# A Convenient Synthesis of Polysubstituted Phthalic Acid Derivatives via Side-Chain Nitration of Polymethylbenzoic Acids

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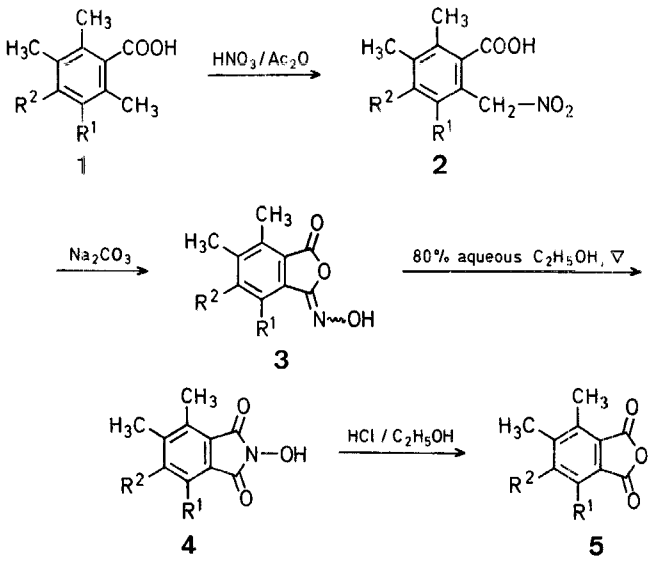
Phthalic acid derivatives are potentially valuable synthetic intermediates. Among these, the polysubstituted phthalic acid derivatives are hard to prepare, because of the difficulties encountered in the selective oxidation of polymethylbenzenes as well as in the introduction of new substituents into the aromatic ring of phthalic acid or the anhydride.

We report here a simple method for the preparation of some phthalic acid derivatives **5** by selective side-chain nitration of polymethylbenzoic acids (**1**) followed by Nef reaction[1] of the resulting phenylnitromethane compounds **2**. Thus, benzoic acids **1** having methyl groups at the 2, 3, and 6-positions react with fuming nitric acid in acetic anhydride to give selectively 2-carboxyphenylnitromethanes **2**. These are easily converted to *N*-hydroxyisophthalimides **3** by treatment with cold aqueous sodium carbonate, which rearrange to *N*-hydroxyphthalimides **4** by boiling in 80% aqueous ethanol (Table 1). Heating **4** in ethanol containing hydrochloric acid gives the polysubstituted phthalic anhydrides **5** (Table 2). The different steps involved in the reaction sequence (Scheme **A**) with the isolation of intermediates **2, 3** and **4** are experimentally demonstrated starting from **1a** to give **5a**. However, it is also possible to carry out the synthesis of **5** from **1** in an one-pot procedure without the isolation of **2, 3** or **4** by the successive treatments described above.

Recently much interest have been shown in side-chain nitration of polysubstituted benzenes with respect to the *ipso*-substitution mechanism whereas synthetic applications[2,3] have aroused only scant interest. The mechanism of side-chain nitration of polymethylbenzenes has been well investigated[4]. Compound **2** also seems to result from the *ipso*-intermediate formed by an attack of nitronium ion at the *meta*-position of the carboxyl group of **1**. The conversion of **2** to **3** would appear to proceed by way of an intramolecular nucleophilic reaction of the carboxyl group at the imine bond of the nitronic acid form of **2** to afford **6**, which immediately looses water to give **3** (which rearranges to **4**) as shown in Scheme **B**.

The method described here offers a convenient procedure for the preparation of complex polysubstituted phthalic acid derivatives **4** and **5**.




| 1-5 | $R^1$ | $R^2$ |
|---|---|---|
| a | $CH_3$ | $CH_3$ |
| b | Cl | $CH_3$ |
| c | $CH_3$ | Cl |
| d | H | $CH_3$ |
| e | $CH_3$ | H |

