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Synthesis of Ethyl Arylacetates by Means of Friedel-Crafts Reaction of Aromatic Compounds with Ethyl α-Chloro-α-(methylthio)acetate

YASUMITSU TAMURA,* HONG DAE CHOI, HIROHISA SHINDO, and HIROYUKI ISHIBASHI

Faculty of Pharmaceutical Sciences, Osaka University, 1-6, Yamada-oka, Suita, Osaka, 565 Japan

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Friedel-Crafts reaction of aromatic compounds with ethyl α-chloro-α-(methylthio)-acetate (**1**) gave ethyl α-(methylthio)arylacetates (**2**), which were readily converted into ethyl arylacetates (**3**) by reductive desulfurization with Raney nickel or zinc dust-acetic acid. The reactions were applied to the syntheses of ibufenac (**5**) and alclofenac (**6**), which are anti-inflammatory agents.

Keywords——Friedel-Crafts reaction with ethyl α-chloro-α-(methylthio)acetate; Lewis acid; ethyl α-(methylthio)arylacetate; reductive desulfurization; Raney nickel; zinc dust-acetic acid; ethyl arylacetate; ibufenac; alclofenac; 2-thiopheneacetic acid

We have briefly reported[1] a novel preparative method for ethyl arylacetates (**3**) by Friedel-Crafts reaction of aromatic compounds with ethyl α-chloro-α-(methylthio)acetate (**1**) and successive desulfurization of the resulting ethyl α-(methylthio)arylacetate (**2**). The present paper describes the experimental details of this work and its application to the syntheses of ibufenac (**5**) and alclofenac (**6**), which are anti-inflammatory agents.

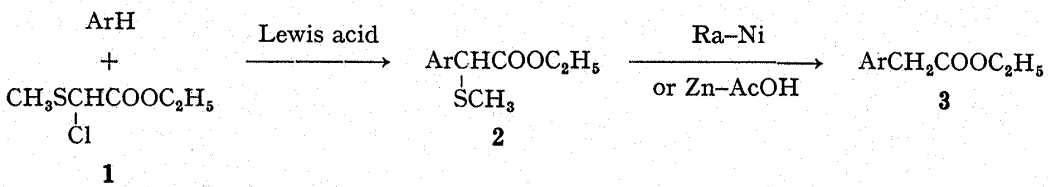


Chart 1

Friedel-Crafts Reaction

Ethyl α-chloro-α-(methylthio)acetate (**1**) was prepared from ethyl α-(methylthio)acetate by chlorination with *N*-chlorosuccinimide (NCS) according to the procedure described by Böhme.[2] When a benzene solution of **1** was treated with one equivalent of stannic chloride ($SnCl_4$) at room temperature, ethyl α-(methylthio)phenylacetate (**2a**, Ar=C_6H_5) was obtained in 91% yield. The structural assignment of **2a** was made on the basis of its composition and spectral data (see "Experimental"). The reaction of benzene with **1** under a variety of conditions (the results are summarized in Table I) shows that (i) the reaction requires one equivalent of catalyst and give no polyalkylated product, (ii) the reaction can also be carried out by using equimolar amounts of benzene and **1** in an inert solvent such as methylene chloride (CH_2Cl_2) and (iii) the order of activity of catalyst is $SnCl_4 \cong$ aluminum chloride ($AlCl_3$) $>$ titanium tetrachloride ($TiCl_4$) $\gg$ zinc chloride ($ZnCl_2$). Further alkylation of **2a** with **1** in the presence of one or two equivalents of $SnCl_4$ was attempted, but failed even under reflux in CH_2Cl_2.

