Tetrahedron Letters,Vol.29,No.5,pp 531-534,1988
Printed in Great Britain

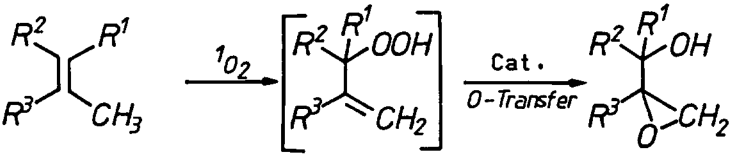
0040-4039/88 $3.00 + .00
Pergamon Journals Ltd.

REGIO-CONTROLLED FUNCTIONALIZATION OF 2,5-DIMETHYL-2,4-HEXADIENE INTO EPOXY ALCOHOLS BY PHOTOOXYGENATION IN THE PRESENCE OF TITANIUM(IV) OR VANADIUM(V)

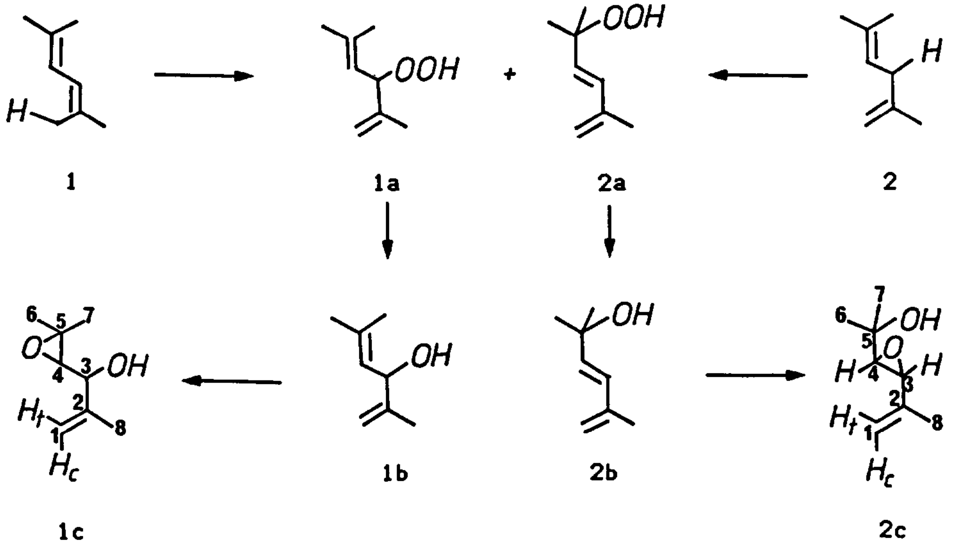
Waldemar ADAM* and Eugen STAAB
Institut für Organische Chemie, Universität Würzburg, D-8700 Würzburg, F.R.G.

SUMMARY: Using $Ti(OiPr)_4$ as oxygen transfer catalyst, the diene **1** afforded exclusively the epoxy alcohol **1c**, but $VO(acac)_2$ gave exclusively the isomerized epoxy alcohol **2c** during its ene reaction with singlet oxygen.

Recently we have shown[1] that olefins can be conveniently transformed into epoxy alcohols via their ene reaction with singlet oxygen in the presence of transition metal catalysts, e.g. $Ti(OiPr)_4$ or $VO(acac)_2$ (Eq. 1). This novel "one-pot" hydroxy-epoxidation of olefins has broad scope[2]. We chose 2,5-dimethyl-2,4-hexadiene (**1**) as olefin substrate. The photooxygenation of this diene **1** has been extensively studied[3] and conflicting results have appeared concerning the hydroperoxides **1a** and **2a**. If the ene reaction can be steered towards hydroperoxide **1a**, then the major product will be epoxy alcohol **1c**, while regioisomer **2c**



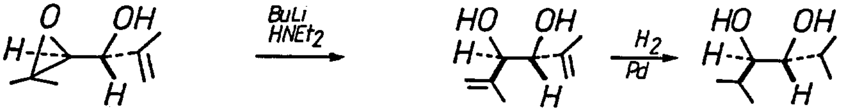
(Eq.1)



