Chemo- and Diastereoselectivity in the Dimethyldioxirane Oxidation of 2,3-Dihydro-4*H*-1-benzothiopyran-4-ones and 4*H*-1-Benzothiopyran-4-ones. Unusual Reactivity of 4*H*-1-Benzothiopyran-4-one 1-Oxides[1]

Tamás Patonay,*[,†] Waldemar Adam,[‡] Albert Lévai,[†] Péter Kövér,[†] Márta Németh,[†] Eva-Maria Peters,[§] and Karl Peters[§]

Department of Organic Chemistry, Faculty of Science, University of Debrecen, H-4010 Debrecen, Hungary, Institute of Organic Chemistry, University of Würzburg, Am Hubland, D-97074 Würzburg, Germany, and Max-Planck-Institut für Festkörperforschung, D-70569 Stuttgart, Germany

tpatonay@tigris.klte.hu

Received October 11, 2000

The oxidation of the 1-thiochromanones **1**−**3** by dimethyldioxirane (DMD) produced the corresponding sulfoxides **4**−**6** or sulfones **7**−**9**; their relative amounts depended on the amount of oxidant used. A low diastereoselectivity was observed in the sulfoxidation of the 2-substituted 1-thiochromanones **2** and **3**, due to the small steric differentiation during the DMD attack. An unusual reactivity pattern was found in the DMD oxidation of the 1-thiochromones **10**−**12**, in that the sulfoxides **13**−**15** were more reactive toward the electrophilic oxidizing agent than the corresponding sulfides. The observed anomaly may be explained in terms of transannular stabilization of the transition structure (TS) for the sulfone formation, promoted through favorable conformational effects in the sulfoxide. Higher sulfoxide/sulfone ratios were found in solvents of greater hydrogen bond donor capacity, which is in accordance with the postulated stabilizing effect.

Introduction

2,3-Dihydro-4*H*-1-benzothiopyran-4-ones and their 2-phenyl derivatives (widely cited by the semitrivial names 1-thiochroman-4-ones and 1-thioflavanones), as well as 4*H*-1-benzothiopyran-4-ones and their 2-phenyl derivatives (1-thiochromones and 1-thioflavones) are the thio analogues of the naturally occurring chromonoid and flavonoid compounds.[2] Some of these substances, particularly their sulfones, have been shown to display antibacterial,[3] fungicidal,[4] antitumor,[3b,5] HIV-inhibitor,[5d] human-cytomegalovirus (HCMV)-protease-inhibitor,[6] serotonin-3-receptor-antagonic,[7] antiallergic,[8] diuretic and antihypertensive,[9] immunosupressive,[10] and weak CNS[11] activities. Despite their interesting pharmacological properties, relatively little has been published on the oxidation chemistry of thiochromonoids and thioflavonoids.

To fill this gap, and in view of our interest in dioxirane chemistry, especially the reactivity of dimethyldioxirane (DMD) toward oxygen-, sulfur-, or nitrogen-containing heterocycles,[12,13] we have examined the dioxirane oxidation of thiochromanone- and thiochromone-type substrates and herein we report our results of this study. As before, we have focused on the chemoselectivity (heteroatom versus double bond and sulfur versus sulfoxide oxidation) and the diastereoselectivity of the oxygen transfer.

* To whom correspondence should be addressed.
† University of Debrecen. Fax: +36 52 453 836. E-mail: tpatonay@tigris.klte.hu.
‡ University of Würzburg. Fax: +49 931 888 4756. E-mail: adam@chemie.uni-wuerzburg.de.
§ Max-Planck-Institut für Festkörperforschung.

Dedicated to Prof. György Bazsa on the occasion of his 60th birthday.

(1) This work has been presented at the 17th International Conference on Heterocyclic Chemistry, Aug 10−15, 1997, Bozeman, MT (OP-V-15).

(2) For reviews, see: (a) Tarbell, D. S. Thiochromans and Related Compounds. In *Heterocyclic Compounds, Vol. 2*; Elderfield, R. C., Ed.; Wiley: New York, 1951; p 533. (b) Schneller, S. W. Thiochromanones and Related Compounds. In *Advances in Heterocyclic Chemistry, Vol. 18*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1975; p 59. (c) Bálint, J.; Bognár, R.; Rákosi, M. Chemistry of Sulfur Containing Flavonoids. In *Studies in Organic Chemistry, 19 (Organic Sulfur Chemistry)*; Bernardi, F., Csizmadia, I. G., Mangini, A., Eds.; Elsevier: Amsterdam, 1985; p 660. (d) Klimenko, S. K.; Kharchenko, V. G.; Stolbova, T. V. *Khim. Get. Soedin.* **1978**, 3.

(3) (a) Nakazumi, H.; Ueyama, T.; Kitao, T. *J. Heterocycl. Chem.* **1984**, *21*, 193. (b) Nakazumi, H.; Ueyama, T.; Kitao, T. *J. Heterocycl. Chem.* **1985**, *22*, 1593.

(4) (a) Nishio, M.; Ito, S. Japanese Patent 72 11.075 1972; *Chem. Abstr.* **1972**, *77*, 34344v. (b) New Japan Pharmaceutical Co. Japanese Patent 60 23.379 1985, *Chem. Abstr.* **1985**, *103*, 6226v. (c) New Japan Pharmaceutical Co. Japanese Patent 60 01.127 1985, *Chem. Abstr.* **1985**, *102*, 191171p.

(5) (a) Holshouser, M. K.; Loeffler, L. J.; Hall, I. H. *J. Med. Chem.* **1981**, *24*, 853. (b) Holshouser, M. K.; Loeffler, L. J. *J. Pharm. Sci.* **1982**, *71*, 715. (c) Holshouser, M. K.; Loeffler, L. J.; Hall, I. H. *J. Pharm. Sci.* **1982**, *71*, 857. (d) Wang, H.-K.; Bastow, K. F.; Cosentino, L. M.; Lee, K.-H. *J. Med. Chem.* **1996**, *39*, 1975.

