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Synthesis of 2-(2-Fluorenyl)propanoic Acid

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Friedel-Crafts reaction of fluorene with methyl α-chloro-α-(methylthio)acetate **1** gave methyl α-methylthio-2-fluoreneacetate **2**. Cicloprofen **8**, a potent antiinflammatory agent, was prepared by methylation of **2** followed by reductive desulfurization of methyl 2-(2-fluorenyl)-2-(methylthio)propionate **6** and hydrolysis of methyl 2-(2-fluorenyl)propionate **7**.

Key words: Friedel-Crafts reaction, Fluorene, Methyl α-chloro-α-(methylthio)acetate, Cicloprofen, Antiinflammatory agent, Methylation, Reductive desulfurization, Hydrolysis

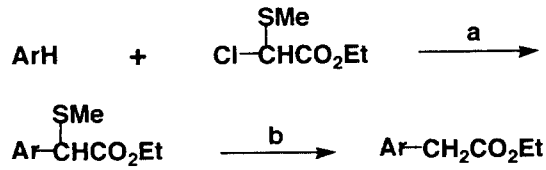
INTRODUCTION

A series of arylalkanoic acid derivatives has been used as potent antiinflammatory and analgesic agents, most of the medicines possess necessarily a phenylacetic acid moiety in aspect of chemical structure. The several syntheses for preparation of the agents were well known, but these are related to the indirect introduction of an acetic acid group into aromatic nuclei (Roth and Kleeman, 1988).

We have developed a novel preparative method for ethyl arylacetates by Friedel-Crafts reaction of aromatic compounds with ethyl α-chloro-α-(methylthio) acetate and successive desulfurization of the resulting ethyl α-(methylthio)arylacetates (Tamura *et al.*, 1982). (see Scheme 1) Recently, the reactions were applied to the syntheses of 4-biphenylacetic acid and 2-(4-cyclohexylphenyl)propionic acid (Choi *et al.*, 1992). The present paper describes the application to convenient syntheses of 2-fluoreneacetic acid **5** and 2-(2-fluorenyl) propanoic acid **8**, which is potent antiinflammatory agents.

MATERIALS AND METHODS

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. The infrared spectra were recorded with a Perkin-Elmer 1320 infrared spectrophotometer. The ^{1}H-NMR spectra were recorded on a Hitachi R-1500 (FT, 60 MHz) spectrometer using tetramethylsilane as an internal standard. The mass spectra were measured on a Hewlett-Packard 5970 GC-MS instrument. Column chromatography was carried out with Kieselgel 60 (70-230 mesh, Merck).



a: Friedel-Crafts Reaction
b: Desulfurization

Scheme 1.

Methyl α-chloro-α-(methylthio)acetate 1

N-Chlorosuccinimide (4.71 g, 0.035 mol) was added to a stirred solution of methyl α-(methylthio)acetate (4.2 g, 0.035 mol) in CCl_4 (20 ml) in small portions at 0℃ and the stirring was continued at room temperature for 10 hrs. The precipitated succinimide was filtered off and the solvent was removed in vacuo. The residual oil was distilled at 42-43℃/2 mmHg (lit. 82-83℃/14 mmHg, Bohme and Krack, 1977) to give **1** (4.4 g, 81%).

IR (neat) cm^{-1}: 1725(CO); ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s, SCH_3), 3.84 (3H, s, $COOCH_3$), 5.37 (1H, s, Cl-CHCOO).

Methyl α-(methylthio)acetate was synthesized accor-

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ding to literature (Herriot and Picker, 1975) for the preparation of unsymmetrical sulfides. Thus, methylmercaptan sodium salt (15% in water; 34.6 g, 0.072 mol), methyl bromoacetate (9.18 g, 0.06 mol), benzene (30 ml), and trioctylmethylammonium chloride (100 mg) were combined. The reaction mixture was stirred vigorously at room temperature for 2 hrs. The organic layer was separated, washed with water (10 ml×2), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residual oil was distilled at 29-30℃/3 mmHg to give methyl α-(methylthio) acetate (5.62 g, 78%).

