Direct Epoxidation of (*E*)-2'-Hydroxychalcones by Dimethyldioxirane

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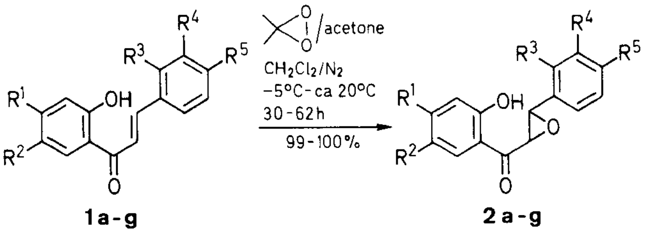
The synthesis of α,β-epoxy-2'-hydroxychalcones (3-aryl-2,3-epoxy-1-(2-hydroxyaryl)propanones) **2** by direct epoxidation of (*E*)-2'-hydroxychalcones [(*E*)-3-aryl-1-(2-hydroxyaryl)propenone] **1** with dimethyldioxirane at subambient temperatures is reported. These acid- and base-sensitive epoxides, which have been hitherto difficult to prepare, were isolated in excellent yields and were completely characterized by spectral and microanalytical data. The now readily available 2'-hydroxy substituted chalcone oxides may serve as convenient precursors to flavonoid-type natural products.

2-Hydroxychalcones constitute a class of naturally occurring substances of great biological interest. They are regarded[2] as precursors in the biosynthesis of all flavonoid-type natural products. Some derivatives have been used in clinical applications[3] for the treatment of ulcers and inflammations, and others have been employed as intermediates in the production of neumatic liquid crystals[4] (telecommunication technology and integrated optics) or photosensitive polymers.[5]

Chalcone oxides are commonly synthesized in plants[6] and are biologically important compounds since they are presumed to act as potent selective inhibitors of the cytosolic epoxide hydrolase; however, little is known about the related 2'-hydroxychalcone oxides, because due to their labile nature towards acids and bases, they have been difficult to prepare. It has been reported[7] that a 2'-hydroxychalone epoxide could be obtained in only 20% yield by peracid epoxidation of the corresponding 2'-hydroxychalcone in boiling chloroform, but its persistence even in neutral aqueous media (pH ca 7) was only a few seconds.[8] On the other hand, the well-known alkaline hydrogen peroxide method, Weitz–Scheffer reaction or its modified form,[9] yielded the corresponding flavonols as a result of base-catalyzed opening of the epoxide ring. A more cumbersome and elaborate approach[10] involved the protection of the 2'-hydroxy functionality by the acid-labile methoxymethyl group, epoxidation with alkaline hydrogen peroxide, and deprotection by acid hydrolysis, but the epoxy ring suffered hydrolysis under these conditions. Furthermore, oxidative cyclization of 2'-hydroxychalcones with the usual oxidants such as SeO_2[11], $Tl(NO_3)_2$[12], $Pb(OAc)_4$[13], $Hg(OAc)_2$[14] afforded complex product mixtures and proved of little synthetic utility.

Dimethyldioxirane, an efficient oxygen-transfer agent, which operates under mild and strictly neutral conditions, was shown[15] to epoxidize electron-poor alkenes such as α,β-unsaturated acids, esters and ketones,[16] β-oxo enol ethers,[17] and flavones.[18] Presently, we describe our results on the epoxidation of various 2'-hydroxychalcones by means of isolated dimethyldioxirane (as acetone solution), which underscores once again the advantages of this novel oxidant for the preparation of labile epoxides.[15]



1,2	R^1	R^2	R^3	R^4	R^5	1,2	R^1	R^2	R^3	R^4	R^5
a	H	Cl	H	H	H	**e**	Me	H	H	H	H
b	H	H	H	H	Cl	**f**	H	Cl	H	H	MeO
c	H	H	MeO	H	H	**g**	H	Me	H	H	MeO
d	H	H	H	MeO	H						