(6) Dhanak, D.; Keenan, R. M.; Burton, G.; Kaura, A.; Darcy, M. G.; Shah, D. H.; Ridgers, L. H.; Breen, A.; Lavery, P.; Tew, D. G.; West, A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3677.

(7) Sano, T.; Saijo, K.; Yokomori, S.; Nakashima, Y.; Hatayama, K. PCT Int. Appl. 92 00.294, 1992; *Chem. Abstr.* **1992**, *116*, 174149j.

(8) Ilvespaa, A.; Haas, G. Eur. Patent Appl. 159.964 1985; *Chem. Abstr.* **1986**, *104*, 207160p.

(9) Bouchara, E. French Patent 2.354.096 1978; *Chem. Abstr.* **1978**, *89*, 163409s.

(10) (a) Lombardino, J. G.; Otterness, I. G.; Muren, J. F. US Patent 4.268.516 1981,*Chem. Abstr.* **1981**, *95*, 62201m. (b) Lombardino, J. G.; Otterness, I. G. *J. Med. Chem.* **1981**, *24*, 830.

(11) Eiden, F.; Felbermeier, G.; Buchborn, H. *Arch. Pharm. (Weinheim)* **1983**, *316*, 921.

(12) For reviews, see: (a) Lévai, A.; Adam, W.; Halász, J.; Nemes, Cs.; Patonay, T.; Tóth, G. *Khim. Get. Soedin.* **1995**, 1345. (b) Patonay, T.; Lévai, A.; Adam, W.; Halász, J.; Nemes, Cs.; Patonay, T.; Tóth, G. Oxidations of Benzopyrans, Benzofurans and Related Compounds: One Step Ahead. In *Flavonoids and Bioflavonoids 1995 Proceedings*; Antus, S., Gábor, M., Vetschera, K., Eds.; Akadémiai Kiadó: Budapest, 1996; p 167.

10.1021/jo001469f CCC: $20.00
Published on Web 03/06/2001

Scheme 1

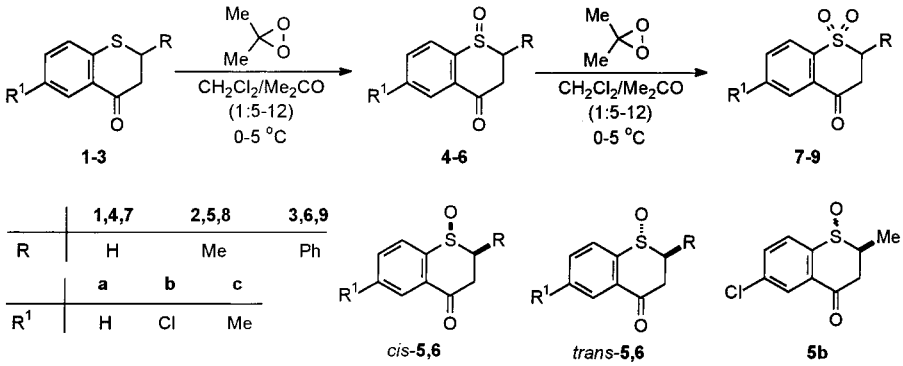


Table 1. Isolated Products in the DMD Oxidation[a] of Thiochromanones 1−3 and Thiochromones 10−12

				sulfoxide		sulfone	
entry	substrate	DMD (equiv)	convn[b] (%)	product	yield[c] (%)	product	yield[c] (%)
1	**1a**	1.42	86	**4a**	93	**7a**	4.8
2	**1a**	3.25	100	**4a**	0	**7a**	96
3	**2a**	2.01	91	**5a**	81	**8a**	14
4	**2a**	3.00	100	**5a**	0	**8a**	85
5	**2b**	2.25	98	**5b**	86	**8b**	1.3
6	**2b**	3.17	100	**5b**	0	**8b**	86
7	**2c**	1.80	100	**5c**	88	**8b**	8.9
8	**2c**	3.50	100	**5c**	0	**8b**	84
9	**3a**	2.12	100	**6a**	77	**9a**	16
10	**3a**	4.10	100	**6a**	0	**9a**	92
11	**10a**	1.20	33	**13a**	11[d]	**16a**	61
12	**10a**	5.28	100	**13a**	0	**16a**	88
13	**10e**	1.20	34	**13a**	32	**16a**	59
14	**10e**	5.00	100	**13a**	0	**16a**	84
15	**11a**	1.20	51	**14a**	10	**17a**	37
16	**11a**	3.50	100	**14a**	0	**17a**	93
17	**12a**	1.20	36	**15a**	28	**17a**	67
18	**12a**	4.70	100	**15a**	0	**17a**	88
19	**12b**	4.47	100	**15b**	0	**17b**	86
20	**12c**	4.56	100	**15c**	0	**17c**	87
21	**12d**	4.56	100	**15d**	0	**17d**	82

[a] For conditions see the Experimental Section. [b] Calculated on the basis of the recovered starting material. [c] Yields refer to isolated products, the values normalized to 100% conversion. [d] Decomposition during column chromatography.

Results and Discussion

First, we studied the oxidation of 1-thiochroman-4-one (**1a**), 2-methyl-6-R[1]-1-thiochroman-4-ones (**2a**−**c**), and 1-thioflavanone (**3a**) with various amounts of DMD. The treatment with an excess (2.5−4.1 equiv) of DMD at subambient temperature afforded the corresponding sulfones **7a**, **8a**−**c**, and **9a** in excellent yields (84−96%), cf. Scheme 1 and Table 1.

