

3.83-3.94 (m, 2 H), 4.57-4.62 (m, 1 H, OCHO), 4.82 (dd, 1 H,  $J_{ab}$  = 19.5 Hz,  $J_{BX}$  = 1.88 Hz,  $C_{21}H$ ), 4.98 (ddt, 1 H,  $J_{AB}$  = 19.5 Hz,  $J_{AX}$  = 1.0 Hz,  $C_{21}H$ ); UV (EtOH)  $\lambda_{max}$  214.9 nm ( $\epsilon$  12500); HRMS calcd 372.2301, found 372.2307 (M - DHP).

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**Registry No.** 1, 20007-99-2; 2, 71563-68-3; 3, 71505-07-2; 4, 71563-69-4; 5, 115649-62-2; 6, 115562-13-5; 6 (hydrazone deriv), 115562-14-6; 7, 115590-14-2; 8, 115562-15-7; 9, 115562-16-8; 10, 115562-17-9; 10 (aldehyde deriv), 115562-18-0; 11, 115590-15-3; 12, 115562-19-1; 13, 115649-63-3; 14, 115562-20-4; 15, 115562-21-5;  $Ph_3P=C=C=O$ , 15596-07-3.

### A Facile and Efficient Preparative Method of Methyl 2-Arylpropanoates by Treatment of Propiophenones and Their Derivatives with Iodine or Iodine Chlorides

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Several 2-arylpropionic acids have been known as important pharmaceutical agents exhibiting nonsteroidal antiinflammatory activities<sup>1</sup> and many preparative methods of the acids have so far been developed.<sup>1b,c</sup> We also presented several new methods for the preparation of the acids or their alkyl esters from propiophenones 1 and related substances via 1,2-aryl group migration.<sup>2-5</sup>

Quite recently a patent work<sup>6</sup> appeared which revealed the formation of methyl 2-arylpropanoates 4 by the treatment of 1 with iodine in trimethyl orthoformate (TMOF). This prompted us to report our similar work on  $I_2$ ,  $ICl$ , or  $ICl_3$ -mediated facile preparation of 4 from 1, its dimethyl ketals 2, and 1-aryl-1-methoxy-1-propenes 3 via aryl migration.<sup>7</sup> The reagent  $ICl_3$  was proved to be very effective for this transformation for the first time. It is worth noting that the reaction of 2-alkyl-2-phenyl-1,3-dioxolanes with  $ICl$  in dichloromethane gave 2-chloroethyl esters of 2-phenylalkanoic acids via 1,2-aryl migration.<sup>8</sup>

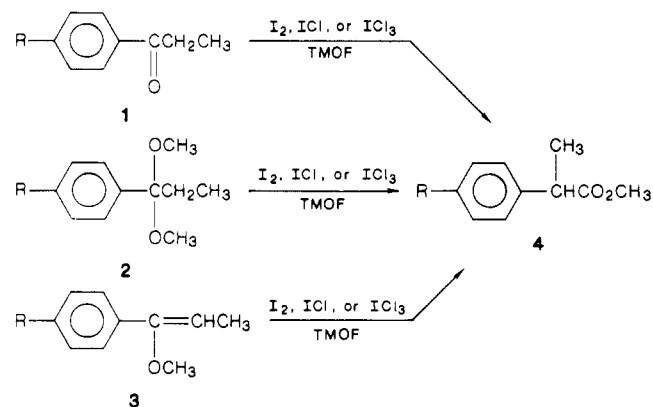
The reactions of 1, 2, or 3 (R = H, Bu<sup>t</sup>, CH<sub>3</sub>O, Br, F) with  $I_2$ ,  $ICl$ , or  $ICl_3$  were generally carried out by the addition

