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Rearrangement of 2,3-Disubstituted Benzofuran Epoxides Prepared by Dimethyldioxirane Oxidation

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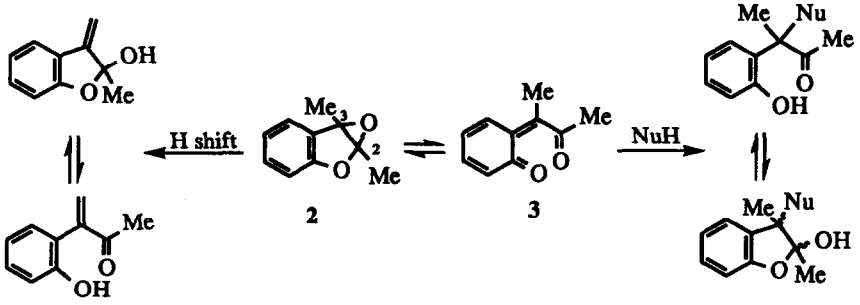
Abstract: Benzofuran epoxides, prepared by dimethyldioxirane (DMD) oxidation of the corresponding 2,3-disubstituted benzofurans, afford on 1,2 migration the respective benzofuranones 4a,d-f , except 3-tert-butyl-2-methylbenzofuran epoxide (2c), which persists even at room temperature; however, on DMD oxidation of 2-methylbenzofuran (1b), the ester 5b is formed by a novel oxidative cleavage of the intermediary epoxide.

Since the first successful isolation of the 2,3-dimethylbenzofuran epoxide (**2**),[1] its chemistry has been extensively studied. It has been shown that this class of epoxides reckons among the most reactive and, thus, least persistent ones known to date. For example, without acid assistance they add methanol at -78 °C[2] (Scheme 1), a reactivity not exhibited even by arene oxides[3]. This high propensity towards nucleophilic

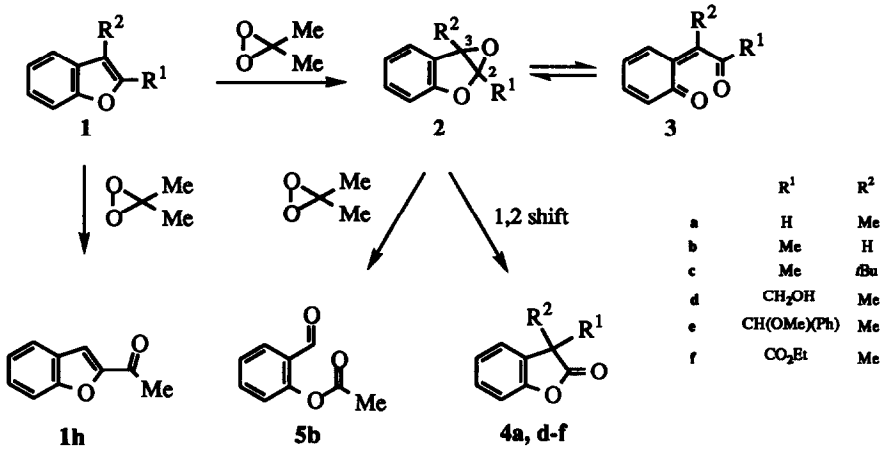
Scheme 1



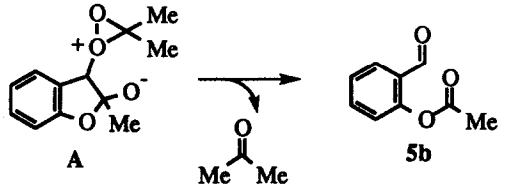
attack is explained in terms of conjugate nucleophilic addition to the respective valence-isomeric quinone methide **3**[2] (Scheme 1). Another reaction feature, which limits the persistence of these unique epoxides, constitutes their rearrangement to the corresponding allylic alcohols by an H shift[1,2] (Scheme 1). Herein we report new results on the effect of C-2 and C-3 substituents on the rearrangement modes of the benzofuran epoxides.