(Eq. 2)

will predominate should the hydroperoxide 2a be formed selectively (Eq. 2). Since isomerization by the metal catalyst could in principle take place at the hydroperoxide stage (1a $\rightleftharpoons$ 2a) or at the allylic alcohol stage (1b $\rightleftharpoons$ 2b) during the oxygen functionalization of diene 1, this particular example provided the opportunity to assess, whether oxygen transfer (1a → 1c or 2a → 2c) can compete with the regioisomerization (1a $\rightleftharpoons$ 2a and/or 1b $\rightleftharpoons$ 2b). Presently we report our results on this "one-pot" oxygen functionalization, showing that depending on the choice of catalyst, either epoxy alcohol 1c (titanium-IV) or epoxy alcohol 2c (vanadium-V) are obtained regioselectively. We also resolve the confusion[3] concerning the hydroperoxide products 1a and 2a derived from the ene reaction of diene 1 with $^1O_2$.

The photooxygenation of a dichloromethane solution of diene 1 at 0°C in the presence of stoichiometric amounts of Ti(OiPr)$_4$ gave a 75% yield (isolated) of the epoxy alcohol 1c[4] in a diastereomeric ratio d.r. ≥95:5 (distilled product mixture). However, when the titanium catalyst was added subsequently to the photooxygenation mixture of diene 1, the 400 MHz ^{1}H NMR indicated a 70:20:10 mixture of epoxy alcohol 1c, of isomerized epoxy alcohol 2c and of the conjugated dienol 2b. The configurational assignment of the major diastereomer R*,S*-1c was accomplished according to the chemical correlation shown in Eq. 3. In view of the poor agreement between the observed and the reported melting points of diol R*,R*-1d, catalytic reduction to diol R*,R*-1e was performed.



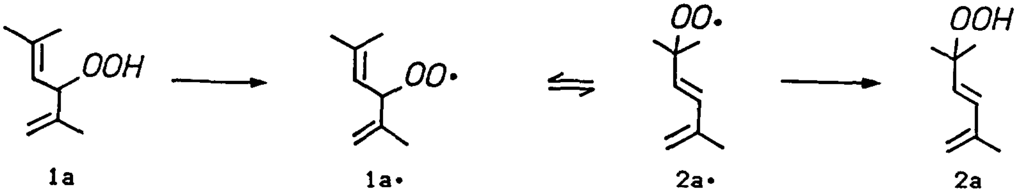
(Eq. 3)

R*,S*-1c R*,R*-1d R*,R*-1e

m.p. 53-55°C (lit.[5]:41.5°C) m.p. 80-82°C (lit.[6]:80-82°C)

Using VO(acac)$_2$ (5 mol%) as catalyst in chloroform at 0°C, a 90:10 mixture of the rearranged epoxy alcohol 2c and the dienol 2b was obtained, but no epoxy alcohol 1c could be detected in the crude photooxygenation mixture by 400 MHz ^{1}H NMR. Pure epoxy alcohol 2c was obtained in 61% yield from the above product mixture by chromatography (silica gel), eluting with 5:1 CH_2Cl_2/petroleum ether. Control experiments with pure epoxy alcohols 1c and 2c demonstrated that neither Ti(OiPr)$_4$ nor VO(acac)$_2$ caused interconversion of these two.