IR (neat) cm^{-1}: 1720(CO); ^{1}H-NMR ($CDCl_3$) δ: 2.22 (3H, s, SCH_3), 3.20 (2H, s, CH_2COO), 3.75 (3H, s, $COOCH_3$).

Methyl α-methylthio-2-fluoreneacetate 2

$SnCl_4$ (607 mg, 2.33 mmol) was added to a stirred solution of fluorene (967 mg, 5.82 mmol) and **1** (300 mg, 1.94 mmol) in CH_2Cl_2 (5 ml) at room temperature, and stirring was continued at the same temperature for 2 hrs. The reaction was quenched by the addition of water, then the mixture was extracted with CH_2Cl_2 (7 ml×2), and the extract was dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was chromatographed (silica gel, benzene) to give **2** (402 mg, 73%, based on **1**) as a white solid.

mp.: 82-83℃ (from n-hexane); IR (KBr) cm^{-1}: 1715 (CO); ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s, SCH_3), 3.76 (3H, s, $COOCH_3$), 3.89 (2H, s, C_9-H on fluorene), 4.58 (1H, s, CHCOO), 7.18-7.96 (7H, m, arom); MS m/z: 284 (M^+), 237, 209, 165, 105, 59.

Dimethyl α,α′-bis(methylthio)-2,7-fluorenediacetate 3

By the same procedure as described above for the preparation of **2**, compound **3** was obtained from fluorene (251 mg, 1.51 mmol) and **1** (700 mg, 4.53 mmol) with $SnCl_4$ (1348 mg, 5.17 mmol). This was purified with silica gel column chromatography (ethyl acetate : n-hexane = 4 : 1) to give **3** (346 mg, 62%, based on fluorene) as a colorless oil.

IR (neat) cm^{-1}: 1710(CO); ^{1}H-NMR ($CDCl_3$) δ: 2.10 (6H, s, SCH_3×2), 3.76 (6H, s, $COOCH_3$×2), 3.90 (2H, s, C_9-H on fluorene), 4.59 (2H, s, CHCOO×2), 7.22-7.97 (6H, m, arom), MS m/z: 402(M^+), 355, 308, 250, 207, 142, 89, 59.

Methyl 2-fluoreneacetate 4

Zinc dust (0.79 g) was added to a solution of **2** (267 mg, 0.94 mmol) in acetic acid (3 ml), and the mixture was refluxed with vigorous stirring for 1 hr, then cooled. Water (10 ml) and CH_2Cl_2 (10 ml) were added to the reaction mixture and the inorganic materials were filtered off. The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (10 ml × 2). The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated off. The residue was recrystallized from n-hexane to give **4** (189 mg, 90%) as a white solid.

mp.: 73-75℃; IR (KBr) cm^{-1}: 1720(CO); ^{1}H-NMR ($CDCl_3$) δ: 3.70 (5H, s, CH_2COOCH_3), 3.87(2H, s, C_9-H on fluorene), 7.14-7.95 (7H, m, arom); MS m/z: 238 (M^+), 179, 152, 126, 89, 76, 51.

2-Fluoreneacetic acid 5

Compound **4** (157 mg, 0.70 mmol) was added to a solution of KOH (197 mg) in water (2 ml) and methanol (2 ml), and the mixture was heated at 70-80℃ for 3 hrs, then cooled. Water (5 ml) was added to the mixture, and the solution was washed with CH_2Cl_2 (7 ml). The aqueous layer was acidified to pH 1 with concentrated HCl, extracted with ethyl ether (10 ml× 2), and dried over anhydrous $MgSO_4$. The solvent was evaporated off. The residue was recrystallized from methanol to give **5** (136 mg, 92%) as a white solid.

mp.: 185-187℃ (lit. 185-186℃, Bachmann and Sheehan, 1940); IR (KBr) cm^{-1}: 3260~2710 (OH), 1690 (CO); ^{1}H-NMR ($CDCl_3$) δ: 3.70 (2H, s, CH_2COO), 3.87 (2H, s, C_9-H on fluorene), 7.08-7.98 (7H, m, arom), 10.17 (1H, br s, COOH).

