million (ppm) downfield relative to tetramethylsilane. ^{19}F NMR chemical shifts are given in parts per million downfield relative to trichlorofluoromethane. IR spectra were recorded on a Perkin-Elmer 1420 spectrometer and are expressed in cm^{-1}. Elemental analyses were performed by the Service de Microanalyse, Université Pierre et Marie Curie, Paris. Mass spectra were determined on a Nermag R30-10 instrument by Professor J. C. Tabet, Université Pierre et Marie Curie, Paris. Ether was diethyl ether. Dichlorofluoromethane (Freon-21) was a generous gift from Atochem and tris(3,6-dioxaheptyl)amine (TDA-1) from Rhône-Poulenc.

7-Chloro-7-fluoro-2,5-dioxabicyclo[4.1.0]heptane (9). Liquid–Liquid PTC. Dichlorofluoromethane (23.2 g, 0.225 mol) was bubbled into a vigorously stirred mixture of dioxene (8; 12.9 g, 0.15 mol), dichloromethane (15 mL), benzyltriethylammonium chloride (0.05 g), and aqueous sodium hydroxide (50% by wt, 45 mL) at 5–10 °C. Stirring at 20 °C was continued for 14 h. Then water (300 mL) was added, and the organic products were extracted with dichloromethane (3 × 200 mL). The extract was washed with brine (100 mL) and dried over sodium sulfate. The solvent was evaporated under vacuum (20 mmHg), and the residue was distilled to give **9** (20.8 g, 0.1365 mol; 91%) as a mixture of two isomers **9c** (cis, 58%) and **9t** (trans, 42%): bp 67–68 °C (20 mmHg); ^1H NMR ($CDCl_3$) 3.6–4.1 (mult); ^{19}F NMR ($CDCl_3$) –145 (cis isomer, t, $^3J_{HF}$ = 14 Hz), –170 (trans isomer, s). Anal. Calcd for $C_5H_6ClFO_2$ (152.55): C, 39.36; H, 3.96. Found: C, 39.76; H, 3.42.

Solid–Liquid PTC. Dichlorofluoromethane (15.45 g, 0.15 mol) was bubbled into a vigorously stirred mixture of dioxene (8.6 g, 0.1 mol), dichloromethane (50 mL), TDA-1 (1.6 g, 5 mmol), and sodium hydroxide reduced to powder (10 g, 0.25 mol) at 5–10 °C. The mixture was stirred for 14 h at 20 °C and then filtered. The solid was washed with dichloromethane (3 × 30 mL), the organic solution was evaporated under vacuum (20 mmHg), and the residue was distilled to give **9** (5.49 g, 0.031 mol; 36%).

Fluoromalonaldehyde Bis(dimethyl acetal) (12a) and 3-Fluoro-2,4-dimethoxy-1,5-dioxacycloheptane (11a). A mixture of **9** (8.05 g, 0.053 mol), methanol (53 mL), and concentrated sulfuric acid (0.35 mL) was refluxed for 8 days. The conversion (verified by ^{19}F NMR) was 86%; 14% of **9t** was still remaining. Water (50 mL) was added. The products were extracted with ether (3 × 50 mL). The organic solution was neutralized with saturated aqueous sodium hydrogen carbonate, then washed with brine (2 × 20 mL), and dried over sodium sulfate. The solvents were evaporated under vacuum (20 mmHg), and the residue was distilled to give a mixture of **11a** (25%) and **12a** (75%) (6.1 g, 63%): bp 88–95 °C (20 mmHg). A second distillation was perfomed in a micro distillation Fischer-Spaltrohr apparatus giving **12a** (4.9 g, 0.027 mol; 51%) and **11a** (0.6 g, 3.3 mmol; 6%). **12a**: bp 87–89 °C (20 mmHg); ^1H NMR ($CDCl_3$, 300 MHz) 3.43–3.44 (2 s, 12 H), 4.3 (t, $^3J_{HH}$ = 4.6 Hz) and 4.44–4.5 (mult) (3 H); ^{19}F NMR ($CDCl_3$) –211 (dt, $^2J_{HF}$ = 47 Hz, $^3J_{HF}$ = 11 Hz); ^{13}C NMR ($CDCl_3$, 75.43 MHz) 57.5 (q), 57.9 (q), 93.1 (dd), 104.3 (dd), 104.4 (d). Anal. Calcd for $C_7H_{15}FO_4$ (182.19): C, 46.15; H, 8.3. Found: C, 46.31; H, 8.4. **11a**: bp 106–110 °C (20 mmHg); ^1H NMR ($CDCl_3$, 300 MHz) 3.45 (mult, 6 H), 3.96 (d mult, 4 H), 4.36 (ddd, 1 H, $^2J_{HF}$ = 47 Hz, $^3J_{HH}$ = 6.5 Hz and 2 Hz), 4.52 (t, 1 H, $^3J_{HF}$ = $^3J_{HH}$ = 6.5 Hz), 5.14 (dd, 1 H, $^3J_{HF}$ = 18 Hz, $^3J_{HH}$ = 2 Hz); ^{19}F NMR ($CDCl_3$) –213 (ddd, $^2J_{HF}$ = 47 Hz, $^3J_{HF}$ = 18 Hz and 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75.43 MHz) 56,8 (q), 58.1 (q), 68.3 (t), 68.4 (t), 92.7 (ddd), 103.9 (dd), 104.5 (dd). Anal. Calcd for $C_7H_{13}FO_4$ (180.17): C, 46.66; H, 7.27. Found: C, 46.25; H, 8.16.