Scheme

The 2'-hydroxychalcones **1a–g** were transformed by dimethyldioxirane into the corresponding epoxides **2a–g** (Scheme) in excellent yields. The results are given in Table 1. The long reaction times (30–62 hours), the subambient temperatures (−5°C to ca. 20°C), the large excess of dimethyldioxirane (up to tenfold), and its addition in portions (12 h intervals) are necessary for achieving the conversion of the 2'-hydroxychalcones **1** into their epoxides **2** in optimal yields. It is important to note that when the epoxidation of **1f** was carried out at ca. 20°C, the epoxide **2f** was contaminated with the corresponding flavonol (*E*/*Z* ratio ca. 2:1). The same mixture of diastereomeric flavonols was also obtained when a chloroform-*d* solution of **2f** was left to stand at room temperature for 24 hours.

The structure assignment of the epoxides **2a–g** rests on the carbonyl band at $\nu = 1640-1685\,cm^{-1}$ in the IR spectra. The epoxide proton signals occur at $\delta = 4.1-4.4$ in the ^1H NMR spectra and the ^{13}C NMR resonances of the C-α and C-β epoxide atoms at $\delta = 56-60$.

In summary, we have described a much superior epoxidation procedure of 2'-hydroxychalcones by using isolated dimethyldioxirane (as acetone solution). Epoxides **2** are now available in excellent yields, and their propensity as useful building blocks for the synthesis of flavonoid-type natural products can now be explored.

All reagents were of commercial quality. Potassium monoperoxosulfate, the triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, was received as a generous gift from Degussa AG (Hanau, Germany) or Peroxid-Chemie GmbH (Munich, Germany). The solvents were purified by following standard literature methods; acetone and H_2O used in the preparation of dimethyldioxirane were doubly distilled over EDTA. Analytical TLC plates were purchased from Macherey-Nagel. Melting points were taken on a Reichert Thermovar hot-stage apparatus. Microanalyses were performed on a Carlo Erba 1106 CHN Analyser. Mass spectra were run on a Varian 8200 Finnigan MAT spectrometer with EI ionization. IR

Table 1. Dimethyldioxirane (DMD) Epoxidation of (*E*)-2′-Hydroxychalcones **1**

Product	Reaction Conditions			Yield (%)[b]	mp (°C) (solvent)	Molecular Formula[c]	IR (CCl_4) ν (cm^{-1})	MS (70 eV) *m/z* (%)
	Time (h)[a]	Temp. (°C)	Ratio **1**/DMD					
2a	59	~20	1 : 6	100	111–113 (CCl_4/PE[d])	$C_{15}H_{11}ClO_3$ (274.7)	1650, 1550, 1505, 1310, 1285, 1210, 1165, 1140, 1060	274 (M^+, 179), 245 (31), 181 (22), 155 (86), 121 (33), 119 (100), 117 (97), 105 (33), 91 (44), 77 (39)
2b	57	~20	1 : 5	100	118–120 ($CHCl_3$/PE[d])	$C_{15}H_{11}ClO_3$ (274.7)	1675, 1605, 1520, 1510, 1310, 1265, 1230, 1175, 1110, 1030	
2c	62	0	1 : 8	100	112–114 (CCl_4/PE[d])	$C_{16}H_{14}O_4$ (270.3)	2950, 1640, 1605, 1480, 1280, 1200, 1150, 1045, 690	
2d	56	0	1 : 7	100	93–94 (CCl_4/PE[d])	$C_{16}H_{14}O_4$ (270.3)	1680, 1610, 1525, 1510, 1460, 1305, 1270, 1225, 1175, 1040	270 (M^+, 13), 241 (35), 213 (9), 150 (15), 121 (100), 107 (38), 105 (8), 93 (13), 91 (20), 77 (16)
2e	30	~20	1 : 3	100	58–60 (CCl_4/PE[d])	$C_{16}H_{14}O_3$ (254.3)	1665, 1600, 1510, 1460, 1305, 1260, 1220, 1170, 1040, 910	254 (M^+, 21), 225 (40), 134 (32), 133 (62), 121 (100), 119 (13), 105 (36), 91 (18), 77 (17)
2f	50	−5	1 : 7	100	97–98 (CCl_4/PE[d])	$C_{16}H_{13}ClO_4$ (304.7)	1685, 1650, 1550, 1500, 1305, 1275, 1210, 1200, 1190, 1055	304 (M^+, 7), 275 (2), 167 (3), 155 (14), 150 (47), 122 (11), 121 (100), 108 (9), 91 (6), 77 (15)
2g	37	0	1 : 5	99	107–108 (CCl_4/PE[d])	$C_{17}H_{16}O_4$ (284.3)	1660, 1630, 1535, 1500, 1420, 1300, 1275, 1265, 1190, 1050	284 (M^+, 11), 255 (4), 150 (21), 136 (14), 135 (100), 121 (72), 119 (6), 107 (11), 91 (10), 77 (20)

