomeric tertiary benzoate **13** was detected by GLC analysis (**12**:**13** = 99:1). In the absence of thiol only ca. 2% of **11** rearranged. The TDT-catalysed rearrangement of **3** also took place quantitatively to give a 6.7:1 mixture of the benzoates **4** and **5**, similar to that obtained by Huyser and Garcia.[2] The regioselectivity of these redox rearrangements is determined by the relative rates of cleavage of the two R–OC$^\bullet$ bonds in the intermediate 2-phenyl-1,3-dioxanyl radicals (Scheme 1, step A) and follows the expected 'enthalpic' trend viz. R = 3°>2°>1°.

Similar results were obtained with the 1,3-dioxolane **14**, except that the effect of thiol catalysis was less dramatic, presumably because direct abstraction of the benzylic hydrogen (Scheme 1, step B) is faster when a five-membered ring is involved.[9] Quantitative rearrangement of **14** to **15** was observed in the presence of TDT under the standard conditions, while 23% conversion of **14** was seen in the absence of thiol; no *tert*-butyl benzoate was detected. Although β-acyl- and β-aroyloxyalkyl radicals (including $BzOCMe_2CH_2^\bullet$) are well known to rearrange by a 1,2-migration of the ester group,[10] the regioselective formation of isobutyl benzoate **15** almost certainly[10,11] results from highly selective opening of the intermediate 2-phenyl-4,4-dimethyl-



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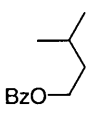

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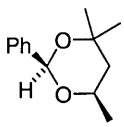

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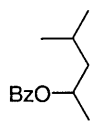

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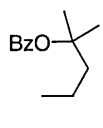

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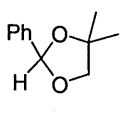

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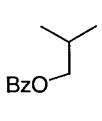

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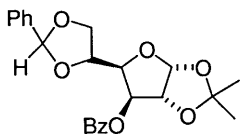

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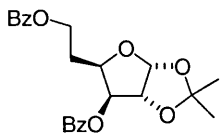

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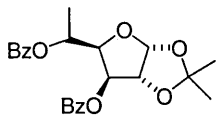
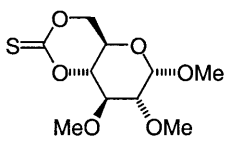


18

1,3-dioxolanyl radical to give directly the more stable tertiary radical $BzOCH_2CMe_2^{\bullet}$.

Thiol catalysis was also applied successfully to some of the carbohydrate benzylidene acetals investigated by Jeppesen et al.[3] Under the standard conditions (DBPB initiator+collidine) in refluxing octane–chlorobenzene (1:1 v/v) solvent, 85% of **6** rearranged to the benzoate **7** when TDT was used as catalyst and conversion could be increased to $\geq 98\%$ by the use of TBST. From the latter reaction mixture **7**[12] was isolated in 89% yield; only a trace of the benzoate **8** was detectable by NMR spectroscopic analysis of the crude product (**7**:**8** = ca. 97:3). Similar treatment of the 5,6-*O*-benzylidene derivative **16**, using TBST as catalyst, resulted in $\geq$ 98% conversion to a mixture of the benzoates **17** and **18** (4.9:1 by ^{1}H NMR), which were isolated in yields of 72 and 14%, respectively.



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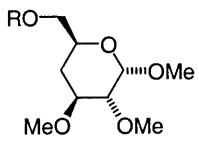
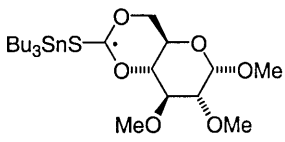


20 R = H
21 R = C(O)SSnBu$_3$



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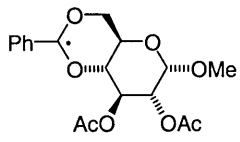

23

It has been reported[13] that treatment of the 4,6-thionocarbonate **19** with tributyltin hydride under radical conditions gives the 4-deoxy compound **20**, after hydrolysis of the initially-formed thiolester **21**, presumably itself derived from regioselective ring-opening β-scission of the intermediate radical **22** to give the *secondary* C-4 alkyl radical. This result contrasts markedly with the highly selective ring opening of the benzylic radical **23**, to give almost exclusively the *primary* C-6 alkyl radical, that occurs in the redox rearrangement of **6** to **7** described above. The latter result also contrasts with the enthalpic control of regioselectivity observed for ring opening of the 2-phenyl-1,3-dioxanyl radicals derived from the monocyclic benzylidene acetals **3**, **9** and **11**. However, Ziegler and Zheng have reported clear-cut examples of contra-thermodynamic ring opening of bicyclic thionocarbonates mediated by tributyltin hydride and rationalised their results in terms of angle strain effects in the transition states for β-scission of radicals related to **22**.[14] There is clearly a need for further studies of the regiochemistry of both types of redox ring-opening reactions.

