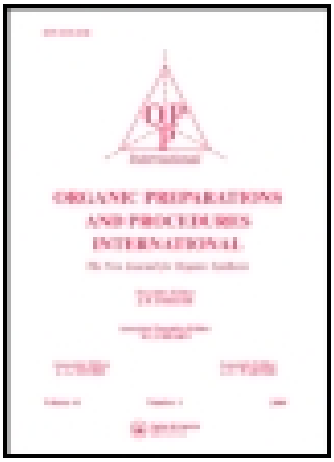

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METHYL 2-CHLORO-4-FLUOROPHENYLTRIOACETATE AS A NEW INTERMEDIATE IN THE SYNTHESIS OF PESTICIDES

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METHYL 2-CHLORO-4-FLUOROPHENYLTHIOACETATE AS A NEW INTERMEDIATE IN THE SYNTHESIS OF PESTICIDES

Submitted by Zhenyuan Xu[†]*, Xiaohua Du[†] and Jianbo Gu[††]
(12/02/02)

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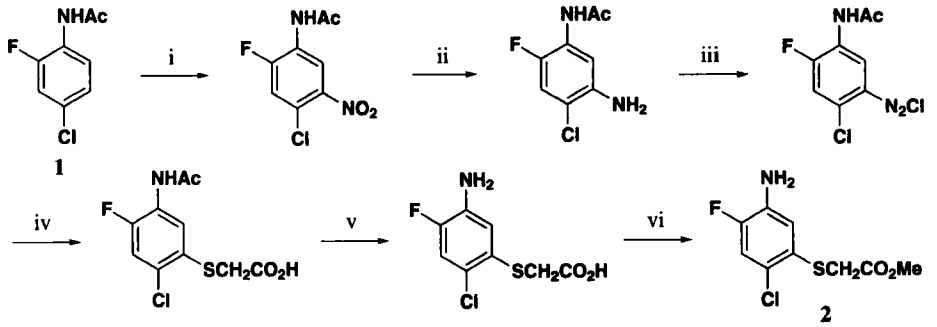
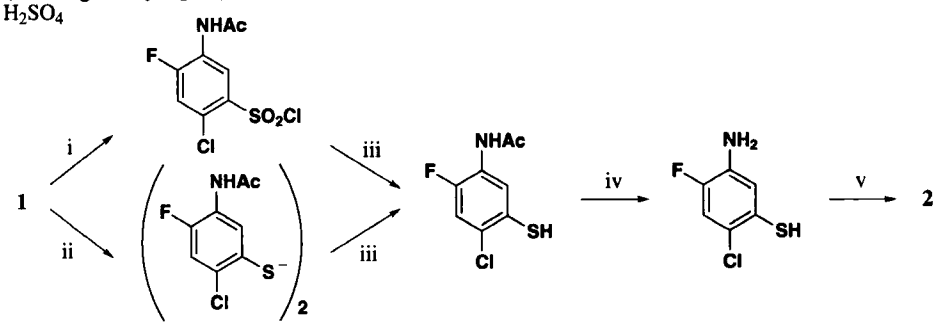
Recently, several types of highly effective herbicides containing the 4-chloro-2-fluoro-5-carbomethoxymethylthiophenyl group have been reported.[1] Methyl 5-amino-2-chloro-4-fluorophenylthioacetate (**2**), a key intermediate in the preparation of these compounds, has been obtained from 4-chloro-2-fluoroacetanilide (**1**) in 19, 30 and 42% yields by routes 1, 2 and 3, respectively[2-5] shown in *Scheme 1*. However, these procedures start from **1** which is expensive and involve lengthy sequences and the use of hazardous reagents such as fuming nitric, and sulfuric acids and sulfuryl chloride.