Scheme A

**Table 1.** Preparation of *N*-Hydroxyphthalimides **4** by Nitration of Polymethylbenzoic Acids **1**

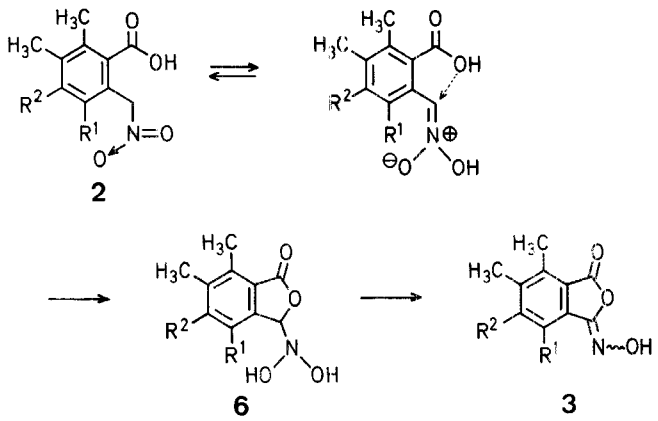
| Product | Nitration Conditions temp. [°C]/time [h] | Yield[a] [%] | m.p. [°C] (solvent) | Molecular Formula[b] | I.R. (KBr)[c] $\nu$ [$cm^{-1}$] | $^1$H-N.M.R. ($CDCl_3$/TMS)[d] $\delta$ [ppm] |
|---|---|---|---|---|---|---|
| **4a** | 0–5°/2 | 67 | 248–249° (80% ethanol) | $C_{12}H_{13}NO_3$ (219.2) | 3210 (OH), 1771 (CO), 1700 (CO) | 2.26 (s, 6H, $CH_3$); 2.64 (s, 6H, $CH_3$); 7.15 (s, 1H, OH) |
| **4b** | 25°/30 | 63 | 247–248° (60% ethanol) | $C_{11}H_{10}ClNO_3$ (239.7) | 3420 (OH), 1770 (CO), 1704 (CO) | 2.35 (s, 3H, $CH_3$); 2.47 (s, 3H, $CH_3$); 2.65 (s, 3H, $CH_3$); 7.38 (s, 1H, OH) |
| **4c** | 25°/30 | 68 | 217–218° (80% ethanol) | $C_{11}H_{10}ClNO_3$ (239.7) | 3100 (OH), 1765 (CO), 1703 (CO) | 2.33 (s, 3H, $CH_3$); 2.64 (s, 3H, $CH_3$); 2.67 (s, 3H, $CH_3$); 7.36 (s, 1H, OH) |
| **4d** | 0–5°/2 | 54 | 181–182° (60% ethanol) | $C_{11}H_{11}NO_3$ (205.2) | 3150 (OH), 1770 (CO), 1710 (CO) | 2.27 (s, 3H, $CH_3$); 2.39 (s, 3H, $CH_3$); 2.62 (s, 3H, $CH_3$); 7.36 (s, 1H, OH); 7.45 (s, 1H, $H_{arom}$) |
| **4e** | 0–5°/2 | 16 | 210–211° (60% ethanol) | $C_{11}H_{11}NO_3$ (205.2) | 3300 (OH), 1770 (CO), 1710 (CO) | 2.33 (s, 3H, $CH_3$); 2.57 (s, 3H, $CH_3$); 2.58 (s, 3H, $CH_3$); 7.30 (s, 1H, OH); 7.26 (s, 1H, $H_{arom}$) |

[a] Yield of **4** isolated in the last step.
[b] Satisfactory microanalyses obtained: C ±0.19, H ±0.27, N ±0.16.
[c] The I.R. spectra were recorded on a Shimadzu IR-430 spectrophotometer.
[d] The $^1$H-N.M.R. spectra were measured at 270 MHz with a JEOL model FX-270 spectrometer.

**Table 2.** Preparation of Phthalic Anhydrides **5** from **4**

| Product | Yield[a] [%] | m.p. [°C] (solvent) | Molecular Formula[b] or Lit. m.p. [°C] | I.R (KBr) $\nu_{C=O}$ [cm$^{-1}$] | $^1$H-N.M.R. ($CDCl_3$/TMS) $\delta$ [ppm] |
|---|---|---|---|---|---|
| **5a** | 95 | 262–263° (benzene) | 260–261°[6] | 1845, 1810, 1775 | 2.65 (s, 6H, $CH_3$); 2.35 (s, 6H, $CH_3$) |
| **5b** | 79 | 211–213° (benzene/hexane) | $C_{11}H_9ClO_3$ (224.6) | 1843, 1772, 1705 | 2.41 (s, 3H, $CH_3$); 2.52 (s, 3H, $CH_3$); 2.68 (s, 3H, $CH_3$) |
| **5c** | 66 | 197–200° (benzene/hexane) | $C_{11}H_9ClO_3$ (224.6) | 1841, 1807, 1772 | 2.51 (s, 3H, $CH_3$); 2.70 (s, 3H, $CH_3$); 2.74 (s, 3H, $CH_3$) |
| **5d** | 47 | 180° (benzene) | $C_{11}H_{10}O_3$ (190.2) | 1840, 1770 | 2.34 (s, 3H, $CH_3$); 2.47 (s, 3H, $CH_3$); 2.68 (s, 3H, $CH_3$); 7.63 (s, 1H, $H_{arom}$) |
| **5e** | 81 | 219–220° (benzene) | $C_{11}H_{10}O_3$ (190.2) | 1840, 1770 | 2.41 (s, 3H, $CH_3$); 2.61 (s, 3H, $CH_3$); 2.63 (s, 3H, $CH_3$); 7.39 (s, 1H, $H_{arom}$) |

[a] Yield of **5** isolated.
[b] Satisfactory microanalyses obtained: C ±0.24, H ±0.17.