Simple methods for the conversion of natural (*R*,*R*)-tartaric acid derivatives to those of unnatural (*R*)-malic acid would be of appreciable interest[15] and we have now shown that thiol-catalysed redox rearrangement of the (*R*,*R*)-benzylidene tartrate **24** can be used as the key step in such a conversion (see Scheme 2). Thus, when **24** was subjected to the usual conditions, using either TDT or TBST as catalyst and refluxing octane–chlorobenzene (3:1 v/v) as the solvent, conversion to diethyl (*R*)-*O*-benzoylmalate **25** was 95% complete; without thiol catalyst only 16% of the tartrate rearranged. Chiral stationary-phase HPLC analysis confirmed that no racemisation of **25** takes place under the reaction conditions. Diethyl tartrate derived from natural tartaric acid is readily converted to **24** and **25** can be easily debenzoylated by treatment with $Ti(OEt)_4$ in ethanol,[15] providing a simple route to unnatural diethyl malate. This procedure represents a significant and environmentally-friendly improvement over the previous methodology[15] which involves classical Hanessian-Hullar[16] ring-opening of **24** by *N*-bromosuccinimide, followed by tributyltin hydride reduction of the derived bromomalate to give **25**.

In conclusion, we emphasise that in the thiol-catalysed redox rearrangement of benzylidene acetals the chain is propagated by thiyl radicals, which are much less reactive and more selective in their hydrogen-atom abstraction reactions than are alkoxyl radicals and seek out specifically the benzylic C–H group. Thus, our procedure is not only higher yielding than the uncatalysed processes of Huyser[2] and of Jeppesen,[3] but is also cleaner and easier to control.

Acknowledgements

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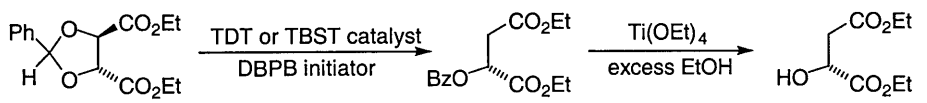

24 **25** **26**
56% yield from **24**

Scheme 2.

6. Available from the Aldrich Chemical Co. as a 50% solution in mineral oil and used as such; the half-life of this peroxide is ca. 1 h at 125°C.
7. This is the isomeric mixture of tertiary thiols as supplied by the Aldrich Chemical Co.
8. Yields were generally improved in the presence of collidine (2,4,6-trimethylpyridine), the role of which is probably to act as a scavenger of acid resulting from reactions between the initiator and the thiol.
9. See, for example: Malatesta, V.; Scaiano, J. C. *J. Org. Chem.* **1982**, *47*, 1455.
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12. NMR (500 MHz for ^{1}H, 125 MHz for ^{13}C, $CDCl_3$ solvent, *J* in Hz); δ_H 1.20 (3H, d, *J* 6.3, Me-6), 1.84 (3H, s, Ac), 2.03 (3H, s, Ac), 3.38 (3H, s, OMe), 3.98 (1H, dq, *J* 9.9 and 6.3, H-5), 4.87–4.92 (2H, m, H-1 and H-2), 5.02 (1H, [t], *J* 9.7, H-4), 5.60 (1H, [t], *J* 9.6, H-3), 7.39 (2H, [t], *J* 7.8, H-*m*), 7.53 (1H, tt, *J* 7.4 and 1.3, H-*p*), 7.96 (2H, dd, *J* 8.4 and 1.3, H-*o*); δ_C 17.3, 20.5, 20.7, 55.2, 65.2, 69.7, 71.3, 74.1, 96.6, 128.4, 129.1, 129.7, 133.3, 165.4, 169.9 and 170.1. The use of [multiplet] indicates an apparent multiplet with line spacing corresponding to an average coupling constant; the apparent triplet from H-3 shows further small splittings due to virtual coupling to H-1 (which is coupled to H-2 and nearly isochronous with it).
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