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# Oxidative 1,2-Aryl Migration of Alkyl Aryl Ketones by Using Diacetoxyphenyliodine: Syntheses of Arylacetate, 2-Arylpropanoate, and 2-Arylsuccinate

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Oxidative 1,2-aryl migration of alkyl aryl ketones (**2**, **5**, and **8**) to 2-arylalkanoates (**3**, **6**, and **9**) was effected by using diacetoxyphenyliodine (**1**). The migration was successfully applied to the preparation of the antiinflammatory agents ibuprofen (**15**) and clidanac (**17**).

**Keywords**——diacetoxyphenyliodine; oxidative 1,2-aryl migration; methyl 2-arylalkanoate; dimethyl 2-arylsuccinate; 2-arylalkanoic acid; 2-arylsuccinic acid; antiinflammatory agent; ibuprofen; clidanac

The oxidative 1,2-aryl migration of alkyl aryl ketones by using thallium(III) nitrate (TTN)[1] provides a general method for the synthesis of 2-arylalkanoic acids, which are widely used as antiinflammatory agents.[2] Thus, McKillop *et al.* have shown that acetophenones (**5**) and propiophenones (**2**) can be rearranged to methyl arylacetates (**6**) and methyl 2-arylpropanoates (**3**) by employing TTN as the oxidant in acidic methanol or trimethylorthoformate.[1] The method, however, is unsuitable for the preparation of pharmaceutical products because of the high toxicity of TTN.[3] This has prompted a number of investigators to devise less toxic reagents, such as silver carbonate,[4] silver (I) nitrate/iodine,[5] iodinemonochloride,[6] lead (IV) acetate,[7,8] and other improved procedures[9] for the migration. Recently we have briefly reported that diacetoxyphenyliodine (**1**), a less toxic reagent, effects the 1,2-aryl migration of propiophenones (**2**) to methyl 2-arylpropanoates (**3**).[10] Since then, the reagent (**1**) has been found to effect the migration of acetophenones (**5**) to methyl arylacetates (**6**) and also the migration of 3-aroylpropionic acids (**8**) to dimethyl 2-arylsuccinates (**9**), which are important synthetic intermediates of indan-1-carboxylic acids possessing antiinflammatory activity.[11] The present paper gives a full account of these results (Chart 1).

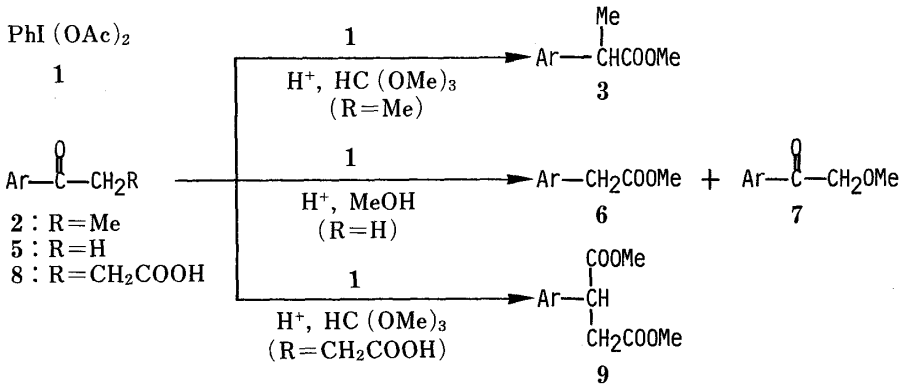



Chart 1

A solution of propiophenone (**2a**) and 1.2 eq of **1** in trimethylorthoformate was treated with acid, resulting in smooth 1,2-aryl migration to give methyl 2-phenylpropanoate (**3a**) in 81% yield (Table I).[10] When the oxidation was carried out in methanol, a 58% yield of 2-methoxy-1-phenylpropanone (**4**) was obtained and the yield of the expected **3a** was only 2%. Attempts to rearrange acetophenone (**5a**) to methyl phenylacetate (**6a**) with **1** and acid in trimethylorthoformate resulted in the formation of a complex mixture. When the oxidation was carried out in methanol, however, **6a** was isolated in 59% yield together with 2-methoxy-1-phenylethanone (**7a**) (17%). The structures of **6a** and **7a** were verified by comparisons of the spectral data with the reported values.[5] Some typical results are summarized in Table II. Next, the migration of 3-aroylpropionic acids (**8**) with **1** and acid was investigated in two solvent systems, methanol and trimethylorthoformate. Treatment of 3-benzoylpropionic acid

