Synthesis of α,β-Epoxy Ketones from Alkyl- and Arylsubstituted Cyclopropanols

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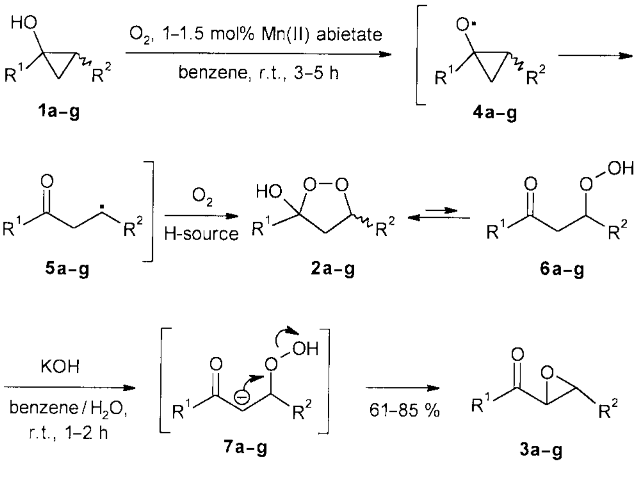
Abstract: A number of aliphatic and arylaliphatic α,β-epoxy ketones were prepared in good yields in a one-pot procedure by a manganese-catalyzed ring cleavage of 1-substituted and 1,2-disubstituted cyclopropanols with oxygen followed by dehydration of the resulting cyclic peroxides with alkali.

Key words: epoxides, ketones, cyclopropanes, oxidations, transition metals

Quite recently, Blanco and coworkers[1,2] reported the copper- and iron-catalyzed oxidation of a number of bicyclo[n.l.0]alkan-1-ols with oxygen which led to the cleavage of the three-carbon ring and the formation of 3-hydroperoxycycloalkanones and/or their bicyclic peroxyhemiketals.[3] These compounds are transformed into 2,3-epoxycycloalkanones by treatment with a base,[2,4] as it is the case for the peroxides which are formed during the oxidation of α,β-unsaturated ketones by alkaline hydrogen peroxide.[5] In the present work, we report the extension of this methodology to the synthesis of aliphatic and arylaliphatic α,β-epoxy ketones, which are attractive intermediates for use in organic synthesis, including the synthesis of natural compounds.[6]

We found that the oxidation of readily available cyclopropanols **1a**–**g**[7] by molecular oxygen effectively proceeds in the presence of manganese(II) abietate or manganese(II) acetylacetonate. It should be noted that our attempts to subject compounds **1a**–**g** to the reaction with O_2 under conditions used for the oxidation of bicyclo[n.l.0]alkan-1-ols[1,2] failed.

For preparative purposes, it is convenient to perform the oxidation of cyclopropanols **1a**–**g** by stirring of their solutions in benzene under an oxygen atmosphere in the presence of 1–1.5 mol% of Mn(II) abietate. Under these conditions, the reaction is complete within 3–5 hours at room temperature providing cyclic peroxy compounds **2a**–**g** as the major products.[8] The latter were converted without isolation into α,β-epoxy ketones **3a**–**g** in 61–85% overall yield by treatment with aqueous potassium hydroxide (Scheme 1). The *E* configuration was assigned to epoxy ketones **3a**–**f** based on their ^{1}H NMR spectra, which showed a coupling constant of 1.8–2.0 Hz for the vicinal oxirane protones.[9] Changing the catalytic species from Mn(II) abietate to Mn(II) acetylacetonate reduced the yield of the target products by approx. 10–15%. The use of tri-*n*-butylvanadate(V) as catalyst led to a mixture of the oxidation products.[10,11]



1–7 a: R^1 = Me, R^2 = n-C$_6$H$_{13}$; **b**: R^1 = Me, R^2 = Ph; **c**: R^1 = Et, R^2 = Ph;
d: R^1 = R^2 = Et; **e**: R^1 = Pr, R^2 = Me; **f**: R^1 = n-C$_6$H$_{13}$, R^2 = Me;
g: R^1 = n-C$_7$H$_{15}$, R^2 = H

