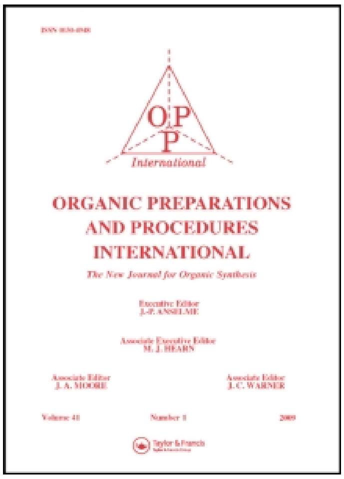

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CONVENIENT LARGE SCALE PREPARATION OF 5-METHYL- AND 4-NITRO- 2-IODOSOBENZOIC AND OF 4-NITRO-2-IODOXYBENZOIC ACIDS

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CONVENIENT LARGE SCALE PREPARATION OF 5-METHYL- AND 4-NITRO- 2-IODOSOBENZOIC AND OF 4-NITRO-2-IODOXYBENZOIC ACIDS

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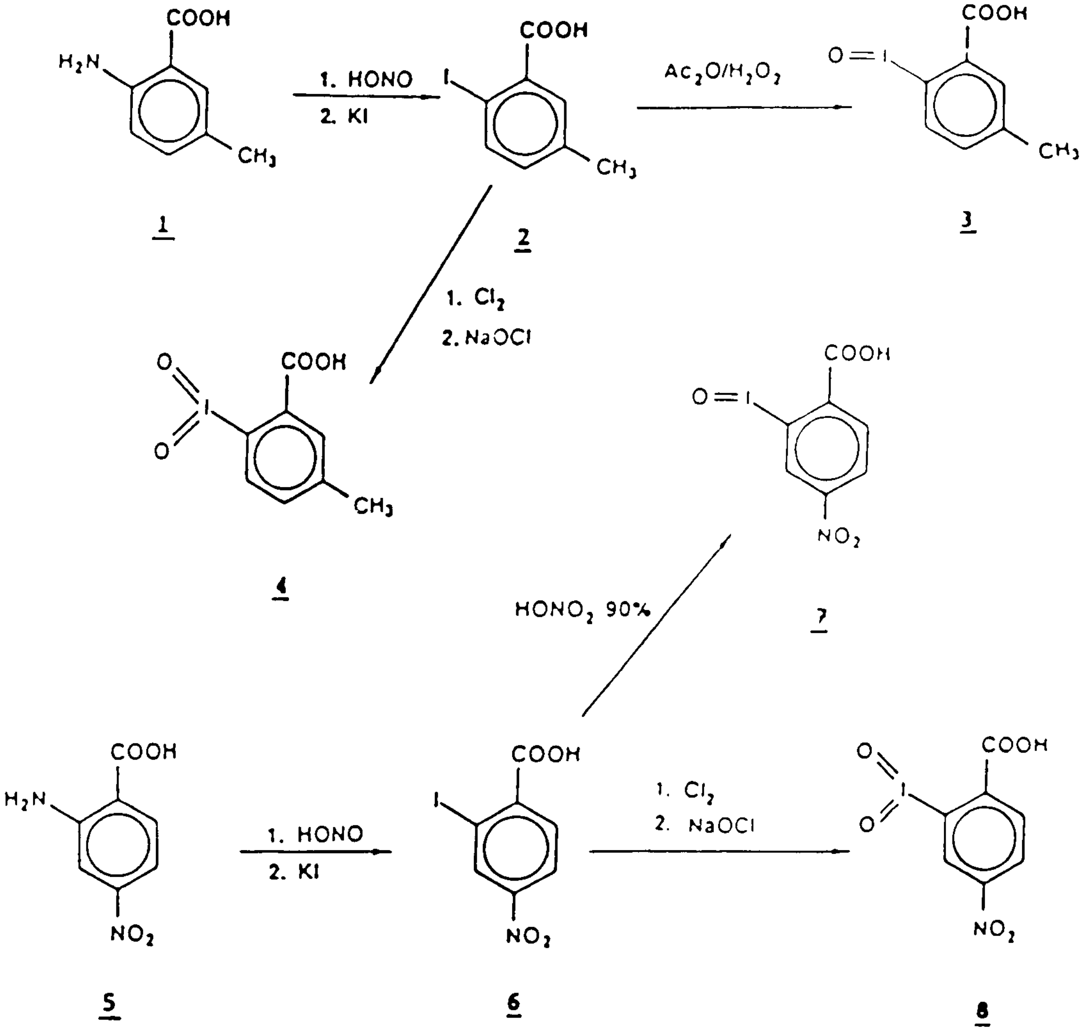
Substituted 2-iodosobenzoic and 2-iodoxybenzoic acids have received renewed attention over the past five years. This has, in part, been due to their ability to act as nucleophilic catalysts for the hydrolytic decomposition of phosphorus esters in cetyltrimethylammonium chloride micellar media.[1-6] 2-Iodoso-4-nitrobenzoic, 2-iodoxy-4-nitrobenzoic, 2-iodoso-5-methylbenzoic and 2-iodoxy-5-methylbenzoic acids were all found to be highly efficient catalysts for this purpose.[5] We now report convenient procedures for the large-scale preparation of these compounds based on methods available from the literature but optimized by the use of new reagents and/or conditions. These procedures should be adaptable to the preparation of a wide variety of analogs.