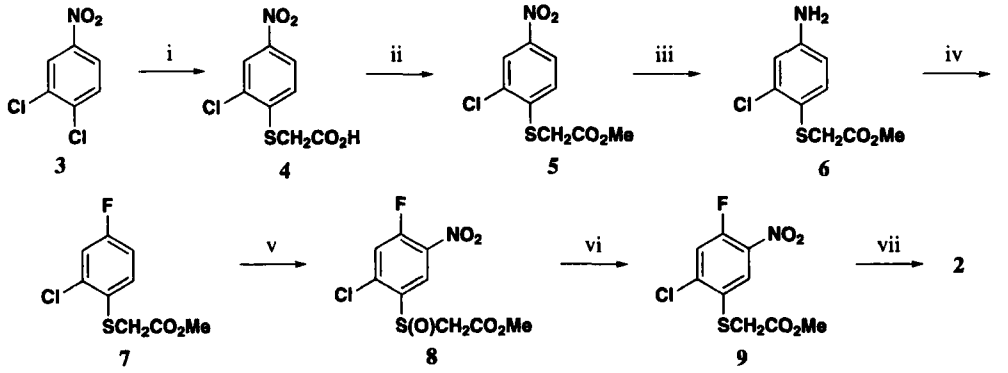
i) Fuming HNO_3, H_2SO_4; ii) Fe, HOAc; iii) $NaNO_2$, HCl; iv) $HSCH_2CO_2H$; v) HCl, H_2O; vi) MeOH, H_2SO_4



i) Fuming H_2SO_4, CCl_4; ii) S_2Cl_2, $AlCl_3$; iii) Zn, HOAc; iv) HCl, H_2O; v) $ClCH_2CO_2Me$

Scheme 1

We now report the synthesis of methyl 2-chloro-4-fluorophenylthioacetate (**7**) from inexpensive and commercially available 3,4-dichloronitrobenzene (**3**) in 34% overall yield. Oxidation and nitration of **7** followed by reduction of **8** gave the desired **2** in 76% yield (*Scheme 2*). Thus compound **2** may be readily obtained from **3** in seven steps in 26% overall yield.



i) $HSCH_2CO_2H$; ii) MeOH, *p*-$CH_3C_6H_4SO_3H$; iii) $SnCl_2$, MeOH iv) $NaNO_2$, HCl, $NaBF_4$; v) HNO_3, H_2SO_4; vi) KI, AcCl; vii) Fe, NH_4Cl

Scheme 2

EXPERIMENTAL SECTION

Melting and boiling points are uncorrected. The purity of products was established on a Fuli GC-9790 gas chromatograph with FID, SE-30 capillary column (3.2mm x 30 m). IR spectra were recorded on a Bruker EQUINOX 55 spectrometer. ^{1}H-NMR spectra were determined on a Bruker AC-400 instrument. Chemical shifts are reported in δ from internal TMS. MS spectra were recorded on a Varian Saturn 2000. Elemental analyses were performed using a Heraus Carlo Erba 1108 analyser.

2-Chloro-4-nitrophenylthioacetic Acid (4).- To a solution of 3,4-dichloronitrobenzene (29.0 g, 0.15 mol) in DMF (150 mL) were added thioglycolic acid (14.0 g, 0.16 mol) and triethylamine (35.0 g, 0.35 mol) with stirring. The resulting mixture was heated to reflux for 2 hours. After completion of reaction, the mixture was cooled to room temperature and slowly poured into 200 mL of 5% HCl with stirring. The precipitated solid was collected, washed several times with water and dried to give **4** (36.1 g, 97%) as a pale yellow solid, mp. 108-110°C. IR (KBr): 1713.9, 1573.8, 1514.5, 1343.5, 884.8 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.29-8.20 (m, 2H), 7.42-7.40 (m, 1H), 6.44 (broad, 1H), 3.85 (s, 2H). MS (m/e): 247 (M^+), 212 (M^+-Cl), 202 (M^+-CO_2H), 156 (202-NO_2), 121 (156-Cl).

Anal. Calcd for $C_8H_6ClNO_4S$: C, 38.80; H, 2.44; N, 5.66, S, 12.95

Found: C, 38.71; H, 2.45; N, 5.57, S, 12.69

Methyl 2-Chloro-4-nitrophenylthioacetate (5).- A solution of **4** (10.0 g, 0.04 mol) and *p*-$CH_3C_6H_4SO_3H$ (0.5 g) in anhydrous methanol (50 mL) was stirred at reflux for 2 hrs. After

cooling to 0°C for 4 hours, the product was collected and dried to give **5** (8.8 g, yield 84%) as pale yellow crystals, mp. 85-86°C. IR (KBr): 3097.6, 2953.0, 1736.1, 1573.7, 1511.2, 1344.3, 884.4, 819.3 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.23-8.09 (m, 2H), 7.43-7.40 (m, 1H), 3.85 (s, 2H), 3.79 (s, 3H). MS (m/e): 261 (M^+), 226 (M^+-Cl), 202 (M^+-CO_2Me), 156 (202-NO_2), 121 (156-Cl).

