Epoxidation of 2,3-Dimethylbenzofurans by Dimethyldioxirane

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The synthesis of epoxides **2** by the reaction of the chloro- and methyl-substituted 2,3-dimethylbenzofurans **1** with dimethyldioxirane at low temperature is reported. These labile epoxides were spectroscopically characterized (^{1}H and ^{13}C NMR) at subambient temperatures. Epoxidation of benzofuran **1c** affords a 31:69 mixture of epoxide **2c** and quinone methide **3c**, the latter presumably being produced by valence isomerization of the epoxide. On warming up above −10°C, the epoxides **2** suffer decomposition. Treatment of epoxide **2i** with methanol yields the tautomeric mixture of adducts **4i** and **4i'**.

Although furan metabolites are known to be highly cytotoxic[2], benzofurans have been widely employed as food additives[3]. Particularly effective is the oxidative metabolic activation by cytochrome P 450[4], which implicates that labile epoxides are responsible for the toxicity. Despite the fact that epoxides of enol ethers are relatively stable compounds[5], to date no furan epoxides have been isolated or detected. Previous traditional epoxidation procedures[6] afforded even at low temperatures the highly reactive *cis*-enediones as the major products, which through their electrophilic nature lead, for example, to DNA adducts[7].

An advantageous oxygen transfer agent for epoxidation, particularly for biological substrates, is dimethyldioxirane[8] (as acetone solution[9]). This efficient oxidant, which operates under mild and strictly neutral conditions, was shown to epoxidize electron-rich alkenes such as enol ethers[5a,b,10], enol silyl ethers[11], enol phosphates[12], vinyl formamides[13], and enol esters and lactones[14]. Recently, this unique epoxidizing peroxide was employed for the preparation of the first furan-type epoxide, namely benzofuran epoxide[15]. This most labile epoxide was necessary in our genetoxicity studies, since it was implicated as being responsible for the high mutagenicity[16] observed for benzofuran dioxetanes in the Ames test.

Presently we report on our results on the epoxidation of chloro- and methyl-substituted 2,3-dimethylbenzofurans by means of dimethyldioxirane. Thereby we extend the scope of this novel epoxidation method, show its generality for the preparation of the biologically relevant benzofuran epoxides, and illustrate the advantage of dimethyldioxirane as the oxidant of choice in the synthesis of labile epoxides.

Results and Discussion

The various 2,3-dimethylbenzofurans **1a–i** were transformed by isolated dimethyldioxirane into the corresponding epoxides **2** in quantitative yields. The results are given in Table 1, in which are stated the % conversion, the temperature and the time of epoxidation. As expected, electron-withdrawing substituents on the benzo moiety reduce the reactivity of the enolic double bond, as witnessed by the longer reaction times for complete conversion. Fortunately, such epoxides are also more persistent.

Epoxides **2** are stable at −20°C for spectral acquisition, but they decompose readily above 0°C, which precluded their rigorous purification for elemental analysis. Thus, the structure assignment of the epoxides rests on NMR-spectral data (cf. Table 2). The signal for the 2- and 3-methyl groups occur at δ = 1.52–1.96, an expected upfield shift from δ = 2.08–2.52 for the 2- and 3-methyl groups of benzofurans **1**. Particularly characteristic are the signals of the epoxide carbon atoms C-2 and C-3 at δ = 94–96 and 66–68 in the ^{13}C-NMR spectrum versus 152–155 and 108–111 for the corresponding olefinic carbon atoms of the benzofurans **1**.

The benzofuran **1c**, in contrast to the other derivatives, afforded on epoxidation with dimethyldioxirane at −78 → −20°C a 31:69 mixture of epoxide **2c** and the respective

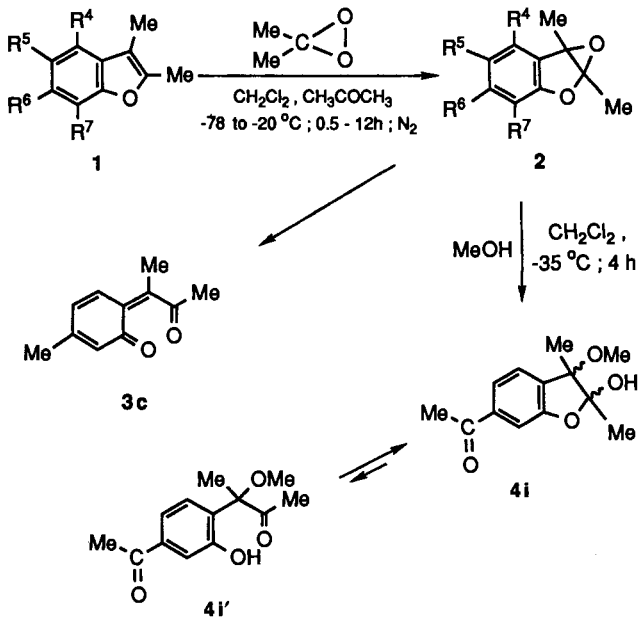

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Table 1. Dimethyldioxirane (DMD) epoxidation[a] of 2,3-dimethylbenzofurans **1**

