

Short Note

## 4,5-Dimethylbenzene-1,2-dimethanol

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**Abstract:** An efficient and cost-effective synthesis of 4,5-dimethylbenzene-1,2-dimethanol is reported. The synthesis is accomplished in three steps with an overall yield of 80%.

**Keywords:** Diels-Alder reaction; dehydrogenation; reduction; reaction optimization

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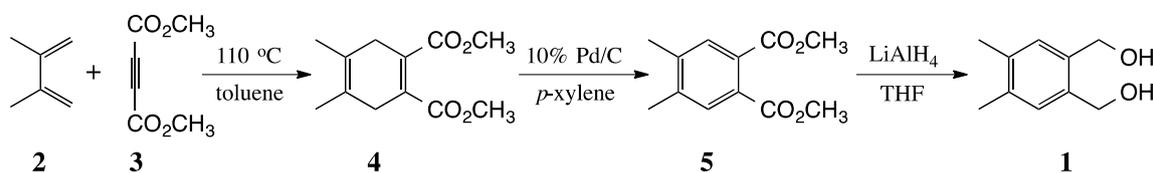
Aromatic rings are important scaffolds in organic synthesis. The rigid planarity of the ring system allows close positioning of reactive centers such that additional fused rings can be readily appended. We recently needed multi-gram quantities of the title compound as a building block to prepare 6,7-dimethylphthalazine for use in the synthesis of dihydrophthalazine-based antibiotics [1–6]. Though the compound is commercially available, it is quite expensive, and the supplier was unable to meet our requirements. Thus, we have designed and optimized a synthesis of this material that is both efficient and cost-effective.

A review of the literature indicates that 4,5-dimethylbenzene-1,2-dimethanol (**1**) has been previously prepared [7]. This early route is similar to the one disclosed here, but was only carried out on a one-gram scale and gave a lower yield. The current approach (Scheme 1) can be scaled up to readily produce the target compound in batches of 12–15 grams with an overall yield of 80%.

Our synthesis began with the Diels-Alder reaction of 2,3-dimethyl-1,3-butadiene (**2**) with dimethyl acetylenedicarboxylate (**3**). Heating this reaction in toluene for 2 h in a sealed pressure vessel afforded the 1,4-cyclohexadiene-based adduct **4** in 99% yield. Following removal of the solvent, the solid product was purified by triturating in hexanes and filtering. This cycloaddition has been previously

performed in benzene under reflux conditions for 12 h with a reported yield of 91% [8]. In our hands, this procedure did not proceed beyond 70% conversion, even in a sealed vessel at this temperature.

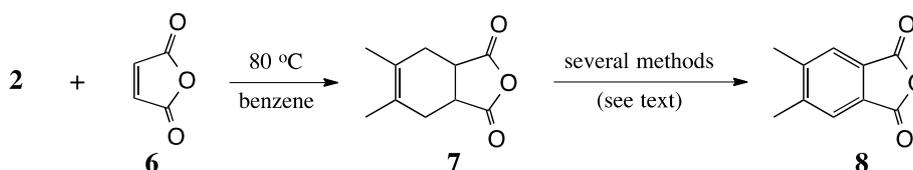
**Scheme 1.** Synthesis of 4,5-dimethylbenzene-1,2-dimethanol (**1**).



In step 2 of the sequence, we needed to aromatize adduct **4** to dimethyl 4,5-dimethylphthalate (**5**). There are many methods available to accomplish this transformation [9], but we found that dehydrogenation of **4** using 10% Pd-C (5 wt %) in refluxing *p*-xylene for 24 h gave **5** in 89% yield. Other methods involving bromine or sulfur (see below) were deemed too hazardous for the large-scale preparation of **5**, while the use of 2 eq of DDQ reported earlier [8] would increase the expense of our synthesis and necessitate chromatographic purification of the product. The solvent for the dehydrogenation proved to be important, with *p*-xylene being far superior to mixed xylenes or lower boiling aromatic solvents. It was not surprising that lower boiling solvents gave incomplete conversion, since this reaction normally demands high temperatures. However, the reaction also failed to go to completion in mixed xylenes, even after 48 h at reflux. We believe that the result in mixed xylenes stems from trace amounts of sulfur compounds present in this solvent, which would deactivate the Pd-C catalyst. Since *p*-xylene requires an additional purification to separate the *ortho* and *para* isomers, these sulfur-containing impurities are presumably removed or greatly reduced in this process. In *p*-xylene, the reaction proceeded to give high yields of the aromatized product without the need for an added hydrogen acceptor.

The final step of the synthesis involved the reduction of diester **5** to give diol **1**. This process was most easily accomplished using LiAlH<sub>4</sub> in tetrahydrofuran. This reduction proceeded smoothly in 4 h and delivered the target diol in 91% yield.

An alternative strategy to generate **1** via the phthalic anhydride derivative **8** was also investigated (Scheme 2). Since maleic anhydride (**6**) is less expensive and more reactive than **3**, we explored the use of this dienophile in the Diels-Alder reaction with **2**. Following the procedure of Kanamitsu and coworkers [10], cycloaddition of **6** with **2** in benzene at 25 °C for 12 h gave adduct **7** in 96% yield. These authors subsequently aromatized product **7** using Br<sub>2</sub> in refluxing acetic acid, but the yield of anhydride **8** was only 37%. Two other research groups employed sulfur in high-boiling solvents for this same transformation [11,12], but the production of H<sub>2</sub>S and yields <70% were strong deterrents to the use of this route. We, therefore, attempted to dehydrogenate this product using 10% Pd-C in *p*-xylene, but found that a much larger quantity of 10% Pd-C (30 wt %) with added dimethyl maleate as a hydrogen acceptor was required to aromatize the cyclohexene-based adduct **7** to the phthalic anhydride derivative **8**. Thus, to avoid the expense of using large amounts of catalyst, as well as the need for removing the hydrogen acceptor, we opted to pursue the synthesis using the slightly more expensive dienophile **3**.