The main advantage of our protocol is the mild conditions; the typical procedure[14−16] developed previously to synthesize 1-thiochroman-4-one 1,1-dioxides utilizes hot H_2O_2 in acetic acid (in situ formation of peracid) as oxidant. Other oxidants such as monoperoxyphthalic acid (3−4 equiv),[15] sodium perborate,[17] and cold $KMnO_4$ in mixtures of acetic acid and water[18] have been employed, limited to only one example.

Table 2. Product Data and Diastereomeric Ratios[a] in the DMD Oxidation[b] of Thiochromanones 1−3 and Thiochromones 10−12

entry	substrate	DMD (equiv)	convn (%)	sulfoxide[c] (%)	dr[d]	sulfone[c] (%)
1	**1a**	1.42	86	97		3
2	**2a**	2.01	94	88	59:41	12
3	**2b**	2.25	96	98	60:40	2
4	**2c**	1.80	100	93	61:39	7
5	**3a**	2.12	100	61	70:30	39
6	**10a**	1.20	31	24		76
7	**10e**	1.20	30	40		60
8	**11a**	1.20	41	32[e]		68[e]
9	**12a**	1.20	32	28		72
10	**12d**	1.20	20	15		85

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture after removal of the solvents, error ≤5% of the stated values; mass balances >90%. [b] For conditions see the Experimental Section. [c] Values normalized to 100% conversion. [d] Diastereomeric (cis/trans) ratio of sulfoxides **5**,**6**. [e] Mass balance 83%.

Treatment of the thiochromanones **1a**, **2a**−**c**, and **3a** with a smaller excess (1.4−2.1 equiv) of DMD afforded the corresponding sulfoxides **4a**, **5a**−**c**, and **6a** in good yields (77−93%), although some of the sulfones **7a**, **8a**−**c**, and **9a** were also formed even at incomplete (80−90%) conversion. However, the sulfoxide/sulfone ratio, measured by ^{1}H NMR spectroscopy, was usually higher than 8−10, which indicates a high chemoselectivity for the attack of DMD on the sulfur atom of the sulfide functionality (Table 2).

A similar chemoselectivity has been observed in the DMD oxidation of 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones.[13h] Earlier oxidations of the parent 1-thiochroman-4-one (**1a**) and its 2- or 3-methyl-substituted derivatives to their sulfoxides have been performed by using ice-cold H_2O_2/acetic acid,[14,19] sodium periodate,[20] or *m*-CPBA,[21] whereas the enantioselective sulfoxidation of the thio-

(13) Other papers published since the reviews cited in ref 12: (a) Adam, W.; Halász, J.; Jámbor, Zs.; Lévai, A.; Nemes, Cs.; Patonay, T.; Tóth, G. *J. Chem. Soc., Perkin Trans. 1.* **1996**, 395. (b) Adam, W.; Halász, J.; Jámbor, Zs.; Lévai, A.; Nemes, Cs.; Patonay, T.; Tóth, G. *Monatsh. Chem.* **1996**, *127*, 683. (c) Patonay, T.; Lévai, A.; Nemes, Cs.; Tímár, T.; Tóth, G.; Adam, W. *J. Org. Chem.* **1996**, *61*, 5375. (d) Adam, W.; Jekõ, J.; Lévai, A.; Majer, Zs.; Nemes, Cs.; Patonay, T.; Párkányi, L.; Sebõk, P. *Tetrahedron: Asymmetry* **1996**, *7*, 2437. (e) Adam, W.; Lévai, A.; Mérour, J.-Y.; Nemes, Cs.; Patonay, T. *Synthesis*, **1997**, 268. (f) Adam, W.; Fell, R. T.; Lévai, A.; Patonay, T.; Peters, K.; Simon, A.; Tóth, G. *Tetrahedron: Asymmetry* **1998**, *9*, 1121. (g) Lévai, A.; Adam, W.; Fell. R. T.; Gessner, R.; Patonay, T.; Simon, A.; Tóth, G. *Tetrahedron* **1998**, *54*, 13105. (h) Patonay, T.; Adam, W.; Jekõ, J.; Kövér, K. E.; Lévai, A.; Németh, M.; Peters, K. *Heterocycles* **1999**, *51*, 85.

(14) Arndt, F.; Flemming, W.; Scholz, E.; Löwensohn, V.; Källner, G.; Eistert, B. *Ber. Dtsch. Chem. Ges.* **1925**, *58*, 1612.

(15) Bognár, R.; Bálint, J.; Rákosi, M. *Liebigs. Ann. Chem.* **1977**, 1529.

(16) Still, I. W. J.; Thomas, M. T. *J. Org. Chem.* **1968**, *33*, 2730.

(17) McKillop, A.; Kemp, D. *Tetrahedron* **1989**, *45*, 3299.

(18) Somogyi, L. *Liebigs Ann. Chem.* **1994**, 959.

(19) (a) Harrison, A. G.; Thomas, M. T.; Still, I. W. J. *Org. Mass Spectrom.* **1970**, *3*, 899. (b) Still, I. W. J.; Thomas, M. T.; Clish, A. M. *Can. J. Chem.* **1975**, *53*, 276. (c) Still, W. J.; Arora, P. C.; Chauhan, M. S.; Kwan, M.-H.; Thomas, M. T. *Can. J. Chem.* **1976**, *54*, 455.

(20) Allenmark, S. G.; Andersson, M. A. *Tetrahedron: Asymmetry* **1996**, *7*, 1089.

chromanone **1a** was accomplished by H_2O_2 in the presence of chloroperoxidase (CPO)[20] or iodosylbenzene and chiral, nonracemic porphyrin catalyst.[22] Very recently two mild and efficient procedures have been published for the oxidation of sulfides including 1-thiochromanone (**1a**) to their sulfoxides, one of them utilizes H_2O_2 in the presence of titanium derivatives supported on silica,[23] whereas ceric ammonium nitrate (CAN) and hydrated silica gel were used in the other case.[24]

1-Thioflavanone 1-oxide (**6a**) was obtained by treatment with ice-cold H_2O_2/acetic acid,[14,25] sodium periodate,[18,25] chloramine-T,[25] or monoperoxyphthalic acid (1 equiv),[15] but in these sulfoxidations also some sulfones were obtained as byproducts. In view of the simple procedure, the high efficiency, and good selectivity, DMD seems to be the oxidant of choice to prepare 1-thiochroman-4-one 1-oxides.