	Substituents				Reaction Conditions: Ratio 1: DMD	Temp. (°C)	Time (h)	Conversion[b] (%)
	R^4	R^5	R^6	R^7				
1a	Me	H	H	H	1 : 1.3	-78→ -20	3	100
1b	H	Me	H	H	1 : 1.5	-78→ -20	2	100
1c	H	H	Me	H	1 : 1.8	-78→ -20	0.5	100
1d	H	H	H	Me	1 : 1.4	-78→ -20	3	80
1e	Cl	H	H	H	1 : 2.9	-40	11	41
1f	H	Cl	H	H	1 : 1.7	-40	12	100
1g	H	H	Cl	H	1 : 1.5	-40	11	100
1h	H	H	H	Cl	1 : 1.4	-40	9	72
1i	H	H	MeCO	H	1 : 1.7	-40	12	100

[a] In CH_2Cl_2/CH_3COCH_3 under N_2. – [b] Estimated by ^1H NMR.

Table 2. Characteristic ^{13}C-NMR data for the benzofurans[a] **1** and the epoxides[b] **2**

Benzofuran	^{13}C Shifts				Epoxide	^{13}C Shifts			
	C-2	C-3	2-Me	3-Me		C-2	C-3	2-Me	3-Me
1a	154.2	109.5	11.7	7.9	**2a**	94.8	67.2	14.7	13.9
1b	152.2	109.4	11.8	7.9	**2b**	94.4	66.3	13.5	11.4
1c	154.0	108.3	11.5	10.5	**2c**	94.8	66.8	14.0	12.0
1d	152.8	109.9	11.7	8.0	**2d**	94.6	67.3	14.2	12.2
1e	154.6	110.1	11.6	9.8	**2e**	94.2	66.6	13.8	13.5
1f	152.2	109.6	11.8	7.8	**2f**	95.8	66.7	13.9	11.7
1g	153.8	109.6	11.8	17.8	**2g**	95.7	66.8	14.4	12.4
1h	152.0	111.0	12.2	8.4	**2h**	95.9	67.3	13.8	11.8
1i	153.1	110.4	11.9	7.7	**2i**	95.9	66.5	13.9	11.7

[a] In $CDCl_3$ at room temperature [Bruker AC 250 (250 MHz)]. – [b] In CD_2Cl_2 at −40°C [Bruker WM 400 (400 MHz)] except **2a,b,f,i** in CD_3COCD_3 at −20°C [Bruker AC 200 (200 MHz)].

quinone methide **3c**. This valence isomerization is analogous to that postulated for the non-isolable, simple furan epoxides into *cis*-enediones. The quinone methide **3c** was too labile for isolation and like the epoxide **2c** decomposed above −10°C into a complex mixture of products. Work is in progress to search for sufficiently stable benzofuran epoxides **2** and/or quinone methides **3** for exploring their chemistry.

The propensity of benzofuran epoxides **2** towards solvolysis is demonstrated in the ease of the reaction with methanol. As an example, the methanolysis of **2i** was investigated. Epoxide **2i** gave with methanol at −35°C the tautomeric alcohols **4i/4i'**, isolated as a 83:17 mixture in 72% yield; the ring tautomer **4i** consisted of two diastereomers in a ratio of 82:18.

In summary, dimethyldioxirane converts benzofurans **1** efficiently into their corresponding, hitherto unknown epoxides **2**. These extremely labile epoxides open up interesting opportunities for synthetic chemistry and the study of cellular DNA damage.