Table I. Preparation of Methyl 2-Arylpropanoates (4)<sup>a</sup>

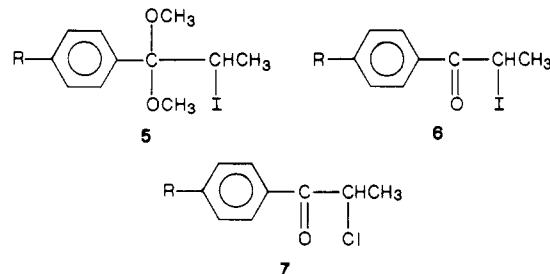
starting compd	reagent (equiv) <sup>b</sup>	product and isolated yield, %			
		4	5	6	7
1 (R = H)	$I_2$ (2.0)	66	0	24	0
1 (R = H)	$ICl_3$ (1.2)	62	<i>d</i>	<i>d</i>	26
1 (R = Bu <sup>t</sup> )	$I_2$ (1.2)	23	69	2	0
1 (R = Bu <sup>t</sup> )	$I_2$ (2.0)	98	0	0	0
1 (R = Bu <sup>t</sup> )	$ICl$ (1.0)	87	0	0	<i>d</i>
1 (R = Bu <sup>t</sup> )	$ICl_3$ (1.1)	97	0	0	<i>d</i>
1 (R = CH <sub>3</sub> O)	$I_2$ (1.2)	85	0	0	0
1 (R = Br)	$I_2$ (2.0)	0	1	48 <sup>e</sup>	0
1 (R = Br)	$ICl$ (1.2)	9	80	<i>d</i>	<i>d</i>
1 (R = Br)	$ICl_3$ (1.2)	73	<i>d</i>	<i>d</i>	18
1 (R = F)	$I_2$ (2.0)	0 <sup>e</sup>	0	0	<i>d</i>
1 (R = F)	$ICl_3$ (1.2)	52	<i>d</i>	<i>d</i>	35
2 (R = H)	$I_2$ (2.0)	60	0	39	0
2 (R = H)	$ICl_3$ (1.2)	55	<i>d</i>	<i>d</i>	32
2 (R = Bu <sup>t</sup> )	$I_2$ (1.2)	30	64	0	0
2 (R = Bu <sup>t</sup> )	$I_2$ (2.0)	93	0	0	0
2 (R = Bu <sup>t</sup> )	$ICl$ (1.2)	74	<i>d</i>	<i>d</i>	<i>d</i>
2 (R = CH <sub>3</sub> O)	$I_2$ (1.2)	98	0	0	0
2 (R = Br)	$I_2$ (2.0)	0 <sup>f</sup>	4	2	0
3 (R = Bu <sup>t</sup> )	$I_2$ (1.0)	20	62	17	0
3 (R = Bu <sup>t</sup> )	$I_2$ (2.0)	98	0	0	0
3 (R = Bu <sup>t</sup> )	$ICl$ (1.2)	80	<i>d</i>	<i>d</i>	<i>d</i>
3 (R = CH <sub>3</sub> O)	$I_2$ (1.2)	88	0	0	0
3 (R = CH <sub>3</sub> O)	$ICl$ (1.0)	81	<i>d</i>	<i>d</i>	<i>d</i>

<sup>a</sup> Carried out using 1 (10 mmol), 2 (10 mmol), or 3 (5 mmol) in TMOF (5.3 g) at 23 °C for 24 h. <sup>b</sup> Equivalent to the starting compound. <sup>c</sup> Recovered 1, 29%. <sup>d</sup> Not determined. <sup>e</sup> Recovered 1, 92%. <sup>f</sup> Recovered 1, 92%.

of an iodine compound to a solution of 1, 2, or 3 in TMOF at 23 °C, and the mixture was stirred for 24 h at the same



temperature. The esters 4, 1-aryl-1,1-dimethoxy-2-iodopropanes 5, and aryl 1-iodoethyl ketones 6, or aryl 1-chloroethyl ketones 7 were the products, the amount of which depended on the reaction conditions. Typical re-



sults are shown in Table I. The reactions in other solvents such as methanol and dichloromethane were slower and gave much lower yields of 4. The data shown in the table disclosed the following: (1) the  $I_2$  (2 equiv to the substrate)/TMOF system is generally suitable for preparation of 4, (2) the reactivity order of iodine compound is  $ICl_3 >$

