Selective Oxidation of 2-Bromo-*m*-xylene to 2-Bromo-3-methylbenzoic Acid or 2-Bromoisophthalic Acid

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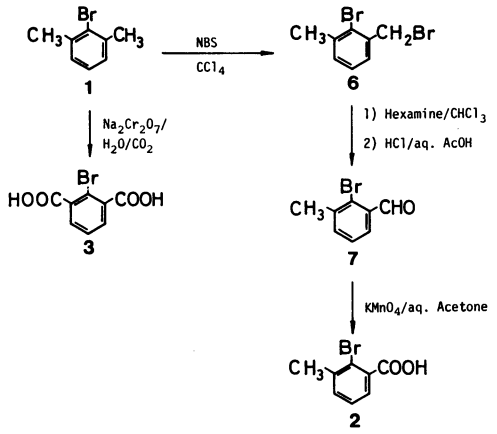
Synopsis. Aqueous sodium dichromate oxidation of 2-bromo-*m*-xylene (**1**) under a carbon dioxide pressure gave 2-bromoisophthalic acid (58%), while NBS-bromination of **1** followed by Sommelet oxidation to aldehyde and then potassium permanganate oxidation enabled the isolation of 2-bromo-3-methylbenzoic acid in 42% yield.

Herein, we wish to report that 2-bromo-*m*-xylene (**1**) serves as readily available starting material for the synthesis of 2-bromo-3-methylbenzoic acid (**2**) and 2-bromoisophthalic acid (**3**) (Scheme 1), both



Scheme 1.

of which have been obtained with difficulty by the literature procedure. In the course of our study on the construction of axially chiral biaryl skeletons,[1] we needed **2** as a coupling component in the Ullmann biaryl synthesis. Unexpectedly, a search of the literature revealed only one precedent synthesis of **2** by Bunnett and Rauhut which involes bromination of *p*-nitrotoluene and then treatment of the resulting 2-bromo-4-nitrotoluene with KCN in water (the von Richter reaction).[2,3] The process was not appealing to us for large scale synthesis because of the low overall yield of **2** (7—8% based on *p*-nitrotoluene) and the tedious handling of massive quantities of toxic cyanide.

We have recently reported an improved oxidation of 1-bromo-2-methylnaphthalene (**4**) to 1-bromo-2-naphthoic acid (**5**) by an aqueous sodium dichromate under a carbon dioxide atmosphere according to the method of Yamashita et al.[4,5] The simplicity of the procedure, along with availability of sufficiently pure **1**,[6] encouraged us to apply it for oxidation of **1**, and Table 1 summarizes the results. In view of the tendency that initially formed monobasic acid **2** was oxidized more readily than starting **1**, probably due to their solubility differences in the aqueous reaction medium, the dichromate oxidation should more advantageously be utilized for selective synthesis of dicarboxylic acid **3**. This was realized by the use of three molar amounts of the oxidant affording **3** in fairly good yield (Run 5). The synthesis of **3** via oxidation of **1** is not new; as long ago as 1937 Coulson used aqueous potassium permanganate as the oxidant.[7,8] However, the procedure has suffered seriously from the concomitant formation of a significant amount of 2-hydroxyisophthalic acid which requires tedious separation from **3**.[7,9] It should be pointed out here that **3** itself is of potential importance as the building block for not only biaryls[7,8] but also diarylamines including acridones of pharmaceutical interest,[11] but that only limited success in the preparation of **3** seems to have restricted its wide use.

As the synthetically passable route to **2**, we eventually resorted to the stepwise oxidation of **1** (Scheme 1) which is essentially an extention of the method used by Bergmann and Szmuszkovicz,[12] and Hall and Turner[13] for transformation of **4** to **5**. Upon treatment with slightly excess amounts of *N*-bromosuccinimde (NBS) almost all of **1** reacted, indicating that preferential bromination of both of the methyl substituents did not so much matter. Crude 2-bromo-3-(bromomethyl)toluene (**6**) was converted to hexamethylenetetramine (hexamine) adduct, which was then hydrolyzed to 2-bromo-3-methylbenzaldehyde (**7**) as needles on standing the reaction mixture (the Sommelet reaction). Conversion of **7** to **2** was effected well with potassium permanganate according to the method of Hall and Turner with slight modifications.[13]

The above procedure was repeated several times with

Table 1. Oxidation of **1** with Aqueous $Na_2Cr_2O_7$ Under CO_2[a]