The DMD oxidation of the 3-methylbenzofuran (**1a**) at 0 °C afforded within 3 h (Table I, entry 1) the known 2-benzofuranone **4a**[4] (Scheme 2). To demonstrate that the furanone **4a** was formed from the respective epoxide **2a**, the latter was prepared at -78 °C by d_6-dimethyldioxirane oxidation of the

Scheme 2



corresponding benzofuran **1a** and characterized by NMR spectroscopy at -55 °C. Indeed, above - 40 °C the latter gave quantitatively the benzofuranone **4a** through 1,2 hydrogen migration. In contrast, benzofuran **1b** (Table 1, entry 2) yielded on oxidation with DMD the known ester **5b**[5]; no epoxide could be observed in this case even at 0 °C. Presumably, this unusual ring cleavage proceeds through the initially formed epoxide **2b**, which subsequently adds dioxirane to give intermediate **A** (Eq. 1) and elimination of acetone with



Eq. 1

concomitant C-2 / C-3 furan bond scisson leads to the ester **5b** (Scheme 2). A precedent for this novel transformation was recently reported for 2-methyl-3-phenylbenzofuran.[6]

DMD oxidation of the benzofuran **1c** (Table 1, entry 3) led to its epoxide **2c**, which persists for days at room temperature. Attempted purification of the latter by column chromatography (silica gel, alumina or Florisil) failed. In contrast to benzofuran **1b**, no further oxidation of epoxide **2c** by DMD was observed, which is not surprising since this sterically hindered epoxide persisted nucleophilic addition even at 20 °C. This *tert*-butyl-stabilized benzofuran epoxide constitutes the most persistent derivative of this highly elusive class of epoxides.

The benzofurans **1d-f** (Table 1, entries 4-6) afforded on DMD oxidation the corresponding benzofuranones **4d-f** (Scheme 2); but surprisingly, the respective allylic alcohols (Scheme 1) were not found. Irrespective of the electronic nature of the C-2 substituents, for the benzofurans **1d-f**, the 1,2 alkyl migration

to the benzofuranones **4d-f** is favored over the H abstraction by the epoxide oxygen atom from the C-3 methyl group to the allylic alcohols (Scheme 1). In the case of the epoxide **1f**, an ester group migrates during the formation of benzofuranone **4f**, for which related 1,2 shifts of electron-withdrawing groups, such as COR, COOR, COSR, $CONR_2$, etc., have been observed in several carbenium ion rearrangements, e.g. the

Table I: Dimethyldioxirane Oxidation[a] of the Benzofurans **1a-g**

Entry	1	Benzofuran R^1	R^2	Temp. [°C]	Time [h]	Yield[b] [%]	Product
1	**a**	H	Me	0[c]	3	98	**4a**
2	**b**[d]	Me	H	20	19	35[e]	**5b**
3	**c**	Me	*t*Bu	0	3	>95[f]	**2c**
4	**d**	CH_2OH	Me	0[c]	3	89	**4d**
5	**e**	CH(OMe)(Ph)	Me	0	9	77	**4e**
6	**f**	CO_2Et	Me	20	48	72	**4f**
7	**g**[d]	CH(OH)(Me)	H	0	12	38[e]	**1h**

[a] As 0.1 M acetone solution, 1.2-1.5 equivalents, nitrogen gas atmosphere.- [b] Conversion and mass balance > 95 %.- [c] Epoxidation by d_6-dimethyldioxirane at -55 °C afforded the respective epoxide, which was characterized by ^1H and ^{13}C NMR spectroscopy .- [d] Three equivalents of dimethyldioxirane were employed .- [e] Mass balance ca. 50 %.- [f] Determined by ^1H NMR spectroscopy.

pinacol, semipinacol, glycidic ester, dienone-phenol, and other Wagner-Meerwein rearrangements.[7] In this context it is worth to mention that epoxides have been proposed as intermediates in certain pinacol rearrangements.[8]

Finally on DMD treatment of the benzofuran **1g**, the known 2-acetylbenzofuran[9] (**1h**) was formed by oxidation of the secondary alcohol. Since the mass balance was rather low (ca. 50 %), epoxidation of the enol ether bond cannot be excluded; nonetheless, such secondary alcohol oxidations by DMD are known.[10]

In summary, the dimethyldioxirane oxidation of the benzofurans initially affords the corresponding epoxides, which subsequently rearrange on 1,2 migration to the respective benzofuranones. For all cases investigated here, the benzofuran epoxides **2** are labile intermediates, except the 3-*tert*-butyl-2-methylbenzofuran epoxide (**2c**), which persists even at room temperature. In the case of the 2-methylbenzofuran (**1b**), the ester **5b** is formed as final product by further reaction of the initially formed epoxide **2b** with DMD, which constitute an unusual reaction mode for dimethyldioxirane.

