Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 16 Feb 2007.

To cite this article: John Scheigetz , Robert Zamboni & Bruno Roy (1995) Synthesis of 5-Methanesulfonamido-6-(2,4-Difluorophenylthio)-1-Indanone, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:18, 2791-2806, DOI: 10.1080/00397919508011826

To link to this article: http://dx.doi.org/10.1080/00397919508011826

SYNTHETIC COMMUNICATIONS, 25(18), 2791-2806 (1995)

SYNTHESIS OF 5-METHANESULFONAMIDO-6-(2,4-DIFLUOROPHENYLTHIO)-1-INDANONE

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Abstract: The ethylene ketal of 5-nitro-6-bromo-1-indanone **6** was prepared via oxidation of N-(6-Bromo-5-indanyl)-acetamide **1**. A subsequent mild displacement and elaboration to 6-thiosubstituted-5-amino indanone derivative **10** is also described.

The search for novel and specific cyclooxygenase-2 enzyme inhibitors led us to the synthesis of indanone derivatives. In the course of our work, the 6-sulfur substituted 5-methanesulfonamido-1-indanones emerged with better overall pharmacological profiles and so a practical method for their synthesis was needed. In this paper we report the synthesis of compound **10**, a novel nonsteroidal anti-inflammatory agent.[1] A synthetic strategy was developed starting with the indane system. Its oxidation to the indanone had to precede the introduction of sulfur at

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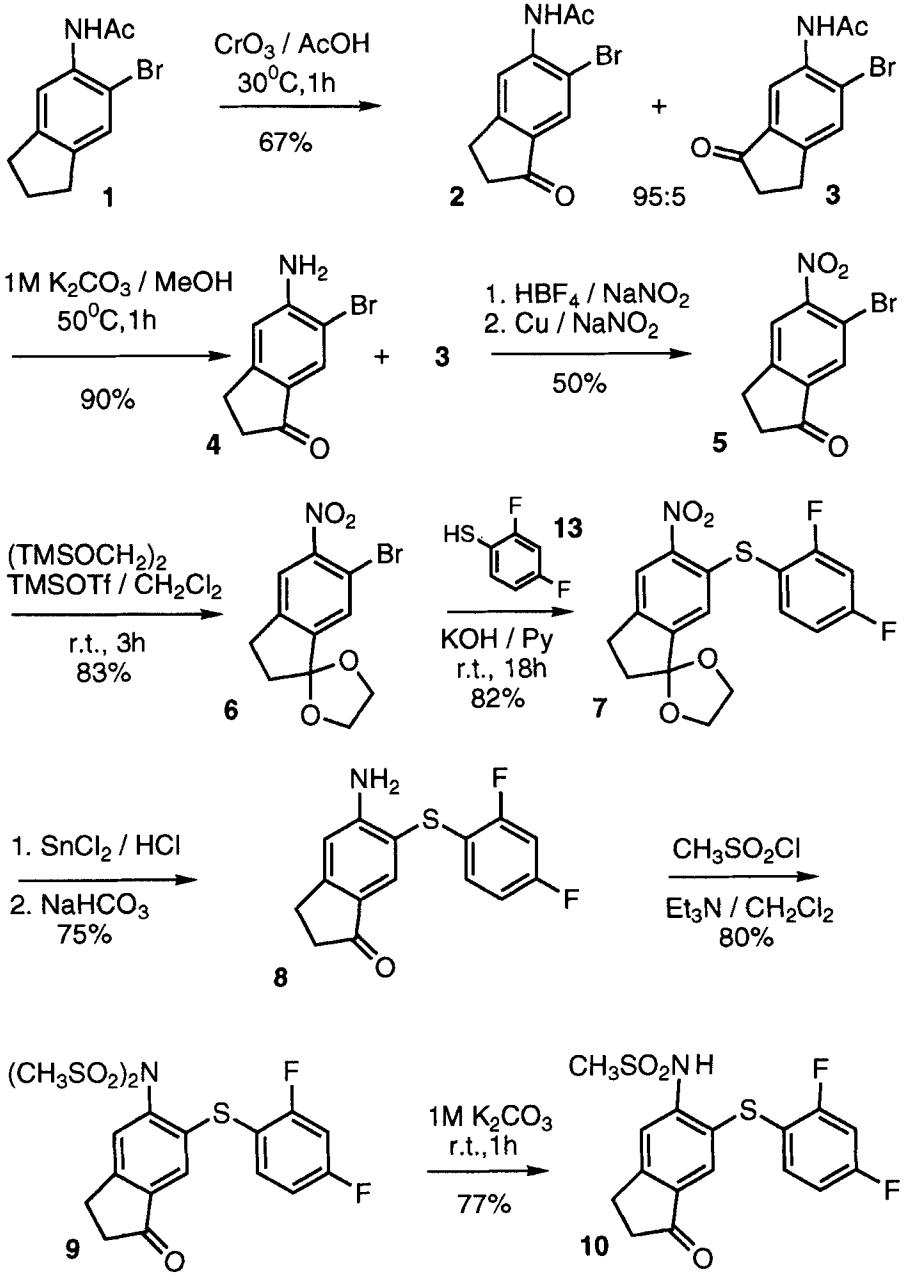
position 6 to avoid oxidation at the sulfur site. A synthon **6** was developed from which the sulfur-linked derivative could be prepared.