[a] Total reaction time of the several batches.
[b] Yield of isolated product **2**.
[c] Satisfactory microanalyses were obtained (C ±0.34, H ±0.13) except **2b** (C +0.58, H +0.10).
[d] PE = petroleum ether (bp 50°–70°C).

Table 2. NMR Data of Epoxides **2**

Product	^{1}H NMR ($CDCl_3$/TMS)[a] δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS)[a] δ
2a	4.14 (d, 1H, J = 1.7), 4.26 (d, 1H, J = 1.7), 7.01 (d, 1H, J = 9.0), 7.36–7.50 (m, 6H), 7.80 (d, 1H, J = 2.5), 11.84 (s, 1H)	59.8 (d), 60.1 (d), 119.3 (s), 120.4 (d), 124.2 (s), 125.8 (d), 128.5 (d), 128.9 (d), 129.4 (d), 134.8 (s), 137.3 (d), 161.2 (s), 196.8 (s)
2b	4.11 (d, 1H, J = 1.8), 4.29 (d, 1H, J = 1.8), 6.89–6.95 (m, 1H), 7.05 (dd, 1H, J_1 = 8.5, J_2 = 0.9), 7.31, 7.39 (AA′BB′, 4H), 7.51–7.58 (m, 1H), 7.80 (dd, 1H, J_1 = 8.1, J_2 = 1.6), 11.85 (s, 1H)	59.1 (d), 59.9 (d), 118.8 (d), 119.5 (d), 127.1 (d), 129.1 (d), 129.3 (d), 133.7 (s), 135.2 (s), 137.5 (d), 162.7 (s), 196.9 (s)
2c	3.82 (s, 3H), 4.09 (d, 1H, J = 1.7), 4.34 (d, 1H, J = 1.7), 6.87–7.04 (m, 5H), 7.29–7.35 (m, 1H), 7.49–7.56 (m, 1H), 7.81 (dd, 1H, J_1 = 8.1, J_2 = 1.5), 11.85 (s, 1H)	55.1 (q), 59.5 (d), 59.6 (d), 110.8 (d), 114.6, 118.0 (d), 118.4 (d), 118.6 (s), 119.3 (d), 129.3 (d), 129.7 (d), 136.5 (s), 137.2 (d), 159.8 (s), 162.3 (s), 197.2 (s)
2d	3.81 (s, 3H), 4.23 (d, 1H, J = 1.9), 4.41 (d, 1H, J = 1.9), 6.88–7.03 (m, 4H), 7.27–7.37 (m, 2H), 7.48–7.55 (m, 1H), 7.88 (dd, 1H, J_1 = 8.1, J_2 = 1.6), 11.92 (s, 1H)	55.3 (q), 56.2 (d), 59.3 (d), 110.3 (d), 118.5 (d), 118.8 (s), 119.3 (d), 120.8 (d), 123.8 (s), 125.5 (d), 129.7 (d), 129.9 (d), 137.2 (d), 158.1 (s), 162.5 (s), 197.9 (s)
2e	2.37 (s, 3H), 4.07 (d, 1H, J = 1.8), 4.32 (d, 1H, J = 1.8), 6.85–6.92 (m, 1H), 7.02 (dd, 1H, J_1 = 8.5, J_2 = 0.9), 7.23 (d, 2H, J = 8.3), 7.26 (d, 2H, J = 8.3), 7.47–7.54 (m, 1H), 7.80 (dd, 1H, J_1 = 8.1, J_2 = 1.6), 11.90 (s, 1H)	21.3 (q), 59.8 (d), 59.9 (d), 118.7 (d), 118.8 (s), 119.4 (d), 125.8 (d), 129.4 (d), 129.5 (d), 132.1 (s), 137.3 (d), 139.2 (s), 162.6 (s), 197.5 (s)
2f	3.82 (s, 3H), 4.07 (d, 1H, J = 1.7), 4.26 (d, 1H, J = 1.7), 6.93, 7.28 (AA′BB′, 4H), 6.97 (d, 1H, J = 9.0), 7.45 (dd, 1H, J_1 = 9.0, J_2 = 2.5), 7.80 (d, 1H, J = 2.5), 11.82 (s, 1H)	55.2 (q), 59.7 (d), 60.0 (d), 114.2 (d), 119.2 (s), 120.2 (d), 124.0 (s), 126.5 (s), 127.1 (d), 128.4 (d), 137.0 (d), 160.4 (s), 161.0 (s), 196.9 (s)
2g	2.25 (s, 3H), 3.80 (s, 3H), 4.05 (d, 1H, J = 1.8), 4.33 (d, 1H, J = 1.8), 6.89–6.95 (m, 3H), 7.27–7.34 (m, 3H), 7.58 (d, 1H, J = 1.3), 11.77 (s, 1H)	20.4 (q), 55.3 (q), 59.7 (d), 59.8 (d), 114.2 (d), 118.4 (d), 118.5 (d), 127.1 (s), 127.2 (d), 128.6 (s), 129.0 (d), 138.4 (d), 160.4 (s), 160.5 (s), 197.4 (s)