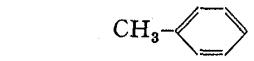
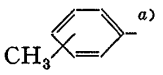
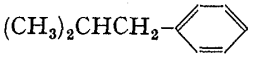
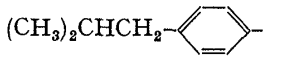
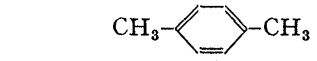
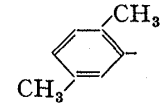
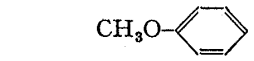
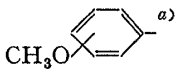
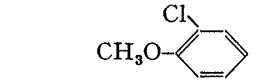
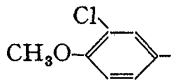
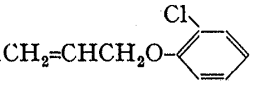
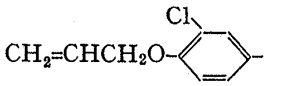
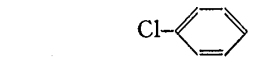
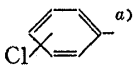
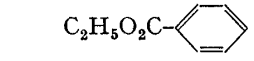
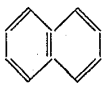
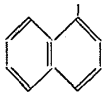
We next examined the reaction of substituted benzenes and naphthalene with one equivalent of **1** in CH_2Cl_2. The results are summarized in Table II. The reaction of toluene, isobutylbenzene, *p*-xylene, or naphthalene took place smoothly at room temperature in the presence of $SnCl_4$ to give the adduct (**2b**, **c**, **d**, or **2i**) in nearly quantitative yield. Similar reaction of anisole was found to give a complex mixture of products with $SnCl_4$ but to give

Table I. Friedel–Crafts Reaction of Benzene with **1** under a Variety of Conditions

Benzene/1	Catalyst	Cat./1	Solvent	Temp.	Time (min)	Yield of **2a** (%)
5	$SnCl_4$	1	—	rt	20	91
5	$SnCl_4$	0.5	—	rt	40	47
5	$TiCl_4$	1	—	rt	20	90
1	$SnCl_4$	1	CH_2Cl_2	rt	40	87
1	$AlCl_3$	1	CH_2Cl_2	rt	40	85
1	$TiCl_4$	1	CH_2Cl_2	rt	40	66
1	$ZnCl_2$	1	CH_2Cl_2	rt	40	5

rt: room temperature.

Table II. Friedel–Crafts Reaction of Substituted Benzenes and Naphthalene with **1** in CH_2Cl_2

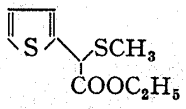
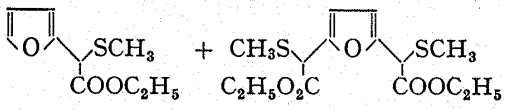
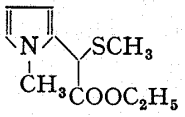
ArH	Catalyst	Temp. (°C)	Time (min)	Product No.	Product Ar in **2**	Yield (%)
	$SnCl_4$	rt	40	**2b**	 a)	92
	$SnCl_4$	rt	40	**2c**		Quant
	$SnCl_4$	rt	40	**2d**		Quant
	$TiCl_4$	0	10	**2e**	 a)	98
	$TiCl_4$	rt	40	**2f**		85
	$TiCl_4$	rt	40	**2g**		86
	$SnCl_4$	refl.	90	**2h**	 a)	90
	$SnCl_4$	refl.	90	—	—	—
	$SnCl_4$	rt	40	**2i**		Quant

a) A mixture of *p*- and *o*-isomers; **2b** (*ca.* 4: 1), **2e** (*ca.* 5: 2), **2h** (*ca.* 4: 1), the ratios were determined by ^{1}H-NMR spectroscopy.
rt: room temperature.

2e quantitatively with $TiCl_4$. The reaction of chlorobenzene with **1** was very sluggish at room temperature in the presence of $SnCl_4$, but, on refluxing the mixture, the adduct (**2h**) was obtained in fairly good yield. Ethyl benzoate failed to react with **1** even under reflux, leading to recovery of the starting materials.

Heteroaromatic compounds such as thiophene, furan, and 1-methylpyrrole, which are sensitive to acidic conditions, were also found to react with **1** in the presence of $TlCl_4$ or $ZnCl_2$. The results are summarized in Table III. In the light of the previous finding[3] that the Friedel-Crafts alkylation of thiophene usually gives a mixture of α- and β-alkylated products, it is of interest that only an α-alkylated product (**2j**) was formed in the reaction of thiophene with **1**. The reaction of furan with **1** afforded an α,α'-dialkylated product (**4**) along with **2k**.