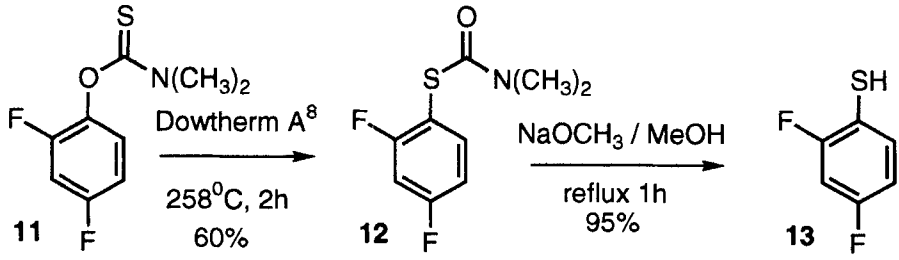
5-Aminoindane was acetylated in accordance with a known procedure[2] and was then brominated to obtain an 85% yield of N-(6-bromo-5-indanyl)-acetamide **1**. Oxidation of **1** using chromium trioxide gives two indanone isomers **2** and **3**. The quantity of the unwanted isomer **3** can be minimized by controlling the oxidation temperature between 25 °C and 30 °C and then crystallizing the product mixture from the reaction medium by dilution with water. The desired 5-acetylamino-6-bromo-1-indanone isomer **2** was obtained (67%) as a 95:5 isomer mixture which circumvents a tedious chromatography. The acetamide **2** was found to be labile and was hydrolysed with 1M potassium carbonate in methanol at 50 °C whereas the isomeric amide **3** was isolated unaltered from these hydrolysis conditions. There was no need to purify the amine **4** at this stage, as the unhydrolysed amide **3** does not react in the subsequent diazonium reaction and is easily removed then from the nitro product **5**. The diazonium fluoroborate formation of **4** was monitored by carrying out a test tube size reaction to the desired product and observing starting material content by TLC. The indanone carbonyl of **5** was protected as the ethylene ketal using the procedure of Nayori[3] to give the key synthon **6**. Subsequent displacement of the bromine functionality with a thiophenol derivative **13** under mild conditions gave compound **7** in over 80%. The coupled nitro ketal **7** was reduced to the amino ketone **8** using tin chloride and

Scheme I



hydrochloric acid. The ketal is hydrolysed first and then the nitro group is reduced slowly. Neutralization of the filtered hydrochloride salt of **8** is necessary to remove the tin residues. Bis mesylation of **8** using methanesulfonyl chloride followed by mild hydrolysis of **9** with 1M potassium carbonate gave the desired 6-sulfur substituted-5-methanesulfonamido-1-indanone **10**.

Scheme II



Thiophenol **13** can be prepared from the corresponding aniline via a diazonium reaction[4] by which method the synthesis of 2,4-difluorothiophenol **13** was already reported[5]. The safety issue of intermediate diazonium xanthates[4] on larger scale and the availability of the appropriately substituted phenol prompted us to investigate an alternate route. Thermal rearrangements of O-aryl dimethylthiocarbamates to S-aryl dimethylthiocarbamates known as the Newman-Kwart rearrangement[6] was considered. Improved methodology on this rearrangement developed in our laboratories[7] did not produce satisfactory results. However, when the pyrolysis was carried out in Dowtherm A[8] at reflux (258 °C)

for 1 h, the rearranged product **12** was isolated in 60% yield. Addition of 1% potassium carbonate in the pyrolysis mixture appeared to minimize decomposition and give a cleaner product mixture. Removal of the blocking group using sodium methoxide in methanol gave an excellent yield of good quality 2,4-difluorothiophenol **13**.

