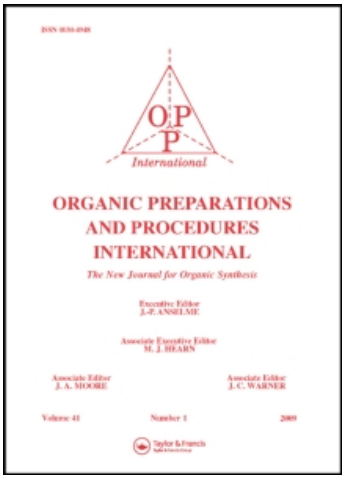

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AN IMPROVED LARGE SCALE SYNTHESIS OF 2,3-DIHYDROXYTEREPHTHALIC ACID AND DIMETHYL 2,3-DIHYDROXYTEREPHTHLATE

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AN IMPROVED LARGE SCALE SYNTHESIS OF 2,3-DIHYDROXYTEREPHTHALIC ACID AND DIMETHYL 2,3-DIHYDROXYTEREPHTHALATE

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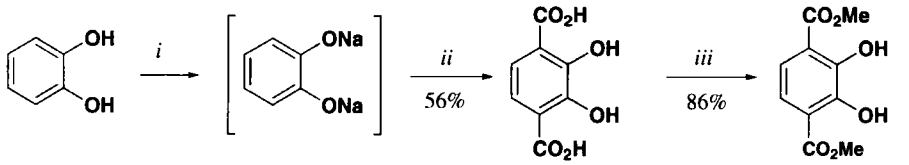
2,3-Dihydroxyterephthalic acid (**3**) and derivatives such as dimethyl 2,3-dihydroxyterephthalate (**4**) are important synthetic intermediates.[1] They are key building blocks in the synthesis of specific sequestering agents for removal of iron (III) from human transferrin[2] and in the synthesis of antidote agents for hazardous radionuclides such as Pu(IV)[3] and Ga(III).[4] They are also used in the preparation of novel synthetic siderophores[5] and molecular receptors[6] as well as in the synthesis of

antiphlogistic, analgesic, and antipyretic agents.[7]

Three different methods have been reported for the synthesis of **3**. First, **3** was prepared by the hydrolysis of 3,6-dicyanocatechol which was obtained from *bis*-2-cyanoethyl sulfide and ethyl oxalate in an unreported yield.[8] Second, **3** was obtained in 11% overall yield from 8-hydroxy-2,3-dimethylchromone in three steps.[9] Finally, **3** was generated by a Kolbe-type reaction using disodium catecholate and carbon dioxide.[2a,10] In a project from our combinatorial drug discovery program, an easy access to **3** and **4** was required. Herein, we describe an improved large scale preparation of these compounds using the Kolbe synthesis.

Treatment of catechol with sodium hydroxide in methanol followed by drying and reaction of the resulting disodium catecholate (**2**) with carbon dioxide[2a] gave only 13% of the desired product **3** and substantial amounts of unreacted catechol and monoacid by-product, 2,3-dihydroxybenzoic acid as shown by HPLC. The low conversion to **3** was attributed to the poor control of the dryness of disodium catecholate **2** prepared, the effect of moisture in the Kolbe reaction has been previously reported.[10] For example, reaction of "dry" disodium catecholate (**2**) with carbon dioxide was reported to give **3** in 28% whereas "damp" afforded none of **3**, 2,3-dihydroxybenzoic acid being obtained instead in 25% yield.[10] Reaction of catechol (**1**) with sodium hydroxide gives in theory two equivalents of water. It was anticipated that this water could be removed by drying the salt at an elevated temperature for a prolonged time. However, it was difficult on scaling the reaction to determine the water content in the dried sample due to the sensitivity of **2** to moisture and oxygen. Compound **2** absorbs moisture and oxygen and darkens rapidly upon exposure to air. Consequently, we decided to substitute sodium methoxide for sodium hydroxide to minimize the water problem. Indeed, treatment of catechol with two equivalents of sodium methoxide in methanol followed by removal of solvent and subsequent reaction of **2** with carbon dioxide smoothly afforded the desired product **3**. 2,3-Dihydroxyterephthalic acid (**3**) was conveniently isolated in 56% yield by dissolving the reaction mixture in water and crystallizing the product by adjusting the pH with HCl.