Scheme 1

Concerning the mechanism of the formation of epoxy ketones **3a**–**g**, it could be assumed that peroxides **2a**–**g** arise via three-carbon ring opening of cyclopropyloxide intermediates **4a**–**g**, and trapping of the resulting β-oxoalkyl radicals **5a**–**g** with O_2 (Scheme 1). It is noteworthy that in the case of 1,2-disubstituted cyclopropanols **1a**–**f**, the cleavage of the most substituted carbon-carbon bond proceeds in a high regioselective manner.

The structures of 1,2-dioxolan-3-ols **2** were confirmed by spectral data of compounds **2d**–**f** isolated by column chromatography. Their ^{1}H NMR spectra showed the cyclic peroxides **2d**–**f** to be a mixture of diastereomers in approx. 1:1 ratio, established from integral intensities of multiplets of the C-5 hydrogen at $\delta = 4.16$–4.74 ppm. In accordance with the ^{1}H NMR data, the ^{13}C NMR spectra of **2d**, **e** exhibited two sets of signals assigned to diastereomers of these compounds. In the IR spectra of compounds **2d**–**f**, along with the strong ν_{OH} band in the 3444–3448 cm^{-1} region, a carbonyl stretching band at 1711–1713 cm^{-1} was observed. These data give evidence for an equilibrium between cyclic hemiacetals **2** and hydroperoxy ketones **6**. The moderate carbonyl absorption in the IR spectra and

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the absence of signals corresponding to C=O carbon atom in the ^{13}C NMR spectra of compounds **2d–f** indicated the low relative contents of keto-forms **6d–f** in the equilibrium mixture. Evidently, epoxy ketones **3** are formed from peroxides **2** through intermediate hydroperoxyenolates **7**. Thus, isolated compounds **2d–f** were transformed into epoxy ketones **3d–f** almost quantitatively under the action of aqueous potassium hydroxide (TLC data).

In summary, we have presented a flexible and convenient method for the preparation of aliphatic and arylaliphatic α,β-epoxy ketones based on manganese-catalyzed oxidation of easily available 1-substituted and 1,2-disubstituted cyclopropanols followed by dehydration of the resulting cyclic peroxides in the presence of potassium hydroxide.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 (200 MHz) and Bruker AC 250 (62.5 MHz) spectrometer, respectively, in $CDCl_3$ using TMS as the internal standard. IR spectra were obtained on a FT-IR Perkin Elmer 1000 spectrophotometer. Cyclopropanols **1a**–**g** were synthesized following literature procedures (**1a**–**c**,[12] **1d**–**g**[13]).

α,β-Epoxy Ketones 3a–g; General Procedure

A solution of corresponding cyclopropanol **1a**–**g** (10 mmol) and Mn(II) abietate (0.07 g, 1 mol%) in anhyd benzene (60 mL) was stirred under an O_2 atm at r.t. for 3–5 h (hazardous procedure). Then aq KOH (0.5 M, 5 mL) was added and the mixture was vigorously stirred at r.t. for 1–2 h. After filtration, the organic layer was separated and the aqueous solution was extracted with benzene (3 × 5 mL). The combined organic phases were washed with sat. NH_4Cl, brine, and dried (Na_2SO_4). The solvent was removed and the crude epoxides **3a**–**g** were purified by distillation under reduced pressure or by recrystallization.

(*E*)-3,4-Epoxydecan-2-one (3a)

Yield: 1.45 g (85%); bp 72–74 °C/2 Torr (Lit.[14] bp 84–85 °C/1 Torr).

^{1}H NMR: δ = 0.93 (t, 3H, J = 6.5 Hz), 1.20–1.54 (m, 8H), 1.55–1.71 (m, 2H), 2.06 (s, 3H), 3.08 (td, 1H, J = 5.0, 1.8 Hz), 3.17 (d, 1H, J = 1.8 Hz).

