Synthesis of Sulfonyl Flosulide

W. Cameron Black,* Benoit Guay

Merck Frosst Centre for Therapeutic Research P.O. Box 1005 Pointe-Claire-Dorval, Quebec, Canada H9R 4P8
Fax +1(514)4283073; E-mail: blackc@merck.com

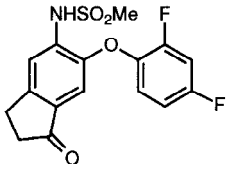
Received 29 December 1997; revised 30 January 1998

Abstract: The sulfone analogue of the selective cyclooxygenase-2 inhibitor flosulide (**1**) has been prepared in an eight step synthesis. A key step involves a thiol conjugate addition reaction followed by nucleophilic aromatic substitution to form the dihydrobenzothiophene ring system.

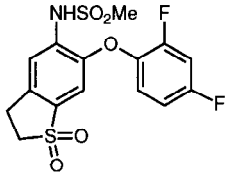
Key words: COX-2 inhibitor, benzothiophene, flosulide

The design of selective inhibitors of inducible cyclooxygenase (COX-2) has become a field of extensive research in recent years. COX-2 plays a major role in the inflammatory response by converting arachidonic acid to pro-inflammatory prostaglandins.[1] It has been proposed that an inhibitor of COX-2 which does not inhibit constitutive cyclooxygenase (COX-1) would be an effective antiinflammatory agent without the side effects commonly associated with current NSAIDs. Indeed, evidence supporting this hypothesis is now beginning to appear.[2]

One of the first compounds reported to be a selective COX-2 inhibitor was flosulide **1**.[3] In the course of exploring the SAR of this class of inhibitor, we noted that the carbonyl group was essential to the drug's activity.[4] It was unclear whether this was due to its acidifying effect on the sulfonamide pharmacophore or due to binding interactions between the enzyme and the carbonyl group itself. To investigate these issues we sought to prepare the sulfone analogue **2** for biological testing.



1

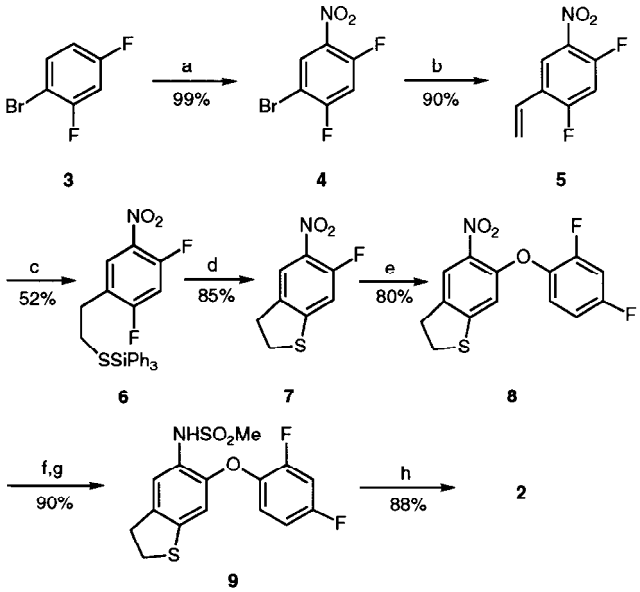


2

The synthesis of **2** turned out to be a significant challenge, and a number of unsuccessful attempts were made using conventional synthetic methods. Ultimately, a new synthesis of the benzothiophene nucleus was devised, taking advantage of a recently developed thiol conjugate addition reaction.[5]

4-Bromo-1,3-difluorobenzene **(3)** underwent regiospecific nitration to provide the 5-nitro derivative **4** in 99% yield. A palladium-catalyzed Stille coupling[6] with vinyltributyltin then provided the styrene **5** in 90% yield. Conjugate addition of triphenylsilanethiol under radical conditions using the recently reported method of Haché and Gareau[5] gave the triphenylsilyl-protected thiol **6** in 52% yield (Scheme). In this reaction, radical initiation could be accomplished with light or benzoyl peroxide, but AIBN was found to provide superior results. Compound **6** was found to be somewhat sensitive to silica gel chromatography, resulting in some loss of material on purification due to desilylation.