Methyl 2-(2-fluorenyl)-2-(methylthio)propionate 6

A solution of **2** (800 mg, 2.81 mmol) in DMF (5 ml) was added to a suspension of sodium hydride (60% dispersion in mineral oil; 113 mg, 2.81 mmol) in DMF (3 ml) at 0℃ under nitrogen atmosphere, and the mixture was stirred at the same temperature until the evolution of hydrogen ceased. Methyl iodide (444 mg, 3.0 mmol) was then added and the mixture was stirred at 0℃ for 30 min and at room temperature for 1 hr. The reaction mixture was poured into a solution of 5% NH_4Cl (10 ml) and extracted with ethyl ether (10 ml×2). The extract was washed with water and dried over anhydrous $MgSO_4$. The solvent was evaporated off. The residue was chromatographed (silica gel, benzene) to give **6** (609 mg, 74%) as a colorless oil.

IR (neat) cm^{-1}: 1715(CO); ^{1}H-NMR ($CDCl_3$) δ: 1.85 [3H, s, $C(SCH_3)\underline{CH_3}$], 2.01 (3H, s, SCH_3), 3.79 (3H, s, $COOCH_3$), 3.87 (2H, s, C_9-H on fluorene), 7.12-7.90 (7H, m, arom); MS m/z: 298(M^+), 251, 223, 191, 165, 120, 95, 40.

Methyl 2-(2-fluorenyl)propionate 7

By the same procedure as described above for the preparation of **4**, compound **7** was obtained from **6** (370 mg, 1.24 mmol) and zinc dust (1.06 g) in acetic

acid (4 ml). The residue was recrystallized from n-hexane to give **7** (240 mg, 77%) as a white solid.

mp.: 72-74℃; IR (KBr) cm^{-1}: 1715(CO); ^{1}H-NMR ($CDCl_3$) δ: 1.54[3H, d, J=7.1 Hz, CH(CH$_3$)COO], 3.67 (3H, s, COOCH$_3$), 3.79 [1H, q, J=7.0 Hz, CH(CH$_3$)COO], 3.88 (2H, s, C$_9$-H on fluorene), 7.11-7.98 (7H, m, arom), MS m/z: 252(M^+), 193, 178, 152, 115, 83, 40.

Cicloprofen [2-(2-Fluorenyl)propanoic acid] 8

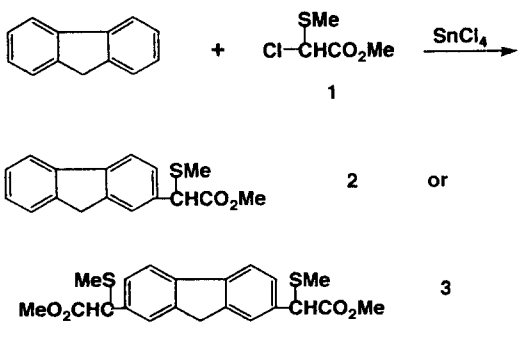
By the same procedure as described above for the preparation of **5**, compound **8** was obtained from **7** (163 mg, 0.65 mmol) and KOH (181 mg). The residual solid was recrystallized from ethanol to give **8** (132 mg, 86%).

mp.: 179-181℃ (lit. 181-183℃, Stiller *et al.*, 1972); IR (KBr) cm^{-1}: 3360~2520(OH), 1690(CO); ^{1}H-NMR ($CDCl_3$) δ: 1.54 [3H, d, J=7.1 Hz, CH(CH$_3$)COO], 3.79 [1H, q, J=7.0 Hz, CH(CH$_3$)COO], 3.84 (2H, s, C$_9$-H on fluorene), 7.08-7.94 (7H, m, arom), 10.44 (1H, br s, COOH).