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Experimental

Melting points: Reichert Thermovar hot stage apparatus. – IR: Perkin-Elmer 1420. – ^1H and ^{13}C NMR: Bruker AC 200 (200 MHz) or Bruker AC 250 (250 MHz); chemical shifts refer to $CDCl_3$, CD_2Cl_2, or [D_6]acetone. – MS: Varian MAT CH-7. – All solvents were purified by following standard literature methods. Acetone and water, used in the preparation of dimethyldioxirane (as acetone solution), were distilled twice over EDTA. Potassium monoperoxysulfate, the triple salt 2 $KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, was used as received. The 2,3-dimethylbenzofurans **1a–i** were prepared according to ref.[17] in moderate overall yields by first forming the 3-(aroyloxy)butan-2-ones from the reaction of the substituted phenols with 2-chlorobutan-2-one, followed by cyclization with concentrated sulfuric acid.

Epoxidation of 2,3-Dimethylbenzofurans **1a–i** *by Dimethyldioxirane. General Procedure:* A cooled (−78°C) solution of dimethyldioxirane (30–200% molar excess) in acetone (0.050–0.084 M), dried over molecular sieve 4 Å at −20°C, was rapidly added to a cooled (−78°C), stirred solution of the benzofurans **1a–i** (0.62–1.10 mmol) in dry CH_2Cl_2 (2 ml) under N_2. The stirring was continued until complete consumption (monitored by TLC) of the benzofuran, while the reaction temperature was allowed to increase to −20°C. For derivatives **1e–i** the reaction temp. was kept constant at −40°C throughout the reaction course. The solvent was removed at −20°C/0.001 Torr to afford essentially quantitatively (cf. Table 1) the hitherto unknown epoxides **2** in high purity (^1H NMR). At 0°C all epoxides deteriorated rapidly.

Epoxide **2a** was obtained quantitatively by following the above procedure at −78°C to −20°C for 3 h, in which a total of 15 ml of a 0.086 M (1.30 mmol) dioxirane solution and 160 mg (1.00 mmol) of **1a** were employed. – ^1H NMR (200 MHz, CD_3COCD_3, −20°C): δ = 1.82 (s, 3H), 1.84 (s, 3H), 2.46 (s, 3H), 6.74–6.78 (m, 2H), 7.12–7.70 (m, 1H). – ^{13}C NMR (50 MHz, CD_3COCD_3, −20°C): δ = 13.9 (q), 14.7 (q), 18.8 (q), 67.2 (s), 94.8 (s), 109.2 (d), 123.7 (d), 128.4 (s), 129.6 (d), 136.6 (s), 160.4 (s).

Epoxide **2b** was obtained quantitatively by following the above procedure at −78 to −20°C for 2 h, in which a total of 12 ml of a 0.086 M (1.03 mmol) dioxirane solution and 110 mg (0.69 mmol) of **1b** were employed. – ^1H NMR (400 MHz, CD_3COCD_3, −40°C): δ = 1.52 (s, 3H), 1.64 (s, 3H), 1.89 (s, 3H), 6.60 (d, J = 8.3 Hz, 1H), 6.86 (dd, J_1 = 8.3, J_2 = 1.0 Hz, 1H), 7.08 (br. s, 1H). – ^{13}C NMR (100 MHz, CD_3COCD_3, −40°C): δ = 11.4 (q), 13.5 (q), 20.1 (q), 66.3 (s), 94.4 (s), 110.2 (d), 124.1 (s), 129.7 (d), 129.8 (d), 132.3 (s), 157.2 (s).

Epoxide **2c** *and Quinone Methide* **3c** were obtained quantitatively as a 39:61 mixture by following the above procedure at −78 to −20°C for 0.5 h, in which a total of 25 ml of a 0.072 M (1.80 mmol) dioxirane solution and 164 mg (1.03 mmol) of **1c** were employed. Epoxide **2c**: ^1H NMR (400 MHz, CD_2Cl_2, −40°C): δ = 1.72 (s, 3H),

1.84 (s, 3H), 2.08 (s, 3H), 6.71 (br. s, 1H), 6.78 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H). – ^{13}C NMR (100 MHz, CD_2Cl_2, –40°C): δ = 12.0 (q), 14.0 (q), 22.4 (q), 66.8 (s), 94.8 (s), 121.3 (d), 123.0 (s), 127.5 (d), 127.7 (d), 140.1 (s), 159.2 (s). – Quinone methide **3c**: ^{1}H NMR (400 MHz, CD_2Cl_2, –40°C): δ = 2.08 (s, 3H), 2.14 (s, 3H), 2.21 (s, 3H), 6.11 (s, 1H), 6.30 (d, J = 9.6 Hz, 1H), 6.73 (d, J = 9.6 Hz, 1H). – ^{13}C NMR (100 MHz, CD_2Cl_2, –40°C): δ = 17.3 (q), 21.4 (q), 26.7 (q), 111.3 (d), 125.4 (d), 126.7 (s), 126.8 (d), 154.0 (s), 162.1 (s), 184.7 (s), 207.7 (s).