Fluoromalonaldehyde Bis(diethyl acetal) (12b) and 3-Fluoro-2,4-diethoxy-1,5-dioxacycloheptane (11b). The same procedure as for the preparation of **12a** and **11a** was followed starting from 6.1 g (0.04 mol) of **9**. After refluxing for 7 days, no more starting material was detected by ^{19}F NMR. The refluxing was stopped. The workup was the same. Distillation afforded a mixture of **11b** (35%) and **12b** (65%) (7.6 g; 80% calculated as if all were **12b**[13]): bp 118–122 °C (12 mmHg); ^1H NMR ($CDCl_3$, 300 MHz) 1.17 (mult), 3.46–3.7 (mult), 3.91 (d mult, 8 lines, OCH_2CH_2O **11b**), 4.25 and 4.3 (2 dt, CHF **11b** and **12b**, $^2J_{HF}$ = 47 Hz, $^3J_{HH}$ = 4.5 Hz), 4.54–4.6 (d mult), 5.1 (dd, CH **11b**, $^3J_{HH}$ = 1.5 Hz, $^3J_{HF}$ = 18.5 Hz); ^{19}F NMR ($CDCl_3$) –211 (dt, $^2J_{HF}$ = 47 Hz, $^3J_{HF}$ = 12 Hz), –213 (ddd, $^2J_{HF}$ = 47 Hz, $^3J_{HF}$ = 7 and 18 Hz); ^{13}C NMR ($CDCl_3$, 75.43 MHz) 17.76 (q), 17.84 (q), 17.91 (q), 65.4 (t, **11b**), 65.9 (t, **12b**), 66.3 (t, **11b**), 68.2 (t, **11b**), 68.35 (t, **11b**), 93.25 (ddd, **11b**), 93.9 (dd, **12b**), 102.46 (dd, **12b**), 102.9 (dd, **11b**), 103.95 (dd, **11b**); MS (chemical ionization, NH_3) 256 [MNH_4^+ (**12b**)], 239 [MH^+ (**12b**)], 226 [MNH_4^+ (**11b**)], 210 [MNH_4^+ (**12b**) – C_2H_5OH], 209 [MH^+ (**11b**)], 180 [MNH_4^+ (**11b**) – C_2H_5OH].

4-Fluoropyrazole (13). A mixture of **11b** and **12b** (2.38 g, 0.01 mol[13]), hydrazine dihydrochloride (1.05 g, 0.01 mol), water (1.5 mL), and ethanol (1 mL) was refluxed for 2 h. Then the mixture was cooled and water (4 mL) and sodium carbonate (2 g) were added. The mixture was filtered and the solid washed with ether (2 × 10 mL). After decantation, the aqueous solution was extracted with ether (2 × 10 mL). The organic solution was washed with brine (2 × 5 mL) and dried over sodium sulfate. The solvents were evaporated under vacuum (20 mmHg). A flash distillation of the residue under vacuum (18 mmHg) gave **13** (0.69 g, 8 mmol; 80%): bp 86–88 °C (18 mmHg) [lit.[1] bp 84 °C (15 mmHg)].

Diethyl Fluoromalonate (14b). To a vigorously stirred solution of **11b** and **12b** (7.14 g; 0.03 mol) in absolute ethanol (60 mL) at 5–10 °C was added the Caro acid[18] prepared from 90% sulfuric acid (42 g) and ammonium persulfate (34.2 g, 0.15 mol). After being stirred for 16 h at room temperature, the mixture was diluted with cold water (200 mL) and extracted with ether (3 × 150 mL). The organic solution was washed with brine (2 × 75 mL) and then dried over sodium sulfate. The solvents were evaporated under vacuum (20 mmHg), and the residue was distilled to give **14b** (2.9 g, 0.0163 mol; 54%): 94–96 °C (12 mmHg) [lit.[17] 110–111 °C (20 mmHg)].

Dimethyl Fluoromalonate (14a). The same procedure as for the preparation of **14b** was followed starting from **12a** (3.3 g, 0.018 mol) in solution in methanol (18 mL). The solvents were distilled at atmospheric pressure, and the residue was distilled to give **16a** (1.5 g, 0.01 mol; 55%): 82–85 °C (15 mmHg) [lit.[17] 111–112 °C (45 mmHg)].

Acknowledgment. This work was supported by Rhône-Poulenc, for which we are grateful. We thank Atochem for a generous gift of dichlorofluoromethane.

Registry No. **8**, 543-75-9; **9c**, 40623-36-7; **9t**, 40623-35-6; **11a**, 122875-58-5; **11b**, 122875-59-6; **12a**, 120131-06-8; **12b**, 120131-05-7; **13**, 35277-02-2; **14a**, 344-14-9; **14b**, 685-88-1; $CHFCl_2$, 75-43-4.

One-Pot Synthesis of β-Keto Sulfones and β-Keto Sulfoxides from Carboxylic Acids

C. Alvarez Ibarra,* R. Cuervo Rodríguez, M. C. Fernández Monreal, F. J. García Navarro, and J. Martín Tesorero

Departamento de Química Orgánica I, Facultad de C. Químicas, Universidad Complutense, Ciudad Universitaria, s/n 28040, Madrid, Spain

Received February 17, 1989

Many synthetic applications of β-oxo sulfones[1–8] and β-oxo sulfoxides[9–30] have been reported in the literature.

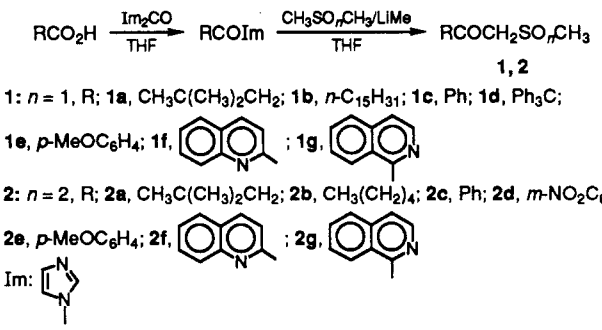
(1) (a) Koutek, B.; Pavlickova, L.; Soucek, M. *Collect. Czech. Chem. Commun.* **1974**, *39*, 192. (b) Julia, M.; Badet, P. *Bull. Soc. Chim. Fr.* **1975**, 1363. (c) Kondo, K.; Tunemoto, D. *Tetrahedron Lett.* **1975**, 1397. (d) Cooper, G. K.; Dolby, I. J. *Tetrahedron Lett.* **1976**, 4765. (e) Ono, N.; Tamura, R.; Kaji, A. *Synthesis* **1977**, 690. (f) Schank, K.; Schmitt, H. G. *Chem. Ber.* **1978**, *11*, 3497. (g) Böhme, K.; Clement, B. *Tetrahedron Lett.* **1979**, 1737. (h) Messinger, P. M.; Kusuma, K. *Synthesis* **1980**, 565. (i) Scholz, D. *Liebigs Ann. Chem.* **1983**, 98.

