Improved Synthesis of a Selective COX-2 Inhibitor, 6-(2,4-Difluorophenoxy)-5-methanesulfonamidoindan-1-one (Flosulide)

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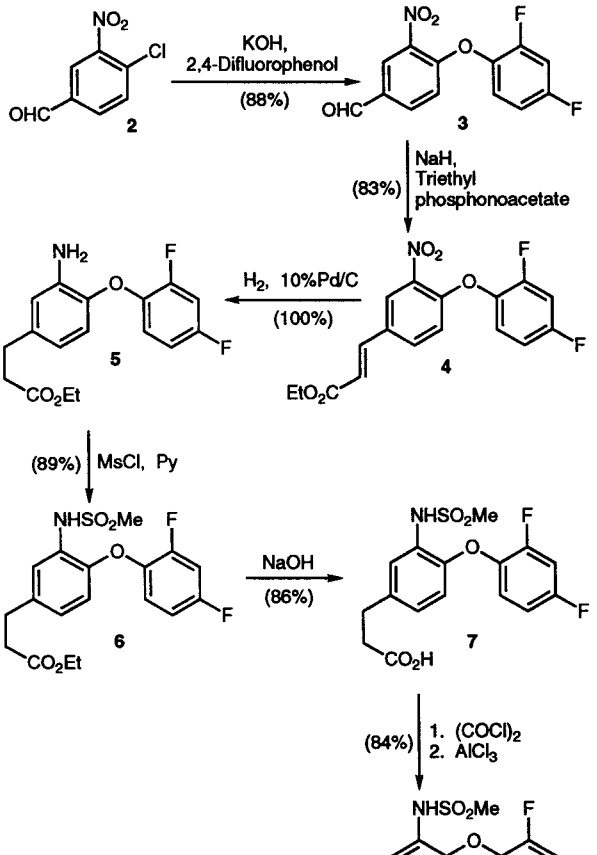
An improved synthesis of Flosulide (**1**), a selective COX-2 inhibitor, from the cheap and commercially available 4-chloro-3-nitrobenzaldehyde (**2**) by using an intramolecular Friedel–Crafts reaction of 4-(2,4-difluorophenoxy)-3-methanesulfonamidophenylpropionic acid (**7**) as the key step is reported.

The mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs) involves inhibition of cyclooxygenase and thus blocking the production of prostanoids.[1] Recent discovery of a novel cyclooxygenase, cyclooxygenase-2 (COX-2), which is responsible for inflammation conditions,[2–5] might provide an opportunity of more effective treatment with potentially fewer side effects.

We and others have shown that 6-(2,4-difluorophenoxy)-5-methanesulfonamidoindan-1-one (**1**), Flosulide (CGP 28238), is a relatively selective COX-2 inhibitor.[6] Therefore, we needed a large quantity of compound **1** for in vitro and in vivo studies. The literature procedure[7] for the preparation of Flosulide is lengthy and requires a non-regioselective benzylic oxidation for the introduction of the carbonyl moiety on the indane ring. We now report our improved synthesis of this useful COX-2 inhibitor, which in the key step uses an intramolecular Friedel–Crafts reaction of a phenylpropionic acid intermediate to form the indanone ring regioselectively, and therefore obviates the need to selectively introduce the carbonyl group.

The cheap and commercially available 4-chloro-3-nitrobenzaldehyde (**2**) was coupled with the potassium salt of 2,4-difluorophenol at 120 °C for 2 h to give 4-(2,4-difluorophenoxy)-3-nitrobenzaldehyde (**3**) in 88 % yield. The potassium salt of 2,4-difluorophenol should be prepared prior to the addition of aldehyde **2** and excess potassium hydroxide should be avoided to prevent the coupling product **3** from undergoing a potential Cannizzaro side reaction. Aldehyde **3** was then reacted with triethyl phosphonoacetate in the presence of sodium hydride to yield ethyl 4-(2,4-difluorophenoxy)-3-nitrocinnamate (**4**) in 83 % yield. The nitro group and the double bond of **4** were simultaneously reduced by hydrogenation to furnish ethyl 3-amino-4-(2,4-difluorophenoxy)phenylpropionate (**5**) in quantitative yield. Sulfonylation with methanesulfonyl chloride in the presence of pyridine provided ethyl 4-(2,4-difluorophenoxy)-3-methanesulfonamidophenylpropionate (**6**). Hydrolysis of the ethyl ester of **6** yielded 4-(2,4-difluorophenoxy)-3-methanesulfonamidophenylpropionic acid (**7**), which was then converted to the corresponding acid chloride. Treatment of the resultant acid chloride in 1,2-dichloroethane with aluminum chloride cleanly gave **1** in 84 % yield. No Friedel–Crafts cyclization product ortho to the methanesulfonamido group was detected.



