Tetrahedron Letters 50 (2009) 5927–5929

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An unexpected 1,2-hydride shift in phosphoric acid-promoted cyclodimerization of styrene oxides under solvent-free conditions. A synthetic route towards 2,4-disubstituted 1,3-dioxolanes

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ARTICLE INFO

Article history:
Received 23 June 2009
Revised 17 July 2009
Accepted 14 August 2009
Available online 20 August 2009

ABSTRACT

A 1,2-hydride shift in the phosphoric acid-promoted cyclodimerization of styrene oxide and its chloro derivatives under solvent-free conditions leading to 2,4-disubstituted 1,3-dioxolanes is described. Methoxy substituents on the aromatic ring of the styrene oxide prevent the 1,2-hydride shift reaction leading to substituted 1,4-dioxanes. A possible mechanism for the formation of the 1,3-dioxolanes is proposed.

The chemistry of epoxides has attracted significant attention mainly as a result of their highly regio- and stereoselective ring-opening reactions and their potential as building blocks for the synthesis of a wide range of biologically active oxygen-containing compounds. Their synthetic utility is based on the fact that they undergo ring-opening with a broad range of nucleophiles.[1–9]

To the best of our knowledge, the preparation of 1,3-dioxolanes utilizing acid-promoted cyclodimerization of epoxides has not been reported. In connection with a project exploiting the use of styrene oxides in synthesis, we report herein our preliminary results on the serendipitous synthesis of 2,4-disubstituted 1,3-dioxolanes via cyclodimerization of styrene oxides under solvent-free conditions. This cyclodimerization reaction was discovered whilst we were investigating the use of phenols in acid-mediated epoxide ring-opening reactions. 1,3-Dioxolanes are often prepared by reactions of oxiranes with carbonyl compounds in the presence of Brønsted or Lewis acids including BF_3, $CuSO_4$, Bi(III), Sn(IV), Ti(IV), Ir, Ru(III) and Re catalysts.[10–12] The alternative route described herein involves a 1,2-hydride shift during the cyclodimerization of styrene oxides.

Styrene oxide **2** was readily prepared from styrene **1** in 88% yield using *m*CPBA (Scheme 1) and initial experiments were performed using **2** as a model substrate. Thus, stirring a solution of epoxide **2** in H_3PO_4 at room temperature gave a 75:25 mixture of *trans*-**3** and *cis*-**3** in good yield. Various organic and inorganic acids were tested, but only perchloric acid was found to be equally effective in promoting the cyclodimerization reaction. The major isomer *trans*-**3** was purified by column chromatography and characterized by NMR spectroscopy.[13] The relative stereochemistry of *trans*-**3** was assigned using 2D NMR experiments, particularly NOESY in which there was correlation observed between H-4 and the methylene protons of the benzyl substituent.

We wondered whether various groups situated at different positions on the phenyl ring of a styrene oxide would have any effect on the cyclodimerization. To this end, *ortho*-, *meta*- and *para*-chlorostyrene oxides **4**, **6** and **8** were prepared using the method described above and then subjected to the solvent-free cyclodimerization conditions to give a mixture of trans/cis isomers of the corresponding dimers **5**, **7** and **9**,[13] respectively, in high yields and stereoselectivity for the trans isomer (Scheme 2). Interestingly, and perhaps somewhat surprisingly, *p*-chlorostyrene oxide gave exclusively the trans-isomer while its *ortho*- and *meta*-analogues gave a 75:25 mixture of trans and cis isomers. The reason for this discrepancy is not clear. On the basis of these findings, it appears that the position of the chloro group on the aromatic ring does not have any effect on the cyclodimerization of styrene oxides to 1,3-dioxalanes. Chlorine is an electron-withdrawing substituent and hence it is assumed that other electron-withdrawing groups would favour the formation of 1,3-dioxolanes.

A possible mechanism for this cyclodimerization reaction would involve protonation and ring-opening of epoxide **2** to give the benzyl cation **10**. Cation **10** is attacked by another molecule of epoxide **2** to give the dimeric benzyl cation **11** which can cyclize to form 1,4-dioxane **12**. In order to form the 1,3-dioxalane, a 1,2-hydride shift occurs to give the cation **13** which is stabilized by resonance structure **13a**. Cyclization of **13** then occurs to give 2-benzyl-4-phenyl-2,3-dioxolane **14** (Scheme 3). The observation that the 1,2-hydride shift in **11** to give **13** was faster than the cyclization reaction to give dioxane **12** was a striking aspect of this work. It can be assumed that stabilization of the carbocation by the oxygen in resonance structures **13** is more pronounced than that by the phenyl group in structure **11**. The electron-withdrawing chlo-

