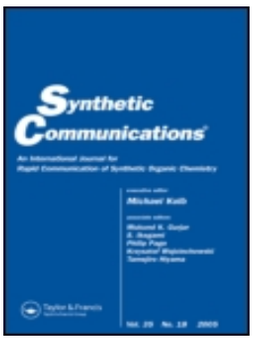

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A NOVEL APPROACH TO THE SYNTHESIS OF 2-ARYL PROPIONATES

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ABSTRACT

A two step conversion of phenyl glyoxylates to 2-aryl-propionates has been accomplished. Esters of phenylglyoxylic acid have been converted to corresponding β,β-dichlorostyrenes. These on further reduction gave esters of 2-arylpropionic acids.

The chemistry of 2-arylpropionic acids is of great importance due to their biological activity.[1,2] The compound **1** widely recognized as Ibuprofen, is extensively used as an antiinflammatory, antipyretic and analgesic. Because of this, the synthesis of these compounds has attracted great interest and has been extensively reviewed.[1–3] The developments in the synthesis of chiral 2-arylpropanoic acid have also been reviewed.[4]

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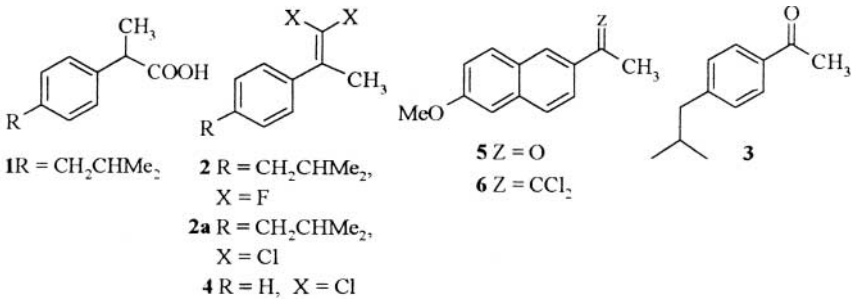
The hydrolysis of β,β-diflurostyrene **2** to provide **1** has been reported[5] in 70% yield. Interestingly the hydrolysis of the corresponding dichlorostyrene **2a** has been reported[6] to be unsuccessful. This led us to re-examine this reaction.



1 R = CH_2CHMe_2

2 R = CH_2CHMe_2, X = F

2a R = CH_2CHMe_2, X = Cl

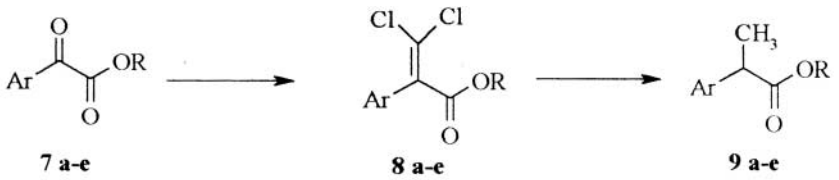
4 R = H, X = Cl

5 Z = O

6 Z = CCl_2

Hydrolysis of the unsubstituted dichlorostyrene **4** readily prepared from acetophenone,[7] was attempted under a variety of conditions viz. CF_3COOH/dil H_2SO_4/dil. HCl, at room temperature or reflux. However under these conditions the desired acid could not be obtained. Hydrolysis of the substituted dichlorostyrenes **6** and **2a** (prepared from the corresponding ketones **5** and **3**) under the above conditions were also unsuccessful.

In an alternative approach it was planned to reduce the dichlorovinyl group to a methyl group. Though several reports of the reduction of a chlorovinyl group to the hydrocarbon are known,[9–11] there is only one report[18] of the reduction of dichlorovinyl group to a methyl. Based on this planning the reaction shown below was attempted and accomplished.