Epoxide **2d** was obtained quantitatively (at 80% conversion) by following the above procedure at –78°C to –20°C for 3 h, in which a total of 15 ml of a 0.080 M (1.20 mmol) dioxirane solution and 140 mg (0.87 mmol) of **1d** were employed. – ^{1}H NMR (400 MHz, CD_2Cl_2, –40°C): δ = 1.81 (s, 3H), 1.96 (s, 3H), 2.29 (s, 3H), 6.93–7.01 (m, 1H), 7.17 (dd, J_1 = 7.4, J_2 = 0.7 Hz, 1H), 7.34 (dd, J_1 = 7.4, J_2 = 0.7 Hz, 1H). – ^{13}C NMR (100 MHz, CD_2Cl_2, –40°C): δ = 12.2 (q), 14.2 (q), 15.0 (q), 67.3 (s), 94.6 (s), 120.7 (d), 121.2 (d), 129.3 (s), 130.9 (d), 137.9 (s), 157.9 (s).

Epoxide **2e** was obtained quantitatively (at 41% conversion) by following the above procedure at –40°C for 12 h, in which a total of 25 ml of a 0.072 M (1.80 mmol) dioxirane and 112 mg (0.623 mmol) of **1e** were employed. – ^{1}H NMR (400 MHz, CD_2Cl_2, –40°C): δ = 1.91 (s, 6H), 6.88 (dd, J_1 = 8.0, J_2 = 0.5 Hz, 1H), 6.97 (dd, J_1 = 8.0, J_2 = 0.5 Hz, 1H), 7.22–7.25 (m, 1H). – ^{13}C NMR (100 MHz, CD_2Cl_2, –40°C): δ = 13.5 (q), 13.8 (q), 66.6 (s), 94.2 (s), 108.7 (d), 109.4 (d), 121.9 (d), 127.5 (s), 130.4 (s), 159.8 (s).

Epoxide **2f** was obtained quantitatively by following the above procedure at –40°C for 12 h, in which a total of 25 ml of a 0.073 M (1.82 mmol) dioxirane solution and 200 mg (1.10 mmol) of **1f** were employed. ^{1}H NMR (200 MHz, CD_3COCD_3, –20°C): δ = 1.78 (s, 3H), 1.88 (s, 3H), 6.98 (dd, J_1 = 8.6, J_2 = 0.3 Hz, 1H), 7.34 (dd, J_1 = 8.6, J_2 = 2.3 Hz, 1H), 7.63 (dd, J_1 = 2.3, J_2 = 0.3 Hz, 1H). – ^{13}C NMR (50 MHz, CD_3COCD_3, –20°C): δ = 11.7 (q), 13.9 (q), 66.7 (s), 95.8 (s), 112.9 (d), 124.8 (d), 125.7 (s), 130.0 (d), 133.0 (s), 158.8 (s).

Epoxide **2g** was obtained quantitatively by following the above procedure at –40°C for 11 h, in which a total of 25 ml of a 0.060 M (1.50 mmol) dioxirane solution and 181 mg (1.00 mmol) of **1g** were employed. ^{1}H NMR (400 MHz, CD_2Cl_2, –40°C): δ = 1.83 (s, 3H), 1.96 (s, 3H), 6.98–7.16 (m, 2H), 7.42 (d, J = 7.9 Hz, 1H). – ^{13}C NMR (100 MHz, CD_2Cl_2, –40°C): δ = 12.4 (q), 14.4 (q), 66.8 (s), 95.7 (s), 121.1 (d), 121.3 (d), 124.8 (d), 128.5 (s), 135.0 (s), 159.9 (s).

Epoxide **2h** was obtained quantitatively (at 72% conversion) by following the above procedure at –40°C for 9 h, in which a total of 20 ml of a 0.060 M (1.20 mmol) dioxirane solution and 150 mg (0.83 mmol) of **1g** were employed. – ^{1}H NMR (400 MHz, CD_2Cl_2, –40°C): δ = 1.78 (s, 3H), 1.92 (s, 3H), 7.03–7.07 (m, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.56 (d, J = 7.2 Hz, 1H). – ^{13}C NMR (100 MHz, CD_2Cl_2, –40°C): δ = 11.8 (q), 13.8 (q), 67.3 (s), 95.9 (s), 115.7 (d), 123.5 (d), 130.2 (d), 132.5 (s), 132.8 (s), 155.6 (s).