Anal. Calcd for $C_9H_8ClNO_4S$: C, 41.31; H, 3.08; N, 5.35; S, 12.25

Found: C, 40.93; H, 3.22; N, 5.11; S, 12.41

Methyl 4-Amino-2-chlorophenylthioacetate (6).- To a solution of $SnCl_2 \cdot 2H_2O$ (45.0 g, 0.199 mol) in methanol (150 mL) was added **5** (15.0 g, 0.057 mol). The mixture was heated to 60°C and stirred at the same temperature for 1 h, and then refluxed for another 1 h to complete the reaction. After cooling to room temperature, the mixture was poured into ice water, neutralized to pH 9 with 10% sodium hydroxide solution, and then extracted with toluene (100 mL x 3). After drying, the solvent was removed and the residue was distilled under vacuum to afford 8.7 g (66%) of product **6** as a pale yellow liquid, bp. 202-208°C/1.5 mmHg. IR (KBr): 1714.6, 1617.5, 1589.5, 1472.6, 1267.3, 1121.9, 896.6, 811.7 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.31-7.24 (m, 1H, Ar), 6.72-6.67 (m, 1H, Ar), 6.48-6.41 (m, 1H, Ar), 4.13 (s, 2H, NH_2), 3.62 (s, 3H, CH_3), 3.47 (s, 2H, CH_2). MS (m/e): 231 (M^+), 196 (M^+-Cl), 172 (M^+-CO_2Me), 158 (172-CH_2), 123 (158-Cl).

Anal. Calcd for $C_9H_{10}ClNO_2S$: C, 46.65; H, 4.35; N, 6.05; S, 13.84

Found: C, 46.38; H, 4.31; N, 5.99; S, 13.78

Methyl 2-Chloro-4-fluorophenylthioacetate (7).- Compound **6** (23.2 g, 0.1 mol) was dispersed in 250 mL of 0.8 M H_2SO_4 and then cooled to -5~0°C in an ice-salt bath. Then with vigorous stirring, a solution of sodium nitrite (6.9 g, 0.1 mol) in water (50 mL) was added dropwise over 40 min., the mixture was then stirred at 0~5°C for 30 min. To the diazonium salt solution thus prepared, a solution of $NaBF_4$ (16.5 g, 0.15 mol) in water (20 mL) was added and the resulting mixture was then stirred at 0°C for an additional 30 min. The diazonium salt (***CAUTION!*** *Diazonium salts are explosive!*) was isolated by suction filtration and washed on the Buchner funnel consecutively with cold water (20 mL x 2) and a 4:1 (v/v) solution of ether and methanol (20 mL x 3). Drying overnight *in vacuo* gave an off-white solid. To a hot solution of *m*-xylene at 130-135°C, the diazonium salt was added portionwise. After the addition, the mixture was heated to reflux for 30 min. to complete the reaction. The mixture was then cooled to room temperature and washed with 10% sodium carbonate. After separation and drying over anhydrous sodium sulfate, the solvent was removed by rotary evaporation and the residue was distilled under vacuum to give **7** (14.6 g, purity 99.5%, yield 62%) as a pale yellow liquid, bp. 106-110°C/0.2 mmHg. IR (KBr): 2953.8, 1733.3, 1586.8, 1465.7, 1257.6, 1207.2, 897.1, 805.0 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.48 (m, 1H, Ar), 7.18 (m, 1H, Ar), 6.97 (m, 1H, Ar), 3.70 (s, 3H, OMe), 3.63 (s, 2H, SCH_2). MS (m/e): 234 (M^+), 199 (M^+-Cl), 175 (M^+-CO_2CH_3), 161 (175-CH_2), 139 (175-HCl), 126 (161-Cl).