EXPERIMENTAL SECTION

Melting points were measured in a Buchi 510 in open capillary tubes and are uncorrected. NMR spectra were obtained on Bruker AM300 and Bruker ARX400 spectrometers and proton chemical shifts are relative to tetramethylsilane as internal standard. Analytical thin-layer chromatography (TLC) was routinely monitored on precoated Analtech glass sheets (Silica Gel GF, 0.25 mm thick) and detection was effected using an 8% cerium molybdate solution in 15% sulfuric acid. Elemental analyses were performed by Guelph Chemical Laboratories, Guelph, Ontario.

N-(6-Bromo-5-indanyl)-acetamide (1)

To a solution of N-(5-indanyl)-acetamide[2] (240 g, 1.37 mol) in glacial acetic acid (4 L) at 10 °C was added bromine (86 mL, 1.66 mol) dropwise over a period of 1 h. After stirring for a further 15 min at 10 °C, the mixture was diluted with water

until no more precipitate formed. The precipitate was collected, washed with water and dried under vacuum to give 297 g (85%) of the title compound **1**; m.p. 145-146°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.50 (s, 1H), 7.35 (s, 1H), 2.78-2.90 (m, 4H), 2.20 (s, 3H), 2.00-2.10 (m, 2H). Anal. Calcd. for $C_{11}H_{12}NBrO$: C, 51.99; H, 4.75; N, 5.51; Br, 31.44; Found: C, 51.88; H, 4.71; N, 5.49; Br, 31.30.

5-Acetylamino-6-bromo-1-indanone (2)

To a mechanically stirred solution of N-(6-bromo-5-indanyl)-acetamide **1** (126 g, 500 mmol) in glacial acetic acid (750 mL) was added dropwise over 30 min a solution of chromium trioxide (150 g, 1.5 mol) in water (300 mL). A first small portion of the chromium trioxide solution was added at room temperature to initiate the reaction. When the internal temperature rose to 27 °C, a cold water bath was placed under the flask and occasionally, amounts of ice added to maintain the internal temperature between 25 °C and 30 °C during the addition. The cold water bath was then removed and the reaction monitored every 10 min by TLC. Samples were added to water until coagulation occurred and then extracted with ethyl acetate. TLC plates were eluted with 50% ethyl acetate in hexane and the indanone isomers observed at R_f 0.4 and R_f 0.3. After 30 min, another portion of chromium trioxide (12.5 g, 125 mmol) in water (25 mL) was added over 3 min and the mixture stirred for another 10 min after which time approximately 5% of

starting material remained. To the mixture was added water (3 x 750 mL) with 2 min of stirring in between additions. Product mixture crystallized out. The flask was recooled in ice and water and the mixture stirred for another 30 min. The product mixture was filtered and washed with water until light in color and then air dried on glass trays in a hood for 24 h. The yield was 91 g (67%) which was contaminated with about 5% of isomeric 6-acetylamino-5-bromo-1-indanone **3**. A sample was purified by silica gel chromatography using 50% ethyl acetate in hexane as eluent to afford the title compound **2**; m.p. 173-174 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.95 (s, 1H), 7.92 (s, 1H), 3.03-3.18 (m, 2H), 2.63-2.78 (m, 2H), 2.30 (s, 3H). Anal. Calcd. for $C_{11}H_{10}NBrO_2$: C, 49.27; H, 3.75; N, 5.22; Br, 29.80; Found: C, 49.34; H, 3.74; N, 5.20; Br, 30.06.