[a] Obtained on a Bruker AC 250 (250 MHz) spectrometer, except **2g** which was run on a Bruker AC 200 (200 MHz).

spectra were measured on a Perkin-Elmer 1420 spectrometer. ^{1}H- and ^{13}C NMR spectra were acquired on a Bruker AC 200 (200 MHz) or AC 250 (250 MHz) spectrometer. (*E*)-2′-Hydroxychalcones **1a–g** were prepared[19] in moderate yields from the NaOH-catalyzed condensation of the appropriate benzaldehydes and substituted 2-hydroxyacetophenones in EtOH by following literature procedures. Dimethyldioxirane (as acetone solution) was isolated as described[16b] and the peroxide content was determined by oxidation of methyl phenyl sulfide to its sulfoxide; the latter was quanitated by ^{1}H NMR.

Epoxidation of (*E*)-2'-Hydroxychalcones 1a–g by Dimethyldioxirane; General Procedure:

The required amount of the dimethyldioxirane solution in acetone (0.057–0.107 M), which was stored over molecular sieves (4 Å) at $-20\,^{\circ}C$, was added rapidly under a N_2 atmosphere to a cooled (cf. Table 1 for specific conditions), stirred solution of the appropriate (*E*)-2'-hydroxychalcone **1** (0.66–1.00 mmol) in absolute CH_2Cl_2 (5 mL). The stirring was continued for 12 h and a new quantity of the dimethyldioxirane solution (0.057–0.107 M) was rapidly added. Every 12 h fresh batches of dimethyldioxirane solution were added until complete consumption of the (*E*)-2'-hydroxychalcone **1** (monitored by TLC), the solvent removed at reduced pressure (0° to ca 20°C at 15 Torr) and the pure epoxides **2a–g** were isolated in excellent yields. The final purification of the epoxide was accomplished by recrystallization from the appropriate solvent. The experimental details are given in Table 1 and the NMR spectroscopic data in Table 2.