The gratifying regioselectivity, i.e. with $^1O_2$/Ti(OiPr)$_4$ exclusively regioisomer 1c and with $^1O_2$/VO(acac)$_2$ exclusively regioisomer 2c are formed, demands rationalization. Since the epoxy alcohols 1c and 2c are not interconverted by the Ti(OiPr)$_4$ and VO(acac)$_2$ catalysts, at what stage does isomerization take place? A control experiment with the authentic allylic alcohols 1b and 2b revealed that VO(acac)$_2$ caused efficient conversion of 1b into the more stable conjugated 2b, but not $Ti(OiPr)_4$. Thus, at least with $VO(acac)_2$ the isomerization route 1b → 2b is evident. However, this does not apply for $Ti(OiPr)_4$ as catalyst, although sequential execution of the oxygen functionalization of diene **1**, i.e. first photooxygenation followed by addition of $Ti(OiPr)_4$, does afford some rearranged epoxy alcohol 2c. The only other logical point for isomerization in this complex transformation must be at the stage of the hydroperoxides 1a and 2a. Unfortunately, control experiments with the authentic hydroperoxide 1a are not possible because $Ti(OiPr)_4$ converts pure 1a efficiently and exclusively into the epoxy alcohol 1c, while $VO(acac)_2$ converts pure 1a into 2c. Thus oxgen transfer during $Ti(OiPr)_4$ functionalization outweighs regioisomerization, but the reverse obtains for $VO(acac)_2$. The propensity for the latter to participate in redox processes, e.g. free radical type reduction of hydroperoxides[8], permits rationalizing the divergent behavior of $VO(acac)_2$. Thus, via a complex redox pathway the vanadium catalyst generates from hydroperoxide 1a its peroxy radical 1a•, which isomerizes to the more stable 2a• and hydrogen abstraction leads to the isomerized hydroperoxide 2a (Eq. 4).



(Eq. 4)

Precedents for such radical-initiated hydroperoxide isomerizations are well documented and believed to operate via the mechanism shown in Eq. 4[9]. Indeed, such hydroperoxide isomerization explains the conflict concerning the composition of the hydroperoxides 1a and 2a in the reaction of diene 1 with $^1O_2$[3]. For example, depending on the solvent used, the presence of radical scavengers (2,6-di-*tert*-butyl-4-methylphenol), or radical initiators [Cu(I)Cl], the ratio of hydroperoxides 1a and 2a in the photooxygenation of diene 1 can range from 90:10 (non-radical conditions) to 10:90 (radical conditions), as illustrated in Table I. Consequently, using $Ti(OiPr)_4$ as oxygen transfer catalyst, the conditions are optimal for the regioselective preparation of epoxy alcohol 1c. In contrast, with $VO(acac)_2$ as catalyst the isomerized epoxy alcohol 2c can be obtained selectively. Such regiocontrol is of obvious synthetic value.

TABLE 1: Product Distribution of the Hydroperoxide Regioisomers 1a and 2a in the Photooxygenation of 2,5-Dimethyl-2,4-hexadiene (1)

Solvent(a)	Additive Type	mol%	Product Ratio(b) 1a:2a
CH_2Cl_2	-	-	69:31
CH_2Cl_2	DTBP(c)	5	90:10
$CDCl_3$	-	-	70:30
$CDCl_3$	DTBP	5	90:10
C_6D_6	-	-	10:90
C_6D_6	DTBP	25	90:10
CD_3CN	-	-	76:24
CD_3CN	Cu(I)Cl	sat.	10:90

a) Run to 100% conversion at 0°C, except C_6D_6 at 8°C; Tetraphenylporphine (TPP) as sensitizer except CD_3CN with Rose Bengal. b) Determined by integration of characteristic signals in the 400 MHz ^1H NMR; error ±2%; normalized to 100%. c) 2,6-Di-*tert*-butyl-4-methylphenol (DTBP).

ACKNOWLEDGEMENTS: We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial help and for spectral services Dr. G. Lange (MS) and Dr. D. Scheutzow (NMR).

REFERENCES AND FOOTENOTES:

