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A Practical Synthesis of 3,4-Dimethoxy-*o*-toluic Acid

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Abstract:

A streamlined, telescoped process has been developed for the preparation of 3,4-dimethoxy-*o*-toluic acid, starting with economical and readily available 2,3-dimethoxybenzaldehyde. Catalytic reduction of the aldehyde functional group generated dimethoxytoluene, which was brominated in situ. The resultant aryl bromide was isolated, converted into a Grignard reagent, and transformed into a carboxylic acid with dry ice. The process was demonstrated on a pilot-plant scale.

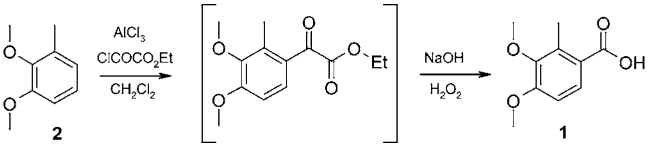
Introduction

2,3-Dimethoxy-*o*-toluic acid (**1**) was required as starting material for a program under development by Roche Palo Alto. Because commercial sources of **1** were not available, an economical and scalable route was required to advance the program in a timely manner. Our goal was to develop a process capable of supplying the short-term needs of the program using our Pilot Plant facilities, and to outsource the process for further scale-up as the program required larger amounts of material.

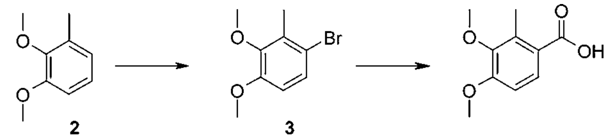
Results and Discussion

Several methods of preparing **1** have been reported in the literature.[1−3] We chose to evaluate the method of Kaufman[3] (Scheme 1). This route involved a Friedel−Crafts acylation of dimethoxytoluene, followed by Baeyer−Villiger oxidation and hydrolysis. A slightly modified version of the published procedure was used to generate 6 kg of acid **1** from 5 kg of 2,3-dimethoxytoluene (**2**). Although this represented a yield of 93%, it was not suitable for batch sizes larger than ca. 5 kg.

Scheme 1



Scheme 2



A study of the Friedel−Crafts reaction revealed that this stage of the process would not be robust to further scale-up. Parameter-ranging experiments showed the process performed best when kept cold (<5 °C) using charges of 3.2 equiv of aluminum trichloride and 1.3 equiv of ethyl oxalyl chloride. Unfortunately, the high charge of aluminum trichloride caused demethylation of the product, which led to both mono- and di-demethyl products being formed. Reducing the charge of Lewis acid resulted in longer reaction times, which also led to demethylation of the product. Increased reaction temperatures did shorten the reaction time, but demethylation was a significant side reaction again. Other Lewis acids such as boron trifluoride etherate, zinc chloride, ytterbium (III) triflate, and various alkyl aluminum chloride reagents failed to generate the desired product. On the basis of these observations and the longer addition and reaction times expected on further scale-up, an alternative route was explored (Scheme 2).

Dimethoxytoluene was known to react with bromine[4] or *N*-bromosuccinimide (NBS)[5,6] to generate the desired aryl bromide **3**. We chose to investigate the use of dibromodimethylhydantoin (DBDMH)[7,8] as a brominating reagent and were pleased to discover that both of the bromines on DBDMH were reactive towards our substrate. Initial reactions were conducted in methylene chloride at ambient temperature and afforded two monobrominated products as a mixture of regioisomers. Fortunately, the desired arylbromide isomer **3** was favored over one of the possible undesired regioisomers in a ratio of 24:1. Following an aqueous workup, bromide **3** was isolated from a mixture of methanol and water.

The process envisioned for scale-up was to charge solid DBDMH to a reactor, add solvent, and then charge **2** as a neat liquid. Abuse studies were conducted with excess DMDMH, which would mimic the early stage of the addition profile. These studies indicated that product **3** was quite slow to react with DBDMH. The dibrominated product was not expected to be formed when the process was scaled, even with extended addition times.