A point of interest was the diastereoselectivity in the sulfoxidation of 2-substituted 1-thiochroman-4-ones **2a**−**c** and **3a** by DMD. Although some sporadic mention has been made on the formation of diastereomers in the literature,[19c,25−27] neither their separation nor the determination of the relative configuration has been carried out. We succeeded in separating the mixtures of the cis and trans diastereomers of **2a** and **2b** by column chromatography, which allowed the unequivocal assignment of the NMR signals to the each diastereomer. Although the ^{1}H NMR[28] and ^{13}C NMR spectra showed characteristic shifts for each diastereomer, the NMR data alone were insufficient to establish the relative configuration unambiguously, since the preferred conformations of the diastereomers are unknown. For this purpose, PM3 calculations[29] were conducted on the diastereomeric sulfoxides, which revealed a conformation with pseudoequatorial methyl groups for both isomers, the sulfoxide oxygen atom is pseudoaxial in the cis[30] and pseudoequatorial in the trans[30] diastereomer.

Definitive configurational assignment was provided by X-ray analysis of the two isomers of **5b**.[31] Thus, the more polar major diastereomer is the cis sulfoxide (*cis*-**5b**), while the less polar minor one is the trans sulfoxide (*trans*-**5b**). On the basis of the relative configurations of the *cis*,*trans*-**5b**, all the remaining diastereomers[32] were assigned with the help of the NMR data. The observed differences in the ^{1}H NMR spectra arise from anisotropy effects of the sulfoxide functionality. Thus, a marked downfield shift (0.67−0.8 ppm) is observed for the 3-H_{ax} ("syn-axial effect")[33] and a smaller upfield shift (0.09−0.24 ppm) for the 2-H and 3-H_{eq} hydrogen atoms of *cis*-**5a**−**c** and *cis*-**6a,** while a small downfield shift (0.09−0.24 ppm) of the 3-H_{eq} and 2-methyl and a small upfield shift (0.08−0.19 ppm) is found for the 2-H hydrogen atoms of *trans*-**5a**−**c** and *trans*-**5a**. On the basis of these NMR data, we may conclude that the sulfoxides **5** and **6** have similar conformations both in solution and in crystal phases. Also, the calculated $\Delta\delta = \delta_{trans} - \delta_{cis}$ values for the 2-methyl, C-2, C-3 and C-8a carbon atoms of the sulfoxides **5a** (+1.9, +5.2, +3.2, and +3.6) and **5b** (+1.7, +5.1, +3.1, and +3.5) may be explained by the "gauche γ steric shift"[33] and furnish further support for the preferred half-chair conformation with pseudoequatorial methyl groups.

The diastereomeric ratio in Table 2 indicates a low cis preference, which falls far behind the diastereoselectivity observed in the sulfoxidation for the 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones.[13h] The observed low diastereoselectivity in the sulfoxidation of 2-substituted 1-thiochroman-4-ones **2a**−**c** and **3a** originates from the poor steric control during the attack of DMD on the half-chair-like conformation of the thiochromanone ring, as exemplified in the calculated[29] conformation (Figure 1) of 2-methyl-1-thiochroman-4-one (**2a**).

DMD oxidation of the 1-thiochromones **10a** and **11a**, 1-thioflavone (**12a**), and their 3-benzyl derivatives **10e** and **12b**−**d** with an excess (3.50−5.28 equiv) of DMD afforded the corresponding sulfones **16a**,**e**, **17a**, and **18a**−**d** in excellent (82−93%) yields; the complete conversion to the sulfones required a higher excess of DMD than in the case of 1-thiochroman-4-ones (Table 1, Scheme 2).

No epoxidation of double bond was observed; even the addition of further batches of DMD left the 1-thiochromone and 1-thioflavone 1,1-dioxides intact. This preferred attack of DMD on the heteroatom in the presence of a double bond is well-documented;[35] also the persistence of the α,β- or β,γ-unsaturated sulfones toward DMD has been demonstrated.[36]

When the substrates **10a**,**e**, **11a**, and **12a**,**d** were treated only with a slight excess (1.2 equiv) of DMD, both ^{1}H NMR analysis of the reaction mixture (Table 2) and the yields of isolated materials (Table 1) revealed a high proportion of sulfone and considerable amounts of unreacted sulfide; the expected sulfoxides were found only as minor products. A literature survey indicated that the sulfones of 1-thiochromones and 1-thioflavones are readily available by oxidation with hot H_2O_2 in acetic acid,[3b,11,14,37,38] hot peracetic acid,[39] hot monoperoxy-