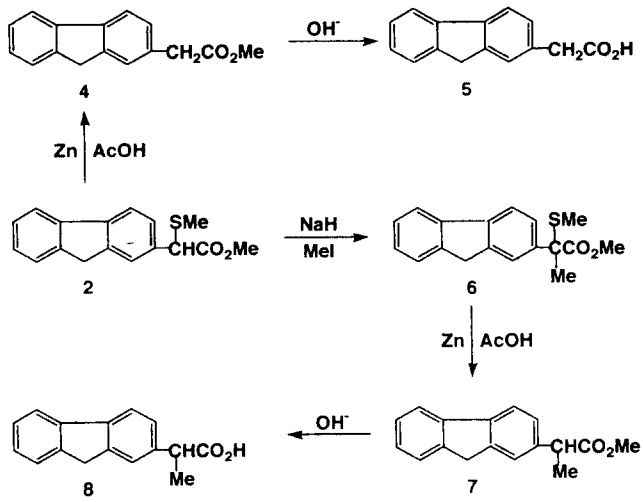
RESULTS AND DISCUSSION

Friedel-Crafts reaction of **3** equimolar amount of fluorene with **1** in the presence of $SnCl_4$ afforded the monoacetate **2** in 73% yield. On the other hand, fluorene gave the diacetate **3** in 62% yield, when treated with 3 equimolar amount of **1**. The structures of compounds **2** and **3** were confirmed by the comparision of their spectral data. ^{1}H-NMR spectra of **2** and **3** showed signals at 7.18-7.96 ppm (7H, m, aromatic protons) and 7.22-7.97 ppm (6H, m, aromatic protons). The mass spectra of **2** and **3** revealed a molecular ion peak [M^+] at m/z 284 and 402, respectively (Scheme 2).

The above result was in accord with our synthetic method for preparation of ethyl 2-methylthio-2-(4-biphenylyl)acetate or diethyl α,α'-di(methylthio)-[1,1'-biphenyl]-4,4'-diacetate obtained from Friedel-Crafts reaction of biphenyl with ethyl α-chloro-α-(methylthio)acetate (Choi *et al.*, 1992).



Scheme 2.



Scheme 3.

Methylation of **2** by treatment with sodium hydride and then methyl iodide in DMF gave methyl 2-(2-fluorenyl)-2-(methylthio)propionate **6** in 74% yield. ^{1}H-NMR spectrum of **6** showed the presence of a new CH$_3$ group (1.85 ppm) and the disappearance of CH group (4.58 ppm) appeared in **2**, and its mass spectrum showed a molecular ion peak [M^+] at m/z 298.

Compounds **2** and **6** were desulfurized by heating with zinc dust in acetic acid to give the corresponding compounds **4** and **7** in 90% and 77% yields. Alkaline hydrolysis of compounds **4** and **7** afforded 2-fluoreneacetic acid **5** and cicloprofen **8** in 92% and 86% yields, respectively.

The synthetic route for compounds **5** and **8** is outlined in Scheme 3. The structural assignment of newly synthesized compounds **2-4** and **6-7** was based on IR, ^{1}H-NMR, MS spectroscopy.

2-Fluoreneacetic acid **5** was previously synthesized from the route through acylation of fluorene with acetic anhydride, followed by Willgerodt-Kindler reaction on 2-acetylfluorene and hydrolysis of 2-fluoreneacetamide (Bachmann and Sheehan, 1940). The known method for preparation of 2-(2-fluorenyl)propanoic acid **8** is acylation of fluorene with ethyloxalyl chloride and hydrolysis of 2-glyoxylate ester, followed by treatment of the resulting acid with methylmagnesium iodide, acidic dehydration of tertiary carbinol and catalytic hydrogenation (Stiller *et al.*, 1972).

In summary, an advantage of our method is that 2-fluorenylalkanoic acid derivatives **5** and **8** could be succesfully obtained from Friedel-Crafts reaction of fluorene with **1**, followed by methylation of **2**, desulfurization of (**2**, **6**), and hydrolysis of (**4**, **7**). The present sequence of reactions can be performed under mild conditions, gives compounds (**5**, **8**) in good yields, and is of preparative value.

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