7 a-e **8 a-e** **9 a-e**

a Ar = Phenyl, R = Me

b Ar = p- tolyl, R = Me

c Ar = p-anisyl, R = Me

d Ar = p-isobutylphenyl, R = Me

e Ar = p-tolyl, R = Et

The esters **7a–e** of phenylglyoxylic acid, prepared in 48–66% yield,[8,17] were characterised by their spectral data. These ketoesters on reaction with

triphenylphosphine and tetrachloromethane in dichloromethane furnished the dichlorostyrene **8a–e** in 62–69% yield. The dihalostyrenes were characterised by their spectral properties and elemental analysis. Though this reagent in THF has been reported[12] to give dichloromethylenation of lactones and acetates, no such reaction was observed in the present conditions and the ester group was recovered unchanged. The dichlorostyrenes were then reduced using 5% Pd–C in methanol to provide the desired esters **9a–e** in 77–87% yield. The methyl ester **9d** was hydrolysed in aq. NaOH to provide (±) Ibuprofen **1** in 92% yield.

Thus a new, simple, two step process for the conversion of phenyl glyoxylate to 2-arylpropionates was accomplished. The interesting feature is the selective dichloromethylenation of keto function of ketoesters. Though a two step process for the conversion of lactone carbonyl to $CH–CH_3$ is known,[18] the present example is an extension for the conversion of a keto group to a $CH–CH_3$ grouping.

EXPERIMENTAL

All melting points and boiling points are uncorrected. The yields of all the compounds reported are of crystallised or distilled pure compounds. All solvents were distilled and dried. Elemental analysis were obtained using Hosli's rapid carbon hydrogen analyser. IR spectra were recorded on Perkin-Elmer FT-IR Model (1615). PMR spectra were recorded on Jeol FX 90Q (90 MHz) instrument in $CDCl_3$, values are given in δ.

General Procedure for the Preparation of Ketones and Arylglyoxylic Esters

These were prepared by the known methods.[8,16,17]

3: Yield 80%, b.p. 265–268° (lit.[16] 94–100°/1.5 mm), ^{1}H NMR: 0.91 (6H, d, $J = 6.5$ Hz, $CH(C\underline{H}_3)_2$), 1.88 (1H, m, $C\underline{H}Me_2$), 2.57 (2H, d, $J = 7.5$ Hz, $Ar–C\underline{H}_2–CH–Me_2$), 2.59 (3H, s, $COCH_3$), 7.37 (2H, d, J = 7.5 Hz, ArH), 8.0 (2H, d, $J = 7.5$ Hz ArH).

5: Gift from Dr. H.R. Sonawane of NCL Pune.

7a: Yield 48%, b.p. 258–260° (lit.[8,17a] b.p. 100–102°/2.3 mm). IR (neat): 1750, 1700 cm^{-1}. ^{1}H NMR: 4.10 (3H, s, $COOC\underline{H}_3$), 7.75 (3H, m, Ar$\underline{H}$), 8.25 (2H, dd, $J = 2.0$ and 8.0 Hz, ArH).

7b: Yield 65%, b.p. 268–270° (Lit.[12,17b] b.p. 122°/5 mm). IR (neat): 1740, 1680 cm^{-1}. ^{1}H NMR: 2.34 (3H, s, $Ar–C\underline{H}_3$), 4.05 (3H, s, $OC\underline{H}_3$), 7.48 (2H, d, $J = 7.5$ Hz, ArH), 8.10 (2H, d, $J = 7.5$ Hz, ArH).

7c: Yield 58%, m.p. 46–47° (Lit.[8,17c] m.p. 46–48°). IR (nujol): 1740, 1680 cm^{-1}. ^1H NMR: 4.00 and 4.10 each (3H, s, $ArOC\underline{H}_3$, $COOC\underline{H}_3$), 7.20 (2H, d, $J = 9.0$ Hz, ArH), 8.30 (2H, d, $J = 9.0$ Hz, ArH).