(21) MacKenzie, N. E.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 395.
(22) Groves, C. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628.
(23) Fraile, J. M.; García, J. I.; Lázaro, B.; Mayoral, J. A. *J. Chem. Soc., Chem. Commun.* **1998**, 1805.
(24) Ali, M. H.; Leach, D. R.; Schmitz, C. E. *Synth. Commun.* **1998**, *28*, 2969.
(25) Bálint, J. Ph.D. Thesis, Kossuth Lajos University, Debrecen, Hungary, 1978.
(26) Still, I. W. J.; Brown, W. L.; Colville, R. J.; Kutney, G. W. *Can. J. Chem.* **1984**, *62*, 586.
(27) Chauhan, M. S.; Still, I. W. J. *Can. J. Chem.* **1975**, *53*, 2880.
(28) ^{1}H NMR spectra of *cis*-**5a** and *cis*-**5b** allowed first order analysis only at ≥360 MHz.
(29) Software package VAMP 5.0: Rauhut, G.; Chandrasekhar, J.; Alex, A.; Steinke, T.; Clark, T. University of Erlangen-Nürnberg, Germany, 1993.
(30) The cis prefix refers to the isomer in which the sulfoxide oxygen and the alkyl/aryl group at the position 2 are on the same side of the heteroring; the *trans*-**5a**−**c** have the 1*R**,2*S**, while the *trans*-**6a** has the 1*R**,2*R** relative configuration, the difference is due to the change in the priority of the substituents at the C-2 atom.
(31) For crystallographic data, see: (a) Peters, K.; Peters, E.-M.; Adam, W.; Kövér, P.; Lévai, A.; Patonay, T. *Z. Kristallogr. NCS* **2000**, *215*, 217 for *cis*-**5b**. (b) Peters, K.; Peters, E.-M.; Adam, W.; Kövér, P.; Lévai, A.; Patonay, T. *Z. Kristallogr. NCS* **2000**, *215*, 219 for *trans*-**5b**.
(32) The 1-thioflavanone 1-oxide diastereomers were separated by fractional crystallization and the relative configuration of the *cis*-**6a** was determined by X-ray analysis, which led to the same assignment, cf. Somogyi, L. *Phosphorous, Sulfur Silicon* **1998**, *143*, 191.
(33) Lett, R.; Marquet, A. *Tetrahedron* **1974**, *30*, 3379.
(34) Zoller, U. Cyclic Sulfones and Sulfoxides. In *The Synthesis of Sulphones, Sulphoxides and Cyclic Sulphides, The Chemistry of Functional Groups*; Patai, S., Rappoport, Z., Eds.; Wiley: Chicester, 1994.
(35) For recent reviews on dioxirane chemistry, see: (a) Adam, W.; Hadjiarapoglou, L. *Top. Curr. Chem.* **1993**, *164*, 45. (b) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811. (c) Adam, W.; Smerz, K. *Bull. Soc. Chim. Belg.* **1996**, *105*, 581. (d) Kazakov, V. P.; Voloshin, A. I.; Kazakov, D. V. *Russ. Chem. Rev.* **1999**, *68*, 253.
(36) Adam, W.; Golsch, D.; Hadjiarapoglou, L.; Lévai, A.; Nemes, Cs.; Patonay, T. *Tetrahedron* **1994**, *50*, 13113.

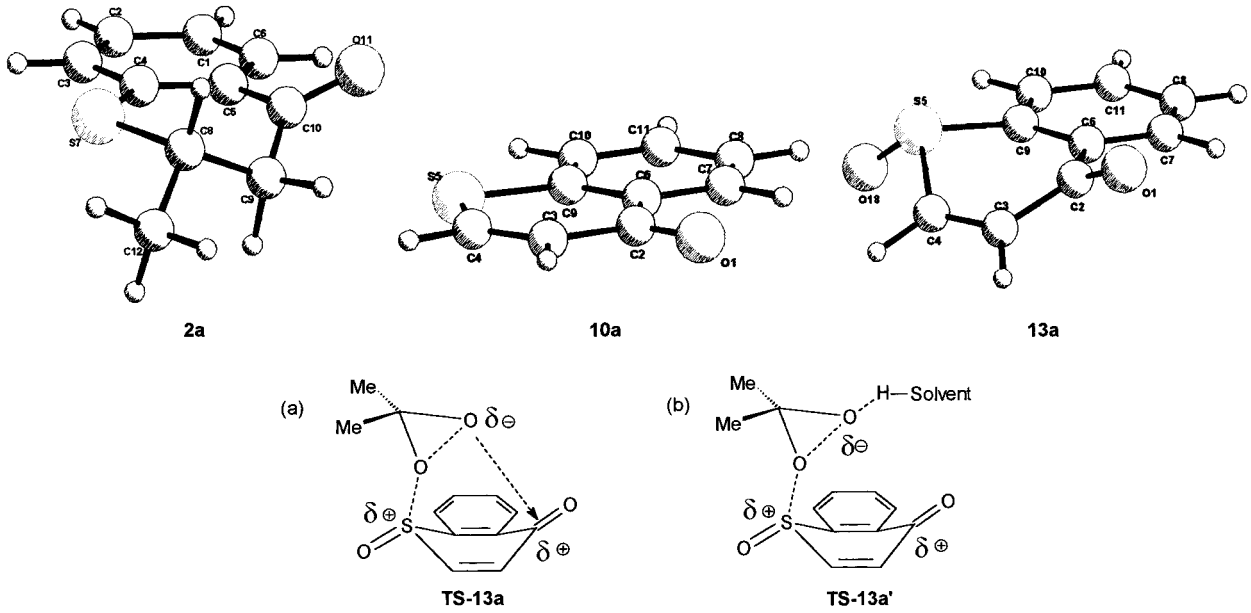
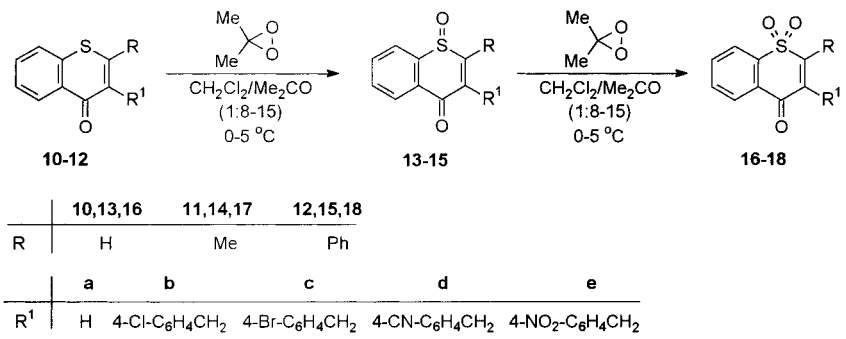


Figure 1. PM3-optimized geometries of 2-methyl-1-thiochromanone (**2a**), 1-thiochromone (**10**), and 1-thiochromone 1-oxide (**13**); postulated transition structures.

