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Synthesis of 4-(2-Thiazolyloxy)phenylalkanoic Acids As An Antiinflammatory Agent

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The efficient synthesis of 4-(2-thiazolyloxy)phenylalkanoic acids (**10a-c**), which are a potent antiinflammatory agent, was achieved in 5~6 steps starting from isopropoxybenzene and methyl α-chloro-α-(methylthio)acetate (**1**). The key intermediate (**4**) was prepared by Friedel-Crafts reaction of isopropoxybenzene with (**1**) followed by desulfurization and the removal of isopropyl protector. Methyl 4-hydroxyphenylalkanoates (**6,8**) were similarly obtained from alkylation of (**3**) and deprotection.

Key words : 4-(2-Thiazolyloxy)phenylalkanoic acids, Antiinflammatory agent, Methyl α-chloro-α-(methylthio)acetate, Friedel-Crafts reaction, Desulfurization, Isopropyl protector, Methyl 4-hydroxyphenylalkanoates, Alkylation, Deprotection

INTRODUCTION

The numerous compounds containing the arylacetic or arylpropionic acid skeleton have been developed as non-steroidal antiinflammatory and antirheumatic agents (Roth and Kleeman, 1988). 4-(2-Thiazolyloxy)phenylalkanoic acids (**10a-c**) are known as having potent antiinflammatory and analgesic activities, especially the compound (**10b**) is more active than ibuprofen but inferior to indomethacin (Hirokuni *et al.*, 1983; Hirose *et al.*, 1984; Sammes and Taylor, 1990; Shionogi & Co.Ltd., 1985). Recently, we reported a convinient method for hexaprofen (Choi *et al.*, 1992) and 2-(2-fluorenyl)propanoic acid (Choi *et al.*, 1994) possessing phenylpropionic acid moiety. Here the key steps involves Friedel-Crafts reaction of aromatic compound with methyl or ethyl α-chloro-α-(methylthio)acetate and successive desulfurization of the resultant methyl or ethyl arylacetate. In a continuing search for the synthesis of antiinflammatory compounds, we wish to describe an efficient synthetic method for 4-(2-thiazolyloxy)phenylalkanoic acids (**10a-c**). We decided to employ our method of preparing the methyl *p*-hydroxyphenylalkanoates (**4, 6, 8**), which consists of an electrophilic aromatic substitution of isopropoxybenzene with methyl α-chloro-α-(methylthio)acetate (**1**) followed by desulfurization and the removal of isopropyl protector at the final stage (see Scheme **1** and **2**).

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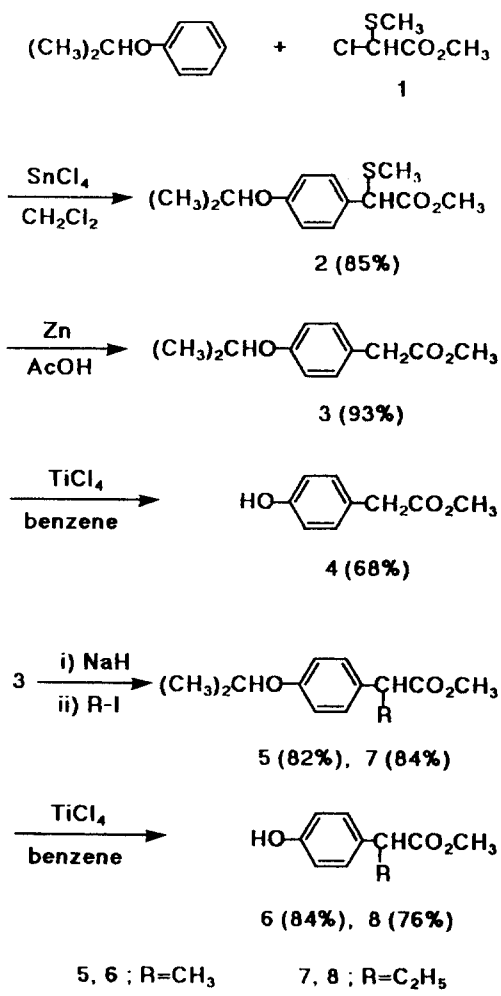
MATERIALS AND METHODS

Stannic chloride, titanium tetrachloride, ethyl iodide and methyl iodide were purchased from Fluka Chemical Company. Sodium hydride and 2-bromothiazole were obtained from Tokyokasei Chemical Company, zinc dust from Aldrich Chemical Company. All other solvents were reagent grade and used without further purification.