Experimental

Melting points were determined with a Reichert Thermovar hot stage apparatus. The IR spectra were recorded with a Perkin Elmer 1420 instrument. ^1H and ^{13}C NMR spectra were run on a Bruker AC 200 (200 MHz) spectrometer. Chemical shifts refer to $CDCl_3$ in TMS. Elemental analyses were performed in the Analytical Division of the Institute of Inorganic Chemistry (University of Würzburg). Dimethyldioxirane (as acetone solution) was prepared according to the published procedure[11]. The dimethyldioxirane solutions were stored over molecular sieves (4 Å) at -20 °C.

2-Methyl-3-*tert*-butylbenzofuran (1c)

A flame-dried, three-necked, round-bottomed flask, equipped with a reflux condenser, mechanical stirrer and dropping funnel, was charged with 374 mg (15.4 mmol) magnesium turnings (activated by a few crystals of I_2) and 10 mL Et_2O, followed by slow addition of a solution of 5 mL Et_2O and 1.47 mL (13.5 mmol) *t*BuCl under reflux for 30 min. The reaction mixture was cooled to room temperature and a solution of 1.00 g (6.77 mmol) 2-methyl-3-benzofuranone[12] in 5 mL Et_2O was added slowly. The resulting reaction mixture was stirred at room temperature for 3 d and then refluxed 2 h after addition of 15 mL of 1N H_2SO_4. The solvent was removed at reduced pressure (ca. 20 °C/ 20 Torr) and the residue was partitioned between dichloromethane (20 mL) and water (20 mL). The combined organic phases were washed with a saturated, aqueous $NaHCO_3$ solution (20 mL) and water (20 mL), and finally dried over $MgSO_4$. The solvent was removed (ca. 20 °C/ 20 Torr) and the crude product was purified by column chromatography (silica gel, 1:3 Et_2O/pentane) to yield 217 mg (17 %) **1c** as colorless needles, mp 45-47 °C (Et_2O).- **1c**: IR (CCl_4): $\tilde{\nu}$ = 2975 cm^{-1}, 2935, 2875, 1455, 1445, 1365, 1255, 1180, 1120, 700.- ^1H NMR (200 MHz, $CDCl_3$): δ = 1.55 (s, 9 H), 2.60 (s, 3 H), 7.19 - 7.27 (m, 2 H), 7.40 - 7.45 (m, 1 H), 7.74 - 7.79 (m, 1 H).- ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.1 (q), 31.0 (q), 32.0 (s), 110.6 (d), 121.4 (d), 121.7 (d), 121.8 (s), 122.6 (d), 129.2 (s), 148.4 (s), 153.7 (s).- Anal. calcd. for $C_{13}H_{16}O$ (188.3) C 82.94, H 8.57; Found C 82.98, H 8.52.

2-(1′-Methoxy)-benzyl-3-methylbenzofuran (1e)

To a stirred solution of 500 mg (3.79 mmol) 3-methylbenzofuran in 5 mL THF under N_2 at 0 °C was added slowly 4.00 mL (4.11 mmol) of 1.35 M solution of *n*BuLi solution in hexane. After 2 h at 0 °C 603 mg (5.69 mmol) benzaldehyde was added and allowed to reach room temperature for 12 h. Then 1.61 g (11.4 mmol) MeI was added to the reaction mixture, which was stirred for another 24 h. The reaction mixture was poured into 50 mL water and extracted three times with 20 mL ether. After drying with $MgSO_4$ and evaporation of the solvent, the crude product was purified by column chromatography (silica gel, 1:3 Et_2O/pentane) afforded 674 mg (71 %) **1e**, mp 68-70 °C. IR (CCl_4): $\tilde{\nu}$ = 3040 cm^{-1}, 3000, 2900, 2795, 1435, 1240, 1180, 1085, 865, 690.- ^1H NMR (200 MHz, $CDCl_3$): δ = 2.37 (s, 3 H), 3.40 (s, 3 H), 5.67 (s, 1 H), 7.06 - 7.49 (m, 9 H).- ^{13}C NMR (50 MHz, $CDCl_3$): δ = 7.9 (q), 56.8 (q), 77.7 (d), 111.6 (d), 114.3 (s), 120.3 (d), 123.2 (d), 125.2 (d), 127.6 (d), 128.4 (d), 129.0 (d), 130.6 (s), 140.6 (s), 151.8 (s), 155.0 (s).- Anal. calcd. for $C_{17}H_{16}O_2$ (252.3) C 80.93, H 6.39; Found C 80.49, H 6.00.

