COMMUNICATION

ChemComm www.rsc.org/chemcomm

The isomerisation of (*Z*)-3-[$^2H_1$]-phenylprop-2-enone as a measure of the rate of hydroperoxide addition in Weitz–Scheffer and Juliá–Colonna epoxidations†

David R. Kelly,*[a] Eva Caroff,[b] Robert W. Flood,[b] William Heal[b] and Stanley M. Roberts*[b]

[a] *Department of Chemistry, Cardiff University, P. O. Box 912, Cardiff, Wales, UK CF10 3TB. E-mail: KellyDR@Cardiff.ac.uk; Fax: (44) 029-20874030; Tel: 029-20874063*

[b] *Department of Chemistry, University of Liverpool, Liverpool, UK L69 3BX. E-mail: smrsm@liverpool.ac.uk; Tel: 0151-7943501*

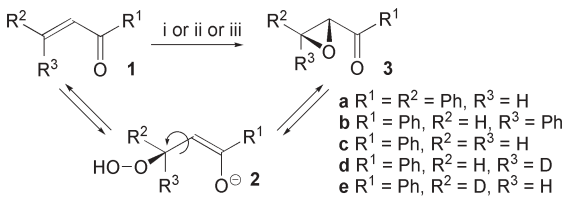
Received (in Cambridge, UK) 23rd March 2004, Accepted 23rd July 2004
First published as an Advance Article on the web 25th August 2004

(*Z*)-3-[$^2H_1$]-Phenylprop-2-enone is isomerised by hydroperoxide to an equimolar mixture of the (*Z*)- and (*E*)-isomers prior to epoxidation. Poly-(L)-leucine (10 mole %) accelerates the addition of hydroperoxide by an order of magnitude and sequesters hydroperoxide from THF.

The Weitz–Scheffer oxidation of α,β-unsaturated ketones **1** by basic peroxide is a two-stage process involving the initial formation of a peroxy-enolate **2** followed by ring closure, with loss of hydroxide ion, to give an epoxide **3** (Scheme 1).[1] Juliá and Colonna discovered an asymmetric variant of the Weitz–Scheffer reaction, by adding a peptide, *e.g.* poly-(L)-leucine (PLL), to aqueous hydrogen peroxide and substrate (*e.g.* (*E*)-chalcone **1a**) in a water immiscible solvent.[2] This triphasic system has been recently complemented by a non-aqueous biphasic protocol in which the organic solvent contains the substrate, the oxidant and the base.[3] The biphasic system exhibits impressively short reaction times (< 1 h, for more reactive enones) and chalcone epoxide **3a** is produced in remarkably high enantiomeric excess (> 95%) given that in the absence of catalyst a substantial amount of racemic chalcone epoxide **3a** (*ca.* 20%)[4] is formed in the same time period. This dichotomy was resolved by a simple experiment.

PLL (100 mg) and UHP (28 mg) were dissolved in THF (1.5 ml) and stirred for 5 min and then DBU (60 μl) was added. After 5 min the supernatant THF was removed and the peroxide content of both the solution and the gel-like PLL was estimated using potassium iodide and thiosulfate in standard fashion. Only 30% of the total peroxide was found in the THF solution; the remainder of the peroxide was associated with the relatively small quantity of polyleucine gel. Thus one of the catalytic modes of polyleucine is sequestration of hydroperoxide.

Early studies of the Weitz–Scheffer reaction demonstrated that the rate of epoxide formation is first order with respect to the concentration of hydroperoxide or α,β-unsaturated ketone and has no definite order with respect to hydroxide or hydrogen peroxide concentration.[5] These results can be equally well rationalised, by postulating slow, rate limiting addition of hydroperoxide anion, followed by fast cyclisation to the epoxide, or fast addition followed by slow rate-limiting cyclisation.