Epoxide **2i** was obtained quantitatively by following the above procedure at –40°C for 12 h, in which a total of 15 ml of a 0.082 M (1.24 mmol) dioxirane solution and 138 mg (0.73 mmol) of **1i** were employed. – ^{1}H NMR (200 MHz, CD_3COCD_3, –20°C): δ = 1.81 (s, 3H), 1.90 (s, 3H), 2.59 (s, 3H), 7.48–7.50 (m, 1H), 7.69–7.71 (m, 2H). – ^{13}C NMR (50 MHz, CD_3COCD_3, –20°C): δ = 11.7 (q), 13.9 (q), 27.0 (q), 66.5 (s), 95.9 (s), 110.6 (d), 122.2 (d), 124.7 (d), 135.9 (s), 139.0 (s), 160.2 (s), 197.3 (s).

Reaction of Epoxide **2i** *with Methanol:* A solution of **2i** [prepared as above from 100 mg (0.53 mmol) of **1i** and 12 ml of 0.061 M (0.80 mmol) dioxirane] in 2 ml of dichloromethane was treated at –35°C with 20 ml of dry methanol. The stirring was continued at this temp. for 4 h, the solvent was evaporated (ca. 20°C/15 Torr) and the residue submitted to column chromatography (silica gel, CH_2Cl_2/AcOEt 9:1) to afford 90 mg (72%) of the 83:17 tautomeric mixture of **4i** (d.r. = 82:18) and **4i'** as a colorless powder, m.p. 100–101°C (ether/petroleum ether 1:2). – IR (CCl_4) for the mixture **4i/4i'**: $\tilde{\nu}$ = 3610 cm^{-1}, 3510, 3370, 3005, 2950, 2840, 1725, 1700, 1590. – ^{1}H NMR (250 MHz, $CDCl_3$), **4i** (major diastereomer): δ = 1.48 (s, 3H), 1.53 (s, 3H), 2.58 (s, 3H), 3.18 (s, 3H), 5.24 (s, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.37 (d, J = 1.5 Hz, 1H), 7.55 (dd, J_1 = 7.9, J_2 = 1.5 Hz, 1H); **4i** (minor diastereomer): δ = 1.62 (s, 3H), 1.71 (s, 3H), 2.57 (s, 3H), 3.03 (s, 3H), 5.10 (br. s, 1H), 7.17–7.59 (m, 3H); **4i'**: δ = 1.73 (s, 3H), 2.16 (s, 3H), 2.56 (s, 3H), 3.36 (s, 3H), 7.17–7.59 (m, 3H), 8.53 (s, 1H). – ^{13}C NMR (63 MHz, $CDCl_3$) for the mixture **4i/4i'**: δ = 14.4 (q), 15.6 (q), 19.2 (q), 20.3 (q), 20.8 (q), 25.8 (q), 26.7 (q), 49.9 (q), 51.9 (q), 79.5 (s), 83.9 (s), 88.0 (s), 110.4 (s), 110.6 (d), 112.7 (s), 113.3 (s), 117.7 (d), 119.9 (d), 120.5 (d), 121.4 (d), 125.1 (d), 127.6 (d), 128.7 (s), 132.4 (s), 134.0 (s), 138.5 (s), 139.5 (s), 139.9 (s), 155.9 (s), 157.9 (s), 158.8 (s), 197.6 (s), 205.3 (s). – MS (70 eV) for the mixture **4i/4i'**: m/z (%) = 236 (6) [M$^+$], 193 (100), 189 (8), 179 (8), 161 (55), 147 (6), 137 (2), 131 (4), 119 (4), 43 (96).

$C_{13}H_{16}O_4$ (236.3) Calcd. C 66.09 H 6.82
Found C 66.34 H 6.65

CAS Registry Numbers

1a: 21417-74-3 / **1b**: 21417-73-2 / **1c**: 7137-22-6 / **1d**: 21417-72-1 / **1e**: 27044-65-1 / **1f**: 3782-17-0 / **1g**: 27044-66-2 / **1h**: 3782-18-1 / **1i**: 1642-79-1 / **2a**: 136795-91-0 / **2b**: 136795-92-1 / **2c**: 136795-93-2 / **2d**: 136795-94-3 / **2e**: 136795-95-4 / **2f**: 136795-96-5 / **2g**: 136795-97-6 / **2h**: 136795-98-7 / **2i**: 131588-88-0 / **3c**: 136795-99-8 / **4i'**: 136796-00-4 / **4i**: 136796-01-5 / dimethyldioxirane: 74087-85-7

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