Nucleophilic cyclization of **6** to the benzothiophene **7** could be accomplished using KOH to remove the triphenylsilyl protecting group while simultaneously generating the reactive potassium thiolate. This reaction could also be carried out using a catalytic amount of either KOH or Bu_4NF, since the fluoride ion generated during the cyclization is able to carry on the deprotection step. With the key functionalized heterocyclic ring system in hand, standard chemical transformations then led to the target molecule. Thus nucleophilic aromatic substitution with 2,4-difluorophenol provided the tricyclic framework **8**. Reduction of the nitro group to the aniline followed by mesylation (MsCl, pyridine) gave sulfonamide **9**. Finally, tungsten-catalyzed oxidation[7] of the benzothiophene gave the cyclic sulfone **2** (sulfonyl flosulide, *N*-[6-(2,4-difluorophenoxy)-1,1-dioxo-2,3-dihydrobenzo[*b*]thiophen-5-yl]-methanesulfonamide), completing the eight step synthesis with an overall yield of 25% (Scheme).



Reagents and conditions: a) HNO_3/H_2SO_4, 0 °C; b) CH_2=$CHSnBu_3$/$Pd_2(dba)_3/Ph_3P$/toluene, reflux; c) Ph_3SiSH/AIBN/benzene, reflux; (d) KOH/EtOH/THF, 0 °C; e) 2,4-difluorophenol/KOH, 100 °C; f) Fe/NH_4Cl/EtOH/THF/H_2O, reflux; g) MsCl/pyridine/CH_2Cl_2, 0 °C; h) H_2O_2/Na_2WO_4/Aliquat 336/EtOAc, 40 °C

Scheme

The chemical shift of the NH in **2** (δ = 8.84) was similar to that of the NH in flosulide (δ = 8.78), suggesting that the indanone and the 1,1-dioxo-2,3-dihydrobenzothiophene had similar electronic character. However, on testing against COX-2 in both whole cell[8] and whole blood[9] assays, sulfonyl flosulide **2** showed no activity (>5 μM and >33 μM, respectively). This result suggests that the acidifying effect of the carbonyl on the sulfonamide NH is by itself not sufficient to retain the activity. The ketone must interact with the enzyme in a way that the sulfone is unable to duplicate with its non-coplanar oxygens. Thus the synthesis of **2** has helped to clarify the nature of the flosulide pharmacophore.

5-Bromo-2,4-difluoronitrobenzene (4):
To a suspension of **3** (12.0 mL, 106 mmol) in concd H_2SO_4 (77 mL) at 0 °C was added dropwise concd HNO_3 (68.0 mL) maintaining an internal temperature below 20 °C. The resulting mixture was stirred for 10 min at 0 °C, then poured into a mixture of Et_2O and ice water with vigorous stirring. The aqueous phase was separated and extracted with Et_2O. The combined organic phases were washed with aq $NaHCO_3$ solution (3 × 200 mL) and brine, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (15% acetone/hexanes) provided 25.2 g (99%) of the title compound as a yellow oil.
IR (film): ν = 3050, 1595, 1480, 1340, 1285, 1157, 1012, 845, 750, 683 cm^{-1}.
^1H NMR (200 MHz, acetone d_6): δ = 8.54 (t, 1 H, J = 7.5 Hz), 7.65 (dd, 1 H, J = 11.0, 8.6 Hz).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.8 (dd, J = 260, 11.6 Hz), 155.4 (dd, J = 266.7, 11.5 Hz), 134.1, 130.7 (t, J = 2.6 Hz), 107.4 (dd, J = 25.1, 1.6 Hz), 104.5 (dd, J = 18.7, 4.4 Hz).
MS (CI): m/z = 240, 238, 223, 221, 112.