Table I. Transformation of **2** to **3**

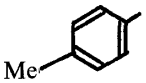
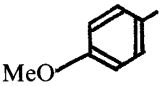
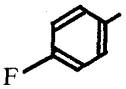
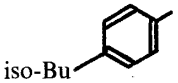
| Compound No. | Ar | Reaction temp. (°C) | Reaction time (min) | Yield (%) |
|---|---|---|---|---|
| **3a** |  | 60 | 10 | 81 |
| **3b** |  | 60 | 5 | 85 |
| **3c** |  | R.T. | 60 | 88 |
| **3d** |  | 60 | 5 | 82 |
| **3e** |  | 60 | 30 | 87 |

Table II. Conversion of **5** into **6** and **7**

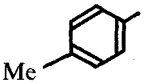
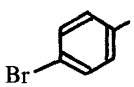
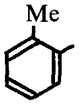
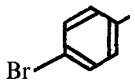
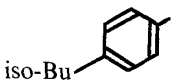
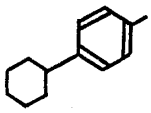
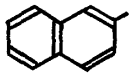
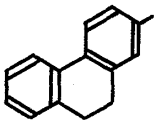
| Substrate No. | Ar | Reaction temp. (°C) | Reaction time (min) | Yield of products (%) **6** | **7** |
|---|---|---|---|---|---|
| **5a** |  | 60 | 60 | 59 | 17 |
| **5b** |  | 60 | 50 | 68 | 18 |
| **5c** |  | 60 | 300 | 44 | 14 |
| **5d** |  | 60 | 60 | 62 | 13 |

TABLE III. Transformation of **8** to **9**

| Compound No. | Ar | Reaction temp. (°C) | Reaction time (h) | Yield (%) |
|---|---|---|---|---|
| **9a** |  | 60 | 2 | 87 |
| **9b** |  | 60 | 2 | 76 |
| **9c** |  | 60 | 1 | 81 |
| **9d** |  | 60 | 2 | 82 |
| **9e** |  | 60 | 1 | 74 |
| **9f** |  | 60 | 5 | 75 |

(**8a**) and 1.2 eq of **1** in methanol with acid gave only the methyl ester of **8a**. The oxidation of **8a** in trimethylorthoformate gave the migration product, dimethyl 2-phenylsuccinate (**9a**) in 87% yield. The structure of **9a** was determined by comparison of the spectral data with the reported values.[12] Data for representative examples are summarized in Table III. As noted above, the 1,2-aryl migration shows a striking dependence on the solvent employed, trimethylorthoformate or methanol. Similar behavior has been observed in analogous migrations using TTN and lead (IV) acetate.[1a,b,8] The role of the solvent, however, is not yet clear.

The mechanism of the above transformations[5] can be represented as shown in Chart 2. The ketone (**2** or **5**) reacts with **1** through the enol form to give the intermediate (**10**), which is acetalized with acid and trimethylorthoformate or methanol to give the acetal (**11**). Loss of iodobenzene with concomitant 1,2-aryl migration leads to the stable carbonium ion (**12**). Reaction of the ion (**12**) with a solvent molecule followed by hydrolysis of the resultant ortho-ester (**13**) gives **3** or **6**. The formation of **4** and **7** can be explained by the methanolysis of the intermediate (**10**; R = Me, H). With respect to the conversion of **8** into **9**, initial esterification of **8** affords the methyl ester (**14**), as confirmed by thin layer and gas chromatography. The mechanism of the migration of **14** to **9** is presumably similar to that outlined in Chart 2.

Finally, the migration was applied to prepare two antiinflammatory agents, ibuprofen (**15**) and clidanac (**17**). Friedel–Crafts reaction of 4-isobutylbenzene with propionyl chloride gave 4′-isobutylpropiophenone (**2e**) in 88% yield. The migration of **2e** with **1** gave an 87% yield of 2-(4-isobutylphenyl)-propanoate (**3e**), which was readily hydrolyzed with 2 N NaOH solution to give ibuprofen (**15**) [2-(4-isobutylphenyl)propanoic acid] in 87% yield (Chart 3). Friedel–Crafts reaction of 4-cyclohexylbenzene with succinic anhydride gave 3-(4-cyclohexylbenzoyl)propionic acid (**8d**) in 86% yield. The migration reaction of **8d** with **1** afforded an 82% yield of 2-(4-cyclohexylphenyl)succinate (**9d**), which was hydrolyzed with 2 N KOH