(2) (a) Bartlett, P. A.; Green III, F. R.; Rose, E. H. *J. Am. Chem. Soc.* **1978**, *100*, 4852. (b) Jurasek, A.; Polakovicova, D.; Kovac, J. *Collect. Czech. Chem. Commun.* **1981**, *46*, 3115. (c) Scholz, D. *Liebigs Ann. Chem.* **1984**, 264. (d) Mandai, T.; Yanagi, T.; Araki, K.; Morisaki, Y.; Kavada, M.; Bebernitz, G. E.; Maynard, S. C.; Spagnolo, C. J. *Tetrahedron Lett.* **1985**, 169. (f) Kuth, M. J.; O'Brien, M. J. *J. Org. Chem.* **1985**, *50*, 3846.

(3) (a) Corey, E. J.; Chaykowsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345. (b) House, H. O.; Larson, J. R. *J. Org. Chem.* **1968**, *33*, 61. (c) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verben, T. R. *Tetrahedron Lett.* **1976**, 3477.

0022-3263/89/1954-5620$01.50/0

Scheme I. Synthesis of β-Keto Sulfones and β-Keto Sulfoxides from Carboxylic Acids



However, a limited number of syntheses of β-oxo sulfones and β-oxo sulfoxides have been described.

The β-oxo sulfones have been obtained by alkylation of metallic arene sulfinates with α-halocarbonyl compounds,[31] oxidation of β-oxo sulfides[32] and β-hydroxy sulfones,[1d] acylation of α-sulfonyl carbanions with esters[1c,3b,33] and nitriles,[34] and acylation of geminal dilithio derivatives of alkyl sulfones with esters[1c,35,36] and acid chlorides.[37] The β-oxo sulfoxides have been obtained by similar methods[3a,10,13,22,38] from esters, aldehydes, and ketones.

In this paper an efficient synthesis of β-oxo sulfones and β-oxo sulfoxides from carboxylic acid is described. The reaction is performed in one-pot procedure by acylation of lithium (methylsulfonyl)methylide or lithium (methylsulfinyl)methylide with 1-acylimidazoles obtained in situ from carboxylic acids and 1,1′-carbonyldiimidazole.

We have prepared several β-oxo sulfones and β-oxo sulfoxides and report for the first time reactions that afford these compounds from 1-acylimidazoles. The general application of this method is tested by using aliphatic, aromatic, and heteroaromatic acids (Scheme I).

The imidazolide is prepared and used without previous isolation from the carboxylic acid (1 equiv) and 1,1′-carbonyldiimidazole in dry THF at room temperature. This reaction mixture is added on a stirred solution of dimethyl sulfone (5 equiv) or dimethyl sulfoxide (5 equiv) and methyllithium (5 equiv) in dry THF–Et_2O. The reaction mixture is stirred at room temperature for 3 h. The mixture is diluted with water and extracted with chloroform. The aqueous phase is acidified by addition of concentrated HCl. The β-oxo sulfone precipitates, and it is filtered and recrystallized from a suitable solvent. The β-oxo sulfoxide is extracted with chloroform. The organic extract is dried, filtered, and evaporated. The crude is recrystallized from a suitable solvent. The yields, melting points, and spectroscopic data for the products are given in the Experimental Section.

The irreversibility of metalation of dimethyl sulfone and dimethyl sulfoxide was achieved with a 1.5 M solution of methyllithium in THF.

The β-oxo sulfones and β-oxo sulfoxides formed in the reaction conditions are quickly deprotonated by any unreacted carbanion, and to avoid a low yield it is necessary to use an excess of base (5 equiv).

Advantages of our method over other procedures previously described include higher yield, greater ease of product isolation, and minimal synthetic steps (only one).

Experimental Section

General Procedures. ^1H and ^{13}C NMR spectra were recorded on a Varian T-60 and FT-80 spectrometers, respectively, and the chemical shifts are quoted as δ values from tetramethylsilane as internal reference. Mass spectra were taken on a Varian MAT-711 instrument (70 eV). Infrared (IR) spectra were recorded on a Perkin-Elmer 781 spectrophotometer.

Tetrahydrofuran (THF) was purified, dried over sodium, and distilled over lithium aluminum hydride under nitrogen immediately before use. Dimethyl sulfoxide (DMSO) was dried over calcium hydride and distilled under vacuum. Dimethyl sulfone (Merck A.G.), 1,1′-carbonyldiimidazole (Merck, A.G.), and carboxylic acids were used without further purifications. Methyllithium was purchased from Aldrich Chemical Co., Janssen Chimica Beerse, and Merck, A.G. Melting points are uncorrected.

β-Oxo Sulfones. Typical Procedure. 4,4-Dimethyl-1-(methylsulfonyl)-2-pentanone (2a). 3,3-Dimethylbutyric acid (1 g, 8.6 mmol), 1,1′-carbonyldiimidazole (1.39 g, 8.6 mmol), and anhydrous THF (20 mL) were stirred at room temperature for 20 min and subsequently used.

(4) (a) Hagiwara, H.; Nakayama, K.; Uda, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3769. (b) Posner, G. H.; Mallamo, J. P.; Muira, K. *J. Am. Chem. Soc.* **1981**, *103*, 2886. (c) Tanikaga, R.; Tamura, T.; Nozaki, Y.; Kaji, A. *J. Chem. Soc. Chem. Commun.* **1984**, *87*.

(5) (a) Diller, D.; Bergmann, F. *J. Org. Chem.* **1972**, *37*, 2147. (b) Komano, T.; Ishihara, S.; Itami, H. *Tetrahedron Lett.* **1972**, 4719. (c) Koutek, B.; Pavlicova, L.; Soucek, M. *Collect. Czech. Chem. Commun.* **1973**, *38*, 3872.

