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

Oleg G. Kulinkovich,* Dmitry A. Astashko, Vladimir I. Tvyorskii, Natalya A. Ilyina
Department of Chemistry, Belarusian State University, Fr. Skorina Av. 4, 220050 Minsk, Belarus
Fax +375(0172)264998; E-mail: kulinkovich@chem.bsu.unibel.by
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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 coworkers1,2 reported the copper- and iron-catalyzed oxidation of a number of bicyclo[n.1.0]alkan-1-ols with oxygen which led to the cleavage of the three-carbon ring and the formation of 3-hydroperoxycyclalkanones and/or their bicyclic peroxycemiketals.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 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 O2 under conditions used for the oxidation of bicyclo[n.1.0]alkan-1-ols1,2 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 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 1H NMR spectra, which showed a coupling constant of 1.8–2.0 Hz for the vicinal oxirane protons.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

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 cyclopropanyloxide intermediates 4a–g, and trapping of the resulting α-oxoalkyl radicals 5a–g with O2 (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 1H 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 δ = 4.16–4.74 ppm. In accordance with the 1H NMR data, the 13C 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 νOH 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...
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 hydroperoxenylates 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 alyarylaliphatic $\alpha$, $\beta$-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, 1d–g).

$\alpha$-$\beta$-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). Thenaq 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$_4$Cl, brine, and dried (Na$_2$SO$_4$). The solvent was removed and the crude$\alpha$-$\beta$-epoxy ketones based on manganese-catalyzed oxidations of cyclic peroxides in the presence of potassium hydroxide.

(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).

(E)-3,4-Epoxy-4-phenylbutan-2-one (3b)
Yield: 1.18 g (73%); mp 55–56°C (MeOH) [Lit.$^{15}$ mp 54–55°C (MeOH)].

(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)].

(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).

(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: $\delta$ = 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): $\nu$ = 2931, 2859, 1712, 1460, 1241, 1376, 1235, 1173, 1141, 1044, 1006, 969, 848 cm$^{-1}$.

$^1$H NMR: $\delta$ = 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).

Alcal. Calcld for C$_7$H$_{14}$O$_3$: C, 70.55; H, 10.66. Found: C, 70.94; H, 10.74.

(E)-3,4-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): $\nu$ = 2929, 2857, 1715, 1379, 1324, 1067, 947, 872, 724 cm$^{-1}$.

$^1$H NMR: $\delta$ = 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. Calcld for C$_7$H$_{14}$O$_3$: 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 2d–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): $\nu$ = 3444, 2970, 2882, 1713, 1463, 1381, 1282, 1212, 1159, 1011, 979, 859 cm$^{-1}$.

$^1$H NMR: $\delta$ = 0.88–1.22 (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: $\delta$ = 87.8, 90.0, 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-1,2-dioxolan-3-ol (2e)
Yield: 1.17 g (80%); colorless liquid (1:1 mixture of diastereomers).

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

$^1$H NMR: $\delta$ = 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: $\delta$ = 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.

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.
1H 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).
13C NMR: δ = 7.4, 10.1, 13.5, 15.9, 17.8, 18.1, 22.8, 25.0, 29.6, 45.5, 45.6, 69.8, 71.3 (The signal due to quaternary C-3 was not observed in the 106–108 ppm region).

References and Notes

(7) For a review, see: Kulinkovich, O. G.; de Meijere, A. Chem. Rev. 2000, 100, 2789.
(8) The rate of oxidation of cyclopropanols 1a–g on air was dramatically depressed, and so intensive bubbling with atmospheric O₂ was required in this case to perform the reaction. The replacement of benzene by the non-flammable chlorinated C₄-hydrocarbons led to the formation of halogen-containing compounds as by-products. (9) Reichel, L.; Neubauer, A. Liebig's Ann. Chem. 1975, 1538.
(10) We found that the reaction of cyclopropanol 1e with O₂ in the presence of tri-n-butylvanadate(V) resulted in the formation of hemiacetal 2e and known β-hydroxy ketone 8e (Scheme 2). After treatment of the reaction mixture produced from the above oxidation of 1e with LiCuCl₂ solution in THF (0.25 M, 50 mol%), compound 8e was obtained in 46% overall yield. For physical and spectral data of 8e, see: Gaudemar-Bardone, F.; Gaudemar, M. J. Organomet. Chem. 1976, 104, 281.

Scheme 2