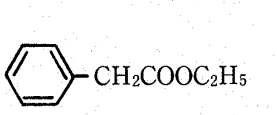
Table III. Friedel–Crafts Reaction of Heteroaromatic Compounds with 1 in CH_2Cl_2

ArH	Catalyst[a]	ArH/1	Temp. (°C)	Time (min)	Product (Yield, %)
	$TiCl_4$	1	0	40	 **2j** (59)
	$TiCl_4$	2	0	40	**2j** (83)[b]
	$ZnCl_2$	1	rt	60	 **2k** (56) **4** (13)[c]
	$ZnCl_2$	2	rt	60	**2k** (68)[b] + **4** (Trace)
	$TiCl_4$	2	0	60	 **2l** (59)[b]

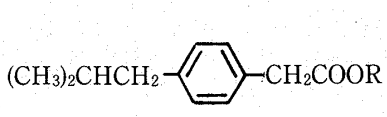
a) Catalyst/1=1.
b) The yields are based on **1**.
c) The yield is based on furan.
rt: room temperature.

Desulfurization

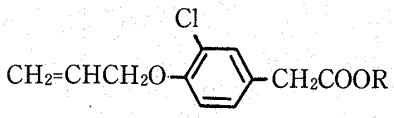
The adducts (**2**) obtained by the above Friedel-Crafts reaction can easily be desulfurized into the corresponding ethyl arylacetates (**3**) by heating with Raney nickel in ethanol or with zinc dust in acetic acid.[4] Thus, the adducts (**2a**, **c**, **g**, **i**, **j**, **k**, and **l**) were converted into ethyl arylacetates (**3a**, **c**, **g**, **i**, **k**, and **l**), respectively, in good yields. Saponifications of **3c** and **3g** with potassium hydroxide in aqueous methanol afforded the anti-inflammatory agents ibufenac (**5**) and alclofenac (**6**), respectively. Saponification of **3j** gives 2-thiopheneacetic acid,[5] a useful reagent for chemical modification of penicillins and cephalosporins.[6]



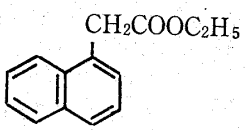
3a



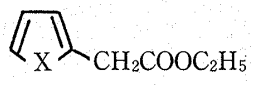
3c : R=C_2H_5
5 : R=H



3g : R=C_2H_5
6 : R=H



3i



3j : X=S
3k : X=O
3l : X=NCH_3

Chart 2

In view of the difficulty in preparing arylacetic esters by Friedel-Crafts reaction with ethyl chloroacetate,[7] the present sequence of the reactions appears to provide a rather useful method for the introduction of an acetic acid group into aromatic nuclei.

Experimental[8]

Ethyl α-Chloro-α-(methylthio)acetate (1)——N-Chlorosuccinimide (6 g, 45 mmol) was added to a stirred solution of ethyl α-(methylthio)acetate (6 g, 45 mmol) in carbon tetrachloride (25 ml) in small portions at 0°C and the stirring was continued at room temperature for 10 h. The precipitated succinimide was filtered off and the solvent was removed *in vacuo*. The residual oil was distilled at 87—89°C (14 mmHg) to give **1** (6.7 g, 89%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.33 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.33 (3H, s, SCH_3), 4.28 (2H, q, J=7 Hz, OCH_2), and 5.35 (1H, s, COCH). *Anal.* Calcd for $C_5H_9ClO_2S$: C, 35.61; H, 5.38. Found: C, 35.39; H, 5.42.

Ethyl α-(methylthio)acetate was synthesized according to our procedure[9] for the preparation of sulfide from sodium thiolate and dialkyl carbonate. Thus, ethyl thioglycolate (24 g, 0.2 mol) and dimethyl carbonate (18 g, 0.2 mol) were added to a stirred solution of sodium ethoxide (16.3 g, 0.24 mol) in ethanol (120 ml) at 0°C, and the resultant mixture was refluxed with vigorous stirring for 15 h. The solvent was evaporated off and the residue was poured into ice-water. The mixture was acidified with concentrated hydrochloric acid, extracted with benzene, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residual oil was distilled to give ethyl α-(methylthio)acetate (18.8 g, 70%), bp 78—79°C (20 mmHg), lit[10] 66°C (12 mmHg). ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.30 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.20 (3H, s, SCH_3), 3.15 (2H, s, $COCH_2$), and 4.17 (2H, q, J=7 Hz, OCH_2).