(6) (a) Truce, W. E.; Klinger, T. C. *J. Org. Chem.* **1970**, *35*, 1834. (b) Hiraki, Y.; Ito, K.; Harada, T.; Tai, A. *Chem. Lett.* **1981**, 131. (c) Julia, M.; Launay, M.; Stacino, J. P.; Verpeaux, J. N. *Tetrahedron Lett.* **1982**, 2465.

(7) (a) Coates, R. M.; Sowerby, R. L. *J. Am. Chem. Soc.* **1972**, *94*, 4758. (b) Kuwajima, I.; Sato, S.; Kurata, Y. *Tetrahedron Lett.* **1972**, 737. (c) Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, 4833. (d) Song, S.; Shiono, M.; Mukaiyama, T. *Chem. Lett.* **1978**, 2625.

(8) Lythgoe, B.; Waterhouse, I. *Tetrahedron Lett.* **1978**, 2625.

(9) Corey, E. J.; Chaykowsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345.

(10) Russell, G. A.; Mikol, G. J. *J. Am. Chem. Soc.* **1966**, *88*, 5498.

(11) Grabowsky, N. *Liebigs Ann. Chem.* **1975**, 348.

(12) Kingsbury, C. A.; Cram, D. J. *J. Am. Chem. Soc.* **1960**, *82*, 1810.

(13) Trost, B. M. Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

(14) Russell, G. A.; Ochrymowycz, L. A. *J. Org. Chem.* **1969**, *34*, 3624.

(15) Gassman, P. G.; Richmond, G. D. *J. Org. Chem.* **1966**, *31*, 2355.

(16) (a) von Asten, J. J. A.; Louw, R. *Tetrahedron Lett.* **1975**, 671. (b) Kunieda, N.; Nokami, J.; Kinoshita, M. *Chem. Lett.* **1974**, 369.

(17) Dehmolow, E. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 170.

(18) Gassman, P. G.; Richmond, G. D. *J. Org. Chem.* **1966**, *31*, 170.

(19) Kuwajima, I.; Iwasawa, H. *Tetrahedron Lett.* **1974**, 107.

(20) Grieco, P. A.; Pogonowski, C. S. *J. Chem. Soc., Chem. Commun.*, **1975**, 72.

(21) (a) Russell, G. A.; Janzen, E. G.; Becker, H. D.; Smentowski, F. J. *J. Am. Chem. Soc.* **1962**, *84*, 2652. (b) Russell, G. A.; Janzen, E. G. Strom, E. T. *J. Am. Chem. Soc.* **1962**, *84*, 4155.

(22) Becker, H. D.; Mikol, G. J.; Russell, G. A. *J. Am. Chem. Soc.* **1963**, *85*, 3410.

(23) Schroeder, E. F.; Dodson, R. M. *J. Am. Chem. Soc.* **1962**, *84*, 1904.

(24) Johnson, C. R.; Sharp, J. C.; Phillips, W. G. *Tetrahedron Lett.* **1967**, 5299.

(25) Johnson, C. R.; Phillips, W. G. *J. Org. Chem.* **1967**, *32*, 1926.

(26) More, T. L. *J. Org. Chem.* **1967**, *32*, 2786.

(27) Russell, G. A.; Mikol, G. J. *J. Am. Chem. Soc.* **1966**, *88*, 5498.

(28) Russell, G. A.; Ochrymowycz, L. A. *J. Org. Chem.* **1970**, *35*, 3007.

(29) Russell, G. A.; Ochrymowycz, L. A. *J. Org. Chem.* **1969**, *34*, 3618.

(30) (a) Russell, G. A.; Sabourin, E. T. *J. Org. Chem.* **1969**, *34*, 2336. (b) Russell, G. A.; Ochrymowycz, L. A. *J. Org. Chem.* **1970**, *35*, 2107.

(31) (a) Vennstra, G. E.; Zwaneburg, B. *Synthesis* **1975**, 519. (b) Wildeman, J.; van Leusen, A. M. *Synthesis* **1979**, 733.

(32) Trost, B. M.; Curran, P. *Tetrahedron Lett.* **1981**, 1287.

(33) (a) Truce, W. E.; Knospe, R. H. *J. Am. Chem. Soc.* **1955**, *77*, 5063. (b) Fields, L.; Lawson, J. E.; McFarland, J. W. *J. Am. Chem. Soc.* **1956**, *78*, 4389. (c) Becker, H. D.; Russell, G. A. *J. Org.* Chem. **1963**, *28*, 1896. (d) Russell, G. A.; Sabourin, E. T.; Hamprecht, G. *J. Org. Chem.* **1969**, *34*, 2339.

(34) Truce, W. E.; Bannister, W. M.; Knospe, R. H. *J. Org. Chem.* **1962**, *27*, 2821.

(35) Mussatto, C. M.; Savoia, D.; Trombin, C.; Umani-Ronchi, A. *J. Org. Chem.* **1980**, *45*, 4002.

(36) Kaiser, E. M.; Solber, L. E.; Schwarz, R. A.; Beard, R. D.; Hauser, C. R. *J. Am. Chem. Soc.* **1971**, *93*, 4237.

(37) Thomsen, M. W.; Handwerker, B. M.; Katz, S. A.; Belser, R. B. *J. Org. Chem.* **1988**, *53*, 906.

(38) Montevio, H. J.; Souza, J. P. *Tetrahedron Lett.* **1975**, 921.