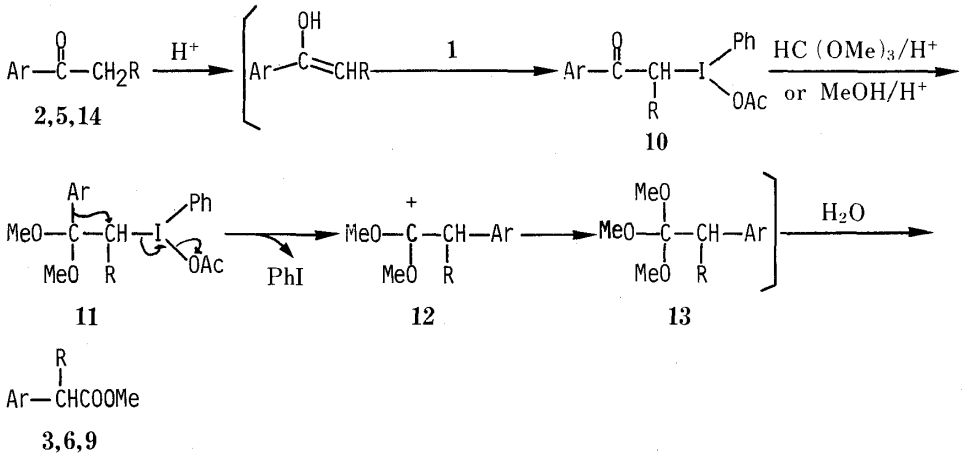


Chart 2

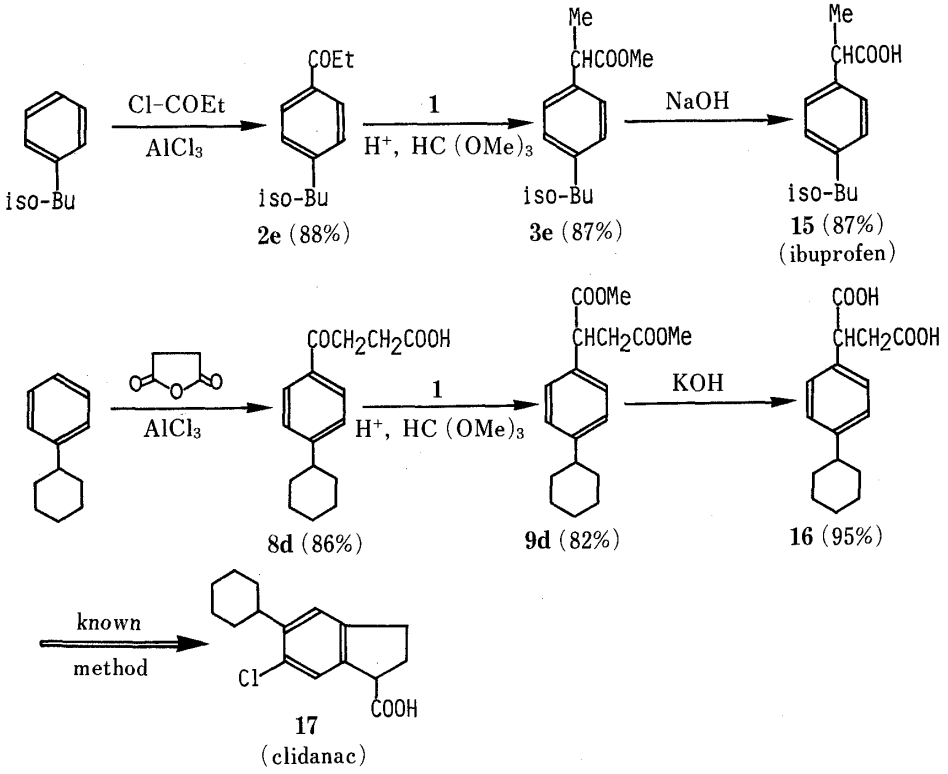


Chart 3

solution to give 2-(4-cyclohexylphenyl)succinic acid (**16**) in 94% yield. The acid (**16**) can be led to clidanac (**17**) [5-cyclohexyl-6-chloroindan-1-carboxylic acid] in high yield according to the reported procedure (Chart 3).[11c]

The present migration of alkyl aryl ketones (**2**, **5**, and **8**) with the reagent (**1**) proceeds smoothly to give the corresponding 2-arylalkanoates (**3**, **6**, and **9**) in moderate to high yields. Such migrations provide versatile procedures for the preparation of 2-arylalkanoic acids and 2-arylsuccinic acids.

## Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-1 spectrometer, and nuclear magnetic resonance (NMR) spectra on a Hitachi R-20A (60 MHz) or a Hitachi R-22

(90 MHz) spectrometer (with tetramethylsilane as an internal standard). Low- and high-resolution mass spectra (MS) were obtained with a JEOL JMS D-300 instrument, with a direct inlet system. Gas chromatography was run on a Shimadzu GC-4B instrument. Column chromatography was carried out on Merck Silica gel 60.

The starting 3-aroylpropionic acids (**8**) were prepared by the reported method.[13]

**General Procedure for the Transformation of Propiophenones (2) to Methyl 2-Arylpropanoates (3)**——Sulfuric acid (2 mmol) was added dropwise to a stirred solution of **1** (1.2 mmol) and **2** (1 mmol) in 3 ml of trimethylorthoformate at room temperature. The reaction mixture was stirred for 5—60 min at 0 or 60 °C, quenched with water (10 ml), and extracted with ether (2 × 10 ml). The organic layer was washed with water (20 ml), then dried over $MgSO_4$. The solvent was evaporated off under reduced pressure and the residue was purified by column chromatography on silica gel or by distillation to give pure **3**. The reaction conditions and yields are summarized in Table I.

Methyl 2-Phenylpropanoate (**3a**): bp 104—105 °C/18 mmHg (lit.[8] bp 104—106 °C/18 mmHg). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1730. $^1$H-NMR ($CDCl_3$) $\delta$: 1.48 (3H, d, $J$=7 Hz), 3.62 (3H, s), 3.70 (1H, q, $J$=7 Hz), 7.24 (5H, s).

Methyl 2-(4-Methylphenyl)propanoate (**3b**): IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1730. $^1$H-NMR ($CDCl_3$) $\delta$: 1.48 (3H, d, $J$=7 Hz), 2.30 (3H, s), 3.60 (3H, s), 3.66 (1H, q, $J$=7 Hz), 7.08 (4H, s). *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.54; H, 7.93.

Methyl 2-(4-Methoxyphenyl)propanoate (**3c**): IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1730. $^1$H-NMR ($CDCl_3$) $\delta$: 1.45 (3H, d, $J$=7 Hz), 3.58 (3H, s), 3.64 (1H, q, $J$=7 Hz), 3.70 (3H, s), 6.68—7.22 (4H, m). *Anal.* Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.01; H, 7.26.

Methyl 2-(4-Fluorophenyl)propanoate (**3d**): IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1735. $^1$H-NMR ($CDCl_3$) $\delta$: 1.48 (3H, d, $J$=7.5 Hz), 3.62 (3H, s), 3.70 (1H, q, $J$=7.5 Hz), 6.80—7.35 (4H, m). *Anal.* Calcd for $C_{10}H_{11}FO_2$: C, 65.92; H, 6.09. Found: C, 66.15; H, 6.11.

Methyl 2-(4-Isobutylphenyl)propanoate (**3e**): bp 107—108 °C/5 mmHg (lit.[8] bp 104—106 °C/1 mmHg). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1725. $^1$H-NMR ($CDCl_3$) $\delta$: 0.90 (6H, d, $J$=6.5 Hz), 1.48 (3H, d, $J$=7.5 Hz), 1.80 (1H, m), 2.44 (2H, d, $J$=7 Hz), 3.62 (3H, s), 3.66 (1H, q, $J$=7.5 Hz), 6.95—7.30 (4H, m). High-resolution MS Calcd for $C_{14}H_{20}O_2$: 220.1463. Found: 220.1465.

**The Reaction of Propiophenone (2a) with 1 in Methanol**——Sulfuric acid (2.06 mmol, 202 mg) was added dropwise to a stirred solution of **1** (1.24 mmol, 400 mg) and **2a** (1.03 mmol, 138 mg) in 3 ml of methanol at room temperature. The reaction mixture was stirred for 2 h at 60 °C, quenched with water (10 ml), and extracted with ether (2 × 10 ml). The organic layer was washed with water (20 ml), then dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using hexane/ethyl acetate (30/1) as an eluent to give **4** (98 mg, 58%) and **3a** (3.4 mg, 2%).

