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Improved One-pot Synthesis of 4,6-Dihydroxyisophthalic Acid and 2,3-Dihydroxyterephthalic Acid

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Abstract: An improved method for the large-scale preparation of 4,6-dihydroxyisophthalic acid and 2,3-dihydroxyterephthalic acid has been developed. Compared to the previous procedures, this new process requires much lower CO_2 pressure of 0.3 Mpa and shorter reaction time, thus providing a convenient access for large-scale synthesis. The yield is high (93% and 65%, respectively), and the oxidation of phenol is nearly inhibited, neither decolorization nor further chromatographic purification is required.

Keywords: One-pot, large-scale, 4,6-dihydroxyisophthalic acid, 2,3-dihydroxyterephthalic acid.

Dihydroxybenzenedicarboxylic acids, such as 4,6-dihydroxyisophthalic acid **2**, 2, 3-dihydroxyterephthalic acid **4**, and 2,5-dihydroxyterephthalic acid and their esters, are very important synthetic intermediates[1]. 4,6-Dihydroxyisophthalic acid derivatives are key building blocks in the preparation of supramolecular self-assembly segments[2], while 2,3-dihydroxyterephthalic acid derivatives are important in the development of specific sequencing antidote agents for radionuclides like Pu(IV) and Ga(III), the removal of Fe(III) from human transferrin[3], and the design of organic light-emitting materials[4]. 2,5-Dihydroxyterephthalic acid is a very important intermediate for the manufacture of organic optoelectronic polymers with improved solubility, which are used to fabricate light-emitting diodes[5].

All of these dihydroxy benzenedicarboxylic acids are Kolbe-Schmitt resultants. Compound **2** have been synthesized according to the Kolbe-Schmitt reaction using sodium salts of resorcinol and pressurized CO_2[6], reaction of resorcinol with K_2CO_3 under CO_2 pressure[7], and carboxylation of resorcinol with dry $KHCO_3$ in a sealed Carius tube[8]. As for the synthesis of compound **4**, three different methods had been reported---hydrolysis of 3,4-dicyanocatechol in unreported yield[9], in three steps from 8-hydroxy-2,3-dimethylchromone with an overall yield of 11%[10], or by an improved Kolbe-Schmitt reaction employing disodium catecholate and pressurized CO_2 as reactants[6,11,12]. Thus it is difficult to prepare these compounds in a large-scale due to the poor yield as well as the difficult operation conditions. Herein, we report an improved, reliable, one-pot preparation based on the direct dicarboxylation of benzenediols with $KHCO_3$ and CO_2,

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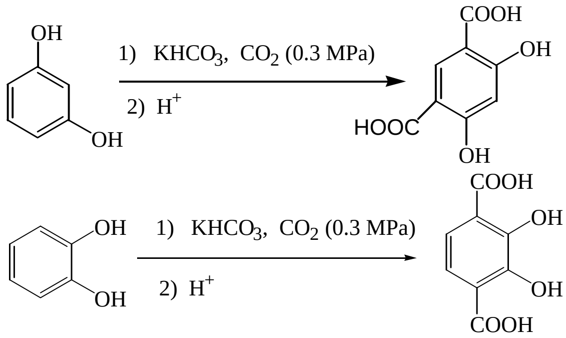
Scheme 1 Synthesis route of the target molecules



which has no harsh requirement for the dryness of benzenediols and $KHCO_3$, where potassium bicarbonate acts as carboxylation agent due to its low decomposition temperature.

Results and Discussion

The Kolbe-Schmitt reaction usually involves two steps. Because the reaction is sensitive to moisture[13], anhydrous sodium phenolates are prepared first by treatment of benzenediols with sodium hydroxide/alkoxide; this process requires prolonged times and often forms by-products, since phenolates are easily oxidized when they exposed to air moisture[13]. The second step is the carboxylation of phenolates with CO_2 under high pressure. High CO_2 pressure and long reaction time are needed, while only relative low yields can be obtained (for compound **2**, 200℃, 8.5-14 MPa, 4 hrs, yield 74 %[6]; for compound **4**, 200℃, 5.7 MPa, 90 hrs, yield 56 %[12], 225℃, 8.5-14 MPa, 8 hrs, yield 81%[6]), and thus makes it difficult to be used in a large scale preparation of dicarboxylic acids.

Carboxylation of resorcinol with anhydrous $KHCO_3$ in a sealed Carius tube at 210℃ is a well-adopted method for preparation of compound **2**[8]. To our knowledge, there is no report employing catechol and $KHCO_3$ for the synthesis of compound **4**. However, the possibility of explosion caused by the CO_2 produced inside the glass tube makes it rather difficult and dangerous to synthesize compound **2** on a large scale, and the yield is only about 45%[8b].

Our improved synthetic procedure by treatment of resorcinol with $KHCO_3$ under a low CO_2 pressure of 0.3 MPa afforded the desired pure product of **2** in 93% yield. The conversion is well-completed that no further purification was needed. When $NaHCO_3$ was utilized instead of $KHCO_3$, a low yield of 30% was obtained. With the similar procedure, a pale-grey solid of compound **4** was obtained due to the easier oxidation of catechol. The crude product required further recrystallization, thus leading to a lower yield (65%). This procedure could be employed to synthesize 2,5-dihydroxytere phthalic acid from hydroquinone, but the main product was the monocarboxylated product 2,5-dihydroxybenzoic acid. The reaction must be carried out in a harsher condition with higher CO_2 pressure and longer reaction time. It has been reported previously the dicarboxylation of hydroquinone is more difficult (225℃, 8.5-14 MPa, 8 hrs, yield 14%)[6].

Experimental

Mass spectra were recorded on a Finnigan-LCQ ESI-MS instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker Advance 600 instrument using tetramethylsilane as internal standard. Melting points were determined on a SEIKO EXSTAR thermoanalyzer. All the reagents were in AR grade and used without further purification.

4,6-Dihydroxyisophthalic acid **2**. Resorcinol (5.5 g, 0.05 mol) and 15.0 g (0.15 mol) of potassium bicarbonate were well mixed and grinded before added to a 500 mL autoclave. The reaction mixture was degassed with argon, and then carbon dioxide was introduced until the internal pressure reached to about 0.3 MPa. The mixture was then heated to 200℃ for 4 hours. After cooling to room temperature, 150 mL of water was added to dissolve the reaction mixture. The solution was acidified with concentrated HCl and the pH was adjusted to 2.0. The resulting slurry was filtered, and the cake was washed with 80℃ water several times to give 9.2 g (93%) of pure product as white powders. mp. 327-328℃(dec.), lit.[14] mp. 326℃(dec.).

2,3-Dihydroxyterephthalic acid **4**. The same procedure when catechol was used instead of resorcinol gave a pale-grey crude product which was recrystallized from ethanol-ether mixture to give 6.4 g (65%) pure white crystal. mp. 309-310℃.

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