5-Amino-6-bromo-1-indanone (4)

To a stirring suspension of 5-acetylamino-6-bromo-1-indanone **2** (167 g, 623 mmol) in methanol (3.25 L) was added in one portion a 1 M potassium carbonate solution (1.5 L). The mixture was heated to 50 °C and the temperature maintained there for 1 h. The 5% isomeric contaminant 6-acetylamino-5-bromo-1-indanone **3** was not hydrolysed. The mixture was concentrated on a rotavap to remove the methanol while keeping the bath temperature at 40 °C or less. The aqueous mixture was diluted with more water (500 mL), filtered and the solid washed well with more water. The product was air dried on the filter funnel for 1 h and then

under vacuum to constant weight to obtain 128 g (90%) yield of the title compound **4** contaminated with about 5% of the isomeric acetamide 6-acetylamino-5-bromo-1-indanone **3**. A sample was purified by silica gel chromatography using 50% ethyl acetate in hexane as eluent to give the title compound **4**; m.p. 199-200 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 6.74 (s, 1H), 4.70 (br s, 2H), 2.85-3.08 (m, 2H), 2.52-2.79 (m, 2H). Anal. Calcd. for C_9H_8NBrO: C, 47.81; H, 3.56; N, 6.19; Br, 35.34; Found: C, 48.01; H, 3.59; N, 6.17; Br, 35.50.

5-Nitro-6-bromo-1-indanone (5)

To a mechanically stirred suspension of 5-amino-6-bromo-1-indanone **4** (100 g, 442 mmol) in 20% fluoroboric acid (440 mL) at 5-7 °C (critical) was added dropwise a solution of sodium nitrite (72.4 g, 1.05 mol) in water (230 mL). The mixture was stirred for 45 min and then a sample of the suspension was added to a test tube containing excess copper powder and sodium nitrite solution. It was shaken well and then extracted with ethyl acetate. TLC using 50% ethyl acetate in hexane as eluent showed the nitro product at R_f 0.8 with starting material still present. Another portion of 20% fluoroboric acid (37 mL) and sodium nitrite (14.5 g, 210 mmol) in water (50 mL) was added and the mixture stirred for another hour after which time a TLC showed only a trace amount of starting material remaining. The stirring was stopped and the diazonium fluoroborate salt

deposited at the bottom of the flask. The aqueous phase was decanted off and the solid washed with cold water (2 x 400 mL) with decanting and then the salt was suspended in cold water (250 mL). The diazonium fluoroborate suspension was then added in portions over 30 min to a stirring 5 °C precooled mixture of copper metal powder (160 g, 2.5 mol), sodium nitrite (500 g, 7.2 mol) and water (1 L). The mixture was stirred for 30 min or until the foaming had subsided and was then extracted with 10% methanol in dichloromethane (4 x 750 mL). The combined organic layers were filtered to remove excess copper powder and then dried with $MgSO_4$. Evaporation of the filtrate gave a black solid. The crude was purified on a silica gel plug using 3% methanol in dichloromethane as eluent. The nitro product eluted first leaving a black tar on the column. The product fractions were concentrated and the yellow solid washed with 50% diethyl ether in hexane to yield 57 g (50%) of the title compound **5**; m.p. 149-152 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.85 (s, 1H), 3.15-3.30 (m, 2H), 2.78-2.92 (m, 2H). MS (DCI, CH_4) m/z 256 $(M+H)^+$. Anal. Calcd. for $C_9H_6NBrO_3$: C, 42.21; H, 2.36; N, 5.47; Br, 31.20; Found: C, 42.36; H, 2.67; N, 5.48; Br, 31.40.

5-Nitro-6-bromo-1-indanone ethylene ketal (6)

To a suspension of 5-nitro-6-bromo-1-indanone **5** (86 g, 335 mmol) and 1,2-bis (trimethylsilyloxy) ethane (193 g, 938 mmol) in dichloromethane (700 mL) was added at room temperature trimethylsilyl trifluoromethanesulfonate (800 μL). The

mixture was stirred for 3 h and the solution quenched with saturated aqueous $NaHCO_3$ (800 mL). The dichloromethane layer was separated, washed with brine, dried over $MgSO_4$, filtered and concentrated on a rotavap. The residue was purified by silica gel chromatography using dichloromethane/ethyl acetate/hexane 10/30/70 as eluent to afford 84 g (83%) of the title compound **6**; m.p. 104-107 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.68 (s, 1H), 4.03-4.15 (m, 2H), 4.15-4.27 (m, 2H), 2.98 (t, 2H), 2.38 (t, 2H). Anal. Calcd. for $C_{11}H_{10}NBrO_4$: C, 44.01; H, 3.35; N, 4.66; Br, 26.62; Found: C, 44.28; H, 3.54; N, 4.54; Br, 26.41.