Ethyl α-(Methylthio)phenylacetate (2a)——a) $SnCl_4$ (464 mg, 1.78 mmol) was added to a stirred solution of **1** (300 mg, 1.78 mmol) in benzene (0.79 ml, 8.9 mmol) at room temperature, and stirring was continued at the same temperature for 30 min. The reaction was quenched by the addition of water and the mixture was extracted with benzene, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed on silica gel using benzene as an eluent to give **2a** (340 mg, 91%), bp 100—110°C (bath temperature) (0.06 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.09 (3H, s, SCH_3), 4.21 (2H, q, J=7 Hz, OCH_2), 4.49 (1H, s, COCH), and 7.25—7.70 (5H, m, arom). MS *m/e*: 210 (M^+). *Anal.* Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71. Found: C, 62.67; H, 6.74.

b) $SnCl_4$ (464 mg, 1.78 mmol) was added to a stirred solution of **1** (300 mg, 1.78 mmol) and benzene (139 mg, 1.78 mmol) in CH_2Cl_2 (0.6 ml) at room temperature. The mixture was stirred at the same temperature for 40 min and worked up to give **2a** (318 mg, 87%). The reactions using the other catalysts listed in Table I were carried out in a similar manner.

Ethyl α-Methylthio-(*p*- and *o*-methylphenyl)acetate (2b), Ethyl α-Methylthio-*p*-isobutylphenylacetate (2c), Ethyl α-Methylthio-2,4-dimethylphenylacetate (2d) and Ethyl α-Methylthio-1-naphthaleneacetate (2i)——$SnCl_4$ (464 mg, 1.78 mmol) in CH_2Cl_2 (1 ml) was added to a stirred solution of **1** (300 mg, 1.78 mmol) and toluene, isobutylbenzene, *p*-xylene, or naphthalene (1.78 mmol) at room temperature, and stirring was continued at the same temperature for 20 min. The reaction was quenched by the addition of water and the mixture was extracted with benzene, and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel using benzene as an eluent to give **2b**, **c**, **d**, or **i** as an oil. The yields are given in Table II. **2b**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.08 (3H, s, SCH_3), 2.34 and 2.40 (3H, 2s, $ArCH_3$ of *p*- and *o*-isomers), 4.18 (2H, q, J=7 Hz, OCH_2), 4.45 and 4.73 (1H, 2s, COCH of *p*- and *o*-isomers), and 7.0—7.5 (4H, m, arom). MS *m/e*: 224 (M^+). *Anal.* Calcd for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.19. Found: C, 64.15; H, 7.18. **2c**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 0.90 [6H, d, $(CH_3)_2$], 1.26 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.50—2.30 [1H, m, $C\underline{H}(CH_3)_2$], 2.07 (3H, s, SCH_3), 2.46 (2H, d, J=7 Hz, $ArC\underline{H}_2$), 4.20 (2H, q, J=7 Hz, OCH_2), 4.47 (1H, s, COCH), and 7.0—7.4 (4H, m, arom). MS *m/e*: 266 (M^+). *Anal.* Calcd for $C_{15}H_{22}O_2S$: C, 67.63; H, 8.32. Found: C, 67.45; H, 8.41. **2d**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.25 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.10 (3H, s, SCH_3), 2.31 (3H, s, $ArC\underline{H}_3$), 2.36 (3H, s, $ArC\underline{H}_3$), 4.18 (2H, q, J=7 Hz, OCH_2), 4.69 (1H, s, COCH), and 7.0—7.3 (3H, m, arom). MS *m/e*: 238 (M^+). *Anal.* Calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61. Found: C, 65.20; H, 7.64. **2i**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.20 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.11 (3H, s, SCH_3), 4.20 (2H, q, J=7 Hz, OCH_2), 5.26 (1H, s, COCH), and 7.4—8.3 (7H, m, arom). MS *m/e*: 260 (M^+). *Anal.* Calcd for $C_{15}H_{16}O_2S$: C, 69.20; H, 6.19. Found: C, 69.01; H, 6.08.