2-(1′-Hydroxy)ethylbenzofuran (1g)

To a stirred solution of 1.00 g (8.46 mmol) benzofuran in 5 mL THF under N_2 at 0 °C was added slowly 6.60 mL (8.60 mmol) of 1.30 M solution of *n*BuLi solution in hexane. After 2 h at 0 °C, 750 mg (19.6 mmol)

acetaldehyde was added and allowed to reach room temperature for 12 h. Then 1.61 g (11.4 mmol) MeI was added to the reaction mixture, which was stirred for another 24 h. The reaction mixture was poured into 50 mL water and extracted three times with 20 mL ether. After drying with $MgSO_4$ and evaporation of the solvent, the crude product was purified by column chromatography (silica gel, 1:2 ether/pentane) afforded 701 mg (52 %) **1g**, mp 36-37 °C. IR (CCl_4): $\tilde{\nu}$ = 3580 cm^{-1}, 2960, 2800, 1430, 1360, 1240, 1090, 900, 700.- ^1H NMR (200 MHz, $CDCl_3$): δ = 1.64 (d, *J* = 6.6 Hz, 3 H), 4. 92 - 5.05 (m, 1 H), 6.60 (s, 1 H), 7.28 - 7.51 (m, 4 H).- ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.3 (q), 64.1 (d), 101.7 (d), 111.1 (d), 121.0 (d), 122.7 (d), 124.1 (d), 128.0 (s), 154.7 (s), 160.1 (s).- Anal. calcd. for $C_{10}H_{10}O_2$ (162.2) C 74.05, H 6.21; Found C 74.28, H 6.09.

2,3-Dihydro-2,3-epoxy-3-methylbenzofuran (2a)

In a NMR tube, a solution of 12.0 mg (0.0910 mmol) 3-methylbenzofuran (**1a**) in 0.05 mL d_6-acetone was treated at -60 °C with 1.00 mL (1.00 mmol) d_6-dimethyldioxirane in d_6-acetone (0.01 *M*), dried over molecular sieves at -20 °C and cooled to -78 °C. ^1H NMR spectroscopy of the reaction mixture showed after 4 h at -55 °C 40 % conversion to epoxide **2a**. ^1H NMR (200 MHz, d_6-acetone, -55 °C): δ = 1.81 (s, 3 H), 6.23 (s, 1 H), 6.95 - 7.31 (m, 4 H).- ^{13}C NMR (50 MHz, d_6-acetone, -55 °C): δ = 12.9 (q), 63.7 (s), 88.7 (d), 111.8 (d), 121.7 (d), 124.5 (d), 129.1 (s), 130.2 (d), 160.7 (s).

2,3-Dihydro-2,3-epoxy-2-methyl-3-*tert*-butylbenzofuran (2c)

To a solution of 30.0 mg (0.160 mmol) benzofuran **1c** in 2 mL absolute CH_2Cl_2 at -20 °C were rapidly added while stirring under N_2 5.0 mL (0.270 mmol) of a solution of dimethyldioxirane in acetone (0.054 M). The stirring was continued for 3 h until complete consumption of the benzofuran **1a** (monitored by TLC), while the reaction temperature was allowed to rise to 20 °C. The solvent was evaporated (0 °C/0.01 Torr, 1-2 h) to yield epoxide **2c** quantitatively as a colorless solid. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.29 (s, 9 H), 2.06 (s, 3 H), 6.92 - 7.70 (m, 4 H).- ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.5 (q), 27.6 (q), 32.6 (s), 74.5 (s), 95.2 (s), 111.5 (d), 120.3 (d), 126.3 (d), 128.4 (s), 129.3 (d), 159.3 (s).

3-Hydroxymethyl-3-methyl-2-benzofuranone (4d)