7d: Yield 66%, b.p. 239°. IR (neat): 1760, 1700 cm^{-1}. ^1H NMR: 0.91 (6H, d, $J = 9.0$ Hz, $-CH(C\underline{H}_3)_2$), 2.0 (1H, m, $CH_2–C\underline{H}(CH_3)_2$), 2.62 (2H, d, $J = 10.0$ Hz, $C\underline{H}_2–CH(CH_3)_2$), 4.10 (3H, s, $OC\underline{H}_3$), 7.54 (2H, d, $J = 9.0$ Hz, ArH), 8.20 (2H, d, $J = 9.0$ Hz, ArH). Analysis: $C_{13}H_{16}O_3$, required: C, 70.91; H, 7.27%. Found: C, 70.72; H, 7.22%.

7e: Yield 56%, b.p. 304° (Lit.[13,17d] b.p. 112°/0.6 mm). IR (neat): 1740, 1680 cm^{-1}. ^1H NMR: 1.43 (3H, t, $J = 7.5$ Hz, $OCH_2C\underline{H}_3$), 2.48 (3H, s, $ArC\underline{H}_3$), 4.60 (2H, q, $J = 7.5$ Hz, $-OC\underline{H}_2CH_3$), 7.60 (2H, d, $J = 9.0$ Hz, ArH), 8.23 (2H, d, $J = 9.0$ Hz, ArH).

General Procedure for the Dichloromethylenation of Ketones or Ketoesters[7]

Triphenyl phosphine (30 mmole) was dissolved in dry dichloromethane (20 mL) and tetrachloromethane (22 mmole) was added to the solution of ketones (10 mmole) or ketoester (10 mmole) at room temperature. The resulting mixture was refluxed for 48 h. After solvent removal, SiO_2 (3 g) was added to the residue and this was loaded on a SiO_2 (30 g) column. The ester was obtained in the hexane-EtOAc (98 : 2) fraction.

4: Yield 70%, b.p. 212–214° (Lit.[6] 92–95°/13 mm). ^1H NMR: 2.10 (3H, s, $H_3C–C{=}CCl_2$), 7.25 (5H, s, $Ar\underline{H}$).

2a: Yield 90%, thick liq. (Lit.[6] oil). IR (neat): 1620, 1470, 930 cm^{-1}. ^1H NMR: 0.91 (6H, d, $J = 6.5$ Hz, $CH(C\underline{H}_3)_2$), 1.88 (1H, m, $CH_2C\underline{H}(CH_3)_2$), 2.20 (3H, s, $CH_3C{=}CCl_2$), 2.48 (2H, d, $J = 6.5$ Hz, $ArC\underline{H}_2$), 7.19 (2H, d, $J = 9.0$ Hz, $Ar\underline{H}$), 7.27 (2H, d , $J = 9.0$ Hz, $Ar\underline{H}$).

6: Yield 65%, m.p. 72–74°. IR (nujol): 1640, 1610, 1510, 1490, 870 cm^{-1}. ^1H NMR: 2.25 (3H, s, $CH_3C{=}CCl_2$), 3.80 (3H, s, $-OCH_3$), 7.18 (3H, m, $Ar\underline{H}$), 7.80 (3H, m, $Ar\underline{H}$). Mass m/z: 270 (11%), 268 (57%), 266 (95%), 225 (17%), 223 (29%), 220 (28%), 218 (96%), 183 (100%). Analysis: $C_{14}H_{12}Cl_2O$, required: C, 62.92; H, 4.49%. Found: C , 62.77; H, 4.43%.

8a: Yield 62%, b.p. 262°. IR: (neat): 1740, 1610, 1600, 1500, 720, 700 cm^{-1}. ^1H NMR: 3.91 (3H, s, $-OC\underline{H}_3$), 7.65 (5H, bs, $Ar\underline{H}$). Analysis: $C_{10}H_8Cl_2O_2$, required: C, 51.95; H, 3.46%. Found: C, 52.05; H, 3.57%.

8b: Yield 65%, yellowish oil. IR (neat): 1740, 1605, 1430, 790 cm^{-1}. ^1H NMR: 2.33 (3H, s, $ArC\underline{H}_3$), 3.70 (3H, s, $COOC\underline{H}_3$), 7.13 (4H, bs, $Ar\underline{H}$). Analysis: $C_{11}H_{10}Cl_2O_2$, required: C, 53.87; H, 4.08%. Found: C, 53.98; H, 4.18%.