The substituted 2-iodobenzoic acid precursors were prepared from commercially available, substituted anthranilic acids using standard techniques. Thus, the substituted anthranilic acids were treated with sulfuric acid and sodium nitrite and the resulting diazonium salt was heated with a solution of potassium iodide to give the iodoarene. The iodo compounds were then oxidized by peracetic acid or by fuming nitric acid to give the iodosobenzoic acids, and by chlorine followed by hypochlorite to give the iodoxybenzoic acids (Fig. 1).

FIG 1. Preparation of substituted iodosobenzoic and iodoxybenzoic acids



Peracetic acid is an efficient, readily obtained reagent for the oxidation of 2-iodo-5-methylbenzoic acid **2**, to 2-iodoso-5-methylbenzoic acid **3**.[6] Peracetic acid is prepared by stirring acetic anhydride and hydrogen peroxide at 40 °C for 4 h.[7] It is important to maintain the temperature within ± 1 °C of this temperature as variations may appreciably decrease the overall yield. The previously reported method for the oxidation of 2-iodo-4-nitrobenzoic acid **6**, to 2-iodoso-4-nitrobenzoic acid **7** using 90% fuming nitric acid,[8] was found to be satisfactory for use on a large scale.

Several methods for the preparation of substituted aryliodoxy compounds have been reported. These include the disproportionation of iodosoarenes *via* steam distillation[9] and the oxidation of iodoarenes with concentrated chloric acid,[10] peracetic acid,[11] Caro's acid,[12] and with chlorine followed by sodium hydroxide and sodium carbonate.[2] We recommend a procedure based on the general method[8,13] of chlorination followed by oxidative hydrolysis of the corresponding 2-(dichloroiodo)-benzoic acids with commercial bleach solution (*ca* 5% aqueous NaOCl). The advantages of this method include the simplicity of workup, high yields, relatively mild conditions and the low cost of the reagent. The latter is especially important when considering large scale-up.

In the procedures described above, attention should be given to the potential explosive hazards associated with the use of peracetic acid. In addition the 2-iodosobenzoic and 2-iodoxybenzoic acids themselves may decompose violently at their melting points.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus equipped with a microscope and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL FX-100 (100 MHz) NMR spectrometer with tetramethylsilane (TMS) as the internal standard. ^{13}C-NMR spectra were recorded on a JEOL FX-100 (25 MHz) NMR spectrometer or on a Varian XL-200 (50 MHz) NMR spectrometer using 5 mm tubes. Solute concentrations were 80-150 mg/mL with $CDCl_3$, D_2O or $(CD_3)_2SO$ as solvent and internal lock as stated. Infrared spectra were recorded as 1-2% nujol mulls between cadmium teluride windows on a Perkin-Elmer 1750 or a Nicolet 10DX FTIR at 2 wavenumber resolution. The instrument sample cavity was purged with bone dry air (*ca* 1 ppm H_2O) before and during data collection. Commercially available reagent grade solvents and reagents were used without further purification.