Methyllithium (26.9 mL of 1.5 M solution, 43 mmol) was added slowly with magnetic stirring under dry nitrogen to a solution of dimethyl sulfone (4.04 g, 43 mmol) in 20 mL of anhydrous THF at room temperature. After 15 min, imidazolide solution, previously prepared, was added by syringe, and the mixture was stirred for 3 h at room temperature. The reaction mixture was hydrolyzed by 40 mL of water and extracted with chloroform. The aqueous phase was acidified to pH 7–8 by addition of concentrated hydrochloric acid. The white precipitate was filtered and recrystallized from water to afford 1.46 g (88%) of white solid; mp 88–89 °C; ^{1}H NMR ($(CD_3)_2CO$) δ 1.04 (s, 9 H, CH_3), 2.65 (s, 2 H, CCH_2CO), 3.04 (s, 3 H, CH_3SO_2), 4.26 (s, 2 H, $COCH_2SO_2$); ^{13}C NMR ($(CD_3)_2CO$) δ 28.9 (CH_3), 30.6 (C), 41.4 (CCH_2CO), 56.0 (CH_3SO_2), 65.6 (CH_2SO_2), 199.6 (CO); IR (KBr) 2990–2860, 1710, 1485, 1475, 1385, 1365, 1320, 1135 cm^{-1}; MS, m/e (rel intensity) 192 ($M^{\bullet+}$, 0.6), 176 (38.5), 137 (31.3), 136 (42.4), 121 (61.5), 113 (13.0), 99 (46.3), 97 (40.4), 79 (16.3), 71 (17.0), 64 (13.0), 57 (100), 56 (19.5). Anal. Calcd for $C_8H_{16}SO_3$: C, 50.0; H, 8.33; S, 16.66. Found: C, 49.82; H, 8.40; S, 16.61.

1-(Methylsulfonyl)-2-heptanone (2b). The β-oxo sulfone was extracted with chloroform at pH 8, and the organic phase was washed with saturated $NaHCO_3$ solution, dried with anhydrous magnesium sulfate, filtered, and evaporated; recrystallized yield from water 42% mp 28–30 °C; ^{1}H NMR ($(CD_3)_2CO$), δ 0.75–1.66 (m, 9 H, $CH_3(CH_2)_3$), 2.69 (t, 2 H, CH_2CO), 3.03 (s, 3 H, CH_3SO_2), 4.29 (s, 2 H, $COCH_2SO_2$); ^{13}C NMR ($(CD_3)_2CO$) δ 14.1 (CH_3), 22.9 (CH_2), 23.2 (CH_2), 31.6 (CH_2), 41.9 (CH_2CO), 44.6 (CH_3SO_2), 64.7 (CH_2SO_2), 200.6 (CO); IR (KBr) 3000–2860, 1715, 1470, 1455, 1370, 1315, 1150 cm^{-1}. Anal. Calcd for $C_8H_{16}SO_3$: C, 50.00; H, 8.33; S, 16.66. Found: C, 50.35; H, 8.29; S, 16.60.

2-(Methylsulfonyl)-1-phenylethanone (2c): recrystallized yield from ethanol 77%; mp 97–99 °C (lit.[34] mp 92–94 °C; lit.[33c] mp 106–107 °C); ^{1}H NMR ($(CD_3)_2CO$) δ 3.15 (s, 3 H, CH_3), δ 4.91 (s, 2 H, CH_2), 8.13–7.52 (m, 5 H, Ar); ^{13}C NMR ($(CD_3)_2CO$) δ 42.3 (CH_3), 61.6 (CH_2), 129.6, 129.9, 134.9, 137.1 (Ar), 190.6 (CO); IR (KBr) 3100–3020, 2950–2910, 1670, 1600, 1580, 1490, 1450, 1320, 1300, 1135, 900, 760, 685 cm^{-1}; MS, m/e (rel intensity) 198 ($M^{\bullet+}$ 2.7), 197 (18), 106 (11.5), 105 (100), 77 (26), 50 (10). Anal. Calcd for $C_9H_{10}SO_3$: C, 55.54; H, 5.05; S, 16.16. Found: C, 54.35; H, 5.19; S, 16.28.

2-(Methylsulfonyl)-1-(*m*-nitrophenyl)ethanone (2d). The imidazolide was prepared at 50 °C. The β-oxo sulfone was extracted with chloroform at pH 8, and the organic phase was washed with saturated $NaHCO_3$ solution, dried with anhydrous magnesium sulfate, filtered, and evaporated; recrystallized yield from methanol–water 34%; mp 90–92 °C; ^{1}H NMR ($(CD_3)_2CO$) δ 3.20 (s, 3 H, CH_3), 5.10 (s, 2 H, CH_2), 7.79–8.83 (m, 4 H, Ar); ^{13}C NMR ($(CD_3)_2CO$) δ 42.4 (CH_3), 62.0 (CH_2), 124.4, 129.0, 131.3, 135.8, 138.3, 148.3 (Ar), 189.4 (CO); IR (KBr) 3100–3020, 2950–2910, 1695, 1610, 1580, 1530, 1470, 1430, 1360, 1320, 1295, 1135, 895, 745, 680 cm^{-1}. Anal. Calcd for $C_9H_9NSO_5$: C, 44.44; H, 3.70; N, 5.76; S, 13.17. Found: C, 44.18; H, 3.99; N, 5.47; S, 13.49.

2-(Methylsulfonyl)-1-(*p*-methoxyphenyl)ethanone (2e): recrystallized yield from methanol–water 71%; mp 136–137 °C (lit.[33c] mp 137–138 °C); ^{1}H NMR (DMSO-d_6) δ 3.16 (s, 3 H, CH_3SO_2), 3.87 (s, 3 H, CH_3O), 5.04 (s, 2 H, CH_2), 7.03–8.10 (m, 4 H, Ar); ^{13}C NMR (DMSO-d_6) δ 42.0 (CH_3SO_2), 55.6 (CH_3O), 60.5 (CH_2), 114.0, 128.8, 131.6, 164.0 (Ar), 188.1 (CO); IR (KBr) 3100–3020, 2990–2920, 2830, 1665, 1600, 1510, 1450, 1325, 1300, 1180, 1150, 1015, 795 cm^{-1}; MS, m/e (rel intensity) 228 ($M^{\bullet+}$, 4), 227 (46), 136 (30), 135 (100), 120 (18), 107 (17.5), 92 (17), 77 (23). Anal. Calcd for $C_{10}H_{12}SO_4$: C, 52.63; H, 5.26; S, 14.04. Found: C, 52.27; H, 5.41; S, 14.32.