5-Nitro-6-(2,4-difluorophenylthio)-1-indanone ethylene ketal (7)

To a mixture of 5-nitro-6-bromo-1-indanone ethylene ketal **6** (61.6 g, 205 mmol) and 2,4-difluorothiophenol **13** (36 g, 249 mmol) in pyridine (200 mL) at 5 °C was added 8N KOH (38.5 mL). The mixture was stirred for 18 h at room temperature, diluted with a saturated solution of NH_4Cl (300 mL) and extracted with ethyl acetate (300 mL). The organic layer was washed with dilute brine (250 mL) and 20% citric acid solution (3 x 250 mL). The ethyl acetate layer was dried over $MgSO_4$, filtered and evaporated to dryness. The brown solid obtained was swished with stirring for 2 h using 5% ethyl acetate in hexane, filtered and dried to give 62 g (82%) of compound **7** as a light brown solid; m.p. 103-106 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.55-7.0 (m, 1H), 6.91-7.09 (m, 2H), 6.70 (s, 1H), 3.92-4.05 (m, 2H), 3.75-3.92 (m, 2H), 2.95 (t, 2H), 2.30 (t, 2H).

Anal. Calcd. for $C_{17}H_{13}NSF_2O_4$: C, 55.88; H, 3.58; N, 3.83; S, 8.77; F, 10.40; Found: C, 55.53; H, 3.65; N, 3.62; S, 8.48; F 10.16.

5-Amino-6-(2,4-difluorophenylthio)-1-indanone (8)

A suspension of 5-nitro-6-(2,4-difluorophenylthio)-1-indanone ethylene ketal **7** (57 g, 156 mmol) in a mixture of stannous chloride (200 g, 1.05 mol), water (325 mL) and concentrated hydrochloric acid (1.0 L) was stirred at room temperature for 24 h. The mixture was filtered and the product as the hydrochloride salt was washed with 1N HCl (250 mL) and with water (250 mL). The solid was suspended in THF (1 L) and saturated $NaHCO_3$ solution (250 mL) added. After stirring for 1 h, ethyl acetate (1 L) and brine 250 mL) were added. The organic phase was separated, dried over $MgSO_4$ and concentrated to about one tenth of its volume. The solid was filtered and washed with ethyl acetate to obtain 34 g (75%) of compound **8**; m.p. 188-190 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 6.98-7.09 (m, 1H), 6.74-6.89 (m, 2H), 6.72 (s, 1H), 4.95 (br s, 2H), 2.95-3.08 (m, 2H), 2.57-2.70 (m, 2H). Anal. Calcd. for $C_{15}H_{11}NSF_2O$: C, 61.84; H, 3.80; N, 4.80; S, 11.00; F, 13.04; Found: C, 61.76; H, 3.65; N, 5.00; S, 10.76; F, 12.77.

5-[N,N-Bis(methanesulfonamido)]-6-(2,4-difluorophenylthio)-1-indanone (9)

To a suspension of 5-amino-6-(2,4-difluorophenylthio)-1-indanone **8** (4.7 g, 162 mmol) in dichloromethane (400 mL), tetrahydrofuran (400 mL) and triethylamine

(81 g, 800 mmol) at 5 °C was added dropwise methanesulfonyl chloride (46 mL, 564 mmol). The mixture was stirred for 1 h at room temperature, washed with 20% citric acid solution, dried over $MgSO_4$ and concentrated to obtain a dark solid residue which after swishing with diethyl ether, filtering and drying gave 59 g (80%) of the title compound **9**; m.p. 212-218 °C.

^1H NMR (400 MHz, $CDCL_3$) δ 7.55-7.62 (m,. 1H), 7.45 (s, 1H), 7.30 (s, 1H), 6.85-7.00 (m, 2H), 3.54 (s, 6H), 3.10-3.19 (m, 2H), 2.65-2.72 (m, 2H). Anal. Calcd. for $C_{17}H_{15}NS_3F_2O_5$: C, 45.62; H, 3.37; N, 3.13; S, 21.49; F, 8.49; Found: C, 45.33; H, 3.58; N, 2.83; S, 21.07; F, 8.29.