To a stirred solution of 100 mg (0.620 mmol) of benzofuran **1d** in 2 ml dichloromethane were added 8 ml (0.800 mmol) of a solution of dimethyldioxirane in acetone (0.1 M) at 0 °C. Stirring was continued for 3 h at this temperature and the solvent removed by distillation on the rotary evaporator (ca. 20 °C/ 20 Torr). Chromatography (silica gel, 1:1 ether/pentane) of the crude product gave 98.0 mg (89 %) **4d** as a colorless oil. IR (CCl_4): $\tilde{\nu}$ = 3600 cm^{-1}, 3545, 2960, 2900, 2840, 1790, 1600, 1460, 1445, 1280, 1220, 1030, 870.- ^1H NMR (200 MHz, $CDCl_3$): δ = 1.40 (s, 3 H), 2.74 (br s, 1 H), 3.78 (AB, *J* = 10.8 Hz, 2 H), 7.06 - 7.34 (m, 4 H).- ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.3 (q), 49.7 (s), 67.5 (t), 110.6 (d), 123.2 (d), 124.3 (d), 128.9 (d), 129.8 (s), 153.1 (s), 179.4 (s).- Anal. calcd. for $C_{10}H_{10}O_3$ (178.2) C 67.41, H 5.66; Found C 67.16, H 5.81.

3-(Methoxyphenyl)methylene-3-methyl-2-benzofuranone (4e)

To a stirred solution of 20.0 mg (0.0800 mmol) of benzofuran **1e** in 2 mL dichloromethane were added 2 mL (0.200 mmol) of a solution of dimethyldioxirane in acetone (0.1 M) at 0 °C. Stirring was continued for 9 h at this temperature and the solvent removed by distillation (ca. 20 °C/ 20 Torr). Chromatography (silica gel, ether) of the crude product gave 17.0 mg (77 %) **4e** as a colorless oil. IR (CCl_4): $\tilde{\nu}$ = 3080 cm^{-1}, 3030,

2990, 2930, 2820, 1800, 1615, 1595, 1475, 1410, 1200, 1160, 1100, 1050.- ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.35 (s, 3 H), 1.71 (s, 3 H), 3.15 (s, 3 H), 3.26 (s, 3 H), 4.48 (s, 1 H), 4.58 (s, 1 H), 6.42 - 7.53 (m, 18 H).- ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.9 (q), 21.7 (q), 52.5 (s), 53.7 (s), 57.5 (q), 57.6 (q), 87.1 (d), 87.4 (d), 110.1 (d), 110.4 (d), 123.1 (d), 123.8 (d), 125.4 (d), 125.7 (d), 127.7 (d), 127.9 (d), 128.2 (d), 128.3 (d), 128.6 (d), 128.7 (d), 128.8 (d), 128.9 (d), 129.2 (s), 135.2 (d) 136.0 (s), 152.7 (s), 153.6 (s), 177.9 (s), 179.7 (s).- Anal. calcd. for $C_{17}H_{16}O_3$ (268.3) C 76.10, H 6.01; Found C 76.47, H 5.82.

3-Ethoxycarbonyl-3-methyl-3-benzofuranone (4f)

To a stirred solution of 100 mg (0.490 mmol) of benzofuran **1d** in 2 mL dichloromethane were added 12 mL (1.20 mmol) of a solution of dimethyldioxirane in acetone (0.1 M) at 0 °C. Stirring was continued for 3 h at this temperature and the solvent removed by distillation (ca. 20 °C/ 20 Torr). Chromatography (silica gel, ether) of the crude product gave 78.0 mg (72 %) **4d** as a colorless oil. IR (CCl_4): $\tilde{\nu}$ = 2960 cm^{-1}, 2900, 1800, 1735, 1600, 1580, 1460, 1445, 1225, 1100, 1025.- ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.1 Hz, 3 H), 1.76 (s, 3 H), 4.16 (ddq, *J* = 7.1 Hz, *J* = 3.4 Hz, *J* = 3.4 Hz, 2 H), 7.03 - 7.09, (m, 2 H), 7.12 - 7.21 (m, 2 H).- ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8 (q), 20.6 (q), 53.8 (s), 62.6 (t), 111.0 (d), 123.3 (d), 124.6 (d), 128.6 (s), 129.9 (d), 153.1 (s), 168.1 (s), 174.2 (s).- Anal. calcd. for $C_{12}H_{12}O_4$ (220.2) C 65.45, H 5.49; Found C 65.81, H 5.60.

2-Acetylbenzofuran (1h)

To a stirred solution of 100 mg (0.610 mmol) of benzofuran **1g** in 2 mL dichloromethane were added 15 mL (1.50 mmol) of a solution of dimethyldioxirane in acetone (0.1 M) at 0 °C. Stirring was continued for 12 h at this temperature and the solvent removed by distillation (ca. 20 °C/ 20 Torr). Chromatography (silica gel, 1:1 ether/pentane) of the crude product gave 38.0 mg (39 %) **1h** whose spectral data match those reported.[9]

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