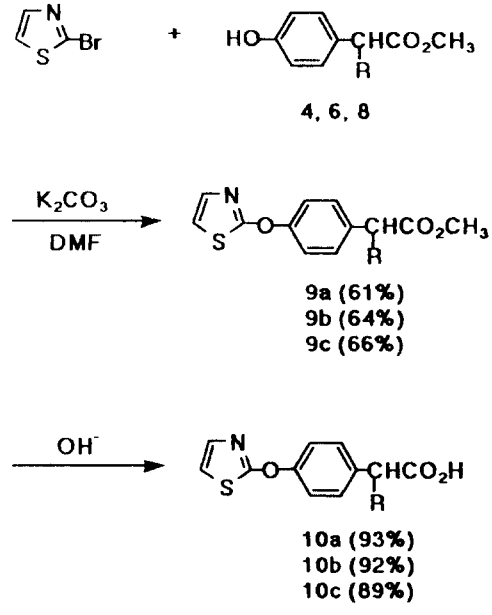
Melting points were determined on a Gallenkamp melting point apparatus and were uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1320 spectrophotometer. Proton nuclear resonance spectra were recorded on a Hitachi R-1500 (FT, 60 MHz) spectrometer using tetramethylsilane as an internal standard. Masss spectra were recorded on a Hewlett Packard 5970 GC/MS system by electron impact method (EI) at 70eV. Analytical thin layer chromatography was performed on plastic sheet (0.2 mm) precoated with silica gel 60 F_{254} (E. Merck). Silica gel 60 (70-230 mesh, E. Merck) was used for column chromatography.

Methyl 2-methylthio-2-(4-isopropoxyphenyl)acetate 2

To a stirred solution of **1** (300 mg, 1.94 mmol) and isopropoxybenzene (264 mg, 1.94 mmol) in methylene chloride (5 ml) at 0°C was added stannic chloride (505 mg, 1.94 mmol) under N_2 atmosphere. The resulting solution was stirred at the same temperature



Scheme 1



Scheme 2

for 30 min. The reaction mixture was quenched by addition of water and extracted with methylene chloride (5 ml×2). The combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (hexane-ethyl acetate, 15 : 1) to afford 2(419 mg, 85%) as a colorless oil. IR(neat) cm^{-1}: 1720(CO); H-NMR ($CDCl_3$) δ: 1.32[6H, d, J=5.8 Hz, $(CH_3)_2CH$], 2.06(3H, s, SCH_3), 3.73(3H, s, $COOCH_3$), 4.22~5.02 [1H, m, $(CH_3)_2CH$], 4.45 (1H, s, CHCOO), 6.83(2H, d, J=8.8 Hz, ArH), 7.35(2H, d, J=8.8 Hz, ArH); MS m/z (relative int.): 254(M^+, 7), 207(21), 165(65), 137(100), 77(19), 43(23).

Methyl 4-isopropoxyphenylacetate 3

To a solution of **2** (700 mg, 2.76 mmol) in acetic acid (7 ml) was added zinc dust (2.30 g) at room temperature. The mixture was refluxed for 1h and cooled. The reaction mixture was diluted with water (10 ml) and methylene chloride (10 ml), and the inorganic materials were filtered off. The organic phase was separated and the aqueous phase was extracted with methylene chloride (5 ml×2). The combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure.The residue was purified by column chromatography (hexane-ethyl acetate, 4 : 1) to give **3** (533 mg, 93%) as a colorless oil. IR(neat) cm^{-1}: 1730(CO); H-NMR($CDCl_3$) δ: 1.32[6H, d, J=6.4 Hz, $(CH_3)_2CH$], 3.36(2H, s, CH_2COO), 3.68(3H, s, $COOCH_3$), 4.22~4.82[1H, m, $(CH_3)_2CH$], 6.82(2H, d, J=8.8 Hz, ArH), 7.19(2H, d, J=8.8 Hz, ArH); MS m/z (relative int.): 208(M^+, 42), 166(98), 149(27), 121(12), 107(100), 77(95), 43(76).

Methyl 4-hydroxyphenylacetate 4

A solution of **3** (486 mg, 2.35 mmol) in benzene (6 ml) was treated with titanium tetrachloride (891 mg, 4.70 mmol) at room temperature and stirred for 8h. The reaction mixture was quenched by addition of water (10 ml). The organic phase was separated and the aqueous phase was extracted with benzene (5 ml×2). The combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (hexane-ethyl acetate, 4 : 1) to afford **4**(264 mg, 68%) as a colorless oil. IR(neat) cm^{-1}: 3410(OH), 1710(CO); H-NMR($CDCl_3$) δ: 3.56(2H, s, CH_2COO), 3.69(3H, s, $COOCH_3$), 5.21(1H, s, ArOH), 6.74(2H, d, J=8.8 Hz, ArH), 7.13(2H, d, J=8.8 Hz, ArH).