2-(Methylsulfonyl)-1-(2-quinolinyl)ethanone (2f): recrystallized yield from ethyl acetate–hexane 53%; mp 162–164 °C; ^{1}H NMR (DMSO-d_6) δ 3.33 (s, 3 H, CH_3), 5.43 (s, 2 H, CH_2), 7.8–8.7 (m, 6 H, Ar); ^{13}C NMR (DMSO-d_6) δ 42.5 (CH_3), 59.4 (CH_2), 118.1, 128.4, 129.7, 129.9, 130.3, 131.1, 138.4, 146.7, 151.8 (Ar), 191.2 (CO); IR (KBr) 3100–3000, 2970, 1685, 1590, 1560, 1500, 1450, 1430, 1315, 1135, 1030, 790, 765, 745 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NSO_3$: C, 57.83; H, 4.42; N, 5.62; S, 12.85. Found: C, 57.60; H, 4.63; N, 5.23; S, 13.01.

2-(Methylsulfonyl)-1-(1-isoquinolinyl)ethanone (2g). The imidazolide was prepared at 50 °C; recrystallized yield from ethyl acetate–hexane 67%; mp 129–130 °C; ^{1}H NMR (DMSO-d_6) δ 3.25 (s, 3 H, CH_3), 5.40 (s, 2 H, CH_2), 7.76–8.95 (m, 6 H, Ar); ^{13}C NMR (DMSO-d_6) δ 42.4 (CH_3), 61.7 (CH_2), 125.7, 126.2, 127.6, 130.2, 131.0, 136.8, 141.2, 150.0 (Ar), 192.7 (CO); IR (KBr) 3060–3000, 2960, 1680, 1580, 1500, 1450, 1390, 1325, 1305, 1135, 960, 755, 745 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NSO_3$: C, 57.83; H, 4.42; N, 5.62; S, 12.85. Found: C, 57.51; H, 4.71; N, 5.28; S, 12.93.

β-Oxo Sulfoxides. Typical Procedure. 2-(Methylsulfinyl)-1-phenylethanone (1c). Benzoic acid (1 g, 8.2 mmol), 1,1′-carbonyldiimidazole (1.33 g, 8.2 mmol), and anhydrous THF (20 mL) were stirred at room temperature for 20 min and subsequently used.

Methyllithium (25.8 mL of 1.6 M solution, 40.99 mmol) was added slowly with magnetic stirring under nitrogen to a mixture of dimethyl sulfoxide (2.9 mL, 40.99 mmol) and THF (20 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 40 min. Then, the imidazolide solution, previously prepared, was added slowly by syringe, and the mixture was stirred for 3 h at room temperature. The reaction mixture was hydrolyzed with water (30 mL) and extracted with chloroform. The aqueous phase was acidified at pH 6–7 by addition of concentrated hydrochloric acid and extracted with chloroform, and the organic phase dried with anhydrous magnesium sulfate, filtered, and evaporated. The unreacted DMSO was removed by vacuum distillation (0.1 mmHg), and the residue was recrystallized from ethyl acetate–hexane to yield 1.21 g of colorless needles (81%): mp 84–85 °C (lit.[22] mp 85 °C, lit.[10] mp 86–86.5 °C); ^{1}H NMR (Cl_3CD), δ 2.77 (s, 3 H, CH_3), 4.12–4.67 (AB system, 2 H, δ_A 4.48, δ_B 4.32, J_{AB} = 14.5 Hz, CH_2), 8.07–7.23 (m, 5 H, Ar); ^{13}C NMR (Cl_3CD) δ 38.7 (CH_3), 61.5 (CH_2), 128.3, 128.3, 133.8, 135.3 (Ar), 191.8 (CO); IR (KBr) 3060, 2940, 2900, 1665, 1595, 1575, 1490, 1450, 1375, 1030, 750, 690 cm^{-1}; MS, m/e (rel intensity) 182 ($M^{\bullet+}$, 5.9), 120 (69.4), 105 (100), 91 (36.7), 77 (46.9), 51 (16.3). Anal. Calcd for $C_9H_{10}SO_2$: C, 59.32; H, 5.53; S, 17.59. Found: C, 59.41; H, 5.26; S, 17.90.

4,4-Dimethyl-1-(methylsulfinyl)-2-pentanone (1a): recrystallized yield from diisopropyl ether–hexane 65%; mp 47–48 °C; ^{1}H NMR (Cl_3CD) δ 1.02 (s, 9 H, CH_3), 2.48 (s, 2 H, CCH_2CO), 2.68 (s, 3 H, CH_3SO), 3.75 (s, 2 H, $COCH_2SO$); ^{13}C NMR (Cl_3CD) δ 29.1 (CH_3), 30.8 (C), 38.5 (CH_3SO), 56.5 (CH_2CO), 65.5 (CH_2SO), 201.9 (CO); IR (KBr) 2970, 2920, 2890, 1710, 1370, 1020 cm^{-1}; MS, m/e, (rel intensity) 176 ($M^{\bullet+}$, 13.9), 159 (48.7), 120 (22.2), 99 (26.4), 97 (18.1), 63 (18.1), 61 (38.9), 57 (100), 43 (20.8), 41 (18.1). Anal. Calcd for $C_8H_{16}SO_2$: C, 54.51; H, 9.15; S, 18.19. Found: C, 54.20; H, 9.30; S, 17.95.

1-(Methylsulfinyl)-2-heptadecanone (1b). The β-oxo sulfoxide was extracted to pH 3–4; recrystallized yield from hexane 78%; mp 91–92 °C; ^{1}H NMR (Cl_3CD) δ 1.28, (br s, 29 H), 2.48 (m, 2 H, CH_2CO), 2.67 (s, 3 H, CH_3SO), 3.73 (br s, 2 H, $COCH_2SO$); ^{13}C NMR (Cl_3CD) δ 13.9 (CH_3), 22.2, 22.9, 28.7, 29.1, 29.2, 29.4, 31.7 (CH_2), 38.4 (CH_3SO), 45.2 (CH_2CO), 63.8 (CH_2SO), 202.3 (CO); IR (KBr) 2910, 2850, 1695, 1375, 1025, cm^{-1}; MS, m/e (rel intensity) 316 ($M^{\bullet+}$ 0.3), 300 (22.6), 299 (100), 120 (59.7), 97 (27.4), 95 (35.5), 83 (33.9), 81 (25.8), 71 (40.3), 69 (30.6), 61 (38.7), 57 (59.7), 55 (40.3), 43 (67.7), 41 (32.3). Anal. Calcd for $C_{18}H_{36}SO_2$: C, 68.30; H, 11.46; S, 10.13. Found: C, 68.10; H, 11.29; S, 10.23.