(*E*)-3,4-Epoxy-4-phenylbutan-2-one (3b)

Yield: 1.18 g (73%); mp 55–56 °C (MeOH) [Lit.[15] mp 54–55.5 °C (MeOH)].

^{1}H NMR: δ = 2.19 (s, 3H), 3.48 (d, 1H, J = 1.8 Hz), 4.00 (d, 1H, J = 1.8 Hz), 7.21–7.42 (m, 5H).

(*E*)-1,2-Epoxy-1-phenylpentan-3-one (3c)

Yield: 1.3 g (74%); mp 50–51 °C (pentane) [Lit.[16] mp 52–53 °C (petroleum ether)].

^{1}H NMR: δ = 1.11 (t, 3H, J = 7.0 Hz), 2.34–2.68 (m, 2H), 3.57 (d, 1H, J = 1.8 Hz), 3.97 (d, 1H, J = 1.8 Hz), 7.20–7.42 (m, 5H).

(*E*)-4,5-Epoxyheptan-3-one (3d)

Yield: 0.78 g (61%); bp 59–61 °C/10 Torr (Lit.[17] bp 61–62 °C/10 Torr).

^{1}H NMR: δ = 1.03 (t, 3H, J = 7.0 Hz), 1.08 (t, 3H, J = 7.0 Hz), 1.54–1.78 (m, 2H), 2.33 (dq, 1H, J = 18.5, 7.0 Hz), 2.50 (dq, 1H, J = 18.5, 7.0 Hz), 3.04 (td, 1H, J = 5.2, 1.8 Hz), 3.24 (d, 1H, J = 1.8 Hz).

(*E*)-2,3-Epoxyheptan-4-one (3e)

Yield: 0.90 g (70%); bp 61–63 °C/10 Torr (Lit.[18] bp 44–45 °C/3 Torr).

^{1}H NMR: δ = 0.92 (t, 3H, J = 7.2 Hz), 1.42 (d, 3H, J = 5.0 Hz), 1.50–1.72 (m, 2H), 2.24 (dt, 1H, J = 17.0, 7.0 Hz), 2.41 (dt, 1H, J = 17.0, 7.0 Hz), 3.13 (qd, 1H, J = 5.0, 2.0 Hz), 3.20 (d, 1H, J = 2.0 Hz).

(*E*)-2,3-Epoxydecan-4-one (3f)

Yield: 1.28 g (75%); colorless liquid; bp 72–73 °C/2 Torr (Lit.[19] bp 77–78 °C/1.5 Torr).

IR (film): ν = 2931, 2859, 1712, 1460, 1421, 1376, 1235, 1173, 1141, 1044, 1006, 969, 848 cm^{-1}.

^{1}H NMR: δ = 0.88 (t, 3H, J = 6.3 Hz), 1.27 (m, 6H), 1.40 (d, 3H, J = 5.0 Hz), 1.46–1.66 (m, 2H), 2.27 (dt, 1H, J = 17.2, 7.0 Hz), 2.45 (dt, 1H, J = 17.2, 7.0 Hz), 3.14 (qd, 1H, J = 5.0, 2.0 Hz), 3.17 (d, 1H, J = 2.0 Hz).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.94; H, 10.74.

1,2-Epoxydecan-3-one (3g)

The title compound was prepared according to General Procedure except that 1.5 mol% Mn(II) abietate was used.

Yield: 1.11 g (65%); colorless liquid; bp 86–89 °C/3 Torr.

IR (film): ν = 2929, 2857, 1715, 1466, 1379, 1234, 1067, 947, 872, 724 cm^{-1}.

