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An Improved Synthesis of Methyl p-Hydroxyphenylalkanoates

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Friedel-Crafts reaction of isopropoxybenzene with methyl α-chloro-α-(methylthio)acetate **1** afforded methyl α-methylthio-p-isopropoxyphenylacetate **2d**, which was readily converted into methyl p-isopropoxyphenylacetate **3** by reductive desulfurization with zinc dust in acetic acid. Methylation of **3** with sodium hydride and methyl iodide gave methyl α-(p-isopropoxyphenyl)propionate **5**. Methyl p-hydroxyphenylalkanoates (**4, 6**), useful intermediates for some medicines, were easily prepared by treatment of **3** and **5** with titanium tetrachloride, respectively.

Key words: Friedel-Crafts reaction, Methyl α-chloro-α-(methylthio)acetate, Methyl α-methylthio-p-isopropoxyphenylacetate, Reductive desulfurization, Methylation, Methyl p-hydroxyphenylalkanoates, Titanium tetrachloride

INTRODUCTION

As shown in Fig. 1, p-hydroxyphenylalkanoic acids are the valuable key intermediates for synthesizing some medicines. For example, zoliprofen I (Shionogi & Co. Ltd., 1985) and benoxaprofen II (Dunwell *et al.*, 1975), which are potent antiinflammatory agents, possess p-hydroxyphenylpropionic acid moiety. Also β-receptor blockers, atenolol III (Lednicer and Mitscher, 1980) contains the partial structure of p-hydroxyphenylacetic acid.

The unique report concerning the synthesis of p-hydroxyphenylacetic acid is the route through nitration of phenylacetonitrile followed by reduction of nitro group, formation of aryldiazonium salt from amino group, displacement of diazonium group by reaction with hot aqueous acid, and hydrolysis of nitrile group (Roth and Kleemann, 1988). But the above sequence of reactions requires somewhat long steps and drastic conditions.

Recently, we reported a convenient method for preparation of 2-(2-fluorenyl)propanoic acid by means of Friedel-Crafts reaction of fluorene with **1** and successive desulfurization of the resulting methyl α-methylthio-2-fluoreneacetate (Choi *et al.*, 1994).

In this paper, we wish to describe an efficient synthetic method of methyl p-hydroxyphenylalkanoates (**4, 6**) according to the procedure outlined for introduction of an acetic acid or a propionic acid into aromatic nuclei (see Scheme 1 and 2).

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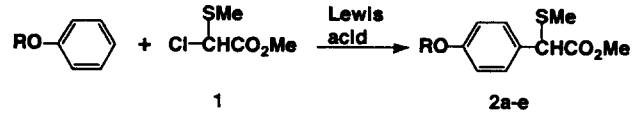
MATERIALS AND METHODS

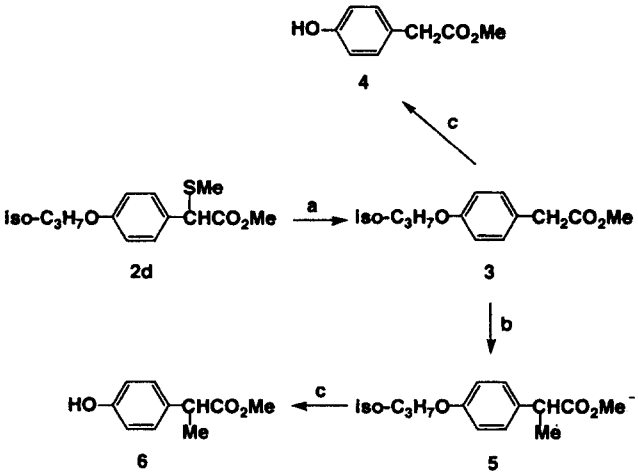
IR spectra were recorded on a Perkin-Elmer 1320 IR spectrophotometer. ^{1}H-NMR spectra were obtained on a Hitachi R-1500 NMR spectrometer using tetramethylsilane as an internal standard. Mass spectra were measured on a Hewlett-Packard 5970 GC/MS system. Analytical TLC used Merck silica gel 60 F_{254} plates, and column chromatography was performed on silica gel (Merck, Kieselgel 60, 70-230 mesh). Chloride compound **1** was prepared as previously described in literature (Choi *et al.*, 1993).