8c: Yield 69%, b.p. 299°. IR (neat): 1720, 1590, 1485, 850 cm^{-1}. ^1H NMR: 3.90, 3.92 (each 3H, s, $-OC\underline{H}_3$), 7.17 (2H, d, $J = 9.0$ Hz, ArH), 7.60 (2H, d, $J = 9.0$ Hz, ArH). Analysis: $C_{11}H_{10}Cl_2O_3$, required: C, 50.57; H, 3.83%. Found: C, 50.79; H, 3.93%.

8d: Yield 65%, b.p. 315°. IR (neat): 1735, 1640, 1610, 1590, 1510, 870 cm^{-1}. ^1H NMR: 0.94 (6H, d, $J = 9.0$ Hz, $H_2C–CH(C\underline{H}_3)_2$), 1.84 (1H, m, $H_2C–C\underline{H}(CH_3)_2$), 2.54 (2H, d, $J = 9.0$ Hz, $-C\underline{H}_2–CH(CH_3)_2$), 3.94 (3H, s, $-OC\underline{H}_3$), 7.37 (2H, d, $J = 8.0$ Hz, ArH), 7.51 (2H, d, $J = 8.0$ Hz, ArH). Analysis: $C_{14}H_{16}Cl_2O_2$, required: C, 58.53; H, 5.57%. Found: C, 58.79; H, 5.71%.

8e: Yield 66%, b.p. 207°. IR (neat): 1735, 1610, 1590, 1510, 850 cm^{-1}. ^1H NMR: 1.23 (3H, t, $J = 6.0$ Hz, $-CH_2C\underline{H}_3$), 2.40 (3H, s, $ArC\underline{H}_3$), 4.40 (2H, q, $J = 6.0$ Hz $COOC\underline{H}_2CH_3$), 7.48 (4H, m, $Ar\underline{H}$). Analysis: $C_{12}H_{12}Cl_2O_2$, required: C, 55.59; H, 4.63%. Found: C, 55.7; H, 4.72%.

Attempted Hydrolysis of β,β-Dichlorostyrene 2a, 4, and 6

β,β-Dichlorostyrene (20 mmole) and HCl or H_2SO_4 (dil. or conc.) or TFA (22 mmole) in benzene (25 mL) were stirred at room temperature for 72 h. As the reaction did not take place (TLC) the mixture in each case was then refluxed for 72 h. Even then there was no product formation (TLC). Usual work up (by ether extraction) gave an oil identified by TLC, IR as the starting dichlorostyrenes.

General Procedure for the Preparation of α-Arylpropanoic Esters 9a–e from 8a–e

To a solution of arylpropanoic ester (**8**, 1 mmole) in methanol (40 mL) in thick glass hydrogenation bottle, 5% palladium over charcoal (~40 mg) was added. This mixture is shaken with hydrogen (~90 lb/in^2) in hydrogenation apparatus at room temperature until uptake of hydrogen ceases (16 h). The catalyst was removed by filtration and washed with methanol. After complete removal of solvent, product was purified by passage through silica gel column using hexane–EtOAc (98 : 2).

9a: Yield 77%, b.p. 220–221° (Lit.[14] 104–106°/18 mm). IR (neat): 1736, 1600 cm^{-1}. ^1H NMR: 1.46 (3H, d, $J = 7.5$ Hz, $Ar–CHC\underline{H}_3$), 3.71 (3H, s, $COOC\underline{H}_3$), 3.80 (1H, q, $J = 7.5$ Hz, $ArC\underline{H}–CH_3$), 7.48 (5H, s, $Ar\underline{H}$).