In summary, we have developed an efficient and selective synthesis of Flosulide. The present synthesis is more staightforward and convenient than the original preparation, which involved two non-selective steps and lower overall yield.

Satisfactory microanalyses obtained for all new compounds: C ± 0.12, H ± 0.24, N ± 0.09.

4-(2,4-Difluorophenoxy)-3-nitrobenzaldehyde (3):

To powdered KOH (6.5 g, 0.11 mol) was added 2,4-difluorophenol (18.0 g, 0.14 mol). The mixture was stirred and heated at 110 °C for 30 min. 4-Chloro-3-nitrobenzaldehyde (**2**; 23.0 g, 0.12 mol) was added in one portion. The mixture was then further stirred at 120 °C for 2 h. After cooling to r.t., the mixture was partitioned between EtOAc and H_2O. The EtOAc layer was separated, washed successively with 1 M aq NaOH, brine, 1 M aq HCl and brine, dried ($MgSO_4$) and evaporated to give a yellow solid. The residue was suspended in EtOH, stirred for 30 min and filtered to give **3** as a pale yellow solid; yield: 29.5 g (88 %). Recrystallization from EtOH provided an analytically pure sample; mp 93–94 °C.

^{1}H NMR ($CDCl_3$): δ = 10.0 (s, 1 H, CHO), 8.49 (d, J = 2.0 Hz, 1 H_{arom}), 8.01 (dd, J = 8.6, 2.0 Hz, 1 H_{arom}), 7.30–6.95 (m, 4 H_{arom}).
MS (CI/CH_4): m/z = 280 (M + 1).

Ethyl 4-(2,4-Difluorophenoxy)-3-nitrocinnamate (4):
To a suspension of 80% NaH (600 mg, 20 mmol) in 1,2-dimethoxyethane (DME, 40 mL) at 0 °C was added dropwise triethyl phosphonoacetate (4.6 g, 20.7 mmol) over a period of 15 min. The mixture was stirred at r.t. for 15 min and a homogeneous solution resulted. The mixture was cooled to 0 °C and a solution of **3** (5.0 g, 17.9 mmol) in DME (10 mL) was added. The mixture was stirred at 60 °C for 1 h, cooled to r.t. and quenched with 1 M aq AcOH (20 mL). The mixture was then diluted with H_2O (100 mL). The precipitate formed was collected, washed successively with H_2O and EtOH, and dried under vacuum to give **4** as a white powder; yield: 5.2 g (83%). Recrystallization from EtOH provided an analytically pure sample; mp 116–117 °C.

^{1}H NMR ($CDCl_3$): δ = 8.12 (d, J = 2.0 Hz, 1 H_{arom}), 7.60 (m, 2 H, 1 H_{arom}, CH=C), 7.20–6.90 (m, 3 H_{arom}), 6.85 (d, J = 8.8 Hz, 1 H_{arom}), 6.43 (d, J = 16.0 Hz, 1 H, C=$CHCO_2$), 4.27 (q, J = 7.2 Hz, 2 H, OCH_2), 1.34 (t, J = 7.2 Hz, 3 H, CH_3).
MS (CI/CH_4): m/z = 350 (M + 1).

Ethyl 3-Amino-4-(2,4-difluorophenoxy)phenylpropionate (5):
A mixture of **4** (5.2 g, 14.9 mmol) and 10% Pd/C (1 g) in EtOAc (100 mL) was hydrogenated at 3.4 bar and at r.t. for 2 h. The catalyst was filtered and the filtrate was concentrated in vacuo to provide **5** as a colorless oil; yield: 4.8 g (quantitative).

^{1}H NMR ($CDCl_3$): δ = 7.05–6.50 (m, 6 H_{arom}), 4.12 (q, J = 7.2 Hz, 2 H, OCH_2), 2.84 (t, J = 7.5 Hz, 2 H, CH_2), 2.57 (t, J = 7.5 Hz, 2 H, CH_2), 1.24 (t, J = 7.2 Hz, 3 H, CH_3).
MS (FAB+): m/z 321 (M + 1).