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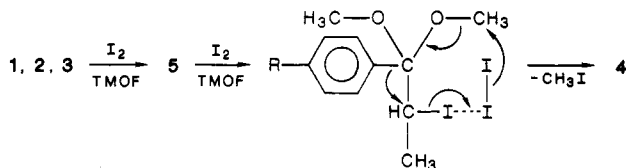
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$\text{ICl} > \text{I}_2$  and the reagent  $\text{ICl}_3$  is especially useful for the rearrangement of 1 (R = Br, F), (3) treatment of 1 (R = H, Br, F), or 2 (R = H) with  $\text{ICl}_3$  afforded 4 with the formation of 7, and (4) the reactivity of the substrate is in the order of R =  $\text{CH}_3\text{O} > \text{Bu}^i > \text{H} > \text{Br} > \text{F}$  as expected. The formation of 6 (R = H) and 6 (R = Br) from the corresponding 1 with 2 equiv of  $\text{I}_2$  and the formation of 5 (R =  $\text{Bu}^i$ ) from 1 (R =  $\text{Bu}^i$ ) with 1.2 equiv of  $\text{I}_2$  suggest that 4 was formed via these compounds. In fact, we confirmed separately that the ketal 5 (R =  $\text{Bu}^i$ ) is converted to 4 (R =  $\text{Bu}^i$ ) quantitatively by treatment with 1 equiv of  $\text{I}_2$  in TMOF at 23 °C for 24 h, while 6 (R =  $\text{Bu}^i$ ) scarcely afforded 4 (R =  $\text{Bu}^i$ ) under similar conditions. Thus the ester 4 seems to be formed via 5 as shown below, methyl iodide being trapped and identified spectroscopically.



### Experimental Section

$^1\text{H}$  NMR spectra were recorded with a JEOL FX-40 Q (90 MHz) instrument in  $\text{CDCl}_3$  with  $\text{Me}_4\text{Si}$  as an internal standard. GLC analysis was carried out with a Shimadzu GC-7AS apparatus using 10% DC-200 on a Chromosorb W (AW-DMCS) column (3 mm  $\times$  3 m).

Propiophenones 1 (R = H,  $\text{CH}_3\text{O}$ , Br, F), solvent, and inorganic materials were commercial products of the purest standard. Compounds 1 (R =  $\text{Bu}^i$ )<sup>4</sup> and 2<sup>9</sup> were prepared by the reported methods. The yield and boiling point of 2 prepared from 1 are as follows: 2 (R = H) 71%, bp 75–77 °C/10 Torr; 2 (R =  $\text{Bu}^i$ ) 94%, bp 92–97 °C/1 Torr; 2 (R =  $\text{CH}_3\text{O}$ ) 68%, bp 90–93 °C/1 Torr; 2 (R = Br) 98%, bp 93–96 °C/2 Torr.

**Preparation of 3 (R =  $\text{Bu}^i$ ) and 3 (R =  $\text{CH}_3\text{O}$ ).** A mixture of 2 (R =  $\text{Bu}^i$ ) (11.8 g, 50 mmol) and methanesulfonic acid (0.1 g, 1 mmol) was heated at 100–105 °C for 2 h. The resulting mixture was distilled in vacuo to give an isomeric mixture of (*E*)- and (*Z*)-1-(4-isobutylphenyl)-1-methoxy-1-propene (3, R =  $\text{Bu}^i$ ) as a colorless oil (8.1 g, 79.3%), *E/Z* = 27/73, by  $^1\text{H}$  NMR:<sup>10</sup> bp 92–96.5 °C/1 Torr; *Z* isomer  $\delta$  0.93 (6 H, d), 1.81 (3 H, d), 1.84 (1 H, m), 2.49 (2 H, d), 3.55 (3 H, s), 5.35 (1 H, q), 7.2–7.4 (4 H, m); *E* isomer  $\delta$  0.93 (6 H, d), 1.72 (3 H, d), 1.84 (1 H, m), 2.49 (2 H, d), 3.63 (3 H, s), 4.78 (1 H, q), 7.2–7.4 (4 H, m). Anal. Calcd for  $\text{C}_{14}\text{H}_{20}\text{O}$ : C, 82.30; H, 9.87. Found: C, 82.35; H, 9.82. Similarly, an isomeric mixture of (*E*)- and (*Z*)-1-methoxy-1-(4-methoxyphenyl)-1-propene (3, R =  $\text{CH}_3\text{O}$ ) was prepared in 88% yield at bp 90–93 °C/0.8 Torr, *E/Z* = 34/66, by  $^1\text{H}$  NMR:<sup>10</sup> *Z* isomer  $\delta$  1.76 (3 H, d), 3.49 (3 H, s), 3.77 (3 H, s), 5.20 (1 H, q), 6.75–8.4 (4 H, m); *E* isomer  $\delta$  1.65 (3 H, d), 3.58 (3 H, s), 3.77 (3 H, s), 4.72 (1 H, q), 6.75–8.40 (4 H, m). Anal. Calcd for  $\text{C}_{11}\text{H}_{14}\text{O}_2$ : C, 74.13; H, 7.92. Found: C, 73.97; H, 8.08.