Anal. Calcd for $C_9H_8ClFO_2S$: C, 46.06; H, 3.44; S, 13.66. Found: C, 46.13; H, 3.42; S, 13.59

Carbomethoxymethyl (2-Chloro-4-fluoro-5-nitrophenyl) Sulfoxide (8).- Compound **7** (2.1 g, 9.0 mmol) was added dropwise during 15 min to a mixture of 95% HNO_3 (3.0 g, 45 mmol) and 98% H_2SO_4 (9.2 g, 92 mmol) with vigorous stirring at room temperature. After the addition, the mixture was stirred at room temperature for 40 min and then poured into ice-water. The product was extracted with ether (10 mL x 2), washed with water and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation and the residue was purified through a silica gel column with ethyl acetate/petroleum ether (5/5, v/v) as eluent to give product **8** (2.4 g, 90%) as pale yellow crystals, mp. 93-95°C. IR (KBr): 3078.4, 2967.2, 1735.4, 1593.6, 1538.4, 1382.0, 1304.1, 1055.0, 888.2 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.60 (d, 1H, ArH, J 7.6 Hz), 7.49 (d, 1H, ArH, J 9.5 Hz), 4.09 (d, 1H, SOCH, J 13.9 Hz), 3.78 (d, 1H, SOCH, J 13.9 Hz), 3.79 (s, 3H, OMe). MS (m/e): 295 (M^+), 250 (M^+-NO_2+1), 234 (250-O), 222 (M^+-CH_2CO_2Me), 177 (250-CH_2CO_2Me).

Anal. Calcd for $C_9H_7ClFNO_5S$: C, 36.56; H, 2.39; N, 4.74; S, 10.84

Found: C, 36.71; H, 2.41; N, 4.66; S, 10.71

Methyl 2-Chloro-4-fluoro-5-nitrophenylthioacetate (9).- To a solution of **8** (1.3 g, 4.4 mmol) in acetic acid (10 mL), was added KI (1.7 g, 10.2 mmol) and the mixture was stirred at room temperature. Acetyl chloride (0.7 g, 8.8 mmol) was slowly added over a period of 20 min. and the mixture was stirred for a further 40 min at room temperature; a TLC test (ethyl acetate/petroleum ether 1/9, v/v) indicated that the reaction was completed. The mixture was poured into ice-water, neutralized with 10% NaOH solution, and then extracted with chloroform (10 mL x 2). The chloroform extract was washed with water and then dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation and the residue was purified through a silica gel column with ethyl acetate/petroleum ether (1/9, v/v) as eluent to give product **9** (1.1 g, 89%) as a pale yellow crystal, mp. 65-66°C. IR (KBr): 3082.9, 1742.2, 1611.2, 1529.1, 1449.4, 1337.5, 1256.0, 1120.2, 883.5 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.17 (d, 1H, ArH, J 7.4 Hz), 7.40 (d, 1H, ArH, J 10.0 Hz), 3.77 (s, 3H, OMe), 3.74 (s, 2H, SCH_2). MS (m/e): 279 (M^+), 244 (M^+-Cl), 220 (M^+-CO_2Me), 174 (220-NO_2), 139 (174-Cl), 59 (CO_2Me).

Anal. Calcd for $C_9H_7ClFNO_4S$: C, 38.65; H, 2.52; N, 5.01; S, 11.47

Found: C, 38.59; H, 2.44; N, 4.89; S, 11.63

Methyl 5-Amino-2-chloro-4-fluorophenylthioacetate (2).- A 50 mL 3-necked flask was charged with water (20 mL), iron powder (1.0 g, 17.9 mmol) and NH_4Cl (0.2 g). The mixture was heated to 80°C with stirring. A toluene (10 mL) solution of compound **9** (1.0 g, 3.6 mmol) was added dropwise during a period of 20 min. After the addition, the mixture was refluxed gently for 30 min. After cooling to room temperature, the toluene phase was separated, washed with water and then dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation and the residue was purified through a silica gel column with ethyl acetate/petroleum ether (3/7, v/v) as eluent to give product **2** (0.85 g, 95%) as an off-white crystal, mp. 52-54°C (*lit.*[5] oil). IR (KBr): 3427.5, 3331.6, 1720.6, 1631.8, 1484.8, 1286.4, 1131.6, 881.4 cm^{-1}. ^1H

NMR ($CDCl_3$): δ 7.04 (d, 1H, ArH, J 10.8 Hz), 6.92 (d, 1H, ArH, J 9.0 Hz), 3.78 (s, 2H, NH_2), 3.70 (s, 3H, OMe), 3.60 (s, 2H, SCH_2). MS (m/e): 249 (M^+), 214 (M^+-Cl), 190 (M^+-CO_2Me), 176 (190-CH_2).

Anal. Calcd for $C_9H_9ClFNO_2S$: C, 43.29; H, 3.63; N, 5.61; S, 12.84

Found: C, 43.12; H, 3.77; N, 5.54; S, 12.61

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