**Scheme 2.** A possible alternative approach to 4,5-disubstituted phthalates.

The entire three-step synthesis proceeded in 80% overall yield, required no chromatography, and gave a product with spectral data and a melting point that matched those in the literature [7]. Analysis of our process indicated that the entire sequence to produce 13.6 g of **1** could be carried out in three days at a cost that is significantly less than that of the commercial material. The conversion of this diol to 6,7-dimethylphthalazine has been previously reported [13].

## Experimental

### 4,5-Dimethylbenzene-1,2-dimethanol (**1**)

In a 250-mL, heavy-walled, round-bottomed pressure vessel (CHEMGLASS CG-1880-R-03) equipped with a magnetic stirrer was placed 2,3-dimethyl-1,3-butadiene (**2**, 10.0 g, 121.7 mmol), dimethyl acetylenedicarboxylate (**3**, 17.3 g, 121.7 mmol) and toluene (70 mL). The container was sealed, placed in an oil bath, and heated at 110–120 °C for 2 h. The reaction was cooled and subjected to TLC analysis (9:1 hexanes/ether), which indicated complete consumption of starting materials. The crude reaction mixture was concentrated under vacuum at 50 °C to afford a viscous, yellow oil, which crystallized to a waxy, yellow solid. Purification by triturating this solid in hexanes and filtering under vacuum gave **4** (27.1 g, 99%), which was sufficiently pure for the next stage of the synthesis, mp 63–66 °C. An analytical sample of **3** was obtained by PTLC (9:1 hexanes/ether), which gave a white solid, mp 70–71 °C [14].

In a 1-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer and a condenser, were placed **4** (25.0 g, 111.5 mmol), 10% Pd-C (1.25 g, 5 wt %), and *p*-xylene (250 mL). The reaction mixture was heated at reflux for 24 h at which time TLC indicated complete conversion of the starting materials, see Table 1 [15]. The reaction was cooled to room temperature and filtered through a pad of Celite<sup>®</sup> under N<sub>2</sub> atmosphere. The Celite<sup>®</sup> was washed with CH<sub>2</sub>Cl<sub>2</sub> (3 × 25 mL), and the combined filtrate was concentrated under vacuum at 60 °C to give **5** as a viscous, yellow oil, which crystallized to a yellow solid (22.0 g, 89%) at room temperature, mp 56–57 °C (lit. [7] mp 54–55 °C) [16].

In a 1-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer, an addition funnel, and a condenser, were placed **5** (20 g, 90 mmol) and THF (300 mL). The yellow solution was cooled to 0–5 °C, and LiAlH<sub>4</sub> (7.5 g, 197.8 mmol) was added portion-wise with stirring over a period of 45 min. This suspension was stirred at 0–5 °C for 30 min, warmed to room temperature for 1 h, and then refluxed for 2 h. TLC analysis (4:1 hexanes/EtOAc) indicated complete conversion of the diester. The reaction was cooled to 0–5 °C and slowly quenched with of saturated aq. Na<sub>2</sub>SO<sub>4</sub> until a total of 33 mL had been added. The flask was warmed to room temperature, and the suspended salts gradually changed from gray to white. Ice water (20 mL) was then added, and the mixture was filtered through a pad of Celite<sup>®</sup>. The collected salts were washed with THF (95 mL). To the combined THF washes was

added solid NaHCO<sub>3</sub> until layer separation was observed. The layers were separated, and the organic phase was washed with 30% aq. NaCl (2 × 100 mL), dried (MgSO<sub>4</sub>), and concentrated under vacuum at 45 °C to give **1** as a white solid (12.7 g). Further saturation of the aqueous layer with NaCl and extraction with THF gave additional white solid (total yield 13.6 g, 91%), mp 95–96 °C (lit. [7] mp 95–98 °C). IR: 3245 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.12 (s, 2H), 4.68 (s, 4H), 2.83 (s, 2H), 2.26 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 136.80, 136.76, 131.31, 63.97, 19.32.

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### Author Contributions

The authors discussed and equally contributed to the design of the synthesis. K.K.G. performed the research and analyzed the data. R.A.B. confirmed the data analysis and wrote the paper. All authors read and approved the final manuscript.

### Conflicts of Interest

The authors declare no conflicts of interest.

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14. IR: 1725  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.78 (s, 6H), 2.92 (s, 4H), 1.66 (s, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.42, 132.76, 121.53, 52.16, 34.13, 17.96.
15. The optimization results for the dehydrogenation of **4** to **5** on a 1-g scale are summarized in the table below. Since the **4** and **5** are chromatographically difficult to separate, it is necessary to get complete conversion to **5**. This occurs most efficiently and economically using 5 wt % of 10% Pd-C in refluxing *p*-xylene for 24 h.

**Table 1.** Optimization for the dehydrogenation of **4** to **5**.

wt % of 10% Pd-C	Time (h)	Yield of <b>5</b> (%)
20	6	92
15	10	91
10	16	90
5	24	89
2.5	48	72 <sup>a</sup>

<sup>a</sup> Some starting material **4** remained after 48 h.

16. IR: 1729  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.49 (s, 2H), 3.88 (s, 6H), 2.31 (s, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  168.24, 140.22, 130.02, 129.39, 52.43, 19.62.