Scheme 2



phthalic acid,[15] or with H_2O_2 in trifluoroacetic acid at room temperature.[40] All attempts to synthesize the corresponding sulfoxides by using less oxidant and/or milder conditions failed in that only mixtures of sulfide, sulfoxides, and sulfones were obtained.[3a,15,41] Indeed, the pure 1-thiochromone 1-oxide (**13a**)[41] and 1-thioflavone 1-oxide (**15a**)[15] can only be prepared by dehydrobromination of the respective 3-bromo-1-thiochroman-4-one derivatives. No explanation appears to have been offered so far for this unexpected behavior of 1-thiochromones and 1-thioflavones toward oxidation. Presumably, it may be attributed to the β-acylvinyl-sulfide functionality, since neither simple vinyl sulfides[36] nor 1-thioaurone[36] with an α-acylvinyl sulfide functionality showed this unique oxidative reactivity.

To obtain better mechanistic insight into the enhanced chemoselectivity for sulfone formation, competion experiments were performed. First, a 1:1 mixture of 1-thioflavanone (**3a**) and 1-thioflavone (**12a**) was treated with a stoichiometric amount of DMD and the composition of the oxidation mixture was determined by ^{1}H NMR spectroscopy after removal of the solvent. ^{1}H NMR analysis indicated 48% unreacted 1-thioflavanone (**3a**), 52% 1-thioflavanone 1-oxide (**6a**) as a mixture of diastereomers, and 100% 1-thioflavone (**12a**) in the oxidation mixture. Neither 1-thioflavone 1-oxide (**15a**) nor 1-thioflavone 1,1-dioxide (**18a**) were detected; *i.e.*, under these conditions 1-thioflavone (**12a**) persisted oxidation. These product data indicate that the reactivity of 1-thioflavanone (**3a**) is at least 1 order of magnitude higher than that of 1-thioflavone (**12a**) in acetone−CH_2Cl_2 (53:47). The decreased reactivity of the 1-thiochromone substrate toward the electrophilic[35,42] DMD may be rationalized by the lower electron density at the sulfur atom due to the electron-accepting efficacy of enone functionality (Figure 2).

Indeed, the electron-attracting feature of the enone unit is supported by PM3 calculations,[29] which indicate a significantly greater net atomic charge on the sulfur atom (+0.232) of 1-thioflavone (**12a**) than on the sulfur atom (+0.080) of 1-thioflavanone (**3a**), see Table 3.

In the second competion experiment, a 1:1 mixture of 1-thioflavone (**12a**) and 1-thioflavone 1-oxide (**15a**) was treated with 1.2 equiv of DMD. ^{1}H NMR analysis, after

(37) Dosemund, J.; Geuschow, B. *Arch. Pharm. (Weinheim)* **1984**, *317*, 27.
(38) Watanabe, S.; Nakazumi, H.; Akagi, N.; Maeda, K.; Kitao, T. *J. Heterocycl. Chem.* **1990**, *27*, 1241.
(39) Chen, C. H.; Reynolds, G. A.; Luss, H. R.; Perlstein *J. Org. Chem.* **1986**, *51*, 3282.
(40) Cozzi, P.; Pillan, A. *J. Heterocycl. Chem.* **1988**, *25*, 1613.
(41) Still, I. W. J.; Arora, P. C.; Sokolowsky, S. N. *Org. Prep. Proced. Int.* **1975**, *7*, 159.
(42) (a) Adam, W.; Golsch, D. *Chem. Ber.* **1994**, *127*, 1111. (b) Adam, W.; Golsch, D.; Görth, F. C. *Chem. Eur. J.* **1996**, *2*, 255. (c) Adam, W.; Golsch, D. *J. Org. Chem.* **1997**, *62*, 115.

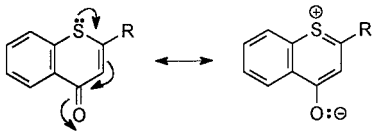


Figure 2. Mesomeric structure of 2-substituted-1-thiochromones **10**−**12**.

Table 3. Calculated[a] HOMO Energies, HOMO−LUMO Energy Gaps, and Net Atomic Charges on the Sulfur Atoms

	sulfides				sulfoxides		
	HOMO (eV)	$\Delta\epsilon^b$ (eV)	net charge on sulfur		HOMO (eV)	$\Delta\epsilon^b$ (eV)	net charge on sulfur
10a	−8.93	8.77	0.240	**13a**	−9.45	9.29	1.073
1a	−8.86	8.70	0.089	**4a**	−9.44	9.28	0.993
12a	−8.88	8.72	0.232	**15a**	−9.30	9.14	1.076
3a	−8.83	8.67	0.080	*cis*-**6a**	−9.33	9.17	0.977
				trans-**6a**	−9.29	9.13	0.977

[a] Reference 29. [b] $\Delta\epsilon = \mathrm{LUMO_{DMD}} - \mathrm{HOMO_{substrate}}$; $\mathrm{LUMO_{DMD}} = -0.16$ eV.

removal of the solvent, showed a mixture of 48% unreacted 1-thioflavone (**12a**), 27% 1-thioflavone 1-oxide (**15a**), and 25% 1-thioflavone 1,1-dioxide (**18a**). Thus, 96% of the starting material **12a** was left behind unreacted and most of observed sulfone **18a** was formed from the sulfoxide **15a** added at the beginning of the oxidation. This composition clearly shows the higher oxidative reactivity of the sulfoxide than the parent sulfide toward the DMD oxidant. From the observed product data (Tables 1 and 2), we may conclude that the *sulfoxide **15a** is at least 10 times more reactive than its parent sulfide **12a***.[43] This reactivity pattern is unexpected since sulfides are usually much more reactive toward oxidation by DMD than sulfoxides;[35,44] e.g., *p*-tolyl methyl sulfide is >300 times more reactive than its sulfoxide.[35b] A lower nucleophilicity may be expected for the sulfide due to the enone functionality,[44c] but this electronic effect of the enone should also apply to the sulfoxide and cannot explain the reverse reactivity. Neither the HOMO−LUMO energy gap nor the net atomic charges on the sulfur atoms of the sulfides and sulfoxides (Table 2) explain the observed anomalous reactivity that the sulfoxide is more effectively oxidized than the corresponding sulfide.