5-Methanesulfonamido-6-(2,4-difluorophenylthio)-1-indanone (10)

To a solution of the bis mesylate **9** (47 g, 105 mmol) in tetrahydrofuran (300 mL) and methanol (300 mL) was added 1M K_2CO_3 (300 mL). The mixture was stirred for 1 h at room temperature, acidified with 3N HCl and extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromotographed over silica gel eluting with ethyl acetate/hexane/dichloromethane 50/40/10 to obtain 29.8 g (77%) of a beige colored solid. Recrystallization from ethyl acetate gave the title compound as pure indanone **10**, white crystals; m.p. 169-170 °C.

^1H NMR (400 MHz, $CDCl_3$ δ 8.05 (s, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.20-7.38 (m, 1H), 6.75-6.95 (m, 2H), 3.16 (t, 2H), 3.06 (s, 3H), 2.70 (t, 2H). Anal. Calcd.

for $C_{16}H_{13}NS_2F_2O_3$: C, 52.02; H, 3.55; N, 3.79, S, 17.35; F, 10.28; Found: C, 52.36; H, 3.48; N, 3.82; S, 17.59; F, 9.78.

O-(2,4-Difluorophenyl) dimethylthiocarbamate (11)

To a stirred mixture of 80% sodium hydride (38 g, 1.2 mol) in dimethylformamide (1 L) cooled in cold water and under a nitrogen stream was added 2,4-difluorophenol (100 g, 0.769 mol) in dimethylformamide (200 mL) over 30 min. After stirring for 1 h, a clear solution was obtained. Dimethylthiocarbamoyl chloride (163 g, 1.3 mol) dissolved in dimethylformamide (250 mL) was added at room temperature to the anion mixture over 15 min. After stirring for 18 h, the reaction was poured gradually into a stirring mixture of ice (3 L) and concentrated HCl (1 L). After stirring for another 30 min, more water (1.5 L) was added and the solid filtered and washed with water (2 x 500 mL). The light yellow solid was purified on a large silica gel plug eluting with ethyl acetate/hexane/dichloro-methane 70/15/15 to yield 175 g (52%) of the title compound **11**; m.p. 120-123 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03-7.15 (m, 1H), 6.80-6.98 (m, 2H), 3.45 (s, 3H), 3.35 (s, 3H). Anal calcd. for $C_9H_9NSOF_2$: C, 49.76; H, 4.17; N, 6.44; Found: C, 50.00; H, 4.12; N, 6.40.

S-(2,4-Difluorophenyl) dimethylthiocarbamate (12)

A mixture of O-(2,4-difluorophenyl) dimethylthiocarbamate **11** (80 g, 368 mmol) in Dowtherm A[8] (400 mL) containing potassium carbonate (800 mg) was refluxed

for 2 h at 258 °C under nitrogen atmosphere. The total mixture was purified on a large silica gel plug eluting with 20% ethyl acetate in hexane to obtain 48 g (60%) of the title compound **12**; m.p. 58-60 °C.

^{1}H NMR (300 MHz, $CDCL_3$) δ 7.35-7.55 (m, 1H), 6.80-7.03 (m, 2H), 3.00 (br s, 3H), 3.10 (br s, 3H). Anal calcd. for $C_9H_9NSOF_2$: C, 49.76; H, 4.17; N, 6.44; Found: C, 49.40; H, 3.95; N, 6.30.

2,4-Difluorothiophenol (13)

To a sodium methoxide solution freshly prepared by the addition of sodium metal (8.5 g, 369 mmol) to dry methanol (540 mL) under nitrogen atmosphere was added in one portion S-(2,4-difluorophenyl) dimethylthiocarbamate **12** (54 g, 249 mmol). The mixture was refluxed for 1 h and then concentrated on a rotavap. The residue was dissolved in water (150 mL), 3N HCl (150 mL) added dropwise and the resultant mixture extracted with diethyl ether (2 x 300 mL). The combined organic fractions were dried over $MgSO_4$ and evaporated to obtain 36 g (95%) of the title compound **13** as a dark red oil; b.p. 75 °C (16 mm).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.35 (m, 1H), 6.75-6.95 (m, 2H), 3.50 (s, 1H).

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(Received in the USA 13 February 1995)