Methyl 2-(4-isopropoxyphenyl)propionate 5

To a suspension of 60% sodium hydride (148 mg,

3.70 mmol) in N,N-dimethylformamide (2 ml) was added a solution of **3** (728 mg, 3.50 mmol) in N,N-dimethylformamide (4 ml) at 0°C under N_2 atmosphere, and the mixture was stirred at the same temperature until the evolution of hydrogen ceased. Methyl iodide (497 mg, 3.50 mmol) was then added and the mixture was stirred at 0°C for 30 min, and at room temperature for 1h. The reaction mixture was quenched by the addition of 5% NH_4Cl (10 ml) and extracted with diethyl ether (10 ml × 2). The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel using hexane-ethyl acetate(4 : 1) as an eluent to give **5** (637 mg, 82%) as a colorless oil. IR(neat) cm^{-1}: 1720(CO); H-NMR($CDCl_3$) δ: 1.31[6H, d, J=6.4 Hz, $(CH_3)_2CH$], 1.47[3H, d, J=7.0 Hz, $CH(CH_3)COO$], 3.44~4.03[4H, m, $CH(CH_3)COOCH_3$], 4.24~4.82[1H, m, $(CH_3)_2CH$], 6.81(2H, d, J=8.8 Hz, ArH), 7.20(2H, d, J=8.8 Hz, ArH); MS m/z(relative int.): 22(M^+, 12), 180(12), 163(10),121(100), 91(32), 77(22), 27(20).

Methyl 2-(4-hydroxyphenyl)propionate 6

By the same procedure as described above for preparation of **4**, compound **6** was obtained from **5** (526 mg, 2.37 mmol) and titanium tetrachloride (899 mg, 4.74 mmol) in 84% yield (358 mg) as a colorless oil. IR(neat) cm^{-1}: 3410(OH), 1700(CO); H-NMR($CDCl_3$) δ: 1.47[3H, d, J=7.6Hz, $CH(CH_3)COO$], 3.40~3.98[4H, m, $CH(CH_3)COOCH_3$], 5.18(1H, s, ArOH), 6.76(2H, d, J=8.8 Hz, ArH), 7.18(2H, d, J=9.4 Hz, ArH); MS m/z(relative int.): 180(M^+, 22), 149(2), 121(100), 93(12), 65(10), 39(15).

Methyl 2-(4-isopropoxyphenyl)butyrate 7

By the same procedure as described above for the preparation of **5**, compound **7** was obtained from **3** (720 mg, 3.05 mmol), 60% sodium hydride (128 mg, 3.20 mmol), and ethyl iodide (499 mg, 3.20 mmol) in 84% yield (605 mg) as a colorless oil. IR(neat) cm^{-1}: 1720(CO); H-NMR($CDCl_3$) δ: 0.87[3H, t, J=7.6 Hz, $CH(CH_2CH_3)COO$], 1.32[6H, d, J=5.8 Hz, $(CH_3)_2CH$], 1.59~2.23[2H, m, $CH(CH_2CH_3)COO$], 3.39[1H,t, J=7.6 Hz, $CH(CH_2CH_3)COO$], 3.65 (3H, s, $COOCH_3$), 4.17~4.76[1H, m, $(CH_3)_2CH$], 6.81(2H, d, J=8.8 Hz, ArH), 7.20(2H, d, J=8.2 Hz, ArH); MS m/z(relative int.): 236(M^+, 20), 194(16), 177(9), 135(100), 107(44), 91(11), 59(5), 41(16).

Methyl 2-(4-hydroxyphenyl)butyrate 8

By the same procedure as described above for the preparation of **4**, compound **8** was obtained from **7** (500 mg, 2.12 mmol) and titanium tetrachloride (804 mg, 4.24 mmol) in 76% yield (313 mg) as a colorless oil. IR(neat) cm^{-1}: 3390(OH), 1695(CO); H-NMR($CDCl_3$) δ: 0.87[3H, t, J=7.0 Hz, $CH(CH_2CH_3)COO$], 1.58~2.22[2H, m, $CH(CH_2CH_3)COO$], 3.40[1H, t, J=7.6 Hz, $CH(CH_2CH_3)COO$], 3.66(3H, s, $COOCH_3$), 5.10(1H,s, ArOH), 6.76(2H, d, J=8.4 Hz, ArH), 7.14(2H, d, J=8.8 Hz, ArH); MS m/z(relative int.): 194(M^+, 31), 165(6), 135 (97), 107(100), 91(15), 77(20), 51(13), 39(20).