3-(Methylsulfinyl)-1,1,1-triphenyl-2-propanone (1d). The imidazolide was prepared at 50 °C. The β-oxo sulfoxide was obtained as a brown oil which was chromatographed on a flash silica gel column, eluting with ethyl acetate–methanol (50:50) to give a colorless oil which solidified upon treatment with hexane; recrystallized from ethyl acetate–hexane as colorless needles (88%); mp 143–144 °C; ^{1}H NMR (Cl_3CD) δ 2.50 (s, 3 H, CH_3), 3.42–4.27 (AB system, 2 H, δ_A 4.11, δ_B 3.58, J_{AB} = 5.5 Hz, CH_2), 7.27 (s, 15 H, Ar); ^{13}C NMR (Cl_3CD) δ 39.5 (CH_3), 64.4 (CH_2), 72.7 (C), 127.0, 128.2, 129.8, 144.4 (Ar), 199.2 (CO); MS, m/e (rel intensity) 286 (M −62, 0.4), 244 (20), 243 (100), 165 (22.8). Anal. Calcd for $C_{22}H_{20}O_2S$: C, 75.83; H, 5.79; S, 9.20. Found: C, 75.44; H, 5.92; S, 9.51.

2-(Methylsulfinyl)-1-(*p*-methoxyphenyl)ethanone (1e): recrystallized yield from ethyl acetate–hexane 78% (colorless needles); mp 103–104 °C (lit.[10] double mp at 96 and 104–105 °C); ^{1}H NMR (Cl_3CD) δ 2.73 (s, 3 H, CH_3SO), 3.87 (s, 3 H, CH_3O), 4.08–4.58 (AB system, 2 H, δ_A 4.43, δ_B 4.25, J_{AB} = 13.5 Hz, CH_2), 7.98–7.00 (m, 4 H, Ar); ^{13}C NMR (Cl_3CD) δ 38.9 (CH_3SO), 55.2 (CH_3O), 61.4 (CH_2), 113.7, 128.6, 130.9, 164.1 (Ar), 189.9 (CO); MS, m/e (rel intensity) 212 ($M^{\bullet+}$, 8.4), 150 (61.8), 136 (11.8), 135

(100), 121 (26.5), 92 (11.8), 77 (11.8). Anal. Calcd for $C_{10}H_{12}SO_3$: C, 56.58; H, 5.70; S, 15.11. Found: C, 56.37; H, 5.97; S, 15.35.

2-(Methylsulfinyl)-1-(2-quinolinyl)ethanone (1f): recrystallized yield from ethyl acetate–hexane 56%; mp 131–132 °C; ^{1}H NMR (Cl_3CD) δ 2.83 (s, 3 H, CH_3), 5.12–4.53 (AB system, 2 H, δ_A 4.96, δ_B 4.72, J_{AB} = 12.0 Hz, CH_2), 8.17–7.16 (m, 3 H, Ar); ^{13}C NMR (Cl_3CD) δ 39.3 (CH_3), 60.7 (CH_2), 117.4, 127.3, 128.9, 129.4, 130.0, 137.0, 146.5, 151.2 (Ar), 193.0 (CO); IR (KBr) 3060, 3020, 3000, 2900, 1690, 1365, 1030 cm^{-1}; MS, m/e (rel intensity) 233 ($M^{\cdot+}$, 1.1), 218 (100), 171 (13.8), 170 (14.4), 156 (33.3), 129 (22.2), 128 (88.9). Anal. Calcd for $C_{12}H_{11}O_2NS$: C, 61.78; H, 4.75; N, 6.00; S, 13.75. Found: C, 61.45; H, 4.82; N, 6.35; S, 13.67.

2-(Methylsulfinyl)-1-(1-isoquinolinyl)ethanone (1g). The imidazolide was prepared at 50 °C. The β-keto sulfoxide was obtained as brown oil which was chromatographed on a flash silica gel column, eluting with ethyl acetate–methanol (60:40) to give a oil that was not solidified (65%); ^{1}H NMR (Cl_3CD) δ 2.80 (s, 3 H, CH_3), 5.03–4.52 (AB system, 2 H, δ_A 4.86, δ_B 4.69, J_{AB} = 14.0 Hz, CH_2), 9.23–7.60 (m, 6 H, Ar); ^{13}C NMR (Cl_3CD) δ 38.4 (CH_3), 63.3 (CH_2), 125.3, 125.4, 126.5, 129.2, 129.9, 136.3, 140.3, 149.0 (Ar), 194.5 (CO); IR (neat) 3060, 3000, 2920, 1680, 1365, 1035, 755, cm^{-1}. Anal. Calcd for $C_{12}H_{11}O_2NS$: C, 61.78; H, 4.75; N, 6.00; S, 13.75. Found: C, 61.39; H, 5.05; N, 6.25; S, 13.5.

Acknowledgment. R.C.R. greatfully acknowledges the Ministry of Education and Science for an F.P.I. grant. This work has been supported by the Comisiôn Asesora de Investigaciôn Cientifica y Têcnica (CAICYT, No. PR84-0352; C03-03), Ministerio de Educaciôn y Ciencia (Madrid, Spain).