Ethyl α-Methylthio-(*p*- and *o*-methoxyphenyl)acetate (2e)——$TiCl_4$ (338 mg, 1.78 mmol) was added to a stirred solution of **1** (300 mg, 1.78 mmol) and anisole (192 mg, 1.78 mmol) in CH_2Cl_2 (1 ml) at 0°C, and stirring was continued at the same temperature for 10 min. The reaction was quenched by the addition of water, then the mixture was extracted with benzene, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed on silica gel using benzene as an eluent to give **2e** (418 mg, 98%) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.06 and 2.13 (3H, 2s, SCH_3 of *p*- and *o*-isomers), 3.78 and 3.82 (3H, 2s, OCH_3 of *p*- and *o*-isomers), 4.17 (2H, q, J=7 Hz, OCH_2), 4.41 and 4.90 (1H, 2s, COCH of *p*- and *o*-isomers), and 3.7—7.4 (4H, m, arom). MS *m/e*: 240 (M^+).

Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.97; H, 6.71. Found: C, 59.93; H, 6.62.

Ethyl α-Methylthio-3-chloro-4-methoxyphenylacetate (2f) and Ethyl α-Methylthio-4-allyloxy-3-chlorophenylacetate (2g)——$TiCl_4$ (676 mg, 3.56 mmol) was added to a stirred solution of **1** (600 mg, 3.56 mmol) and *o*-chloroanisole or *o*-(allyloxy)chlorobenzene[11] (3.56 mmol) in CH_2Cl_2 (10 ml) at 0°C, and stirring was continued at room temperature for 40 min. The reaction was quenched by the addition of water and the mixture was extracted with benzene, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed on silica gel using benzene as an eluent to give **2f** (833 mg, 85%) or **2g** (920 mg, 86%) as an oil. **2f**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.23 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.03 (3H, s, SCH_3), 3.86 (3H, s, OCH_3), 4.18 (2H, q, J=7 Hz, OCH_2), 4.36 (1H, s, COCH), and 6.8—7.6 (3H, m, arom). MS *m/e*: 274 (M^+). *Anal.* Calcd for $C_{12}H_{15}ClO_3S$: C, 52.46; H, 5.50. Found: C, 52.26; H, 5.31. **2g**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.27 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.08 (3H, s, SCH_3), 4.20 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.38 (1H, s, COCH), 4.60 (2H, bd, OCH_2C=C), 5.1—6.4 (3H, m, CH=CH_2), and 6.7—7.5 (3H, m, arom). MS *m/e*: 300 (M^+). *Anal.* Calcd for $C_{14}H_{17}ClO_3S$: C, 55.90; H, 5.70. Found: C, 55.59; H, 5.73.

Ethyl α-Methylthio-(*p*- and *o*-chlorophenyl)acetate (2h)——$SnCl_4$ (464 mg, 1.78 mmol) was added to a stirred solution of **1** (300 mg, 1.78 mmol) and chlorobenzene (200 mg, 1.78 mmol) in CH_2Cl_2 (1 ml) at room temperature and the resultant solution was refluxed for 90 min. The reaction was quenched by the addition of water, then the mixture was extracted with benzene, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed on silica gel using benzene as an eluent to give **2h** (393 mg, 90%) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.07 and 2.14 (3H, 2s, SCH_3 of *p*- and *o*-isomers), 4.20 (2H, q, J=7 Hz, OCH_2), 4.45 and 5.04 (1H, 2s, COCH of *p*- and *o*-isomers), a d 7.3—7.4 (4H, m, arom). MS *m/e*: 244 (M^+). *Anal.* Calcd for $C_{11}H_{13}ClO_3S$: C, 53.99; H, 5.35. Fou d: C, 53.97; H, 5.29.