General Procedure for Preparation of Methyl α-methylthio-(alkoxyphenyl)acetates (2a-e)

To a stirred solution of **1** (300 mg, 1.94 mmol) and alkoxybenzenes (1.94 mmol) in methylene chloride (3-5 ml) was added dropwise $SnCl_4$ or $TiCl_4$ (1.94 mmol) at 0℃ under a N_2 atmosphere, and the mixture was stirred for 30 min at the same temperature. The reaction mixture was quenched by the addition of water (5 ml) and extracted with methylene chloride (5 ml× 2). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (benzene) to afford **2a-e** as colorless oil. The reaction con-



Scheme 1



Scheme 2

Table I. Friedel-Crafts Reaction of Alkoxybenzenes with **1** in CH_2Cl_2[a]

Alkoxybenzene	Cat.[b]	Product No	RO-C_6H_4- in **2**	Yield (%)
anisole	$TiCl_4$	**2a**	CH_3O-[c]	80
	$SnCl_4$			75
ethoxybenzene	$TiCl_4$	**2b**	C_2H_5O-[c]	63
	$SnCl_4$			58
n-propoxybenzene	$TiCl_4$	**2c**	n-C_3H_7O-[c]	63
	$SnCl_4$			58
isopropoxybenzene	$TiCl_4$	**2d**	iso-C_3H_7O-	63
	$SnCl_4$			58
n-butoxybenzene	$TiCl_4$	**2e**	n-C_4H_9O-[c]	63
	$SnCl_4$			58

[a] Reactions were carried out for 30 min at 0°C, [b] Alkoxybenzene/1/Cat=1/1/1, [c] A mixture of p- and o-isomers: **2a** (ca. 5 : 2), **2b** (ca. 2 : 1), **2c** (ca. 3 : 1), **2e** (ca. 5 : 1), the ratios were determined by ^{1}H-NMR spectroscopy.

ditions and yields of **2a-e** are summerized in Table I. The compounds **2a-e** had the following physical properties.

Methyl α-methylthio-(p- and o-methoxyphenyl)acetate 2a

IR (neat) cm^{-1}: 1740(CO); ^{1}H-NMR ($CDCl_3$) δ: 2.06 and 2.13 (total 3H, both s, SCH_3 of p- and o-isomers), 3.73(3H, s, $COOCH_3$), 3.80 and 3.85 (total 3H, both s, OCH_3 of p- and o-isomers), 4.47 and 4.98 (total 1H, both s, CHCOO of p- and o-isomers), 6.70-7.65(4H, m, ArH); MS m/z (rel. int.): 226(M^+, 15), 179(70), 151(95), 135(17), 108(18), 77(45), 51(60), 15(100).

Methyl α-methylthio-(p- and o-ethoxyphenyl)acetate 2b

IR (neat) cm^{-1}: 1725(CO); ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7.0 Hz, $\underline{CH_3}CH_2O$), 2.06 and 2.13 (total 3H, both s, SCH_3 of p- and o-isomers), 3.73(3H, s, $COOCH_3$), 4.02 and 4.06 (total 2H, both q, J=7.0 Hz, $CH_3\underline{CH_2}O$ of p- and o-isomers), 4.46 and 4.95 (total 1H, both s, CHCOO of p- and o-isomers), 6.62-7.40(4H, m, ArH); MS m/z (rel. int.): 240(M^+, 10), 193(62), 153(34), 137(100), 78(20), 51(45), 29(51).

Methyl α-methylthio-(p- and o-propoxyphenyl)acetate 2c

IR (neat) cm^{-1}: 1720(CO); ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, t, J=7.1 Hz, $\underline{CH_3}CH_2CH_2O$), 1.48-2.0(2H, m, $CH_3\underline{CH_2}CH_2O$), 2.06 and 2.13(total 3H, both s, SCH_3 of p- and o-isomers), 3.73(3H, s, $COOCH_3$), 3.92 and 3.98 (total 2H, both t, J=6.4 Hz, $CH_3CH_2\underline{CH_2}O$ of p- and o-isomers), 6.71-7.60(4H, m, ArH); MS m/z (rel. int.): 254(M^+, 35), 207(100), 165(76), 137(82), 107(9), 77(22), 59(20), 41(54).