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(2) Hepworth, J. D. In Katritzky and Rees *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon Press: Oxford, 1984; Vol. 3, p 874.

(3) Vanstone, A. E.; Maile, G. K., German Patent (DOS) 2810253; *Chem. Abstr.* **1979**, *90*, 22628.

(4) Hanemann, K.; Schubert, H.; Demus, D. French Patent 2133788; *Chem. Abstr.* **1973**, *78*, 159226.

(5) Kato, M.; Hasegawa, M.; Ichijo, T. US Patent 3873500; *Chem. Abstr.* **1975**, *83*, 29065.

(6) Wong, E. In *Chemistry and Biochemistry of Plant Pigments;* Goodwin, T. W., Ed.; Academic Press: New York, 1976; p 464–526.

(7) Ramakrishnan, V. T.; Kagan, J. *J. Org. Chem.* **1970**, *35*, 2898.

(8) Main, L.; Old, K. B. *Tetrahedron Lett.* **1977**, 2809.

(9) Donnelly, J. A.; Farrell, D. F. *J. Org. Chem.* **1990**, *55*, 1757.
Arringa-Giner, F. J.; Iunuma, M.; Tanaka, T.; Mizuno, M.; Scheele, C.; Wollenweber, E. *Z. Naturforsch.* **1987**, *42c*, 1063.
Takahashi, H.; Kubota, Y.; Fank, L.; Onda, M. *Heterocycles* **1986**, *24*, 1099.
Saxena, S.; Makrand, J. K.; Grover, S. K. *Synthesis* **1985**, 110.

(10) Augustiyn, J. A. N.; Bezuidenhoudt, B. C. B.; Ferreira, D. *Tetrahedron* **1990**, *46*, 2651.
Takahashi, H.; Kubota, Y.; Miyazaki, H.; Onda, M. *Chem. Pharm. Bull.* **1984**, *32*, 4852.

(11) Srivastava, S. D.; Srivastava, S. K. *Indian J. Chem.* **1987**, *26B*, 57.

(12) Bezuidenhoudt, B. C. B.; Brandt, E. V.; Feweiva, D. *J. Chem. Soc., Perkin Trans 1* **1987**, 1081.

(13) Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 1456.
Kurosawa, K.; Higuchi, J. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1132.

(14) Sekizaki, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1407.

(15) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205.
Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187.
Curci, R. In *Advances in Oxygenated Processes*; Baumstark, A. L., (Ed.); JAI Press: Greenwich, 1990; Vol. 2, p 1.
Murray, R. W. In *Molecular Structure and Energetics. Unconventional Chemical Bonding*; Liebman, J. F., Greenberg, I., Eds.; VCH Publishers: New York, 1988; Vol. 6, p 311.
Adam, W.; Curci, R.; Hadjiarapoglou, L.; Mello, R. In *Organic Peroxides*; Ando, W., Ed.; John Wiley Interscience, in press.

(16) Adam, W.; Hadjiarapoglou, L.; Nestler, B. *Tetrahedron Lett.* **1989**, *30*, 331.
Adam, W.; Hadjiarapoglou, L.; Smerz, A. *Chem. Ber.* **1991**, *124*, 227.
Amstrong, A.; Ley, S. V. *Synlett* **1990**, 323.

(17) Adam, W.; Hadjiarapoglou, L. *Chem. Ber.* **1990**, *123*, 2077.

(18) Adam, W.; Golsch, D.; Hadjiarapoglou, L.; Patonay, T. *Tetrahedron Lett.* **1991**, *32*, *1041*.
Adam, W.; Golsch, D.; Hadjiarapoglou, L.; Patonay, T. *J. Org. Chem.*, submitted.

(19) Smith, M. A.; Neumann, R. N.; Webb, R. A. *J. Heterocycl. Chem.* **1968**, *5*, 425.