2-Methoxy-1-phenylpropanone (**4**): IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1690. $^1$H-NMR ($CDCl_3$) $\delta$: 1.48 (3H, d, $J$=7.5 Hz), 3.38 (3H, s), 4.62 (1H, q, $J$=7.5 Hz), 7.2—8.1 (5H, m).[1a] MS $m/z$: 164 ($M^+$).

**General Procedure for the Reaction of Acetophenones (5) with 1**——Sulfuric acid (1.2 mmol) was added dropwise to a stirred solution of **1** (1.2 mmol) and **5** (1 mmol) in 3 ml of methanol at room temperature. The reaction mixture was stirred for 50—300 min at 60 °C, quenched with water (10 ml), and extracted with ether (2 × 10 ml). The organic layer was washed with water (20 ml), then dried over $MgSO_4$. The solvent was evaporated off under reduced pressure and the residue was purified by column chromatography on silica gel to give pure **6** and **7**. The reaction conditions and yields are summarized in Table II. The spectral data for **6a**—**d** are in accord with those reported.[5]

Methyl Phenylacetate (**6a**): bp 90—92 °C/5 mmHg (lit.[1a] bp 96—98 °C/6 mmHg). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1730. $^1$H-NMR ($CDCl_3$) $\delta$: 3.60 (2H, s), 3.66 (3H, s), 7.25 (5H, s). MS $m/z$: 150 ($M^+$).

Methyl (4-Methylphenyl)acetate (**6b**): IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1730. $^1$H-NMR ($CDCl_3$) $\delta$: 2.32 (3H, s), 3.55 (2H, s), 3.66 (3H, s), 7.10 (4H, s). MS $m/z$: 164 ($M^+$).

Methyl (4-Bromophenyl)acetate (**6c**): mp 113 °C (lit.[5] mp 113—114 °C). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1730. $^1$H-NMR ($CDCl_3$) $\delta$: 3.55 (2H, s), 3.66 (3H, s), 7.0—7.6 (4H, m). MS $m/z$: 229 ($M^+$).

Methyl (2-Methylphenyl)acetate (**6d**): IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1730. $^1$H-NMR ($CDCl_3$) $\delta$: 2.30 (3H, s), 3.60 (2H, s), 3.64 (3H, s), 7.10 (4H, s). MS $m/z$: 164 ($M^+$).

2-Methoxy-1-phenylethanone (**7a**): IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1700. $^1$H-NMR ($CDCl_3$) $\delta$: 3.49 (3H, s), 4.67 (2H, s), 7.3—8.1 (5H, m). MS $m/z$: 150 ($M^+$); these spectral data are in accord with those reported.[5]

2-Methoxy-1-(4-methylphenyl)ethanone (**7b**): IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1695. $^1$H-NMR ($CDCl_3$) $\delta$: 2.41 (3H, s), 3.48 (3H, s), 4.63 (2H, s), 7.20 (2H, d, $J$=8.5 Hz), 7.79 (2H, d, $J$=8.5 Hz). MS $m/z$: 164 ($M^+$).

2-Methoxy-1-(4-bromophenyl)ethanone (**7c**): IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1700. $^1$H-NMR ($CDCl_3$) $\delta$: 3.48 (3H, s), 4.60 (2H, s), 7.45—7.90 (4H, m). MS $m/z$: 229 ($M^+$). *Anal.* Calcd for $C_9H_9BrO_2$: C, 47.19; H, 3.96. Found: C, 47.26; H, 3.88.

2-Methoxy-1-(2-methylphenyl)ethanone (**7d**): IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1690. $^1$H-NMR ($CDCl_3$) $\delta$: 2.51 (3H, s), 3.48 (3H, s), 4.51 (2H, s), 7.00—7.76 (4H, m). MS $m/z$: 164 ($M^+$). *Anal.* Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.08; H, 7.16.