Methyl α-methylthio-p-isopropoxyphenylacetate 2d

IR (neat) cm^{-1}: 1720(CO); ^{1}H-NMR ($CDCl_3$) δ: 1.32 [6H, d, $(\underline{CH_3})_2CH$], 2.06(3H, s, SCH_3), 3.73(3H, s, $COOCH_3$), 4.22-5.02[1H, m, $(CH_3)_2\underline{CH}$], 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 (rel. int.): 254(M^+, 7), 207(21), 165(65), 137(100), 121(12), 77(19), 43(23).

Methyl α-methylthio-(p- and o-butoxyphenyl)acetate 2e

IR (neat) cm^{-1}: 1725(CO); ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=5.8 Hz, $\underline{CH_3}CH_2CH_2CH_2$), 1.16-1.98(4H, m, $CH_3\underline{CH_2}CH_2CH_2$), 2.06 and 2.13 (total 3H, both s, SCH_3 of p-and o-isomers), 3.73(3H, s, $COOCH_3$), 3.95(2H, t, J=5.8 Hz, $CH_3CH_2CH_2\underline{CH_2}$), 4.46 and 4.98 (total 1H, both s, CHCOO of o- and p-isomers), 6.64-7.46(4H, m, ArH); MS m/z (rel. int.): 268(M^+, 10), 221(51), 190 (3), 165(85), 137(98), 77(22), 51(20), 29(100).

Methyl p-isopropoxyphenylacetate 3

A solution of **2d** (700 mg, 2.76 mmol) in acetic acid (7 ml) was treated with zinc dust (2.30 g) at room temperature, and themixture was refluxed for 1 h, then cooled. The reaction mixture was diluted with water (10 ml) and methylene chloride (10 ml), the inorganic materials were filtered off. The organic layer was separated and the aqueous layer was further extracted with methylene chloride (10 ml×2). The combined organic layer was dried ($MgSO_4$) and concentrated under re-

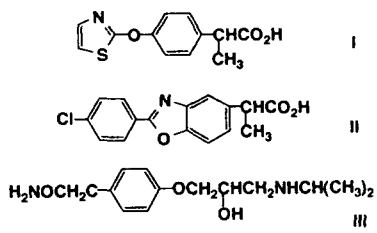


Fig. 1

duced pressure. The residue was 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); ^{1}H-NMR ($CDCl_3$) δ: 1.32[6 H, d, $(CH_3)_2CH$], 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 (rel. int.): 208(M^+, 42), 166(98), 149(27), 121(12), 107 (100), 77(95), 43(76).

Methyl p-hydroxyphenylacetate 4

To a solution of **3** (486 mg, 2.35 mmol) in benzene (6 ml) was added $TiCl_4$ (891 mg, 4.70 mmol) at room temperature. The mixture was stirred for 8 h atthe same temperature and quenched by the addition of water. The organic layer was separated and the aqueous layer was further extracted with benzene (7 ml×2). The combined organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel using hexane/ethylacetate (4/1) as an eluent to give **4** (264 mg, 68%) as a colorless oil.

IR (neat) cm^{-1}: 3400(OH), 1710(CO); ^{1}H-NMR ($CDCl_3$) δ: 3.56(2H, s, CH_2COO), 3. 69(3H, s, $COOCH_3$), 5.21(1 H, s, ArOH) 6.74(2H, d, J=8.8 Hz, ArH), 7.13(2H, d, J=8.8 Hz, ArH). This ester was identical with authentic sample prepared by the usual esterification (HCl-methanol) of p-hydroxyphenylacetic acid.