In another control experiment we treated the sulfoxide **15a** with 1.4 equiv of DMD and the ^{1}H NMR analysis of the reaction mixture, after removal of the solvent, gave a 38:62 mixture of sulfoxide **15a** and sulfone **18a**, but no sulfide **12a** could be detected. This observation excludes any disproportionation of the sulfoxide **15a** into the sulfide **12a** and sulfone **18a**, furthermore it makes the existence of an independent and direct route from sulfide **12a** to sulfone **18a** improbable. In this context, previously Asensio and co-workers[45] have postulated a direct route to the sulfone through a cyclic sulfurane intermediate as a major pathway in the oxidation of phenyl methyl sulfide, dibenzyl sulfide, and dibutyl sulfide by methyl(trifluoromethyl)dioxirane.

One possible explanation for the observed anomalous reactivity pattern may be found in the calculated[29] preferred ground-state conformations of the 1-thiochromone 1-oxide (**13a**) and 1-thiochromone (**10a**). As shown in Figure 1, in contrast to the planar structure of 1-thiochromone (**10a**), 1-thiochromone 1-oxide (**13a**) exists in a "boat-type" conformation, which brings the lone pair of the sulfoxide sulfur atom and the carbon atom of the carbonyl group in closer proximity. As a consequence, in the dipolar transition structure (TS-**13a**),[42b,44] the developing partial negative charge on the remote dioxirane oxygen atom may interact with the partially positive carbon atom of the carbonyl group, which should stabilize the transition structure and decrease the energy of activation to favor sulfone formation (Figure 1). A similar transannular interaction between the oxygen atom of the dioxirane and the electron-deficient sulfur atom of a remote sulfoxide group has been postulated to account the observed the chemo- and diastereoselectivity in the oxidation of thianthrene-5-oxide.[42b]

To support this proposed transannular stabilization of the TS, the solvent effect was examined. Indeed, the sulfoxide (**15a**)/sulfone (**18a**) ratio compiled in Table 4 changed from 7:93 for the oxidation in pure carbon tetrachloride solution to 66:34 in carbon tetrachloride−acetic acid (1:1). A similar (60:40) ratio was obtained in pure chloroform.

These data clearly show that solvents of higher hydrogen-bonding donor (HBD) capacity favor the formation of sulfoxide. Such an advantageous effect of the increasing HBD character (e.g., $CHCl_3 > Me_2CO > CCl_4$ order), or the addition of traces of water, on the rate and

Table 4. Solvent Effect on the Sulfoxidation of 1-Thioflavone (12a) by Dimethyldioxirane (DMD)[a] and *m*-Chloroperbenzoic Acid (*m*-CPBA)[b]

entry	solvent	oxidant	convn (%)	sulfoxide/sulfone[c] (**15a**/**18a**)
1	CCl_4[d]	DMD	29	7:93
2	CCl_4−Me_2CO (9:1)[d]	DMD	25	12:88
3	Me_2CO	DMD	15	35:65
4	CCl_4−MeOH (1:1)[d]	DMD	29	48:52
5	$CHCl_3$[d]	DMD	21	60:40
6	CCl_4−AcOH (1:1)[d]	DMD	25	66:34
7	CCl_4[d]	*m*-CPBA	46	9:91
8	$CHCl_3$[d]	*m*-CPBA	68	17:83

[a] 1-Thioflavone (0.500 mmol), DMD (0.600 mmol), and solvent (6−15 mL) at 0 °C for 24 h. [b] 1-Thioflavone (0.500 mmol), *m*-CPBA (0.610 mmol), and solvent (6−15 mL) at 25 °C for 24 h, washed with saturated $NaHCO_3$ before solvent evaporation. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture after removal of the solvent, error ≤5% of the stated values. Mass balances >90%. [d] Acetone-free DMD solution, see ref 47e.

(43) On the basis of the reported[35b,d] second-order kinetics, the kinetics of the substrates **12a** and **15a** with DMD may be described by the differential equations

$$\mathrm{d}[\mathbf{12a}]/\mathrm{d}t = -k_1[\mathbf{12a}][\mathrm{DMD}]$$

$$\mathrm{d}[\mathbf{15a}]/\mathrm{d}t = k_1[\mathbf{12a}][\mathrm{DMD}] - k_2[\mathbf{15a}][\mathrm{DMD}]$$

$$\mathrm{d}[\mathrm{DMD}]/\mathrm{d}t = -k_1[\mathbf{12a}][\mathrm{DMD}] - k_2[\mathbf{15a}][\mathrm{DMD}]$$

$$\mathrm{d}[\mathbf{18a}]/\mathrm{d}t = k_2[\mathbf{15a}][\mathrm{DMD}]$$

where k_1 is the rate constant for the oxidation of **12a** into **15a** and k_2 is the rate constant for the oxidation of **15a** into **18a**. No simple solution was found in the literature, but simulation (Mathematica for Windows, Student Version 2.2, Wolfram Research, Inc., Champaign, Illinois, USA, 1993) at the starting concentrations $[\mathbf{12a}]_0 = 2.8 \times 10^{-2}$ mol/dm^3, $[\mathbf{15a}]_0 = 2.83 \times 10^{-2}$ mol/dm^3 and $[\mathrm{DMD}]_0 = 1.53 \times 10^{-2}$ mol/dm^3 gave the best fit of the observed product ratio with rate constant values $k_1 \sim 1 \times 10^{-3}$ and $k_2 \sim 1 \times 10^{-2}$ mol/dm^3·s.