**General Procedure for the Transformation of 3-Aroylpropionic Acids (8) to Dimethyl 2-Arylsuccinates (9) with 1**——A 60% $HClO_4$ solution (4 mmol) was added dropwise to a stirred solution of **1** (1.2 mmol) and **8** (1 mmol) in 8 ml of trimethylorthoformate at room temperature. The reaction mixture was stirred for 1—5 h at 60 °C, quenched

with water (10 ml) and extracted with ether (2 × 10 ml). The organic layer was washed with water (20 ml), then dried over $MgSO_4$. The solvent was evaporated off under reduced pressure and the residue was purified by column chromatography on silica gel to give pure **9**. The reaction conditions and yields of **9** are summarized in Table III. The spectral data for **9a**—**c** are in accord with those reported.[12)]

Dimethyl 2-Phenylsuccinate (**9a**): IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1730. $^1$H-NMR ($CDCl_3$) $\delta$: 2.62 (1H, dd, $J$=6, 17 Hz), 3.26 (1H, dd, $J$=10, 17 Hz), 3.63 (6H, s), 4.07 (1H, dd, $J$=6, 10 Hz), 7.23 (5H, s).

Dimethyl 2-(4-Bromophenyl)succinate (**9b**): IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1735. $^1$H-NMR ($CDCl_3$) $\delta$: 2.61 (1H, dd, $J$=6, 17 Hz), 3.19 (1H, dd, $J$=9.5, 17 Hz), 3.66 (6H, s), 4.05 (1H, dd, $J$=6, 9.5 Hz), 7.10 (2H, d, $J$=8.5 Hz), 7.42 (2H, d, $J$=8.5 Hz).

Dimethyl 2-(4-Isobutylphenyl)succinate (**9c**): IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1730. $^1$H-NMR ($CDCl_3$) $\delta$: 0.88 (6H, d, $J$=7 Hz), 1.5—2.1 (1H, m), 2.44 (2H, d, $J$=7 Hz), 2.60 (1H, dd, $J$=5, 17 Hz), 3.19 (1H, dd, $J$=10, 17 Hz), 3.63 (6H, s), 4.03 (1H, dd, $J$=5, 10 Hz), 7.09 (4H, s).

Dimethyl 2-(4-Cyclohexylphenyl)succinate (**9d**): mp 71.5—72 °C (pet. ether). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1730. $^1$H-NMR ($CDCl_3$) $\delta$: 1.0—2.1 (10H, m), 2.2—2.6 (1H, m), 2.59 (1H, dd, $J$=6, 16 Hz), 3.20 (1H, dd, $J$=10, 16 Hz), 3.64 (6H, s), 4.04 (1H, dd, $J$=6, 10 Hz), 7.13 (4H, s). *Anal.* Calcd for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 70.89; H, 8.02.

Dimethyl 2-(2-Naphthyl)succinate (**9e**): mp 63—64 °C (pet. ether). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1730. $^1$H-NMR ($CDCl_3$) $\delta$: 2.73 (1H, dd, $J$=6, 16.5 Hz), 3.33 (1H, dd, $J$=9.5, 16.5 Hz), 3.65 (6H, s), 4.25 (1H, dd, $J$=6, 9.5 Hz), 7.1—7.8 (7H, m). *Anal.* Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.36; H, 5.87.

Dimethyl 2-(9,10-Dihydrophenanthr-2-yl)succinate (**9f**): mp 100—101 °C (pet. ether). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1730. $^1$H-NMR ($CDCl_3$) $\delta$: 2.63 (1H, dd, $J$=6, 17 Hz), 2.83 (4H, s), 3.22 (1H, dd, $J$=10, 17 Hz), 3.65 (3H, s), 3.66 (3H, s), 4.06 (1H, dd, $J$=6, 10 Hz), 7.05—7.80 (7H, m). *Anal.* Calcd for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: C, 73.66; H, 6.23.

**Preparation of 4′-Isobutylpropiophenone (2e)**——Isobutylbenzene (0.037 mol, 5 g) and propionyl chloride (0.04 mol, 3.7 g) were added dropwise to a stirred suspension of anhydrous aluminum chloride (0.038 mol, 5.1 g) in 10 ml of carbon disulfide at −5 °C. The reaction mixture was stirred for 1.5 h below 5 °C, then overnight at room temperature. The resultant mixture was poured into a mixture of ice (30 g) and conc. HCl (10 ml), and extracted with ether (2 × 30 ml). The extract was dried over $MgSO_4$. The solvent was evaporated off under reduced pressure and the residue was purified by distillation to give pure **2e**; yield: 88%. bp 155 °C/20 mmHg (lit.[9g)] bp 86—87 °C/0.3 mmHg). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1690. $^1$H-NMR ($CDCl_3$) $\delta$: 0.91 (6H, d, $J$=6.5 Hz), 1.21 (3H, t, $J$=7 Hz), 1.90 (1H, m), 2.52 (2H, d, $J$=6.5 Hz), 2.96 (2H, q, $J$=7 Hz), 7.16 (2H, d, $J$=8.5 Hz), 7.83 (2H, d, $J$=8.5 Hz). MS $m/z$: 190 ($M^+$).