Methyl α-(p-isopropoxyphenyl)propionate 5

To a suspension of sodium hydride (60% dispersion in mineral oil, 148 mg, 3.70 mmol) in DMF (2 ml) was added a solution of **3** (728 mg, 3.50 mmol) in DMF (4 ml) at 0℃ under a 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℃ for 30 min and at room temperature for 1 h. The reaction mixture was quenched by the addition of 5% NH_4Cl (10 ml) and extracted with ethyl ether (10 ml×2). The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographyed 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); ^{1}H-NMR ($CDCl_3$) δ: 1.31[6 H, d, $(CH_3)_2CH$], 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(2 H, d, J=8.8 Hz, ArH); MS m/z (rel. int.): 222(M^+, 12), 180(12), 163(10), 121(100), 91(32), 77(22), 27(20).

Methyl α-(p-hydroxyphenyl)propionate 6

By the same procedure as described above for the preparation of **4**, compound **6** was obtained from **5** (526 mg, 2.37 mmol) and TiCl4 (899 mg, 4.74 mmol) in 84% yield (358 mg) as a colorless oil.

IR (neat) cm^{-1}: 3400(OH), 1700(CO); ^{1}H-NMR ($CDCl_3$) δ: 1.47[3H, d, $CH(CH_3)COO$], 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 (rel. int.): 180(M^+, 22), 149(2), 121(100), 93(12), 65(10), 39 (15).

RESULTS AND DISCUSSION

Friedel-Crafts reaction of alkoxybenzenes with **1** under a variety of conditions showed that (i) the reaction can also be carried out by using equimolar amounts of alkoxybenzenes and **1** in an inert solvent such as methylene chloride, (ii) the order of activity of Lewis acid is stannic chloride=titanium tetrachloride (for anisole, ethoxybenzene, n-propoxybenzene, n-butoxybenzene) and stannic chloride≫titanium tetrachloride (for isopropoxybenzene), (iii) by examination of ^{1}H-NMR spectra, compounds (**2a-c, e**) are the mixture of p- and o-isomers and methyl α-methylthio-p-isopropoxyp-henylacetate **2d** is only p-substituted product. ^{1}H-NMR spectra of **2d** exhibited proton resonances of typical p-substituted benzene ring at δ 6.83 and 7.35 ppm (2H, d, J=8.8 Hz, each). The results are summarized in Table I.

In a series of Friedel-Crafts reactions, **2d** was obtained in 29% yield from isopropoxybenzene with **1** in the presence of $TiCl_4$. As reported by Sala in 1979 (Sala and Sargent, 1979), consequently, the remarkable decrease of yield means that cleavage of ether bond of **2d** would be accomplished by exposure to $TiCl_4$.

Compound **2d** was desulfurized by heating of zinc dust in acetic acid to give methyl p-isopropoxyphenylacetate **3** in 93% yield. Methylation of **3** by treatment with sodium hydride and then methyl iodide in dimethylformamide afforded methyl α-(p-isopropoxyphenyl) propionate **5** in 82% yield. ^{1}H-NMR spectra of **5** showed a new doublet methyl proton resonance at δ 1.47 ppm (J=7.0 Hz) and disappearence of a methylene proton signal at δ 3.36 ppm in ^{1}H-NMR spectra of **3**. The mass spectra of **5** showed a molecular ion peak at m/z 222 and 121 as base peak for the frag-

ment.

Methyl p-hydroxyphenylalkanoates (**4, 6**) were prepared from compounds **3** and **5** by dealkylation with titanium tetrachloride in benzene according to the procedure for the removal of isopropyl protector (Sala and Sargent, 1979). The structural assignment of the newly synthesized compounds **2a-e** and (**3, 5, 6**) was based on IR, ^{1}H-NMR, MS spectroscopy.

In summary, products (**4, 6**) were successfully obtained from Friedel-Crafts reaction of isopropoxybenzene with **1**, desulfurization of **2d**, methylation of **3**, and followed by dealkylation of compounds (**3, 5**). The present sequence of reactions can be carried out under rather mild conditions in good yields, and hence provides a useful synthetic route. Now we are continuing to develop several synthetic approach for some medicines starting from key intermediates **4** and **6**.

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