**Treatment of 1, 2, or 3 with Iodine Compound for the Preparation of 4, 5, and/or 6.** A typical experimental procedure is as follows. Iodine (3.05 g, 12 mmol) was added to a solution of 1 (R =  $\text{Bu}^i$ ) (1.90 g, 10 mmol) in TMOF (5.3 g) at 23 °C and the mixture was stirred for 24 h. Aqueous sodium thiosulfate (10%, 20 mL) was added and the resulting brown solution was extracted with  $\text{CHCl}_3$  (2  $\times$  30 mL). The extract was dried ( $\text{MgSO}_4$ ) and the solvent was evaporated under reduced pressure. An oily residue was purified by column chromatography on  $\text{SiO}_2$  [hexane– $\text{EtOAc}$  (30:1–20:1) as eluent] to give methyl 2-(4-isobutylphenyl)propanoate (4, R =  $\text{Bu}^i$ )<sup>5</sup> (0.5 g, 23% yield) and 1,1-dimethoxy-1-(4-isobutylphenyl)-2-iodopropane (5, R =  $\text{Bu}^i$ ) (2.50 g, 69% yield) together with a small amount of 6 (R =  $\text{Bu}^i$ ) (2% yield) as a colorless oil, respectively. 5 (R =  $\text{Bu}^i$ ):  $\delta$  0.90 (6

H, d), 1.73 (3 H, d), 1.6–2.1 (1 H, m), 2.48 (2 H, d), 3.19 (3 H, s), 3.32 (3 H, s), 4.58 (1 H, q), 7.0–7.5 (4 H, m). Anal. Calcd for  $\text{C}_{15}\text{H}_{23}\text{O}_2\text{I}$ : C, 49.73; H, 6.40. Found: C, 49.80; H, 6.33. Similar treatment of 1 (R =  $\text{Bu}^i$ ) with  $\text{I}_2$  (5.04 g, 20 mmol) afforded 2.13 g (98% isolated yield) of 4 (R =  $\text{Bu}^i$ ). For identification of the produced methyl iodide, the reaction mixture was distilled directly under reduced pressure, the vapor was trapped by a cold trap at –78 °C, and the trapped liquid substance (a mixture of  $\text{CH}_3\text{I}$  and TMOF) was analyzed by  $^1\text{H}$  NMR and GLC.

The treatment of 1 (R = Br) (2.13 g, 10 mmol) with iodine (5.04 g, 20 mmol) in TMOF (5.3 g) at 23 °C for 24 h afforded 1-(4-bromophenyl)-1,1-dimethoxy-2-iodopropane (5, R = Br) (47 mg, 0.12 mmol, 1.2% yield) and 4-bromophenyl 1-iodoethyl ketone (6, R = Br) (1.62 g, 4.8 mmol, 48% yield). 5 (R = Br)  $\delta$  1.70 (3 H, d), 3.16 (3 H, s), 3.27 (3 H, s), 4.52 (1 H, q), 7.3–7.5 (4 H, m). Anal. Calcd for  $\text{C}_{11}\text{H}_{14}\text{O}_2\text{BrI}$ : C, 34.31; H, 3.66. Found: C, 34.02; H, 3.53. 6 (R = Br):  $\delta$  2.03 (3 H, d), 5.38 (1 H, q), 7.4–7.9 (4 H, m). Anal. Calcd for  $\text{C}_9\text{H}_9\text{OBrI}$ : C, 31.89; H, 2.18. Found: C, 29.67; H, 2.20.