**Preparation of 3-(4-Cyclohexylbenzoyl)propionic Acid (8d)**——Anhydrous aluminum chloride (0.312 mol, 41.5 g) was added dropwise to a stirred suspension of cyclohexylbenzene (0.156 mol, 25 g) and succinic anhydride (0.156 mol, 15.6 g) in 120 ml of nitrobenzene at 0 °C. The reaction mixture was stirred at 0 °C for 3 h, then overnight at room temperature. The resultant mixture was poured into cold HCl solution. The whole was stirred for 10 min, then nitrobenzene was removed by steam distillation. The residue was cooled and the precipitated solid was collected by filtration. The solid was washed with water and then dissolved in 5% KOH solution. The alkaline solution was acidified with conc. HCl to precipitate crude **8d**, which was recrystallized from benzene to give pure **8d** (35 g, 86%); mp 136—138 °C (lit.[14)] mp 134 °C). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1710, 1680. $^1$H-NMR ($CDCl_3$) $\delta$: 1.1—2.2(10H, m), 2.3—3.0 (1H, m), 2.6—2.9 (2H, m), 3.1—3.4 (2H, m), 7.24 (2H, d, $J$=8.5 Hz), 7.88 (2H, d, $J$=8.5 Hz). MS $m/z$: 260 ($M^+$).

**Hydrolysis of 3e to 15**——A solution of **3e** (5 mmol, 1.1 g) in 3 ml of 2 N aqueous NaOH was refluxed for 3.5 h. After cooling, the reaction mixture was washed with $CHCl_3$ (5 ml). The aqueous layer was acidified with conc. HCl to precipitate crude **15**, which was recrystallized from hexane to give pure **15**; yield: 87%. mp 74—75 °C (lit.[8)] mp 75—76 °C, lit.[15)] mp 73—75 °C). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1705. $^1$H-NMR ($CDCl_3$) $\delta$: 0.88 (6H, d, $J$=6.5 Hz), 1.48 (3H, d, $J$=7 Hz), 1.82 (1H, m), 2.44 (2H, d, $J$=7 Hz), 3.68 (1H, q, $J$=7 Hz), 6.80—7.40 (4H, m), 11.68 (1H, br s).

**Hydrolysis of 9d to 16**——A solution of **9d** (0.62 mmol, 189 mg) in 10 ml of 2 N aqueous KOH was refluxed for 3 h. After cooling, the reaction mixture was washed with $CHCl_3$ (10 ml). The aqueous layer was acidified with conc. HCl to precipitate crude **16**, which was recrystallized from ethyl acetate to give pure **16**; yield: 95%. mp 188—189 °C (lit.[11c)] mp 188—189 °C). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1705. $^1$H-NMR ($CDCl_3$) $\delta$: 1.1—1.2 (10H, m), 2.2—2.9 (1H, m), 2.59 (1H, dd, $J$=5.5, 16.5 Hz), 3.15 (1H, dd, $J$=10, 16.5 Hz), 4.02 (1H, dd, $J$=5.5, 10 Hz), 7.20 (4H, s), 9.2 (2H, br s).

## References and Notes


1) *a*) A. McKillop, B. P. Swann, and E. C. Taylor, *J. Am. Chem. Soc.*, **95**, 3340 (1973); *b*) E. C. Taylor, R. L. Robey, K.-T. Liu, B. Favre, H. T. Bozimo, R. A. Conley, C.-S. Chiang, A. McKillop, and M. E. Ford, *ibid.*, **98**, 3037 (1976); *c*) E. C. Taylor, C.-S. Chiang, A. McKillop, and J. F. White, *ibid.*, **98**, 6750 (1976).

2) *a*) T. Y. Shen, *Angew. Chem.*, **84**, 512 (1972); *idem, Angew. Chem. Int. Ed. Engl.*, **11**, 460 (1972); *b*) S. H. Ferreira and J. R. Vane, "Antiinflammatory Drugs," Springer-Verlag, New York, 1979, p. 321.