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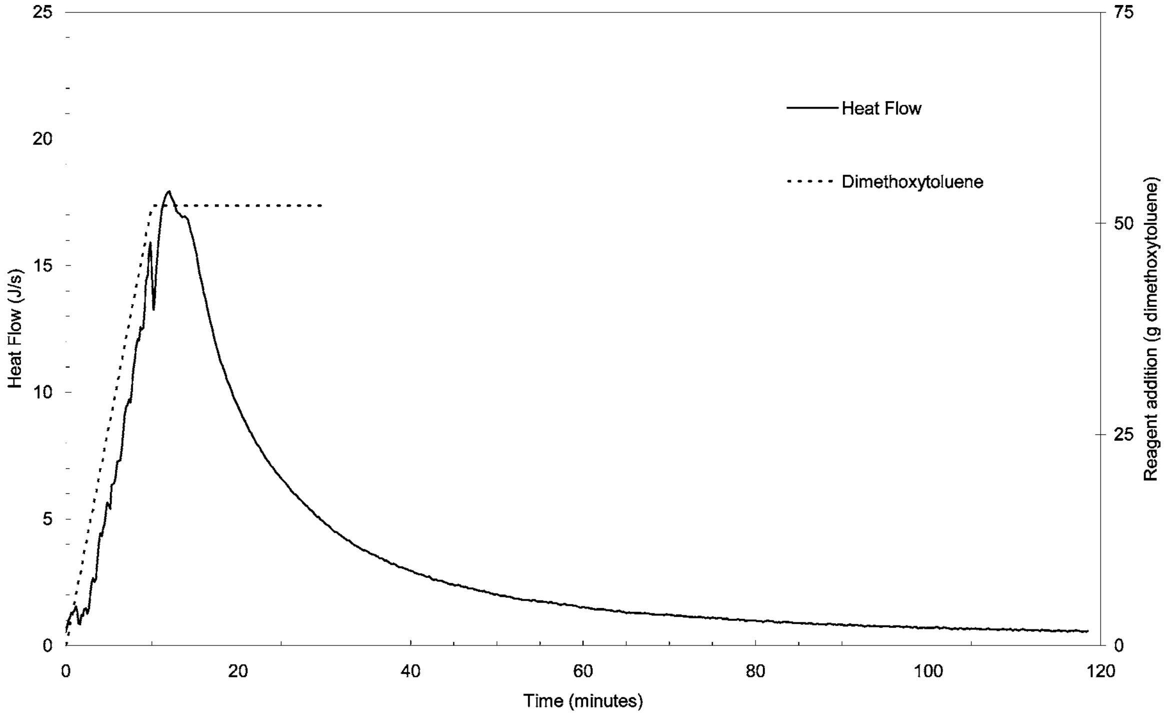


Figure 1. **RC1 heat flow for bromination of dimethoxytoluene in methylene chloride.**

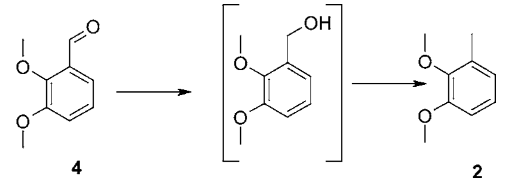
Prior to scale-up, the only item to be addressed was the rather unusual temperature profile which was observed in the laboratory during the bromination. A small endotherm, followed by a delayed exotherm was observed when dimethoxytoluene was charged to a slurry of DBDMH in methylene chloride. The temperature then cycled between increases and decreases in reaction temperature before it drifted back to ambient temperature. The reaction between DBDMH and dimethoxytoluene was investigated using a reaction calorimeter to obtain a better understanding of the thermal events.