(44) (a) Murray, R. W.; Jeyaraman, R.*J. Org. Chem.* **1985**, *50*, 2847. (b) Murray, R. W.; Jeyaraman, R.; Krisna Pillay, M. *J. Org. Chem.* **1987**, *52*, 740. (c) Ballistreri, F. P.; Tomaselli, G. A.; Toscano, R. M.; Bonchio, M.; Conte, V.; DiFuria, F. *Tetrahedron Lett.* **1994**, *35*, 8041.

(45) Asensio, G.; Mello, R.; González-Núòez, M. E. *Tetrahedron Lett.* **1996**, *37*, 2299.

stereoselectivity of dioxirane epoxidations is well documented.[46c,f,47] A Kamlet−Taft analysis of DMD epoxidations pointed out that the HBD capacity is the dominating factor while the solvent's hydrogen-bonding acceptor (HBA) capacity, the solubility parameter and the ability of the solvent to stabilize a charge or dipole are of less importance.[47b] In the present case the higher HBD capacity of the solvent stabilizes the partially negative charge on the remote dioxirane oxygen intermolecularly (see TS-**13a′** in Figure 1) and, consequently, the intramolecular stabilizing effect of the carbonyl group is decreased. The dominance of the intermolecular stabilizing effect, which is effective for both sulfide **10a** and sulfoxide **13a**, over the intramolecular stabilizing effect results in the loss of discrimination between substrates **10a** and **13a** based on the different conformation (see Figure 1) and shifts the product ratio toward the "regular" one.

Since the electrophilic dioxiranes and peracids are considered to have similar transition structures for oxygen transfer, it was of interest to assess the solvent effect in the oxidation of the 1-thioflavone (**12a**) by peracids under the same conditions as with dioxiranes. ^{1}H NMR analysis of the reaction mixture of sulfide **12a** and *m*-chloroperbenzoic acid (*m*-CPBA) revealed a similar trend, i.e., more sulfoxide in chloroform than carbon tetrachloride (Table 4, entries 7 and 8), although the solvent effect is less pronounced. This decreased sensitivity of the peracid oxidation toward the HBD capacity of the solvent may be rationalized in terms of the effective *internal* hydrogen bond in the peracid, which makes the interaction with the external hydrogen-bonding donor less important.

In summary, dimethyldioxirane is a convenient and useful oxidizing agent in the synthesis of 1-thiochroman-4-one sulfoxides and sulfones, the chemoselectivity depends on the amount of oxidant used. The sulfoxidation of 2-substituted 1-thiochroman-4-ones takes place in low diastereoselectivity because of the low steric differentiation between the two possible attacks. A unique reversed reactivity pattern, i.e., a higher reactivity of sulfoxides versus the corresponding sulfide, was discovered in the DMD oxidation of 1-thiochromones and 1-thiochromone 1-oxides. This anomaly may be explained in terms of a transannular stabilizing effect by the carbonyl group in the TS for the sulfoxide oxidation in view of a favorable conformational effect. Solvents of high HBD capacity were found to increase the sulfoxide/sulfone ratio, probably due to the formation of a hydrogen bond between the solvent and the dipolar TS which disrupts the internal stabilization.

Acknowledgment. This work was supported by the European Community (COST D12/0019/98), by the Deutsche Forschungsgemeinschaft (Schwerpunktprogramm "Peroxidchemie: Mechanistische und prepärative Aspekte des Sauerstofftransfers"), Fonds der Chemischen Industrie, and by the Hungarian Scientific Research Found (OTKA T29171). The generous gift of Curox (potassium monoperoxysulfate), the triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, from Peroxid-Chemie GmbH (Höllriegelskreuth, Germany) is gratefully appreciated. Special thanks are due to Prof. Vilmos Gáspár for his helpful discussions.

Supporting Information Available: General experimental techniques, synthesis of **11a**, details of oxidation experiments, physical constants, and spectroscopic data of the compounds prepared herein. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001469F

(46) (a) Baumstark, A. L.; McCloskey, C. J. *Tetrahedron Lett.* **1987**, *37*, 3311. (b) Murray, R. W.; Gu, D. *J. Chem. Soc., Perkin Trans. 2.* **1993**, 2203. (c) Adam, W.; Smerz, A. K. *Tetrahedron* **1995**, *51*, 13039. (d) Adam, W.; Smerz, A. K. *J. Org. Chem.* **1996**, *61*, 3506. (e) Adam, W.; Mitchell, C. M.; Paredes, R.; Smerz, A. K.; Veloza, L. A. *Liebigs Ann./Recueil* **1997**, 1365. (f) Adam, W.; Paredes, R.; Smerz, A. K.; Veloza, L. A. *Eur. J. Org. Chem.* **1998**, *349*, 9.

(47) (a) Baumstark, A. L.; Vasquez, P. C. *J. Org. Chem.* **1988**, *53*, 3437. (b) Murray, R. W.; Gu, D. *J. Chem. Soc., Perkin Trans. 2* **1993**, 2203. (c) Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M. *Tetrahedron Lett.* **1995**, *36*, 2437. (d) Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M. *J. Org. Chem.* **1996**, *61*, 1830. (e) Gibert, M.; Ferrer, M.; Sánchez-Baeza, F.; Messeguer, A. *Tetrahedron* **1997**, *53*, 8643.