Registry No. **1a**, 123005-08-3; **1b**, 51840-11-0; **1c**, 2813-22-1; **1d**, 123005-09-4; **1e**, 2813-23-2; **1f**, 123005-10-7; **1g**, 123005-11-8; **2a**, 123005-04-9; **2b**, 14723-73-0; **2c**, 3708-04-1; **2d**, 123005-05-0; **2e**, 27918-36-1; **2f**, 123005-06-1; **2g**, 123005-07-2; $CH_3(CH_2)_4CO_2H$, 142-62-1; $PhCO_2H$, 65-85-0; m-$NO_2C_6H_4CO_2H$, 121-92-6; p-$MeOC_6H_4CO_2H$, 100-09-4; $CH_3(CH_2)_{14}CO_2H$, 57-10-3; Ph_3CCO_2H, 595-91-5; 1,1'-carbonyldiimidazole, 530-62-1; dimethyl sulfone, 67-71-0; dimethyl sulfoxide, 67-68-5; 3,3-dimethylbutyric acid, 1070-83-3; 2-quinolinecarboxylic acid, 93-10-7; 1-isoquinolinecarboxylic acid, 486-73-7; 1-(1-imidazolyl)-3,3-dimethylbutanone, 4122-55-8; 1-(1-imidazolyl)-1-hexanone, 60988-34-3; (1-imidazolyl)phenone, 10364-94-0; 1-imidazolyl(3-nitrophenyl)-methanone, 61652-82-2; 1-imidazolyl(4-methoxyphenyl)-methanone, 10364-93-9; 1-imidazolyl-2-quinolinylmethanone, 123005-03-8; imidazol-1-ylisoquinolinylmethanone, 123026-29-9; 1-imidazol-1-yl-1-hexadecanone, 26227-65-6; 1-imidazol-1-yl-2,2,2-triphenylethanone, 123005-12-9.

Synthesis and Analytical Characterization of a Major Desferrioxamine B Metabolite

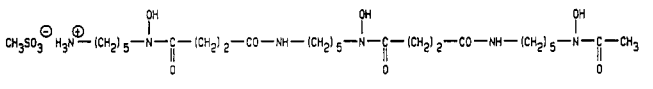
John B. Dionis, Hans-Beat Jenny, and Heinrich H. Peter*

Biotechnology Research Laboratories, Pharmaceutical Division, CIBA-GEIGY Limited, CH-4002 Basel, Switzerland

Received April 6, 1989

Introduction

Over the past 2 decades desferrioxamine B (1, Desferal, Ciba-Geigy) has been used therapeutically to treat transfusional iron overload in patients afflicted with thalassemia.[1] In addition, the drug has been used in the treatment



1

of acute iron poisoning and as a diagnostic aid for the determination of abnormal iron stores.[2] A more recent application has been in the removal of aluminum from patients with impaired renal function undergoing chronic haemodialysis.[3,4] While desferrioxamine has been established as a very safe drug with minimal toxicity in iron-overloaded patients, there have been isolated reports of toxic side effects.[5] This dissimilarity in drug tolerability could be a direct result of differences related to the metabolism of the drug.

Several early studies in desferrioxamine metabolism demonstrated the ability of plasma to degrade the iron-free compound rapidly.[6,7] This enzymatic activity was most pronounced in the plasma of the rat and mouse with lower activity observed in dog and human plasma. In contrast, the iron-bound ligand, ferrioxamine, was not metabolized to any appreciable extent.[7] The recovery of three human urinary metabolites of desferrioxamine was reported 25 years ago by Keberle.[8] The principle metabolite, known as "metabolite C" (2), was isolated and described as the product of an oxidative deamination reaction resulting in the corresponding carboxylic acid derivative. More recently an HPLC method has been developed that permits determination and quantitation of desferrioxamine B and metabolites as their iron(III) complexes in mammalian plasma.[9] Pharmacokinetic data from a patient who had received desferrioxamine i.m. (500 mg) revealed that the drug was rapidly converted into two main metabolites whose iron complexes exhibited spectral characteristics similar to those of ferrioxamine. It was suggested that the metabolites were N-terminal modified desferrioxamine derivatives.

It is evident that the synthesis and evaluation of desferrioxamine metabolites could prove quite useful in investigations correlating the formation of metabolites with the onset of toxic side effects. In this paper we describe the synthesis of "metabolite C" (2), a desferrioxamine carboxylic acid analogue, as well as the corresponding alcohol derivative (3), also a potential metabolite. In addition, a general procedure for the preparation of ferric and aluminum complexes of hydroxamate ligands is reported. Last, we have investigated the chromatographic behavior of these metabolites in the free and metal-bound forms in comparison to desferrioxamine B and its Fe(III) and Al(III) complexes utilizing high-performance liquid chromatography.

Results and Discussion

Bergeron and Pegram have recently described[10] an elegant total synthesis of desferrioxamine B. The synthesis is noteworthy in that the synthetic scheme is highly flexible thus providing access to various desferrioxamine analogues as well as proceeding in high overall yield. A key intermediate was the tri-O-benzyl-protected cyanodesferrioxamine derivative **6**. The synthesis described herein (Scheme II) is predicated on this important intermediate. The synthetic strategy was centered on the conversion of this intermediate into the fully protected deaminated

(1) Modell, B.; Berdoukas, V. Desferrioxamine, In *The Clinical Approach to Thalassaemia*; Grune and Stratton: London, 1984; p 217.
(2) Singh, A. K. *J. Med.* **1971**, 345.
(3) Chang, T. M. S.; Barre, P. *Lancet* **1983**, 1051.
(4) Drueke, T. *Med. Klin.* **1985**, *80*, 311.
(5) Borgna-Pignatti, C.; DeStefano, P.; Broglia, A. M. *Lancet* **1984**, 681.
(6) Meyer-Brunot, H. G.; Keberle, H. *Biochem. Pharmacol.* **1967**, *16*, 527.
(7) Peters, G.; Keberle, H.; Schmid, K.; Brunner, H. *Biochem. Pharmacol.* **1966**, *15*, 93.
(8) Keberle, H. *Ann. N.Y. Acad. Sci.* **1964**, *119*, 758.
(9) Kruck, T. P. A.; Teichert-Kuliszewska, K.; Fisher, E.; Kalow, W.; McLachlan, D. R. *J. Chromatogr.* **1988**, *433*, 207.
(10) Bergeron, R. J.; Pegram, J. J. *J. Org. Chem.* **1988**, *53*, 3131.

0022-3263/89/1954-5623$01.50/0