Methyl 4-(2-thiazolyloxy)phenylacetate 9a

A solution of **4** (415 mg, 2.50 mmol) and 2-bromothiazole (410 mg, 2.50 mmol) in N,N-dimethylformamide (5 ml) was treated with potassium carbonate (415 mg, 3.0 mmol), and heated for 5h at 150°C. The reaction mixture was diluted with 10% NH_4Cl (10 ml) and extracted with diethyl ether (10 ml × 2). The combined organic phase was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography (hexane-ethyl acetate, 2 : 1) to afford **9a** (380 mg, 61%) as a colorless oil. IR(neat) cm^{-1}: 1720(CO); H-NMR($CDCl_3$) δ: 3.62(2H, s, CH_2COO), 3.70(3H, s, $COOCH_3$), 6.72-7.46(6H, m, ArH); MS m/z(relative int.): 249(M^+, 83), 190(49), 162(100), 118(19), 89(44), 59(27), 45(20).

Methyl 2-[4-(2-thiazolyloxy)phenyl]propionate 9b

By the same procedure as decribed above for the preparation of **9a**, compound **9b** was obtained from **6** (281 mg, 1.56 mmol), 2-bromothiazole (255 mg, 1.56 mmol), and potassium carbonate (216 mg, 1.56 mmol) in 64% yield (284 mg) as a colorless oil. IR (neat) cm^{-1}: 1720(CO); H-NMR($CDCl_3$) δ: 1.50[3H, d, J=7.1 Hz, $CH(CH_3)COO$], 3.52~4.00[4H, m, $CH(CH_3)COOCH_3$], 6.76~7.46(6H, m, ArH); MS m/z(relative int.): 263(M^+, 53), 204(100), 176(88), 132(7), 103(14), 77(17), 59(10), 39(9).

Methyl 2-[4-(2-thiazolyloxy)phenyl]butyrate 9c

By the same procedure as described above for the preparation of **9a**, compound **9c** was obtained from **8** (247 mg, 1.27 mmol), 2-bromothiazole (208 mg, 1.27 mmol), and potassium carbonate (176 mg, 1.27 mmol) in 66% yield (232 mg) as a colorless oil. IR (neat) cm^{-1}: 1715(CO); H-NMR($CDCl_3$) δ: 0.89[3H, t, J =7.6 Hz, $CH(CH_2CH_3)COO$], 1.50~2.36[2H, m, $CH(CH_2CH_3)COO$], 3.48[1H, t, J=7.6 Hz, $CH(CH_2CH_3)COO$], 3.66[3H, s, $CH(CH_2CH_3)COOCH_3$], 6.69~7.56(6H, m, ArH); MS m/z(relative int.): 277(M^+, 48), 248(5), 218(100), 190(56), 162(17), 130(4), 115(16), 91(19), 77 (15), 39(12).

4-(2-Thiazolyloxy)phenylacetic acid 10a

Compound **9a** (270 mg, 1.08 mmol) was added to a solution of potassium hydroxide (303 mg, 5.40 mmol) in water (3 ml) and methanol (3 ml), and the

mixture was heated at 60-70°C for 3h, then cooled. To the mixture was added water (5 ml) and washed with methylene chloride (8 ml). The aqueous phase was acidified to pH 1 with concentrated hydrochloric acid, extracted with diethyl ether (10 ml × 2), and dried ($MgSO_4$). The solvent was evaporated off and the residue was recrystallized from diisopropyl ether to give **10a** (237 mg, 93%) as a white solid. mp: 148~149°C; IR(KBr) cm^{-1}: 3220~2400(OH), 1700(CO); H-NMR($CDCl_3$) δ: 3.64(2H,s, CH_2COO), 6.70~7.58(6H, m, ArH), 9.44(1H, br s, COOH).

2-[4-(2-Thiazolyloxy)phenyl]propionic acid 10b

By the same procedure as described above for the preparation of **10a**, compound **10b** was obtained from **9b** (411 mg, 1.56 mmol) and potassium hydroxide (438 mg, 7.80 mmol) in 92% yield (356 mg) as a white solid. mp: 119~120°C [from diisopropyl ether, lit. 120~121°C, Shionogi & Co. Ltd., 1985]; IR (KBr) cm^{-1}: 3280~2460(OH), 1700(CO); H-NMR ($CDCl_3$) δ: 1.51[3H, d, J=7.0 Hz, $CH(C\underline{H}_3)COO$], 3.45[1H, q, J=7.6 Hz, $C\underline{H}(CH_3)COO$], 6.76~7.60(6H, m, ArH), 9.22(1H, br s, COOH).