1. a) Adam,W.; Griesbeck,A.; Staab,E. Angew. Chem. 98 (1986) 279; b) Adam.,W; Griesbeck,A.; Staab,E. Tetrahedron Lett. 27 (1986) 2839; c) Adam,W.; Pasquato,L. Tetrahedron Lett. 28 (1987) 311; d) Adam,W.; Lupon,P. Chem. Ber. 1987, in press.
2. Staab,E., Dissertation, Universität Würzburg, 1987.
3. a) Hasty,N.M.; Kearns,D.R. J. Am. Chem. Soc. 95 (1973) 3380; b) Manring,L.E.; Foote,C.S. J. Am. Chem. Soc. 105 4710; c) Gorman,A.A.; Rodgers,M.A. J. Chem. Phys. Lett. 55 (1978) 52; d) Gollnick,K.; Griesbeck,A. Tetrahedron 40 (1984) 3235; e) Matsumoto,M.; Dobashi,S.; Kuroda,K.; Kondo,K. Tetrahedron 41 (1985) 2147.
4. (R*,S*-1c): colorless liquid, bp. 80°C (oven)/0.1 mm, 75% yield
   IR (CCl_4): 3610 cm^{-1}, 3520, 3080, 2970, 2930, 1450, 1380, 1240, 1210, 905.- ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.24 and 1.26 (s, 6H, 6,7-Me), 1.70 (dd, *J*[8-Me, 1t] = *J*[8-Me,1c] = 1.4 Hz, 3H, 8-Me), 2.72 (d, *J*[4,3] = 8.0 Hz, 1H, 4-H), 3.30 (br s, 1H, OH), 3.81 (br d, *J*[3,4] = 8.0 Hz, 1H, 3-H), 4.83 (ddq, *J*[1t,8-Me] = 1.4, *J*[1t, 1c] = 0.9, *J*[1t,3] = 0.5 Hz, 1H, 1t-H), 4.96 (ddq, *J*[1c,8-Me] = 1.4, *J*[1c,1t] = *J*[1c,3] = 0.9 Hz, 1H, 1c-H).- ^{13}C-NMR ($CDCl_3$, 22 MHz): δ = 18.4 (q), 19.1 (q), 24.3 (q), 59.4 (d), 66.6 (d), 73.1 (s), 111.5 (t), 143.4 (s).- MS (70eV): m/z(%) = 142 (0.3, M^+), 109 (2), 93 (3), 83 (25), 72 (77), 59 (47), 57 (74), 43 (55), 41 (100), 39 (62).
   $C_8H_{14}O_2$ (142.2): Calcd. 67.57, H 9.92 Found C 67.35, H 10.23
5. Wiemann,J.; Thi-Thuan,L. Bull. Soc. Chim. Fr. 1955, 95.
6. Mangoni,L.; Adinolfi,M.; Barone,G.; Parrilli,M. Gaz. Chim. Ital. 105 (1975) 377.
7. (R*,S*-2c): colorless liquid, 61% yield
   IR ($CDCl_3$): 3570 cm^{-1}, 3090, 2980, 2930, 1455, 1370, 1245, 1185, 1140, 960.- ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.21 and 1.29 (s, 6H, 6,7-Me), 1.63 (br.s, 3H, 8-Me), 2.05 (br.s, 1H, OH), 2.86 (d, *J*[4,3] = 2.3 Hz, 1H, 4-H), 3.41 (d, *J*[3,4] = 2.3 Hz, 1H, 3-H), 4.96 (dq, *J*[1t,1c] = *J*[1t,8-Me] = 1.4 Hz, 1H, 1t-H) 5.10 (dq, *J*[1c,1t] = 1.4, *J*[1c,8-Me] = 0.7 Hz, 1H, 1c-H).- ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 17.0 (q), 24.9 (q), 27.6 (q), 57.4 (d), 64.4 (d), 67.8 (s), 114.9 (t), 140.7 (s).- MS (70 eV): m/z(%) = 142 (0.1, M^+), 99 (7), 86 (5), 71 (11), 59 (24), 58 (22), 57 (17), 43 (100), 41 (29), 18 (40).
   $C_8H_{14}O_2$ (142.2): Calcd. C 67.57, H 9.92 Found C 67.72, H 10.34
8. Sheldon,R.A. in Aspects of Homogeneous Catalysis (R. Ugo, Ed.), Vol. IV, D. Reidel, Dordrecht 1984.
9. a) Porter,N.A. Acc. Chem. Res. 19 (1986) 262; b) Brill,W.F. J. Chem. Soc., Perkin Trans. II, 1984, 621; c) Chan,H. W.-S.; Levett,G.; Matthew,J.A. J. Chem. Soc., Chem. Commun., 1978, 756; d) Beckwith, A.L.J.; O'Shea,D.M.; Roberts, D.H. J. Am. Chem. Soc. 108 (1986) 6408.

(Received in Germany 10 November 1987)