2,4-Difluoro-5-vinylnitrobenzene (5):
A mixture of $Pd_2(dba)_3$ (200 mg, 0.21 mmol) and Ph_3P (220 mg, 0.84 mmol) was dissolved in toluene (20 mL), degassed and stirred 10 min at r.t. A solution of **4** (1.0 g, 4.2 mmol) in toluene (20 mL) was then added, followed by vinyltributyltin (1.84 mL, 6.3 mmol). The mixture was refluxed for 2 h, then poured into a mixture of aq NaF and Et_2O. The aqueous phase was separated and extracted with Et_2O. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (7% acetone/hexanes) provided 700 mg (90%) of the title compound as pale yellow crystals.
IR (film): ν = 3085, 1630, 1585, 1490, 1345, 1290, 1045, 850, 775 cm^{-1}.
^1H NMR (200 MHz, acetone-d_6): δ = 8.41 (t, 1 H, J = 8.0 Hz), 7.45 (t, 1 H, J = 10.7 Hz), 6.87 (dd, 1 H, J = 17.6, 11.3 Hz), 6.10 (d, 1 H, J = 17.6 Hz), 5.60 (d, 1 H, J = 11.3 Hz).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.3 (dd, J = 258.6, 11.0 Hz), 156.1 (dd, J = 263.5, 13.6 Hz), 127.4, 126.0 (m), 123.7 (dd, J = 14.7, 5.3 Hz), 120.3 (dd, J = 2.4, 1.9 Hz), 107.7 (dd, J = 28.1, 24.9 Hz).
MS (CI): m/z = 185, 169, 156.
Anal. $C_8H_5F_2NO_2$ (185.1): Calcd C, 51.89; H, 2.72; N, 7.60; Found C, 51.24; H, 2.76; N, 7.65.

2,4-Difluoro-5-[2-(triphenylsilylsulfanyl)ethyl]nitrobenzene (6):
To a solution of **5** (2.0 g, 10.8 mmol) and triphenylsilanethiol (4.74 g, 16.2 mmol) in benzene (36 mL) was added AIBN (532 mg, 3.24 mmol). The mixture was refluxed for 45 min, then cooled to r.t. and concentrated. Purification by flash chromatography (10 % acetone/hexanes) provided 2.65 g (52%) of the title compound as a white solid.
IR (KBr): ν = 3062, 1625, 1587, 1530, 1425, 1342, 1285, 1105, 705, 695 cm^{-1}.
^1H NMR (200 MHz, acetone-d_6): δ = 7.97 (t, 1 H, J = 8.0 Hz), 7.65 (m, 6 H), 7.45 (m, 9 H), 7.32 (dd, 1 H, J = 11.1, 10.0 Hz), 2.81 (m, 4 H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.2 (dd, J = 258.4, 11.0 Hz), 165.1 (dd, J = 264.8, 12.8 Hz), 135.6, 132.7, 130.3, 128.7, 128.6, 128.2, 124.4 (dd, J = 17.8, 4.1 Hz), 106.1 (dd, J = 26.9, 24.2 Hz), 30.9 (d, J = 28.1 Hz), 26.8 (d, J = 3.5 Hz).
MS (CI): m/z = 478, 400, 259, 199.
Anal. $C_{26}H_{21}F_2NO_2SSi$ (477.6): Calcd C, 65.38; H, 4.43; N, 2.94. Found C, 65.61; H, 4.49; N, 3.09.