2-Iodo-5-methylbenzoic acid (2) - To a stirred solution of 2-amino-5-methylbenzoic acid (37.75 g, 0.25 mol), water (450 mL), ice (300 g), and concentrated sulfuric acid (50 mL), a solution of sodium nitrite (18.63 g, 0.27 mol) in water (150 mL) was added dropwise, while keeping the temperature below 5 °C. The mixture was stirred at 0-5 °C for 2 h and then a solution of potassium iodide (57.0 g, 0.34 mol) in water (125 mL) was added over a period of 10 min at the same temperature. The mixture was heated on a steam bath for 2 h, then cooled in an ice bath. The solid which separated was filtered, dissolved in ether (500 mL), and washed with 20% aqueous thiosulfate solution (3 x 300 mL). The organic layer was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The solid residue was recrystallized from water and dried *in vacuo* to give 2-iodo-5-methylbenzoic acid (53.6 g, 82%) as off-white needles, m.p. 118-119 °C (Lit.[14] m.p. 118-119 °C). ^{13}C-NMR δ($CDCl_3$): 20.8, CH_3; 90.6, C2; 132.8, C5; 132.9, C6; 134.6, C4; 138.2, C1; 141.7, C3; 171.8, C=O. ^{1}H-NMR δ($CDCl_3$): 11.24, s, COOH; 7.88, d, J = 8.1 Hz, H3; 7.83, d, J = 2.2 Hz, H6; 7.00, dd, J = 8.2 and 2.3 Hz, H4; 2.33, s, CH_3.

2-Iodoso-5-methylbenzoic acid (3) - A mixture of 30% hydrogen peroxide (25 mL) and acetic anhydride (105 mL) was stirred in a water bath at 40 °C for 4 h. To this was added 2-iodo-5-methylbenzoic acid (22.3 g, 85 mmol) and the mixture was stirred at room temperature for 24 h. The crystalline precipitate was collected by vacuum filtration, washed with water (100 mL) and with chloroform (50 mL) and dried *in vacuo*. The mother liquor was diluted to 1000 mL with water and stirred for 1 h. A second crystalline crop was collected, washed with water (100 mL) and chloroform (50 mL) and then dried. The combined precipitates were recrystallized from water to give 2-iodoso-5-methylbenzoic acid as fine colorless needles (18.0 g, 76%), m.p. 215-216 °C (Lit.[15] m.p. 210-212 °C). ^{13}C-NMR δ(DMSO-d_6): 20.2, CH_3; 116.7, C2; 126.0, C3; 131.5, C1,C6; 135.2, C4; 140.5, C5; 167.8, C=O; and its sodium salt, δ(DMSO-d_6/D_2O): 20.8, CH_3; 116.9, C2; 125.3, C3; 131.8, C6; 133.4, C1; 134.6, C4; 140.0, C5; 169.8, C=O. FTIR: 3400 (br), 1619 (97), 1587 (84), 1571 (88), 1456 (90), 1404 (72), 1344 (50), 1318 (92), 1253 (56), 1216 (56), 1189 (46), 1140 (42), 1120 (41), 909 (50), 822 (48), 792 (76), 785 (82), 673 (52), 576 (83), 532 (64), 510 (52), 437 (59) cm^{-1} (%).

2-Iodoxy-5-methylbenzoic acid (4) - Chlorine gas was bubbled into an ice-cold solution of 2-iodo-5-methylbenzoic acid (22.3 g, 85 mmol) in chloroform (100 mL) for 30 min. The solid precipitate was collected by filtration, treated with 150 mL of commercial bleach (*ca* 5% aqueous NaOCl) and the mixture was stirred for 24 h at room temperature. The solution was acidified with concentrated H_2SO_4 and the resultant precipitate was collected, washed with water (100 mL) and ethyl acetate (50 mL), and then dried. Recrystallization from acetone gave 2-iodoxy-5-methylbenzoic acid (18.2 g, 73%) as white needles, m.p. 199-201 °C. ^{13}C-NMR (Sodium salt), δ(D_2O/NaOCl): 21.5, CH_3; 123.7, C3; 131.9, C1; 132.0, C6; 135.1, C4; 144.1, C5; 146.1, C2; 172.1, C=O. FTIR: 3400 (br), 1643 (95), 1587 (54), 1458 (72), 1413 (37), 1378 (52), 1326 (71), 1302 (65), 1258 (53), 908 (35), 823 (69), 786 (92), 777 (91), 680 (49), 618 (66), 602 (45), 508 (44), 434 (61) cm^{-1} (%).