1 2 3 4

i) NaOMe, MeOH; ii) CO_2 then HCl, H_2O; iii) TMSCl, MeOH

Dimethyl 2,3-dihydroxyterephthalate (**4**) was previously prepared in 82% yield by reaction of **3** with methanol using an excess gaseous hydrogen chloride.[2a] The reaction mixture was heated at reflux for 60 hours. We decided to use chlorotrimethylsilane (trimethylsilyl chloride, TMSCl)[11] instead of gaseous HCl. Use of TMSCl is more advantageous not only because it is more convenient to use and measure, but also because it acts as a water scavenger so that the esterification is faster

and cleaner. Thus, treatment of **3** in refluxing methanol in the presence of TMSCl afforded **4** in 86% yield after crystallization.

In summary, an improved method has been developed for the large scale preparation of **3** and **4**. Compared to the previous methods, this new method gave higher yields and more convenient manipulations. Chromatographic purification of product was not required.

EXPERIMENTAL SECTION

Melting points were taken on a Uni-Melt apparatus in open capillaries and are uncorrected. Infrared spectra were recorded as KBr pellets on a Nicolet Magna 560 instrument. Proton and carbon-13 NMR spectra were recorded in DMSO-d_6 on a Bruker ARX-400 instrument using tetramethylsilane as internal standard. Catechol and TMSCl were purchased from Aldrich Company and used as received.

2,3-Dihydroxyterephthalic Acid (3).- To a 2L Parr high pressure reactor was added a 25 wt% solution of sodium methoxide in methanol (240 mL, 1.05 mol). After degassing the solution with argon for 15 minutes, catechol (55.06g, 0.5 mol) was added as a solid in one portion. The reaction mixture was stirred at room temperature for 15 minutes. Methanol was distilled off under argon until the pot temperature reached 105-115°. The resulted disodium catecholate was dried under argon in the reactor at 105-115° for 16 hours. After cooling to room temperature and brief grinding of the solid in the reactor with a spatula, carbon dioxide gas was charged until the internal pressure reached about 800psi. The reaction mixture was heated to 195-200° while the pressure was adjusted to 1100psi and was then gently stirred for 90 hours at 195-200°. After cooling to room temperature, the reaction mixture was transferred into a 2L three-necked round bottomed flask equipped with a mechanical stirrer. Water (900 mL) and charcoal (10g) were added. The mixture was heated with stirring to 100-105° for 30 min. After filtration and washing the black cake with hot water (100 mL), the filtrate was cooled to about 40° and the pH was adjusted from 10.0 to 2.0 using con. HCl (~80 mL). The resulting slurry was stirred at room temperature overnight and filtered. The cake was washed with water (3x200mL) and dried in a vacuum oven at 60° for 18 hours to give 55.3g (56%) of **3**, mp. 289-290°, lit.[2a] mp. 289-290°. IR: 3520, 3446, 3064, 1662, 1622, 1228, 752 cm^{-1}; ^1H NMR: δ 7.21 (s, 2H), 9.10 (br s, 4H); ^{13}C NMR: δ 172.14, 151.79, 118.17, 118.09.

Dimethyl 2,3-Dihydroxyterephthalate (4).- To a 2L three-necked round bottomed flask equipped with a mechanical stirrer and condenser was added **3** (50.0g, 0.252 mol) and methanol (750 mL). The mixture was stirred under nitrogen at room temperature to give a solution. TMSCl (250 mL, 1.97 mol) was added over 5 min. The reaction mixture was heated to reflux and stirred for 16 hours. After cooling to room temperature, water (750 mL) was added to the resulting slurry. The product mixture was cooled with an ice water bath, stirred for 45 min. The resulting slurry was filtered with suction, washed with water (3x100 mL), and dried to give 49.1g (86%) of **4**, mp. 142-143°, lit.[2a] mp. 141-143°. IR: 3165, 2958 1697, 1626, 1213, 748 cm^{-1}; ^1H NMR: δ 10.5 (s, 2H), 7.28 (s, 2H), 3.92 (s, 6H); ^{13}C NMR: δ 168.89, 149.81, 118.98, 117.41, 53.10; MS (M+H) 227.1.

Anal. Calcd. for $C_{10}H_{10}O_6$: C, 53.10; H, 4.46. Found: C, 53.11; H 4.44

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