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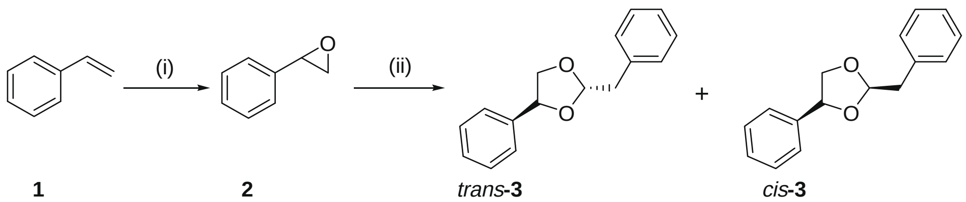
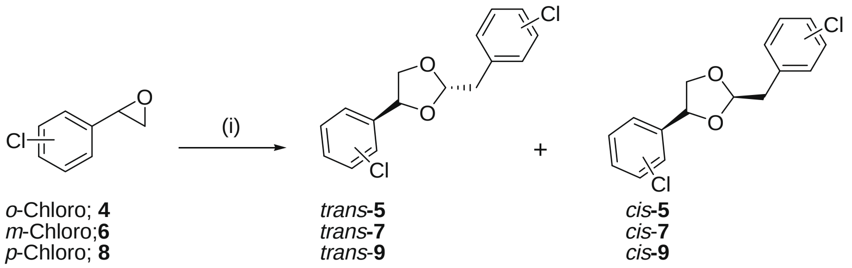
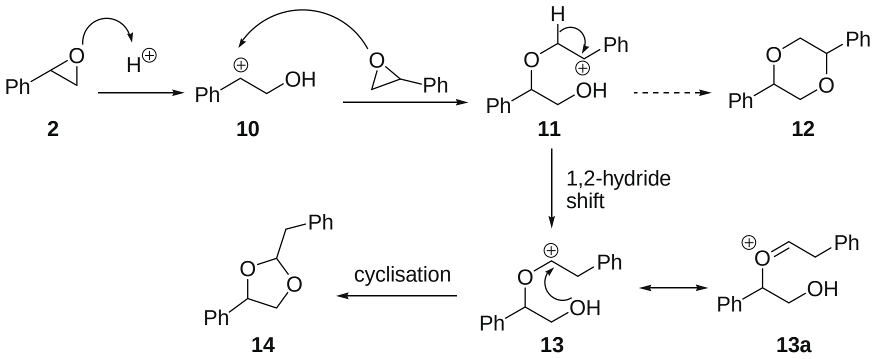
doi:10.1016/j.tetlet.2009.08.044



Scheme 1. Reagents and conditions: (i) *m*CPBA, CH_2Cl_2, $NaHCO_3$, 25 °C, 88%; (ii) H_3PO_4, 25 °C, 61% (*trans*-**3**:*cis*-**3**, 75:25).



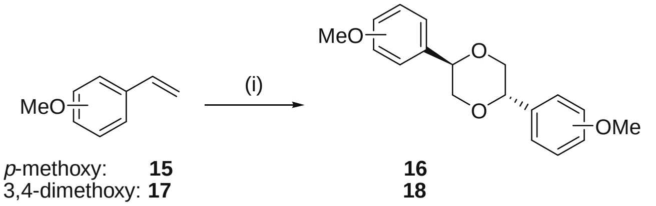
Scheme 2. Reagents and conditions: (i) H_3PO_4, 25 °C, 72% [**5** (*trans*-**5**:*cis*-**5** 75:25)], 62% [**7** (*trans*-**7**:*cis*-**7** 75:25)], 65% [**9** (*trans*-**9**:*cis*-**9** 100:0)].



Scheme 3. A possible mechanism for the cyclodimerization of styrene oxide to 1,3-dioxolanes.

rine atom on the phenyl ring further destabilizes the benzyl carbocation of **11** and therefore accelerates the 1,2-hydride shift.

Next, we decided to investigate the effects of methoxy groups (electron-donating) on the aromatic ring on the cyclodimerization. To this end, methoxystyrenes **15** and **17** were subjected to the epoxidation conditions and interestingly, and perhaps somewhat surprisingly, 1,4-dioxanes **16** and **18**[13] were isolated in good yields instead of the expected epoxides (Scheme 4). Concellon et al. have reported the cyclodimerization of epoxides to 1,4-dioxanes promoted by Lewis acids.[14] It is therefore logical to suggest that this cyclodimerization reaction is promoted by the *m*-chlorobenzoic acid generated during the epoxidation reaction. We suggest that the methoxy group further stabilizes benzyl cation **11** by resonance thereby preventing the occurrence of 1,2-hydride shift. It is reasonable to expect that other electron-donating groups on the aromatic ring of styrene oxide would also prevent the 1,2-hydride shift.