Ethyl α-Methylthio-2-thiopheneacetate (2j)——$TiCl_4$ (338 mg, 1.78 mmol) was added to a stirred solution of **1** (300 mg, 1.78 mmol) and thiophene (150 mg, 1.78 mmol) in CH_2Cl_2 (20 ml) at 0°C, and stirring was continued at the same temperature for 40 min. The reaction was quenched by the addition of water, and the mixture was extracted with benzene, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed on silica gel using benzene as an eluent to give **2j** (227 mg, 59%) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.29 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.12 (3H, s, SCH_3), 4.24 (2H, q, J=7 Hz, OCH_2), 4.77 (1H, s, COCH), and 6.8—7.4 (3H, m, arom); these spectral data are in accord with those reported.[12]

Ethyl α-Methylthio-2-furanacetate (2k) and Diethyl α,α′-Di(methylthio)-2,5-furandiacetate (4)——$ZnCl_2$ (243 mg, 1.78 mmol) was added to a stirred solution of **1** (300 mg, 1.78 mmol) and furan (121 mg, 1.78 mmol) in CH_2Cl_2 (20 ml) at 0°C, and stirring was continued at room temperature for 1 h. The reaction was quenched by the addition of water, then the mixture was extracted with benzene, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed on silica gel using benzene as an eluent to give **2k** (198 mg, 56%) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.29 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.18 (3H, s, SCH_3), 4.20 (2H, q, J=7 Hz, OCH_2), 4.57 (1H, s, COCH), 6.2—6.6 (2H, m, arom), and 7.3—7.45 (1H, m, arom). MS *m/e*: 200 (M^+, Calcd for $C_9H_{12}O_3S$: 200.0505. Found: 200.0494). Further elution with the same solvent gave **4** as an oil (39 mg, 13% based on furan). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.33 (6H, t, J=7 Hz, $CH_2C\underline{H}_3\times2$), 2.13 (6H, s, $SCH_3\times2$), 4.24 (4H, q, J=7 Hz, $OCH_2\times2$), 4.55 (2H, s, $COCH\times2$), and 6.41 (2H, s, arom). MS *m/e*: 332 (M^+). *Anal.* Calcd for $C_{14}H_{20}O_5S_2$: 332.0751. Found: 332.0766).

Ethyl α-Methylthio-1-methyl-2-pyrroleacetate (2l)——$TiCl_4$ (338 mg, 1.78 mmol) was added to a stirred solution of **1** (300 mg, 1.78 mmol) and 1-methylpyrrole (289 mg, 3.56 mmol) in CH_2Cl_2 (8 ml) at 0°C and stirring was continued at the same temperature for 1 h. The reaction was quenched by the addition of water, then the mixture was extracted with CH_2Cl_2, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was chromatographed on silica gel using benzene as an eluent to give **2l** (226 mg, 59% based on **1**) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.30 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.01 (3H, s, SCH_3), 3.58 (3H, s, NCH_3), 4.28 (2H, q, J=7 Hz, OCH_2), 4.50 (1H, s, COCH), 5.97 (1H, dd, J=4 and 3 Hz, arom), 6.24 (1H, dd, J=4 and 2 Hz, arom), and 6.54 (1H, bt, arom). MS *m/e*: 213 (M^+). *Anal.* Calcd for $C_{10}H_{15}NO_2S$: 213.0824. Found: 213.0829).

Ethyl Phenylacetate (3a)——Raney nickel (W-1) was added to a solution of **2a** (190 mg, 0.9 mmol) in ethanol (40 ml), and the mixture was refluxed for 3 h. The Raney nickel was filtered off and the solvent was removed *in vacuo* to give **3a** quantitatively. This ester was identified by comparison of spectral data with those of a commercial sample.

Ethyl *p*-Isobutylphenylacetate (3c)——Zinc dust (650 mg) was added to a solution of **2c** (200 mg, 0.15 mmol) in acetic acid (3 ml), and the resultant mixture was heated with vigorous stirring at 100—110°C for 1 h, then cooled. Water (20 ml) and CH_2Cl_2 (30 ml) were added, and the inorganic materials were filtered off. The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$) and the solvent was evaporated off. The residue was chromatographed on silica gel using benzene as an eluent to give **3c** (152 mg, 92%) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 0.90 [6H, d, J=7 Hz, $(CH_3)_2$], 1.25 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.4—2.3

(1H, m, $CH_2C\underline{H}$), 2.44 (2H, d, J=7 Hz, $C\underline{H}_2CH$), 3.53 (2H, s, CH_2CO), 4.12 (2H, q, J=7 Hz, OCH_2), and 7.04 (4H, s, arom). This ester was characterized by the following transformation into ibufenac (**5**).