Scheme 1 *Reagents and conditions*: (i) Weitz–Scheffer: H_2O_2, NaOH, co-solvent, *e.g.* CH_3OH. (ii) Juliá–Colonna triphasic system: PLL (20 mole %), 30% H_2O_2 (30 equiv.), 5 M NaOH (4 equiv.), toluene, 24 h. (iii) Biphasic system: PLL (5–10 mole %), urea–hydrogen peroxide complex (UHP, 1.3 equiv.), DBU (1.3 equiv.), THF, ½ h. All at rt.

(*E*)-Chalcone **1a** and (*Z*)-chalcone **1b**, under both Weitz–Scheffer[6] and Juliá–Colonna conditions, give the *trans*-epoxide **3a** (racemic or scalemic respectively), *via* (*E*)-chalcone **1a** and this behaviour is typical of other alkenes. Rate studies suggest that isomerisation of the (*Z*)-alkene to the (*E*)-alkene[7] occurs by fast addition of hydroperoxide to give a peroxy-enolate **2**, which has a sufficient lifetime to allow rotation of the α,β-bond before elimination of hydroperoxide. Definitive conclusions could not be drawn from the previous studies, because the relative rate of hydroperoxide addition to the (*Z*)- and (*E*)-alkenes was unknown. Furthermore there was uncertainty as to why the peroxy-enolate derived from the (*Z*)-alkene did not cyclise, whereas that from the (*E*)-alkene did.

An opportunity to resolve this conundrum was provided by the observation that phenylprop-2-enone **1c** (phenyl vinyl ketone) was converted into (2*R*,3)-epoxyphenylpropanone **3c** (> 95% ee)[8] using PLL, UHP and either DBU or BEMP in THF. Therefore, the (*Z*)-deuterio-analogue **1d** was synthesised[9] which is presumed to be sterically and electronically unbiased in the addition step and to undergo free rotation as the peroxy-enolates **2d**, **2e**.[10]

Addition of DBU to (*Z*)-alkene **1d** in THF caused isomerization to the (*E*)-alkene **1e**, due to the reversible addition of the base.[11] However, no isomerisation occurred when (*Z*)-alkene **1d** was dissolved in THF containing BEMP, until UHP was added. Then a relatively slow isomerization of the (*Z*)-alkene **1d** to the (*E*)-alkene **1e** was observed.[12] A plot of the excess of (*Z*)-alkene **1d** (%) against time (Fig. 1) showed that isomerisation reached the halfway point after *ca.* 1 h and was incomplete even after 3 h. Epoxide formation was near to completion after ten hours.

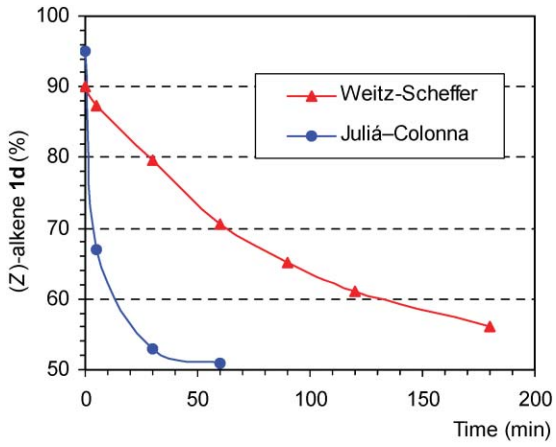


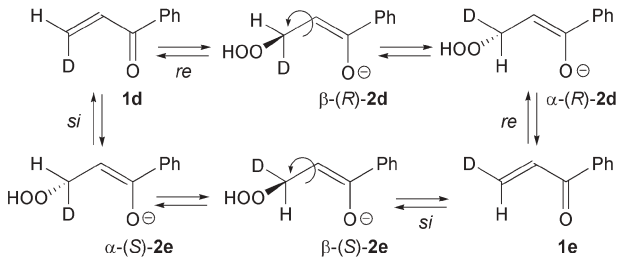
Fig. 1 Isomerisation of (*Z*)-3-[$^2H_1$]-phenylprop-2-enone **1d**. *Reagents and conditions*: UHP (1.2 equiv.), THF, without and with PLL (10 mole %) stirred for 10 min and BEMP (1.2 equiv.) added. Reaction monitored by ^{1}H-NMR and HPLC.

† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b4/b404389h/

DOI: 10.1039/b404389h

When the (*Z*)-alkene **1d** was subjected to biphasic Juliá–Colonna conditions, the epoxidation reaction was complete after 2 h. HPLC analysis showed a 78% enantiomeric excess, while ^{1}H-NMR spectroscopy indicated an equimolar mixture of (2*R*,3*R*)-epoxide **3d** and (2*R*,3*S*)-epoxide **3e** isotopomers.[13] The excess of (*Z*)-alkene **1d** over (*E*)-alkene **1e** was reduced from 45% to 17% in just five minutes and complete isomerization was observed after 1 h (Fig. 1). This isomerisation is at least an order of magnitude faster than that observed under Weitz–Scheffer conditions.[14]

There are three main conclusions that can be drawn from these reactions. Firstly, polyleucine increases the rate of addition of hydroperoxide to the (*Z*)-alkene **1d** (and presumably **1c**, **1e**). Secondly, the peroxy-enolate intermediate **2d** undergoes rotation, even without a steric driving force, and finally epoxide formation is directed solely by the orientation of the hydroperoxide moiety relative to the enolate. The increased rate presumably occurs by stabilisation of the peroxy-enolates **2d**, **2e** and the latter two observations are a consequence of the following conformational constraints. Addition and elimination of hydroperoxide must occur *via* the same transition state, with hydroperoxide or the hydroperoxy moiety of the peroxy-enolate **2** in alignment with the orbitals of the π-system. Additionally, when epoxide is formed the O–O bond must be anti-periplanar to the π-system to enable overlap with the O–O anti-bonding orbital. Therefore we view the rapid rate of addition relative to epoxidation, as a failure to achieve the requisite O–O bond orientation in the majority of the additions.

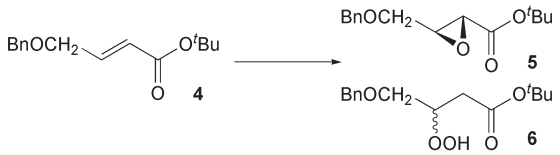


Scheme 2 Stereochemistry of alkene isomerisation. α and β refer to the orientation of the hydroperoxy moiety.

There are two distinguishable mechanisms for alkene isomerisation/epoxidation. The first possibility involves face selective addition (*re* or *si*, Scheme 2), followed by random elimination or epoxidation while the second invokes random facial addition, followed by conformationally controlled elimination of hydroperoxide or hydroxyl from the α- or β-conformers. The (2*R*)-stereochemistry of the epoxides **3d**, **3e**, in the Juliá–Colonna reaction, shows that epoxide formation occurs from the β-(*R*)-**2d** and β-(*S*)-**2e** conformers, when the O–O-bond is optimally orientated.

Evidence to distinguish between the two mechanisms was provided by epoxidation of an α,β-unsaturated ester. These are usually inert under triphasic Juliá–Colonna epoxidation conditions, but when *tert*-butyl (*E*)-3-benzyloxybut-2-enoate **4** was subjected to biphasic epoxidation conditions the optically active epoxide **5** (20%, > 85% ee)[15] and the hydroperoxide **6** (58% yield) were isolated (Scheme 3). The hydroperoxide **6** was reduced with triphenylphosphine to the corresponding alcohol, and converted into (*S*)-Mosher's esters. ^{1}H-NMR spectra showed the presence of equal amounts of two diastereoisomers, indicating that the alcohol was racemic. The hydroperoxide **6** did not form racemic or optically active epoxide **5** when re-subjected to the Juliá–Colonna conditions.

We interpret this result as follows. Ester enolates are less stable than ketone enolates, hence the peroxy-enolate was protonated before β-elimination or epoxide formation. Moreover,



Scheme 3 *Reagents and conditions*: UHP (2 equiv.), DBU (2.1 equiv.), PLL (20 mole %), THF, 72 h, rt.

we conjecture that the orientation of the hydroperoxide moiety of the peroxy-enolate **2** and facilitation of O–O bond cleavage are due to hydrogen bonding to the peptide.[16] This might be thwarted by an intramolecular hydrogen bond between the hydroperoxide proton and the ether or an intermolecular hydrogen bond between the peptide and the ether. Whatever the explanation, this result clearly indicates random facial addition of hydroperoxide to this substrate.