^{1}H NMR: δ = 0.88 (t, 3H, J = 7.0 Hz), 1.28 (m, 8H), 1.48–1.65 (m, 2H), 2.20–2.54 (m, 2H), 2.87 (dd, 1H, J = 6.0, 2.2 Hz), 2.99 (dd, 1H, J = 6.0, 4.8 Hz), 3.42 (dd, 1H, J = 4.8, 2.2 Hz).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.68; H, 10.63.

Isolation of 1,2-Dioxolan-3-ols 2d–f; General Procedure

A solution of the corresponding cyclopropanol **1d**–**f** (10 mmol) and Mn(II) abietate (0.07 g, 1 mol%) in anhyd benzene (60 mL) was stirred under an O_2 atm at r.t. for 3–5 h (hazardous procedure). The solvent was removed under reduced pressure and peroxides **2d**–**f** were isolated by column chromatography on silica gel (EtOAc–cyclohexane, 1:1).

3,5-Diethyl-1,2-dioxolan-3-ol (2d)

Yield: 0.91 g (62%); colorless liquid (1:1 mixture of diastereomers).

IR (film): ν = 3444, 2970, 2882, 1713, 1463, 1381, 1282, 1212, 1159, 1011, 979, 905, 859 cm^{-1}.

^{1}H NMR: δ = 0.88–1.12 (m, 6H), 1.62–1.92 (m, 4H), 2.14–2.30 (m, 1H), 2.62–2.80 (m, 1H), 3.38 (br s, 1H), 4.16–4.32 (m, 0.5H), 4.34–4.48 (m, 0.5H).

^{13}C NMR: δ = 8.7, 9.0, 10.1, 10.3, 24.9, 27.4, 29.0, 29.4, 49.6, 49.8, 81.7, 83.3, 106.9, 107.8.

5-Methyl-3-propyl-1,2-dioxolan-3-ol (2e)

Yield: 1.17 g (80%); colorless liquid (1:1 mixture of diastereomers).

IR (film): ν = 3446, 2965, 2874, 1712 cm^{-1}.

^{1}H NMR: δ = 0.93 (t, 1.5H, J = 7.0 Hz), 0.94 (t, 1.5H, J = 7.0 Hz), 1.32 (d, 1.5H, J = 6.0 Hz), 1.36 (d, 1.5H, J = 6.0 Hz), 1.39–1.60 (m, 2H), 1.66–1.94 (m, 2H), 2.12–2.28 (m, 1H), 2.64–2.83 (m, 1H), 3.20 (br s, 1H), 4.33–4.52 (m, 0.5H), 4.58–4.74 (m, 0.5H).

^{13}C NMR: δ = 14.2, 16.8, 17.8, 18.1, 20.1, 38.3, 38.6, 52.1, 52.2, 76.5, 77.9, 106.6, 107.7.

Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.88; H, 9.39.

3-Hexyl-5-methyl-1,2-dioxolan-3-ol (2f)

Yield: 1.60 g (85%); colorless liquid (1:1 mixture of diastereomers).

IR (film): ν = 3448, 2961, 2874, 1711, 1465, 1378, 1271, 1216, 1148, 1059, 966 cm^{-1}.

^{1}H NMR: δ = 0.82 (m, 3H), 1.10–1.50 (m, 13H), 1.62–1.80 (m, 1H), 2.04–2.22 (m, 1H), 3.14 (br s, 1H), 4.26–4.46 (m, 0.5H), 4.52–4.68 (m, 0.5H).

^{13}C NMR: δ = 7.4, 10.1, 13.5, 15.9, 17.8, 18.1, 22.8, 25.0, 29.6, 29.9, 45.5, 45.6, 69.8, 71.3 (The signal due to quaternary C-3 was not observed in the 106–108 ppm region).

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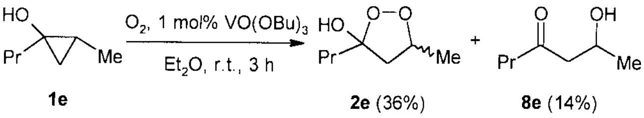

Scheme 2

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