Ibufenac (*p*-Isobutylphenylacetic Acid, 5)——Compound **3c** (155 mg, 0.7 mmol) was added to a solution of potassium hydroxide (180 mg, 3.2 mmol) in water (2 ml) and methanol (3 ml), and the mixture was heated at 60°C for 3 h, then cooled. Water was added, and the solution was washed with CH_2Cl_2 The aqueous layer was acidified to pH 1 with concentrated hydrochloric acid, extracted with ether, and dried ($MgSO_4$). The solvent was evaporated off to give ibufenac (**5**) quantitatively, mp 80—82°C (from *n*-hexane), lit.[13a] 85—87°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 0.89 [6H, d, J=7 Hz, $(CH_3)_2$], 1.4—2.3 (1H, m, $CH_2C\underline{H}$), 2.41 (2H, d, J=7 Hz, $C\underline{H}_2CH$), 3.54 (2H, s, CH_2CO), 7.03 (4H, s, arom), and 10.23 (1H, bs, COOH).

Ethyl 4-Allyloxy-3-chlorophenylacetate (3g)——By the same procedure as described above for the preparation of **3c**, compound **3g** was obtained from **2g** (325 mg, 1.08 mmol) in 92% yield (253 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.53 (2H, s, $ArC\underline{H}_2$), 4.14 (2H, q, J=7 Hz, OCH_2), 5.57 (2H, bd, OCH_2C=C), 5.1—6.4 (3H, m, CH=CH_2), and 6.7—7.5 (3H, m, arom). This ester was characterized by the following transformation into alclofenac (**6**).

Alclofenac (4-Allyloxy-3-chlorophenylacetic Acid, 6)——By the same procedure as described above for the preparation of **5**, alclofenac (**6**) was obtained from **3g** (263 mg, 0.99 mmol) in quantitative yield, mp 89—90°C (from cyclohexane), lit.[13b] 92—93°C. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 3.55 (2H, s, $ArC\underline{H}_2$), 4.59 (2H, bd, OCH_2), 5.1—6.4 (3H, m, CH=CH_2), 6.7—7.4 (3H, m, arom), and 7.7—8.3 (1H, br, COOH).

Ethyl 1-Naphthaleneacetate (3i)——By the same procedure as described above for the preparation of **3c**, compound **3i** was obtained from **2i** (330 mg, 1.27 mmol) in 92% yield (250 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.20 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.00 (2H, s, $ArC\underline{H}_2$), 4.11 (2H, q, J=7 Hz, OCH_2), and 7.1—8.0 (7H, m, arom). This ester was identical with an authentic sample prepared by the usual esterification (HCl–ethanol) of 1-naphthaleneacetic acid.

Ethyl 2-Thiopheneacetate (3j)——By the same procedure described above for the preparation of **3c**, compound **3j** was obtained from **2j** (507 mg, 2.35 mmol) in 93% yield (370 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.30 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.84 (2H, s, $ArC\underline{H}_2$), 4.20 (2H, q, J=7 Hz, OCH_2), and 6.85—7.4 (3H, m, arom). MS m/e: 170 (M^+). This ester was identical with an authentic sample prepared by the usual esterification (HCl–ethanol) of 2-thiopheneacetic acid.

Ethyl 2-Furanacetate (3k)——By the same procedure as described above for the preparation of **3c**, compound **3k** was obtained from **2k** (194 mg, 0.97 mmol) in 67% yield (100 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.62 (2H, s, $ArC\underline{H}_2$), 4.13 (2H, q, J=7 Hz, OCH_2), 6.1—6.3 (2H, m, arom), and 7.2—7.3 (1H, m, arom); these spectral data are in accord with those reported.[14]

Ethyl 1-Methyl-2-pyrroleacetate (3l)——By the same procedure as described above for the preparation of **3c**, compound **3l** was obtained from **2l** (177 mg, 0.88 mmol) in 71% yield (98 mg) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720. ^{1}H-NMR (10% solution in CCl_4) δ: 1.23 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.42 (2H, s, $ArC\underline{H}_2$), 3.49 (3H, s, NCH_3), 4.04 (2H, q, J=7 Hz, OCH_2), 5.78 (2H, bd, arom), and 6.34 (1H, bt, arom); these spectral data are in accord with those reported.[15]

References and Notes

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