Run	$Na_2Cr_2O_7$/**1** mol/mol	T/°C	t/h	Yield[b]/% **2**	Yield[b]/% **3**	Recovered[c] **1**/%
1	0.8	230	8	15	13	28
2	1.0	230	8	12	14	21
3	1.0	260	5	1.0	1.4	3.1
4	1.5	230	8	8.2	37	12
5	3.0	230	5	1.3	58	11

a) Reaction conditions: **1**, 26—30 mmol; H_2O, 90 ml; initial CO_2 press., 20 atm. b) Isolated by crystallization. c) Isolated by bulb-to-bulb distillation of the nonacidic components.

slightly changing the reaction variables giving the overall yields of **2** ranging from 25 to 42% based on starting **1**. As frequently encountered in the Sommelet reaction,[14] the low yield in the hydrolysis step is one limiting factor, but the straightforward and simple reaction sequence provides a considerable improvement over the conventional preparation of **2**.[2]

Experimental

Preparation of 3 (Run 5 in Table 1). A mixture of **1** (5.38 g, 0.0291 mol), $Na_2Cr_2O_7 \cdot 2H_2O$ (26.0 g, 0.0872 mol), and 90 ml of water placed in a 300 ml autoclave was allowed to react[4] under the conditions cited in Table 1. After the reaction, acidic products were taken into ether and treated as usual. Removal of the solvent left white solid, which was heated at reflux in 100 ml of toluene and filtered hot. The solid was then recrystallized from 2 M HCl (1 M=1 mol dm^{-3}) to give **3** as colorless needles (4.15 g, 0.0169 mol); mp 218—220 °C (lit,[7] mp 218 °C); δ (acetone-d_6) 7.3—7.9 (3H, m, ring-Hs) and 11.0 (2H, br, -COOH); IR (KBr) 1710 and 1685 cm^{-1} (νCO). Anal. ($C_8H_5BrO_4$) C, H, Br.

The toluene filtrate was concentrated to about 20 ml volume. After precipitated solid had been filtered off (70 mg, mp 216—220 °C), the solvent was removed from the filtrate and then crystallization from H_2O–EtOH gave **2** (80 mg, 0.37 mmol), mp 133—136 °C.

Preparation of 2. A mixture of **1** (25.8 g, 0.139 mol), NBS (25.8 g, 0.145 mol), and 0.1 g of benzoyl peroxide was refluxed in 75 ml of CCl_4 for 3 h. The cool reaction mixture was filtered, and evaporation of the solvent left crude **6** as a pale yellow oil; δ (CCl_4) 2.35 (3H, s, $-CH_3$), 4.50 (2H, s, $-CH_2Br$), and 7.0—7.4 (3H, m, ring-Hs).

To the mechanically stirred **6** in 180 ml of $CHCl_3$ was added 24.4 g of hexamethylenetetramine (0.174 mol). After 1 h heating at reflux, the amine adduct was filtered and dried under reduced pressure. The adduct was boiled in 280 ml of 50% aqueous AcOH for 2 h, and then for further 1 h after adding 30 ml of concd HCl. The mixture was allowed to stand overnight at room temperature to give **7** as needles[15] (13.7 g, 49.4% based on **1**); mp 53—54 °C; δ ($CDCl_3$) 2.40 (3H, s, $-CH_3$), 7.2—7.8 (3H, m, ring-Hs), and 10.4 (1H, s, -CHO); IR (KBr) 1680 cm^{-1} (νCO). Combustion analysis suggested the presence of about 5—6% of 2-bromoisophthalaldehyde (Found: C, 46.57; H, 3.38; Br, 38.45%. C_8H_7BrO requires C, 48.27; H, 3.54; Br, 40.14%).

To a boiling solution of **7** (13.2 g, 66.3 mmol) in 420 ml of acetone was added dropwise a $KMnO_4$ solution (13.8 g, 87.3 mmol) in 250 ml of water for 1/2 h, and the heating was continued for another 1 h. Sulfur dioxide was passed through the cool, dark brown mixture until it became clear solution, to which was added 2 l of water and 200 ml of 28% NH_3. The mixture was passed through a short silica-gel column to remove brown precipitates, acidified with concd HCl, and extracted with ether. After the usual work-up, the solvent was evaporated, and the residue was recrystallized from H_2O–EtOH to give **2** as colorless needles (12.2 g, 85.6% based on **7** and 42.3% based on **1**), mp 135—137 °C (lit,[2a] mp 135—137 °C); δ ($CDCl_3$) 2.40 (3H, s, $-CH_3$), 7.0—7.8 (3H, m, ring-Hs), and 11 (1H, br, -COOH); IR (KBr) 1690 cm^{-1} (νCO). Anal. ($C_8H_7BrO_2$) C, H, Br.

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