2-[4-(2-Thiazolyloxy)phenyl]butyric acid 10c

By the same procedure as described above for the preparation of **10a**, compound **10c** was obtained from **9c** (321 mg, 1.16 mmol) and potassium hydroxide (326 mg, 5.80 mmol) in 89% yield (272 mg) as a white solid. mp: 116~117°C (from diisopropyl ether); IR(KBr) cm^{-1}: 3220~2400(OH), 1700(CO); H-NMR($CDCl_3$) δ: 0.92[3H, t, J=7.6 Hz, $CH(CH_2C\underline{H}_3)COO$], 1.58~2.36[2H, m, $CH(C\underline{H}_2CH_3)COO$], 3.49[1H, t, $C\underline{H}(CH_2CH_3)COO$], 6.64~7.61(6H, m, ArH), 9.38(1H, br s, COOH).

RESULTS AND DISCUSSION

Methyl α-chloro-α-(methylthio)acetate (**1**) was prepared from methyl α-(methylthio)acetate by chlorination with N-chlorosuccinimide according to the previously reported method (Choi *et al.*, 1994).

Methyl 4-hydroxyphenylalkanoates (**4, 6, 8**) were prepared as outlined in Scheme **1**. Friedel-Crafts reaction of isopropoxybenzene with the compound (**1**) in the presence of stannic chloride gave methyl 2-methylthio-2-(4-isopropoxyphenyl)acetate (**2**) in 85% yield. On the other hand, the above reaction afforded the ester (**2**) in 29% yield when treated with titanium tetrachloride. This case of low yield, as reported by Sala and Sargent in 1979, is probably due to the cleavage of ether bond of the compound (**3**) by exposure to titanium tetrachloride. The H-NMR spectrum of **2** exhibited the signals for the aromatic protons at δ 6.83 and 7.35 ppm (2H, d, J=8.8 Hz, each), which suggested the compound (**3**) to be a para-disubstituted benzene ring.

The compound (**2**) can easily be desulfurized into methyl 4-isopropoxyphenylacetate (**3**) in an excellant yield by heating with zinc dust in acetic acid. We examined the method (Sala and Sargent, 1979) for the removal of isopropyl protector in the phenolic hydroxy group of the compound (**3**). The treatment of **3** with titanium tetrachloride in benzene at room temperature furnished methyl 4-hydroxyphenylacetate (**4**) in 68% yield.

Alkylation of benzylic position of **3** by the treatment of sodium hydride and then methyl iodide or ethyl iodide in N,N-dimethylformamide gave the corresponding methyl 2-(4-isopropoxyphenyl)alkanoates **5** and **7** in 82% and 84% yields, respectively. Such as the above described manner leading from **3** into **4**, the deprotection of the compounds (**5, 7**) was accomplished by titanium tetrachloride in benzene to give methyl 2-(4-hydroxyphenyl)alkanoates **6** and **8** in 84% and 76% yields, respectively.

As shown in Scheme **2**, a mixture of the phenol (**4, 6, 8**) and 2-bromothiazole was heated in refluxing N, N-dimethylformamide in the presence of potassium carbonate for 5h. The expected condensation products (**9a-c**) was obtained in good yields. Finally, alkaline hydolysis of the ester compounds (**9a-c**) afforded 4-(2-thiazolyloxy)phenylalkanoic acid derivatives (**10a-c**) in 89~93% yields.

The synthesis of the compound (**10b**) developed by Shionogi Company (Shionogi & Co. Ltd., 1985) begins with the formation of the corresponding isopropyl ester from *p*-hydroxyphenylacetic acid, which is obtained in **4** steps starting from benzyl cyanide. The compound (**10b**) is prepared by the cyclocondensation of isoproyl *p*-hydroxyphenylacetate with isobutoxy-2-chloroethyl isothiocyanate, elimination of isobutanol, methylation, and then hydrolysis.

In summary, the desired 4-(2-thiazolyloxy)phenylalkanoic acids (**10a-c**) were successfully obtained in 5~6 steps by using Friedel-Crafts reaction of isopropoxybenzene with the chloride (**1**) followed by desulfurization of the ester (**2**), the removal of isopropyl protector or alkylation of the compound (3), the condensation of the phenol (**4, 6, 8**) with 2-bromothiazole, and finally hydrolysis of the compounds (**9a-c**). The presence sequence of reactions can be carried out under rather mild conditions in high yields, and hence provides a useful synthetic route to target compounds (**10a-c**).

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