6-Fluoro-2,3-dihydro-5-nitrobenzo[*b*]thiophene (7):
A solution of **6** (1.23 g, 2.57 mmol) in EtOH (45 mL) and THF (90 mL) was cooled in an ice bath and treated with 8 N aq KOH (0.48 mL , 3.84 mmol). The resulting mixture was stirred for 10 min, then quenched with 6 N HCl (0.48 mL, 2.88 mmol) and concentrated. The residue was partitioned between 1 M HCl and Et_2O. The aqueous layer was washed with Et_2O and the combined organics were washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (35 % CH_2Cl_2/hexanes) provided 435 mg (85 %) of **7**.
IR (KBr): ν = 3040, 2940, 1600, 1580, 1510, 1340, 1330, 1235, 990, 960, 750 cm^{-1}.
1H NMR (200 MHz, acetone- d_6): δ = 7.96 (d, 1 H, J = 7.3 Hz), 7.34 (d, 1 H, J = 11.4 Hz), 3.56 (m, 2 H), 3.42 (m, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.7 (d, J = 263.5 Hz), 153.5, 153.4 , 136.5 (d, J = 3.2 Hz), 120.8 (d, J = 2.1 Hz), 110.9 (d, J = 23.6 Hz), 34.6, 34.3.
MS (CI): m/z = 200, 183, 169.
Anal. $C_8H_6FNO_2S$ (199.2): Calcd C, 48.22; H, 3.03; N, 7.06. Found: C, 48.21; H, 3.12; N, 6.99.

6-(2,4-Difluorophenoxy)-2,3-dihydro-5-nitrobenzo[*b*]thiophene (8):
A mixture of **7** (400 mg, 2.0 mmol) and 2,4-difluorophenol (0.25 mL, 2.6 mmol) was heated to 100ºC. To this solution was added dropwise a solution of KOH (173 mg, 2.6 mmol) in H_2O (0.2 mL). The resulting mixture was heated for 1 h at 100ºC, then cooled and partitioned between EtOAc and H_2O. The aqueous phase was extracted with EtOAc and the combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (10% acetone/hexanes) provided 495 mg (80%) of **8** as yellow crystals.
IR (KBr): ν = 1680, 1580, 1500, 1460, 1340, 1245, 1190, 1070, 955, 850, 800 cm^{-1}.
^1H NMR (200 MHz, acetone-d_6): δ = 7.91 (s, 1 H), 7.29 (m, 2 H), 7.10 (m, 1 H), 6.96 (s, 1 H), 3.52 (m, 2 H), 3.39 (m, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4 (dd, J = 245.8, 10.4 Hz), 153.8 (dd, J = 251.0, 12.4 Hz), 152.3, 151.8, 138.5 (dd, J = 11.6, 5.6 Hz), 136.2, 135.3, 122.7 (dd, J = 9.9, 1.6 Hz), 121.3, 111.7 (dd, J = 22.7, 3.8 Hz), 110.8, 105.7 (dd, J = 26.6, 21.4 Hz), 34.7, 34.2.
MS (CI): m/z = 310, 293, 180, 93.
Anal. $C_{14}H_9F_2NO_3S$ (277.2): Calcd C, 54.36; H, 2.93; N, 4.55. Found: C, 54.61; H, 3.16; N, 4.53.

5-Amino-6-(2,4-difluorophenoxy)-2,3-dihydrobenzo[*b*]thiophene (8a):
To a solution of **8** (495 mg, 1.6 mmol) in EtOH (24 mL), THF (12 mL), aq NH_4Cl (6 mL) and H_2O (6 mL) was added iron powder (575 mg, 10.2 mmol). The mixture was refluxed for 1 h, then filtered hot through Celite. The filter pad was washed with hot EtOAc (3 × 50 mL). The filtrate was concentrated and the residue was partitioned between EtOAc and brine. The organic phase was dried ($MgSO_4$) and concentrated to provide 453 mg (100 %) of **8a**.
IR (KBr): ν = 3450, 3350, 2930, 1610, 1500, 1475, 1240, 1195, 1133, 1090, 955, 845 cm^{-1}.
^1H NMR (200 MHz, acetone-d_6): δ = 7.17 (m, 1 H), 6.99 (m, 2 H), 6.81 (s, 1 H), 6.60 (s, 1 H), 4.49 (br s , 2 H), 3.28 (m, 2 H), 3.13 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.9 (dd, *J* = 243.5, 10.4 Hz), 152.7 (dd, *J* = 249.2, 12.1 Hz), 143.3, 140.4 (dd, *J* = 11.4, 3.8 Hz), 136.1, 134.3, 120.5 (dd, *J* = 9.4, 1.8 Hz), 112.8, 111.4, 111.3 (dd, *J* = 22.4, 3.5 Hz), 105.0 (dd, *J* = 26.8, 21.8 Hz), 35.8, 33.8.
MS (CI): *m/z* = 280, 279, 260, 138.
Anal. $C_{14}H_{11}F_2NOS$ (279.3): Calcd C, 60.19; H, 3.97; N, 5.04. Found: C, 60.17; H, 4.12; N, 5.01.