3) C. Achenbach, R. Ziskoven, F. Koehler, U. Bahr, and H.-R. Schulten, *Angew. Chem. Int. Ed. Engl.*, **18**, 882 (1979).

4) *a*) C. Giordano, G. Castaldi, F. Casagrande, and L. Abis, *Tetrahedron Lett.*, **23**, 1385 (1982); *b*) C. Giordano, G. Castaldi, F. Casagrande, and A. Belli, *J. Chem. Soc., Perkin Trans. 1*, **1982**, 2575.

5) S. D. Higgins, and C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1*, **1982**, 235.
6) A. Goosen, and C. W. McCleland, *J. Chem. Soc., Chem. Commun.*, **1982**, 1311.
7) B. Myrboh, H. Ila, and H. Junjappa, *Synthesis*, **1981**, 126.
8) K. Fujii, K. Nakao, and T. Yamauchi, *Synthesis*, **1982**, 456.
9) *a*) T. Shioiri and N. Kawai, *J. Org. Chem.*, **43**, 2936 (1978); *b*) Z. Cekovic, J. Bosnjak, and M. Cvetkóvic, *Tetrahedron Lett.*, **1980**, 2675; *c*) G. Tsuchihashi, K. Kitajima, and S. Mitamura, *ibid.*, **22**, 4305 (1981); *d*) G. Tsuchihashi, S. Mitamura, K. Kitajima, and K. Kobayashi, *ibid.*, **23**, 5427 (1982); *e*) S. D. Higgins and C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1483; *f*) G. Castaldi, A. Belli, F. Uggeri, and C. Giordano, *J. Org. Chem.*, **48**, 4658 (1983); *g*) N. Kawai, N. Kato, Y. Hamada, and T. Shioiri, *Chem. Pharm. Bull.*, **31**, 3139 (1983); *h*) S. Uemura, S. Fukuzawa, T. Yamauchi, K. Hattori, S. Mizutaki, and K. Tamaki, *J. Chem. Soc., Chem. Commun.*, **1984**, 426.
10) Y. Tamura, Y. Shirouchi, and J. Haruta, *Synthesis*, **1984**, 231.
11) *a*) S. Noguchi, S. Kishimoto, I. Minamida, M. Obayashi, and K. Kawakita, *Chem. Pharm. Bull.*, **19**, 646 (1971); *b*) G. R. Allen, Jr., R. Littell, F. J. McEvoy, and A. E. Sloboda, *J. Med. Chem.*, **15**, 934 (1972); *c*) P. F. Juby, W. R. Goodwin, T. W. Hudyma, and R. A. Partyka, *ibid.*, **15**, 1297 (1972); *d*) S. Noguchi, S. Kishimoto, I. Minamida, and M. Obayashi, *Chem. Pharm. Bull.*, **22**, 529 (1974); *e*) Y. Sawa, T. Hattori, Y. Kawakami, S. Katsube, and A. Goto, *Yakugaku Zasshi*, **96**, 653 (1976); *f*) T. Aono, S. Kishimoto, Y. Araki, and S. Noguchi, *Chem. Pharm. Bull.*, **25**, 3198 (1977); *g*) T. Aono, M. Imanishi, Y. Kawano, S. Kishimoto, and S. Noguchi, *ibid.*, **26**, 2475 (1978).
12) Recently, we have reported that TTN effects the 1,2-aryl migration of 3-aroylpropionic acids (**8**) to dimethyl 2-arylsuccinates (**9**); Y. Tamura, Y. Shirouchi, J. Minamikawa, and J. Haruta, *Chem. Pharm. Bull.*, **33**, 551 (1985).
13) *a*) L. F. Somerville and C. F. H. Allen, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, 1943, p. 81; *b*) J. D. Reinheimer, and S. Taylor, *J. Org. Chem.*, **19**, 802 (1954); *c*) L. F. Fieser and A. M. Seligman, *J. Am. Chem. Soc.*, **60**, 170 (1938); *d*) L. F. Fieser and R. G. Kennelly, *ibid.*, **57**, 1611 (1935).
14) G. Benoit and R. Delavigne, *Bull. Soc. Chim. Fr.*, **1959**, 1197.
15) J. A. Walker and M. D. Pillai, *Tetrahedron Lett.*, **1977**, 3707.