Scheme **B**

Compounds **1a–e** were prepared by the method described in the literature[5].

**Tetramethylphthalic Anhydride (5a); Typical Procedure for Stepwise Preparation:**

*2-Carboxy-3,4,5,6-tetramethylphenylnitromethane* (**2a**): To a solution of pentamethylbenzoic acid (**1a**; 1.00 g, 5.2 mmol) in acetic anhydride (10 ml), fuming nitric acid (0.66 g, 10.4 mmol, $d$ = 1.52) in acetic anhydride (5 ml) is added at 0 °C and the mixture is stirred for 2 h at the same temperature. The reaction mixture is poured into ice/water (~ 200 g) and stirred overnight. The resulting precipitate is collected, washed with water, and recrystallized from methanol to give **2a**; yield: 0.86 g (70%); m.p. 164 °C (dec.).

| | | | | |
|---|---|---|---|---|
| $C_{12}H_{15}NO_4$ | calc. | C 60.75 | H 6.37 | N 5.90 |
| (237.3) | found | 60.77 | 6.47 | 5.76 |

I.R. (KBr): $\nu$ = 1700 (CO); 1560, 1375 cm$^{-1}$ ($NO_2$).

$^1$H-N.M.R. ($CDCl_3$): $\delta$ = 5.65 (s, 2H, $CH_2$); 5.50 (br.s, 1H, COOH);

2.35 (s, 6H, 2 $CH_3$); 2.27 ppm (s, 6H, 2$CH_3$).

*N-Hydroxytetramethylisophthalimide* (**3a**): After the nitration reaction of **1a** (1.00 g, 5.2 mmol) under the same conditions above described, the resulting reaction mixture is poured into ice/water (~ 200 g), neutralized with solid sodium carbonate (17 g) till the solution becames weakily alkaline, and stirred overnight. The resulting solid is filtered and recrystallized from methanol to give **3a**; yield: 0.71 g (77%); m.p. 234–235 °C.

| | | | | |
|---|---|---|---|---|
| $C_{12}H_{13}NO_3$ | calc. | C 65.74 | H 5.98 | N 6.39 |
| (219.2) | found | 65.63 | 6.01 | 6.30 |

I.R. (KBr): $\nu$ = 3340 (OH), 1786 cm$^{-1}$ (CO).

$^1$H-N.M.R. ($CDCl_3$): $\delta$ = 2.31 (s, 3H, $CH_3$); 2.34 (s, 3H, $CH_3$); 2.55 (s, 3H, $CH_3$); 2.64 (s, 3H, $CH_3$); 7.04 ppm (s, 1H, OH).

*N-Hydroxytetramethylphthalimide* (**4a**): Recrystallization of **3a** (0.5 g, 2.3 mmol) from 80% aqueous ethanol (20 ml) gives **4a**; yield: 0.48 g (96%); m.p. 248–249 °C (Table 1).

*Conversion of* **4a** *to Tetramethylphthalic Anhydride* (**5a**): A solution of *N*-hydroxytetramethylphthalimide (**4a**; 0.5 g, 2.3 mmol) in ethanol (20 ml) containing concentrated hydrochloric acid (10 ml) is heated to reflux for 4 h and cooled. The precipitate formed is filtered and recrystallized from benzene; yield: 0.45 g (95%); m.p. 262–263 °C (Lit.[6], m.p. 260–261 °C) (Table 2).

**Tetramethylphthalic Anhydride (5a); Typical Procedure for One-pot Preparation:**

To a solution of **1a** (3.00 g, 15.6 mmol) in acetic anhydride (30 ml), a solution of fuming nitric acid (1.97 g, 31.2 mmol, $d$ = 1.52) in acetic anhydride (18 ml) is added over 30 min at 0 °C. The reaction mixture is stirred at the same temperature for 2 h, then poured into ice/water (500 ml), neutralized with solid sodium carbonate (55 g), and stirred overnight. The resulting solid is heated in ethanol (100 ml) containing concentrated hydrochloric acid (20 ml) under reflux for 4 h. After cooling, the resulting precipitate is filtered to give **5a**; yield: 2.01 g (63%); m.p. 262–263 °C (benzene) (Lit.[6], m.p. 260–261 °C; Lit.[7], 238–239 °C).

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