The compounds 5 and 6 were also prepared separately as follows and used as authentic samples for  $^1\text{H}$  NMR and GLC. The ketal 2 (R =  $\text{Bu}^i$ ) was treated with 1.2 equiv of  $\text{I}_2$  in TMOF at 23 °C for 24 h and a normal workup procedure of the mixture afforded 5 (R =  $\text{Bu}^i$ ) in 64% yield. A mixture of methanol (20 mL), 2 N sulfuric acid (1 mL), and 5 (R =  $\text{Bu}^i$ ) (1.60 g, 4.4 mmol) was stirred at 60 °C for 1 h. After it had been cooled down, the solvent was evaporated under reduced pressure to leave an oily residue which was added to  $\text{CHCl}_3$  (20 mL) and 2% aqueous sodium thiosulfate (10 mL). An organic layer was separated and the aqueous layer was extracted with  $\text{CHCl}_3$  (10 mL). The combined organic layers were dried ( $\text{MgSO}_4$ ) and evaporated to leave 6 (R =  $\text{Bu}^i$ ) (1.36 g, 97% yield) as a light yellow oil: 6 (R =  $\text{Bu}^i$ )  $\delta$  0.90 (6 H, d), 1.88 (1 H, m), 2.04 (3 H, d), 2.52 (2 H, d), 5.45 (1 H, q), 7.18 (2 H, d), 7.89 (2 H, d). Anal. Calcd for  $\text{C}_{13}\text{H}_{17}\text{OI}$ : C, 49.38; H, 5.42. Found: C, 49.68; H, 5.64.

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**Registry No.** 1 (R = H), 93-55-0; 1 (R = Bui), 59771-24-3; 1 (R =  $\text{CH}_3\text{O}$ ), 121-97-1; 1 (R = Br), 10342-83-3; 1 (R = F), 456-03-1; 2 (R = H), 25310-92-3; 2 (R = Bui), 66202-89-9; 2 (R =  $\text{CH}_3\text{O}$ ), 115943-56-1; 2 (R = Br), 115943-57-2; (*E*)-3 (R = Bui), 115943-58-3; (*Z*)-3 (R = Bui), 115943-59-4; (*E*)-3 (R =  $\text{CH}_3\text{O}$ ), 58889-88-6; (*Z*)-3 (R =  $\text{CH}_3\text{O}$ ), 58889-89-7; 4 (R = H), 31508-44-8; 4 (R = Bui), 61566-34-5; 4 (R =  $\text{CH}_3\text{O}$ ), 50415-73-1; 4 (R = Br), 83636-46-8; 4 (R = F), 50415-71-9; 5 (R = Bui), 87498-05-3; 5 (R = Br), 115943-60-7; 6 (R = H), 6084-15-7; 6 (R = Br), 115943-61-8; 6 (R = Bui), 115943-62-9; 7 (R = H), 6084-17-9; 7 (R = Br), 87010-95-5; 7 (R = F), 81112-09-6;  $\text{I}_2$ , 7553-56-2;  $\text{ICl}_3$ , 865-44-1;  $\text{ICl}$ , 7790-99-0.

### A Versatile and Convenient Multigram Synthesis of Methylidenemalonic Acid Diesters<sup>1</sup>

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Owing to their multifunctionality, dialkyl methylidenemalonates 3 are useful synthetic intermediates in Michael, Diels–Alder, cyclopropanation, and epoxidation reactions<sup>2–4</sup> and in polymer synthesis.<sup>5</sup>

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