In conclusion, it has been shown that for substrate **1d** the first stage of the Weitz–Scheffer and Juliá–Colonna oxidations is the reversible conjugate addition of peroxide anion, which is substantially accelerated by the presence of PLL.

We thank the Swiss National Research Fund, the EPSRC and DTI (Micrograms to Multikilograms LINK Scheme), the BBSRC, and Novartis for funding to EC, RWF and WH.

Notes and references

1 E. Weitz and A. Scheffer, *Ber.*, 1921, **54**, 2327.
2 S. Banfi, S. Colonna, H. Molinari, S. Juliá and J. Guixer, *Tetrahedron*, 1984, **40**, 5207.
3 T. Geller and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1397 and ref. 3 therein.
4 R. Takagi, A. Shiraki, T. Manabe, S. Kojima and K. Ohkata, *Chem. Lett.*, 2000, 366, ref. 12; R. W. Flood, PhD Thesis, University of Liverpool, 2001.
5 C. A. Bunton and G. J. Minkoff, *J. Chem. Soc.*, 1949, 665.
6 R. E. Liutz and W. B. Black, *J. Am. Chem. Soc.*, 1953, **75**, 5990; S. Patai, Z. Rappoport, in *The Chemistry of the Alkenes*, (S. Patai, ed.), Wiley-Interscience, London, 1964, p. 469.
7 H. O. House and R. S. Ro, *J. Am. Chem. Soc.*, 1958, **80**, 2428.
8 Physical data for (2*R*,3)-epoxyphenylpropanone **3c** λ_{max} (film) 1689; δ_H ($CDCl_3$) 2.89 (1 H, dd, *J* 6.5, 2.5), 3.12 (1 H, dd, *J* 6.5, 4.5), 4.23 (1 H, dd, *J* 4.5, 2.5) 7.49–8.08 (5 H, m). δ_C($CDCl_3$) 47.5, 51.2, 128.4, 128.9, 133.9, 135.5, 194.7. Found: C, 72.7; H, 5.4; $C_9H_8O_2$ requires C, 72.95; H, 5.45%. $[\alpha]_D^{22}$ +60.8 (*c* 0.74, CH_2Cl_2), mp 64–66 °C. An authentic sample was obtained in six steps from styryl alcohol using Sharpless asymmetric epoxidation in the first step.
9 Prepared by hydroalumination of 1-phenylprop-2-yn-1-ol with $LiAlH_4$ in THF, quenching the reaction with D_2O (M. J. Kang, J.-S. Jang and S.-G. Lee, *Tetrahedron Lett.*, 1995, **36**, 8829) and Dess–Martin periodinane oxidation (70% overall yield). The ratio (*Z*)-isomer **1d** : (*E*)-isomer **1e** was 95–90 : 5–10.
10 Y. Apeloig, M. Karni and Z. Rappoport, *J. Am. Chem. Soc.*, 1983, **105**, 2784.
11 V. K. Aggarwal and A. Mereu, *Chem. Commun.*, 1999, 2311.
12 The isomerization was followed by ^{1}H NMR spectroscopy.
13 In a separate experiment it was confirmed that epimerisation of the epoxides **3d**, **3e** by deprotonation/reprotonation did not occur under the reaction conditions.
14 If every addition occurs with full bond rotation, then the rate of isomerisation is half the rate of addition. Clearly addition–elimination may occur without bond rotation, particularly when the peroxy-enolate **2** is bound to poly-leucine. Therefore the rate of isomerisation is 50% of the lowest possible rate of addition.
15 The absolute configuration is inferred to be (2*R*,3*S*) by analogy with the results from Juliá–Colonna oxidation of a wide variety of α,β-unsaturated ketones.
16 The role of the peptide in this mechanism is discussed in the following paper, in this issue (DOI: 10.1039/b404390c).