Scheme 4. Reagents and conditions: (i) *m*CPBA, CH_2Cl_2, $NaHCO_3$, 25 °C, 85% (**16**), 96% (**18**).

In summary we have reported a 1,2-hydride shift in the cyclodimerization of styrene oxides which proceeds under fairly mild conditions to give 1,3-dioxolanes. We have also shown that chloro groups on the phenyl ring of styrene favour the 1,2-hydride shift leading to substituted 1,3-dioxolanes while methoxy groups prevent the hydride shift resulting in the formation of substituted 1,4-dioxanes instead. Further studies on the effects of other substituents on the aromatic ring of styrene oxide on the cyclodimerization reaction are currently under investigation in our laboratory.

Acknowledgements

This work was supported financially by the Royal Society of Chemistry. O.M. is grateful to the Chemistry Department, University of Botswana for a fellowship. We thank Miss G. Ramokongwa for assistance with NMR experiments and Dr. K. Sichilongo for mass spectra. We also thank Dr. P. G. Steel (University of Durham, UK) for donating columns for flash chromatography to our laboratory.

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13. Satisfactory spectroscopic and analytical data were obtained for all the new compounds. *trans*-**3**: Colourless gum; ν_{max} (KBr): 3028, 2923, 2875, 1596, 1446, 1024, 754 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.24 (2H, d, J = 5.7, PhCH_2), 3.75 (1H, dd, J = 7.8 Hz, 6.3 Hz, H-5), 4.22 (1H, dd, J = 7.8 Hz, 1.9 Hz, H-5), 5.06 (1H, dd, J = 6.3 Hz, 1.9 Hz, H-4), 5.38 (1H, t, J = 5.7 Hz, H-2), 7.39–7.44 (10H, m, aromatic protons); δ_C (75 MHz, $CDCl_3$): 40.8 (PhCH_2), 72.0 (C-5), 78.5 (C-4), 105.4 (C-2), 126.4 (C-2″, C-6″), 126.7 (C-4″), 128.1 (C-1′), 128.3 (C-3″, C-5″), 128.5 (C-2′, C-6′), 130.0 (C-3′, C-5′), 136.0 (C-1′), 139.4 (C-1″). HRMS (EI) found M$^+$, 240.1692. $C_{16}H_{16}O_2$ requires 240.1601. *cis*-**3**: Yellow gum; ν_{max} (KBr): 3032, 2918, 2885, 1581, 1438, 1031, 768 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.17 (2H, d, J = 4.2 Hz, PhCH_2), 3.73 (1H, dd, J = 6.3 Hz, 1.6 Hz, H-5), 4.41 (1H, t, J = 6.3 Hz, H-5), 5.05 (1H, dd, J = 6.3 Hz, 1.6 Hz, H-4), 5.57 (1H, t, J = 4.2 Hz, H-2), 7.41–7.40 (10H, m, aromatic protons). δ_C (75 MHz, $CDCl_3$): 41.3 (PhCH_2), 72.7 (C-5), 77.7 (C-4), 105.7 (C-2), 126.1 (C-2″, C-6″), 126.5 (C-4″), 127.8 (C-1′), 128.7 (C-3″, C-5″), 128.5 (C-2′, C-6′), 130.2 (C-3′, C-5′), 136.4 (C-1′), 139.1 (C-1″). HRMS (EI) found M$^+$, 240.1641. $C_{16}H_{16}O_2$ requires 240.1601. *trans*-**5**: Colourless gum; ν_{max} (KBr) 3057, 2937, 1579, 1427, 1257, 1128, 1024, 750 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.36 (2H, d, J = 4.8 Hz, PhCH_2), 3.73 (1H, dd, J = 7.8 Hz, 2.1 Hz, H-5), 4.35 (1H, t, J = 7.8 Hz, H-5), 5.35 (1H, dd, J = 7.8 Hz, 2.1 Hz, H-4), 5.42 (1H, t, J = 4.8 Hz, H-2), 7.26–7.48 (8H, m, aromatic protons); δ_C (75 MHz, $CDCl_3$): 37.9 (PhCH_2), 71.1 (C-5), 75.0 (C-4), 103.9 (C-2), 126.8 (C-5′), 127.0 (C-5″), 127.2 (C-4′), 128.8 (C-3′), 128.9 (C-3″), 129.1 (C-6″), 129.4 (C-6′), 129.7 (C-4″), 131.5 (C-2″), 133.8 (C-2′), 133.9 (C-1″), 138.1 (C-1′). HRMS (EI) found M$^+$, 309.0168. $C_{16}H_{14}O_2Cl_2$ requires 309.0148. *trans*-**7**: White gum; ν_{max} (KBr): 2923, 1569, 1427, 1247, 1134, 788, 746 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.60 (2H, d, J = 4.2, PhCH_2), 3.64 (1H, dd, J = 6.3 Hz, 1.5 Hz, H-5), 4.13 (1H, t, J = 6.3 Hz, H-5), 4.94 (1H, dd, J = 6.3 Hz, 1.5 Hz, H-4), 5.25 (1H, t, J = 4.2 Hz, H-2), 7.21–7.27 (8H, m, aromatic protons); δ_C (75 MHz, $CDCl_3$): 40.7 (PhCH_2), 71.8 (C-5), 77.6 (C-4), 104.8 (C-2), 124.3 (C-6″), 126.4 (C-6′), 126.9 (C-4′), 128.2 (C-2′), 128.3 (C-2″), 129.4 (C-4″), 129.8 (C-5″), 130.1 (C-5′), 134.1 (C-3″), 134.5 (C-3′), 137.6 (C-1″), 141.5 (C-1′). HRMS (EI) found M$^+$, 309.0183. $C_{16}H_{14}O_2Cl_2$ requires 309.0148. *trans*-**9**: White Gum; ν_{max} (KBr): 3076, 2846, 1587, 1479, 1271, 1215, 1095, 825, 727 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.09 (2H, d, J = 4.2 Hz, PhCH_2), 3.63 (1H, dd, J = 6.3 Hz, 1.5 Hz, H-5), 4.15 (1H, t, J = 6.9 Hz, H-5), 4.96 (1H, dd, J = 6.9 Hz, 1.5 Hz, H-4), 5.25 (1H, t, J = 4.2 Hz, H-2), 7.48 (4H, d, J = 8.4 Hz, aromatic protons), 7.90 (4H, d, J = 8.4 Hz, aromatic protons); δ_C (75 MHz, $CDCl_3$): 39.8 (PhCH_2), 71.9 (C-5), 77.7 (C-4), 104.9 (C-2), 127.6 (C-3″, C-5″), 128.3 (C-3′, C-5′), 128.7 (C-2″, C-6″), 131.3 (C-2′, C-6′), 12), 132.8 (C-4″), 133.9 (C-4′), 134.1 (C-1′), 137.2 (C-1″). HRMS (EI) found M$^+$, 309.0168. $C_{16}H_{14}O_2Cl_2$ requires 309.0148. Compound **16**: yellow gum; ν_{max} (KBr): 2923, 2856, 1606, 1290, 1251, 1118, 1029 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.71 (6H, s, 2 × MeO), 3.81 (2H, dd, J = 12.1 Hz, 3.9 Hz, H-3a, 6a), 3.94 (2H, dd, J = 12.1 Hz, 7.8 Hz, H-3b, 6b), 6.05 (2H, dd, J = 7.8 Hz, 3.9 Hz, H-2, 5), 6.83 (4H, d, J = 8.7 Hz, H-2′, 6′, 2″, 6″), 7.33 (4H, d, J = 8.7 Hz, H-3′, 5′, 3″, 5″); δ_C (75 MHz, $CDCl_3$): 55.2 (2 × MeO), 65.5 (C-3, 6), 77.6 (C-2, 6), 114.1 (C-2′, 6′, 2″, 6″), 128.2 (3′, 5′, 3″, 5″), 129.1 (1′, 1″), 159.7 (4′, 4″). HRMS (EI) found M$^+$, 300.1435. $C_{18}H_{20}O_4$ requires 300.1362. Compound **18**: brown gum; ν_{max} (KBr): 2914, 2829, 1593, 1456, 1247, 1134, 1020, 806, 746 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 3.82 (6H, s, 2 × MeO), 3.85 (6H, s, 2 × MeO), 3.87 (2H, s, H-3a, 6a), 4.00 (2H, dd, J = 12.1 Hz, 8.1 Hz, H-3b, 6b), 6.01 (2H, dd, J = 8.1 Hz, 3.9 Hz, H-2, 5), 6.81 (2H, d, J = 8.1 Hz, H-5′, 5″), 6.94 (2H, d, J = 1.8 Hz, H-2′, 2″), 6.96 (2H, dd, J = 8.1 Hz, 1.8 Hz, H-6′, 6″); δ_C (75 MHz, $CDCl_3$): 55.8 (2 × MeO-4′), 55.9 (2 × MeO-3′), 65.6 (C-3, 6), 77.8 (C-2, 6), 110.1 (C-2′, 2″), 111.2 (C-5′, 5′), 119.2 (C-6′, 6″), 129.4 (1′, 1″), 148.9 (3′, 3″), 149.1 (4′, 4″). HRMS (EI) found M$^+$, 360.1559. $C_{20}H_{24}O_6$ requires 360.1573.
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