_N_-[6-(2,4-Difluorophenoxy)-2,3-dihydrobenzo[*b*]thiophen-5-yl]-methanesulfonamide (9):
To a solution of **8a** (450 mg, 1.61 mmol) in CH_2Cl_2 (18 mL) at 0˚C was added pyridine (0.65 mL, 8.05 mmol), followed by $MeSO_2Cl$ (0.50 mL, 6.44 mmol). The mixture was stirred 3 h then quenched with H_2O and separated. The organic layer was washed with 1 M HCl and brine, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (15% acetone/hexanes) provided 515 mg (90 %) of **9** as light pink crystals.
IR (KBr): 3260, 3080, 2930, 1705, 1605, 1500, 1472, 1390, 1330, 1200, 1160, 1137, 960, 850, 755 cm^{-1}.
^{1}H NMR (200 MHz, acetone-d_6): δ = 7.17 (br s, 1 H), 7.4 (s, 1 H), 7.25 (m, 2 H), 7.0 (m, 1 H), 6.67 (s, 1 H), 3.38 (m, 2 H), 3.26 (m, 2 H), 3.02 (s, 3 H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.3 (dd, *J* = 246.4, 10.4 Hz), 154.0 (dd, *J* = 251.0, 12.5 Hz), 148.6, 140.3, 138.2 (dd, *J* = 11.5, 4.1 Hz), 135.5, 123.2 (d, *J* = 8.9 Hz), 122.4, 120.2, 111.7 (dd, *J* = 22.9, 4.0 Hz), 108.5, 105.7 (dd, *J* = 26.6, 21.6 Hz), 39.0 (d, *J* = 1.3 Hz), 35.5, 34.0.
MS (CI): *m/z* = 357, 279, 277, 79.
Anal. $C_{15}H_{13}F_2NO_3S_2$ (357.4): Calcd C, 50.40; H, 3.67; N, 3.94. Found: C, 50.34; H, 3.86; N, 3.92.