Dimethoxytoluene (52 g) was added over 10 min to a mixture of DBDMH (50 g, 0.51 equiv) and methylene chloride while the reactor temperature was maintained at 22 °C. Analysis of the data (Figure 1) showed that the heat output increased linearly with continued dosing, but the reaction was not instantaneous. In fact, approximately 75% of the energy of the reaction was released after dosing stopped. Using the heat flow of the process as a gauge for the extent of reaction, these data showed the reaction required approximately 90 min to reach completion. Although accumulation of reagent did occur, the overall exotherm was quite mild at 54 kJ/mol. The adiabatic temperature rise for the process was 10.3 °C. The bromination of dimethoxytoluene was then conducted in our pilot plant at a 10-kg scale and afforded bromide **3** in a yield of 79% with excellent purity.

As future batches were planned, supply of dimethoxytoluene became an issue. Although several vendors offered this material, the cost and considerable lead time were not acceptable.

In searching for economical and readily available starting materials, 2,3-dimethoxybenzaldehyde (**4**) was an attractive choice. Reports in the literature showed that dimethoxybenzaldehyde could be converted to dimethoxytoluene via catalytic hydrogenation and hydrogenolysis (Scheme 3).[9,10]

Scheme 3



Our experiments indicated that the reaction proceeded well when conducted in ethyl acetate at slightly elevated pressures (5−10 psi above ambient pressure). The throughput of the reaction was also acceptable, requiring only 5 volumes of solvent relative to the charge of starting material.

When the reaction was run with 2.5% (weight/weight basis, relative to substrate) of 50% water-wet palladium on carbon (10% palladium by weight), in-process analysis of the reaction clearly showed the growth and subsequent decay of the benzylic alcohol intermediate (Figure 2). Although the reaction could be pushed to completion under these conditions, it required over 48 h. To use our pilot-plant facilities more efficiently, we chose to increase the catalyst charge from 2.5 to 5 wt %. After being under a hydrogen atmosphere for 3 h, starting aldehyde was not detected, and only 4% benzylic alcohol remained. The reaction mixture was left under a hydrogen atmosphere overnight, after which time in-process monitoring showed there to be 0.4% alcohol remaining.

On a 5-kg scale, an essentially quantitative amount of dimethoxytoluene was produced. Isolation of the product was accomplished by passing the reaction mixture through a filter

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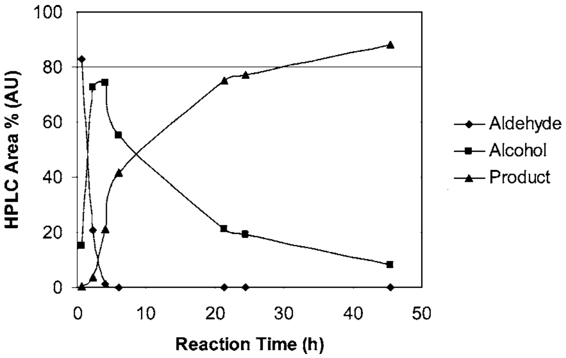

Figure 2. **Reaction profile for reduction of 2,3-dimethoxybenzaldehyde to 2,3-dimethoxytoluene.**

aid such as diatomaceous earth or cellulose (Solka-Floc) and removing the solvent at ambient pressure.

The next stage in developing the process was to couple the reduction stage together with the bromination step. By telescoping the reduction and bromination together, the solvent requirement and unit operations would be reduced, resulting in significant cost savings and better throughput. This was easily accomplished, and as an added benefit, the bromination was even more selective in ethyl acetate, affording the desired regioisomer in a selectivity of 73:1. In the pilot plant, 10 kg of dimethoxybenzaldehyde was reduced to dimethoxytoluene as described above. The catalyst was removed via an in-line cartridge filter and the filtrate added directly to a reactor which contained DBDMH in ethyl acetate. When the bromination was complete, the reaction mixture was quenched with an aqueous sodium sulfite solution. Dropping the lower aqueous layer out of the reactor and switching the solvent to a methanol−water mixture afforded the desired aryl bromide **3** in a yield of 96% from dimethoxybenzaldehyde. The purity of the isolated product was greater than 99% when measured using HPLC.