2-Iodo-4-nitrobenzoic acid (6) - To a stirred solution of 2-amino-4-nitrobenzoic acid (45.5 g, 0.25 mol), water (450 mL), ice (300 g), and concentrated sulfuric acid (50 mL) a solution of sodium nitrite (18.63 g, 0.27 mol) in water (150 mL), was added dropwise while keeping the temperature less than 5 °C. The mixture was stirred at 0-5 °C for 2 h, and then a solution of potassium iodide (57.0 g, 0.34 mol) in water (125 mL) was added over 10 min maintaining the temperature below 5 °C. The mixture was heated on a steam bath for 2 h then cooled in an ice bath. The precipitate that formed was collected by filtration, taken up in ether (500 mL) and washed with 20% aqueous thiosulfate solution (3 x 300 mL). The organic layer was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The solid residue was recrystallized from water to give 2-iodo-4-nitrobenzoic acid (63.1 g, 87%) as orange needles, m.p. 142-143 °C (Lit.[16] m.p. 144-145 and[8] 142 °C). ^{1}H-NMR δ($CDCl_3$): 9.4, b, COOH; 8.73, d, J = 2.2 Hz, H3; 8.23, dd, J = 8.6 and 2.1 Hz, H5; 7.93, dd, J = 8.4 and 1.6 Hz, H6. ^{13}C-NMR δ($CDCl_3$): 93.2, C2; 122.7, C5; 131.0, C6; 135.5, C3; 142.0, C1; 148.5, C4; 167.0, C=O.

2-Iodoso-4-nitrobenzoic acid (7) - A solution of 2-iodo-4-nitrobenzoic acid (14.65 g, 50 mmol) in 90% fuming nitric acid (150 mL) was stirred for 6 h at room temperature. The reaction mixture was poured into ice water (1500 mL) and the resulting solid was collected, washed with water (100 mL), and dried *in vacuo*. After trituration with ethyl acetate (50 mL), the solid was collected, washed with ethyl acetate (50 mL) and ethyl ether (50 mL) then dried to give 2-iodoso-4-nitrobenzoic acid (14.0 g, 86%), m.p. 204-205 °C (Lit.[17] m.p. 201 and[8] 190, 196 and 201 °C). ^{13}C-NMR δ(DMSO-d_6) 121.7, C5; 122.1, C2; 125.9, C3; 132.1, C6; 136.6, C1; 151.5, C4; 166.1, C=O; and its sodium salt, δ(D_2O): 120.9, C5; 121.7, C2; 125.7, C3; 132.4, C6; 137.5, C1; 151.8, C4; 170.2, C=O. FTIR: 3400 (br), 2415 (39), 1611 (86), 1586 (89), 1574 (99), 1541 (86), 1532 (80), 1460 (47), 1398 (50), 1377 (58), 1348 (84), 1336 (81), 1312 (74), 820 (48), 792 (20), 735 (46), 658 (20), 599 (29), 575 (38), 536 (29) cm^{-1} (%).

2-Iodoxy-4-nitrobenzoic acid (8) - Chlorine gas was bubbled into an ice-cold solution of 2-iodo-4-nitrobenzoic acid (14.65 g, 0.05 mol) in chloroform (100 mL) for 30 min. The solid precipitate was collected by vacuum filtration and treated with commercial bleach (*ca* 5% aqueous NaOCl) (100 mL). The mixture was stirred for 24 h at room temperature then filtered. The filtrate was acidified with concentrated H_2SO_4 and cooled in an ice bath. A precipitate formed and was collected by vacuum filtration, washed with water (100 mL) and dried. Recrystallization from water gave 2-iodoxy-4-nitrobenzoic acid (13.6 g, 84%) as pale yellow microcrystals m.p. 202-204 °C (dec) (Lit.[8] m.p. 205 °C). ^{13}C-NMR (Sodium salt), δ(D_2O/NaOCl): 119.2, C5; 129.3, C3; 132.7, C6; 137.3, C1; 149.4, C2; 151.8, C2; 169.8, C=O. FTIR: 3400 (br), 1648 (75), 1602 (68), 1585 (73), 1546 (72), 1533 (74), 1466 (63), 1344 (82), 1246 (69), 1227 (68), 913 (47), 804 (82), 796 (86), 734 (85), 723 (81), 709 (80), 671 (86), 650 (31), 580 (47), 527 (41), 428 (33) cm^{-1} (%).

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