_N_-[6-(2,4-Difluorophenoxy)-2,3-dihydro-1,1-dioxobenzo[*b*]-thiophen-5-yl]methanesulfonamide (2):
To a solution of **9** (60 mg, 0.17 mmol) in EtOAc (0.5 mL) was added Na_2WO_4 (22 mg, 0.07 mmol), 30% aq H_2O_2 (0.07 mL, 0.6 mmol) and Aliquat 336 (0.05 mL). The mixture was warmed to 45 °C, stirred for 0.5 h, then cooled and partitioned between EtOAc and H_2O. The organic phase was washed sequentially with aq $NaHSO_3$ solution, H_2O and brine, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (30 % acetone/hexane) provided 57 mg (88%) of **2** as a white solid.
IR (KBr): ν = 3260, 3070, 2920, 1615, 1590, 1505, 1482, 1400, 1340, 1295, 1245, 1200, 1165, 1110, 960, 850, 760 cm^{-1}.
^{1}H NMR (200 MHz, acetone-d_6): δ = 8.85 (br s, 1 H), 7.7 (s, 1 H), 7.42 (dt, *J* = 9.12, 5.5 Hz, 1 H), 7.30 (ddd, *J* = 11.5, 8.8, 3.1 Hz, 1 H), 7.13 (m, 1 H), 7.01 (s, 1 H), 3.54 (m, 2 H), 3.42 (m, 2 H), 3.22 (s, 3 H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4 (dd, *J* = 243.7, 10.5 Hz), 155.0 (dd, *J* = 248.9, 12.5 Hz), 149.6, 139.3 (dd, *J* = 11.6, 3.2 Hz), 135.8, 134.3, 133.9, 124.8 (dd, *J* = 9.3, 1.3 Hz), 119.8, 113.0 (dd, *J* = 23.0, 3.8 Hz), 107.7, 106.6 (dd, *J* = 27.2, 22.0 Hz), 52.0, 40.5, 25.5.
MS (CI): *m/z* = 390, 311.
Anal. $C_{15}H_{13}F_2NO_5S_2$ (389.4): Calcd C, 46.26; H, 3.36; N, 3.61. Found: C, 46.20; H, 3.43; N, 3.53.

(1) (a) Hla, T.; Neilson, K. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 7384.
(b) Holtzman, M.J.; Turk, J.; Shornick, L.P. *J. Biol. Chem.* **1992**, *267*, 21438.
(c) Herschman, H.R. *Cancer and Metastasis Reviews* **1994**, *13*, 241.
(d) Kennedy, B.P.; Chan, C.-C.; Culp, S.A.; Cromlish, W.A. *Biochem. Biophys. Res. Commun.* **1993**, *197*, 494.
(2) (a) Graul, A.; Martel, A.M.; Castaner, J. *Drugs of the Future* **1997**, *22*, 711.
(b) Lanza, F.; Simon, T.; Quan, H.; Bolognese, J.; Rack, M.F.; Hoover, M.; Wilson, F. *Meeting of the American Gastroenterological Association*, Washington D.C., May 1997; Abstract 395.
(3) Wiesenberg-Böttcher, I.; Schweizer, A.; Green, J.R.; Seltenmeyer, Y.; Müller, K. *Agents Actions* **1989**, *26*, 240.
(4) Li, C.-S.; Black, W.C.; Chan, C.-C.; Ford-Hutchinson, A.W.; Gauthier, J.Y.; Gordon, R.; Guay, D.; Kargman, S.; Lau, C.K.; Mancini, J.; Ouimet, N.; Roy, P.; Vickers, P.; Wong, E.; Young, R.N.; Zamboni, R.; Prasit, P. *J. Med. Chem.* **1995**, *38*, 4897.
(5) Haché, B.; Gareau, Y. *Tetrahedron Lett.* **1994**, *35*, 1837.
(6) Stille, J.K. *Angew. Chem.* **1986**, *98*, 504; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.
(7) (a) Blacklock, T.J.; Butcher, J.W.; Sohar, P.; Lamanec, T.R.; Grabowski, E.J.J. *J.Org. Chem.* **1989**, *54*, 3907.
(b) Schultz, H.S.; Freyermüth, H.B.; Buc, S.R. *J. Org. Chem.* **1963**, *28*, 1140.
(8) Chan, C.-C.; Boyce, S.; Brideau, C.; Ford-Hutchinson, A.W.; Gordon, R.; Guay, D.; Hill, R.G.; Li, C.-S.; Mancini, J.; Penneton, M.; Prasit, P.; Rasori, R.; Riendeau, D.; Roy, P.; Vickers, P.; Wong, E.; Rodger, I.W. *J. Pharmacol. Exp. Ther.* **1995**, *274*, 1531.
(9) Brideau, C.; Kargman, S.; Liu, S.; Dallob, A.L.; Ehrich, E.W.; Rodger, I.W.; Chan, C.-C. *Inflamm. Res.* **1996**, *45*, 68.