The aryl bromide also had desirable solid-state properties. Batch sizes of 12−14 kg were easily filtered using a 13-gal Nutsche filter within 5 min. Drying of the product was accomplished by simply passing a stream of filtered nitrogen through the cake overnight.[11]

With a route to the required aryl bromide secured, attention was shifted to formation of the Grignard reagent and to the quench with dry ice. Several excellent reports are available regarding the safe generation and scale-up of Grignard reagents.[12,13] On the basis of these reports, a process that involved controlled addition of the aryl bromide to a slurry of magnesium metal in tetrahydrofuran was developed. Initial laboratory experiments were quite promising, with the Grignard reaction being initiated smoothly at ambient temperature. However, when aryl bromide more representative of the pilot-plant batches was used, significant induction times were observed. Addition of catalytic amounts of methylmagnesium chloride (in tetrahydrofuran) to the mixture of magnesium and aryl bromide led to more consistent initiation. The exotherm of the reaction was then easily controlled by adjusting the addition rate of the remaining aryl bromide solution.

The Grignard reagent derived from **3** was found to be quite stable. Stress tests in the lab demonstrated that it could be stored under a nitrogen atmosphere overnight with only minimal decomposition. This was an important consideration since the process planned for our pilot plant would require that the Grignard reagent be stored for that period of time.

Control of the Grignard-generating stage of the process was accompanied with a shift in focus to the carboxylation stage. Early experiments used heptane as the solvent to slurry the dry ice. Under these conditions, the yield of carboxylic acid was not acceptable. Examination of the mass balance of the reaction mixture indicated that as much as 15% of the Grignard reagent was converted back to starting dimethoxytoluene. Analysis of the reaction mixture for water content and an investigation into the stability of the Grignard reagent eventually revealed that the loss in yield occurred during the aqueous workup. Addition of the Grignard reagent mixture to heptane resulted in precipitation of the Grignard reagent. This observation led to the conclusion that the Grignard reagent precipitated during the quench into the dry ice/heptane mixture. The precipitated Grignard reagent was then not able to react with the carbon dioxide and remained as an insoluble mass until water was added, when it dissolved and was quenched by water.

Further refinement of the reaction conditions revealed that preparing the dry ice slurry in tetrahydrofuran resulted in less dimethoxytoluene. Subsequent experiments showed that the product carboxylic acid would precipitate from the reaction mixture upon addition of 3 N HCl. Dimethoxytoluene was not entrained by the product and remained entirely in the filtrate.

The process was scaled up to the 5-kg scale, and afforded the desired product in 72% yield. The filtration was rather slow, and fines passed though the cake and filter screen. Experiments in the lab showed that the recovery of product could be increased if the tetrahydrofuran was partially removed prior to acidifying the reaction mixture. Dilute sulfuric acid was substituted for hydrochloric acid to allow stainless steel filters to be used if necessary.

These changes were incorporated into the process, and the chemistry was demonstrated on a 20-kg scale. Once again, formation of the Grignard reagent was smooth when methylmagnesium chloride was used catalytically. The generated Grignard reagent was then quenched into a mixture of tetrahydrofuran and dry ice. The dry ice slurry resulted in an internal reactor temperature of −60 °C,[14] which allowed the reaction mixture to be quenched relatively quickly. Under these conditions, the reaction temperature rose to ca. 0 °C. Attempts to cool the Grignard reagent solution prior to the quench resulted in precipitation of the Grignard reagent. One interesting observation was the need to precool the reactor used to prepare the dry ice slurry prior to charging dry ice. The large surface area of the reactor and ambient temperature

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(11) Aryl bromide **3** melts at 55 °C; therefore, drying the product on the filter was a desirable option.

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(14) A reactor rated for low temperature was used to prepare the dry ice and THF mixture.

caused a significant amount of dry ice to evaporate prior to adding solvent. Since an in-process test was not used to determine the amount of carbon dioxide in the reactor, cooling the reactor before the solid carbon dioxide was added minimized sublimation.

Once the transfer of Grignard reagent was complete, the reaction mixture was warmed to 25 °C, and water was added. By distilling out approximately 60% of the THF prior to adding sulfuric acid, the yield of product increased from 76 to 86% without any detrimental impact on purity.