9b: Yield 78%, b.p. 243–244° (Lit.[14] 111–112°/13 mm). IR (neat): 1720, 1500 cm^{-1}. ^1H NMR: 1.51 (3H, d, $J = 7.5$ Hz, $Ar–CHC\underline{H}_3$), 2.37

(3H, s, ArC$\underline{H}_3$), 3.77 (3H, s, COOC$\underline{H}_3$), 4.23 (1H, q, $J = 7.5$ Hz, Ar–C$\underline{H}$–C$\underline{H}_3$), 7.45 (4H, m, Ar$\underline{H}$).

9c: Yield 85%, b.p. 280°. IR (neat): 1736, 1605 cm^{-1}. ^{1}H NMR: 1.48 (3H, d, $J = 9.0$ Hz, ArCHC$\underline{H}_3$), 3.74 and 3.88 (each 3H, s, COOC$\underline{H}_3$, ArOC$\underline{H}_3$), 4.22 (1H, q, $J = 9.0$ Hz, ArC$\underline{H}$), 7.08 (2H, d, $J = 9.0$ Hz, ArH), 7.46 (2H, d, $J = 9.0$ Hz, ArH). Analysis: $C_{11}H_{14}O_3$, required: C, 68.04; H, 7.21%. Found: C, 68.21; H, 7.38%.

9d: Yield 87%, b.p. 283° (Lit.[14] 104–106°/1.0 mm). IR (neat): 1739, 1495 cm^{-1}. ^{1}H NMR: 0.91 (6H, d, $J = 9.0$ Hz, ArCH$_2$–CH(C$\underline{H}_3$)$_2$), 1.51 (3H, d, $J = 9.0$ Hz, ArCHC$\underline{H}_3$), 1.88 (1H, m, Ar–CH$_2$–C$\underline{H}$(CH$_3$)$_2$), 2.48 (2H, d, $J = 10.0$ Hz, ArC$\underline{H}_2$CH(CH$_3$)$_2$), 3.77 (3H, s, –COOC$\underline{H}_3$), 3.80 (1H, q, $J = 9.0$ Hz, Ar–C$\underline{H}$CH$_3$), 7.20–7.60 (4H, m, Ar$\underline{H}$).

9e: Yield 76%, b.p. 241° (Lit.[15] yellow oil). IR (neat): 1734, 1500 cm^{-1}. ^{1}H NMR: 1.22 (3H, t, $J = 7.5$ Hz, –OCH$_2$C$\underline{H}_3$), 1.51 (3H, d, $J = 7.5$ Hz, CHC$\underline{H}_3$), 2.37 (3H, s, ArC$\underline{H}_3$), 3.77 (1H, q, $J = 7.5$ Hz, –C$\underline{H}$CH$_3$), 4.23 (2H, q, $J = 7.5$ Hz, –COOC$\underline{H}_2$CH$_3$), 7.45 (4H, s, Ar$\underline{H}$).

Hydrolysis of Ester 9d to 2-(4′-Isobutylphenyl) Propanoic Acid 2

The methyl ester **9d** (0.190 g, 0.86 mmole) and sodium hydroxide (2N, 5 mL) was stirred at 80° for 2 h. Usual workup gave a white solid which was recrystallised from 80% methanol. Yield (0.168 g) 92%, m.p. 75° (lit.[14] 75–76°). IR (nujol): 3300–2500 (broad OH), 1718, 1507, 866. ^{1}H NMR: 0.88 (6H, d, $J = 6.5$ Hz, –CH(C$\underline{H}_3$)$_2$), 1.47 (3H, d, $J = 7.5$ Hz, Ar–CH–C$\underline{H}_3$), 1.87 (1H, m, –CH$_2$C$\underline{H}$(CH$_3$)$_2$), 2.47 (2H, d, $J = 6.5$ Hz, C$\underline{H}_2$–CH(CH$_3$)$_2$), 3.73 (1H, q, $J = 7.5$ Hz, Ar–C$\underline{H}$–CH$_3$), 7.07 (2H, d, $J = 8.0$ Hz, Ar$\underline{H}$), 7.35 (2H, d, $J = 8.0$ Hz, Ar$\underline{H}$).

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