Ethyl 4-(2,4-Difluorophenoxy)-3-methanesulfonamidophenylpropionate (6):
To a solution of **5** (4.7 g, 14.6 mmol) and pyridine (4.0 mL, 50 mmol) in CH_2Cl_2 (30 mL) at r.t. was added MsCl (4.5 g, 39.3 mmol). The mixture was stirred at r.t. for 1 h and quenched with H_2O. The CH_2Cl_2 layer was separated, washed successively with saturated aq $NaHCO_3$, 1 M aq HCl, brine, dried ($MgSO_4$) and concentrated. Chromatography over silica gel and elution with hexanes/EtOAc (3:2) gave **6** as a white solid; yield: 5.2 g (89%). Recrystallization from EtOH furnished an analytically pure sample; mp 100.5–101.5 °C.

^{1}H NMR ($CDCl_3$): δ = 7.46 (s, 1 H_{arom}), 7.25–6.85 (m, 4 H_{arom}), 6.82 (s, 1 H, NH), 6.58 (d, J = 8.4 Hz, 1 H_{arom}), 4.11 (q, J = 7.2 Hz, 2 H, OCH_2), 3.01 (s, 3 H, SO_2CH_3), 2.90 (t, J = 7.6 Hz, 2 H, CH_2), 2.58 (t, J = 7.6 Hz, 2 H, CH_2), 1.22 (t, J = 7.2 Hz, 3 H, CH_3).
MS (CI/CH_4): m/z = 400 (M + 1).

4-(2,4-Difluorophenoxy)-3-methanesulfonamidophenylpropionic Acid (7):
A mixture of **6** (5.0 g, 12.5 mmol) and 1 M aq NaOH (50 mL, 50 mmol) in EtOH (100 mL) was refluxed for 2 h and the solvent was evaporated in vacuo. The residue was diluted with H_2O, acidified with 3 M aq HCl and extracted with EtOAc. The EtOAc extract was washed with brine, dried ($MgSO_4$) and concentrated to give an oil, which solidified on standing. The residue was suspended in Et_2O, stirred at r.t. for 30 min and filtered to give **7** as a white solid; yield: 4.0 g (86%). Recrystallization from toluene provided an analytically pure sample; mp 146–148 °C.

^{1}H NMR ($CDCl_3$): δ = 7.47 (s, 1 H_{arom}), 7.24–6.86 (m, 5 H_{arom}), 6.59 (d, J = 8.4 Hz, 1 H_{arom}), 3.01 (s, 3 H, SO_2CH_3), 2.92 (t, J = 7.5 Hz, 2 H, CH_2), 2.65 (t, J = 7.5 Hz, 2 H, CH_2).
MS (CI/CH_4): m/z = 372 (M + 1).

6-(2,4-Difluorophenoxy)-5-methanesulfonamidoindan-1-one (Flosulide) (1):
A mixture of **7** (5.8 g, 15.6 mmol), oxalyl chloride (3.0 g, 23.4 mmol) and DMF (100 µL) in 1,2-dichloroethane (100 mL) was stirred at 0 °C for 30 min and then at r.t. for 30 min. Solvent and excess oxalyl chloride were removed in vacuo to yield the crude acid chloride. The crude acid chloride was dissolved in 1,2-dichloroethane (100 mL) and anhydr. $AlCl_3$ (9.2 g, 69 mmol) was added at r.t. The mixture was further stirred at r.t. for 30 min, cooled to 0 °C and quenched with H_2O. After dilution with CH_2Cl_2, the CH_2Cl_2 layer was separated, washed successively with 1 M aq HCl and brine, dried ($MgSO_4$) and concentrated. Chromatography over silica gel and elution with hexanes/EtOAc (1:1) furnished **1** as a white solid; yield: 5.5 g (84%). Recrystallization from EtOH gave an analytically pure sample; mp 155–156 °C (Lit.[7] mp 156 °C).

^{1}H NMR ($CDCl_3$): δ = 7.71 (s, 1 H_{arom}), 7.34 (s, 1 H, NH), 7.20–6.90 (m, 4 H_{arom}), 3.13 (s, 3 H, SO_2CH_3), 3.09 (t, J = 5.7 Hz, 2 H, CH_2), 2.66 (t, J = 5.7 Hz, 2 H, CH_2).
MS (CI/CH_4): m/z = 354 (M + 1).

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