Conclusions

An economical synthesis of 3,4-dimethoxy-*o*-toluic acid was developed and demonstrated on a pilot-plant scale. The methodology developed could be extended to the preparation of other benzoic acid derivatives.

Experimental Section

3,4-Dimethoxy-2-methyl-1-bromobenzene (3). A mixture of 2,3-Dimethoxybenzaldehyde (10 kg, 60.2 mol), palladium on carbon (10 wt %) (500 g), and ethyl acetate (45 kg) was stirred in a 200-L reactor under 5 psi hydrogen at 20 °C for 15 h. The mixture was filtered through a bag filter and a cotton cartridge filter precoated with 600 and 100 g of Solka-Floc, respectively. The reactor and filters were rinsed forward with ethyl acetate (14 kg). The filtrate was slowly charged into a stirred suspension of 2,3-dibromo-5,5-dimethyhydantoin (9.67 kg, 33.8 mol) in ethyl acetate (18 kg) while the temperature was maintained below 15 °C. The mixture was allowed to react at 15 °C for 12 h. Sodium sulfite (3.79 kg) in water (50 kg) was added slowly, the mixture was stirred for 10 min and then settled, and the phases were separated. The organic layer was concentrated at 70 °C/30 mmHg. Methanol (24 kg) and water (7 kg) were added at 60 °C, and the mixture was cooled to approximately 45 °C where crystallization occurred. The mixture was cooled to 5 °C over 20 h; the crystalline product was collected by filtration, washed three times with a methanol−water mixture (6/10, w/w), and then blown dry with filtered nitrogen over the weekend to give 13.41 kg (96.4%, 99.9% AN HPLC purity) of **3** as a white crystalline solid, mp 60.1−61.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, 1 H, $J = 9$ Hz), 6.65 (d, 1 H, $J = 9$ Hz); 3.83 (s, 3 H), 3.78 (s, 3 H), 2.34 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152, 148, 132, 127, 116, 111, 60, 56, 6.

3,4-Dimethoxy-2-methylbenzoic acid (1). A mixture of magnesium turnings (2.2 kg, 90.5 mol) and tetrahydrofuran (17.7 kg)was stirred at 25 °C in a 200-L reactor. The mixture was treated with approximately 5% (2.78 kg) of a prepared solution of 6-bromo-2,3-dimethoxy toluene (**3**) (20 kg, 86.5 mol) in tetrahydrofuran (35 kg). The reaction was initiated by addition of methylmagnesiumchloride (3 M solution in THF) (0.8 kg, 2.34 mol). After the initial exotherm subsided, the remaining solution of **3** in THF was added slowly over approximately 4 h such that the internal temperature did not exceed 45 °C. The resulting solution was kept overnight at 25 °C under a low flow of nitrogen. The mixture was then added to a mixture of dry ice (38.2 kg, 868 mol) and THF (75 kg) which had been prepared in a 400-L reactor and chilled to −60 °C. The Grignard reagent was added over approximately 50 min while the temperature was maintained below −10 °C. When the addition was complete, the mixture was warmed to 20−25 °C, and water (140 kg) was added over approximately 15 min. The resulting solution was subjected to distillation under reduced pressure (60 mbar) until ca. 60% of THF solution (∼83 kg) was distilled out. Vacuum was released, and the reactor contents were adjusted to 25 °C, acidified with 4.5 M H_2SO_4 (14.6 kg), and stirred at 30 °C for 1 h. The mixture was then cooled to 5 °C and stirred for 1 h, and the product was collected by filtration, washed twice with water (2 × 30 kg), and dried at 65 °C under vacuum to give **6** as a white solid, mp 184 °C (14.76 kg, 86.2%, 98% AN HPLC purity). ^{1}H NMR (300 MHz, DMSO) δ 7.62 (d, 1H, $J = 8.7$ Hz), 6.93 (d, 1H, $J = 8.7$ Hz), 3.84 (s, 3H), 3.67 (s, 3H), 2.41 (s, 3H).

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