

MFB를 이용한 PABA One-Pot 합성법

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Facile One-Pot Synthesis of PABA from MFB

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본 연구의 내용은 Dimethyl terephthalate의 생성 과정 중 필연적으로 생성되는 부산물인 Methyl 4-formylbenzoate를 이용해 one-pot reaction을 통한 *p*-Aminobenzoic acid를 얻는 방법이다. 이 방법은 Methyl 4-formylbenzoate에 chlorine gas와 methylene chloride를 이용해 acid chloride를 형성하고 ammonia gas를 통해 amide를 중간체로 가진다. 생성된 amide는 Hofmann degradation을 통해 *p*-Aminobenzoic acid로 전환된다. 이 방법은 폐기물인 Methyl 4-formylbenzoate를 재활용하여 기존의 *p*-Aminobenzoic acid를 수율 90%로 합성하였으며 이는 기존의 *p*-Aminobenzoic acid 생산과정을 대체할 수 있을 것으로 예상된다.

A facile one-pot synthesis of *p*-aminobenzoic acid from methyl 4-formylbenzoate which is a main by product in dimethyl terephthalate production process has been developed. This process involves the formation of amide intermediate obtained from the reaction of an aldehyde in methyl 4-formylbenzoate with chlorine in methylene chloride and the subsequent treatment of acid chloride with ammonia. The resulting amide was converted into amine using Hofmann degradation to afford a *p*-aminobenzoic acid. This facile one-pot process does not involve any expensive materials and should offer an attractive alternative to *p*-aminobenzoic acid production.

Keywords: Methyl 4-formylbenzoate, *p*-Aminobenzoic acid, Hofmann degradation, Industrial waste, Second pollution

1. Introduction

Significant amount of waste materials in petrochemical industry have been disposed by open burning/detonation[1]. Use of open burning/detonation is becoming unacceptable due to public concern and environmental regulations. Therefore, the chemical conversion study of waste materials to higher value products would be highly desirable.

Recently, we developed new purification protocol of crude Methyl 4-formylbenzoate(1) (MFB) without second pollution[2]. MFB (1) is a main by product in Dimethyl terephthalate (DMT) production process in which *p*-xylene was oxidized with oxygen followed by esterification (Figure 1). MFB (1) have been used as a versatile starting material for the design to different types of valuable products (Figure 2)[3,4].

Herein we describe a one-pot synthesis of *p*-Aminobenzoic acid(2)

(PABA) from MFB (1). Discovered in 1940s, PABA (2) was widely used in sunscreens as a UV filter[5]. It is a UVB absorber, meaning that it can absorb wavelengths between 290-320 nm. The commercial conversion methods for PABA (2) which is used in the pharmaceutical, cosmetics, textile dying and polymer industries were developed from toluene (Figure 3)[6]. However, this conventional synthesis had difficulties because of mainly environmental problems associated with waste disposal.

2. Experimental

2.1. Materials and Measurements

The reagents used for this study was purchased from Aldrich Chem. Co. All proton nuclear magnetic resonance (NMR) spectra were recorded on a Varian Unity Inova spectrometer at 300 MHz and are reported in parts per million (ppm) on the δ scale relative to chloroform- d_1 (δ 7.24) or tetramethylsilane (δ 0.00). IR spectra were recorded on a Varian FT-IR spectrometer using KBr optics. Analytical thin layer chromatography (TLC) was performed with E. Merck pre-coated TLC plates, silica gel 60F-254, layer thickness 0.25 mm.

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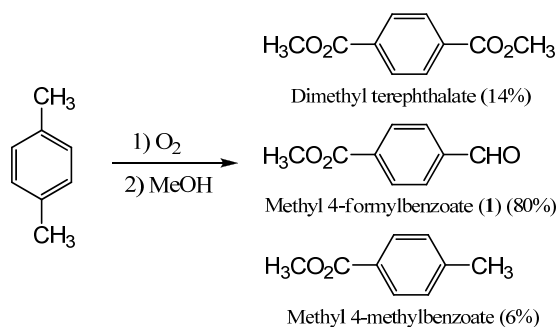


Figure 1. The residues after DMT separation from p-xylene.

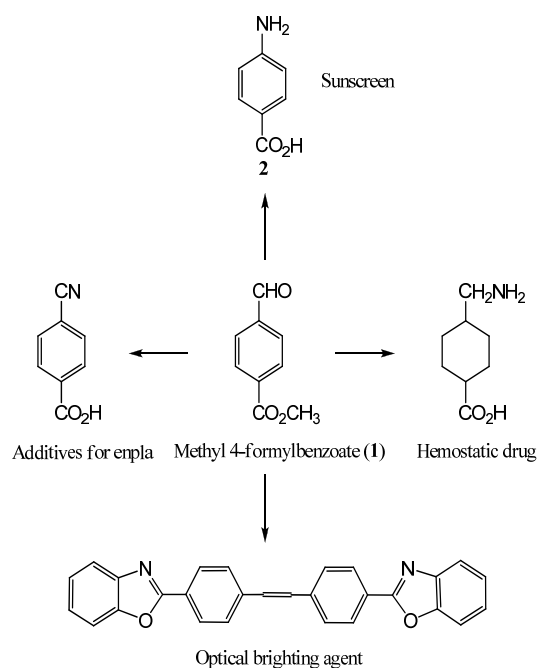


Figure 2. Various fine chemicals from MFB (1).

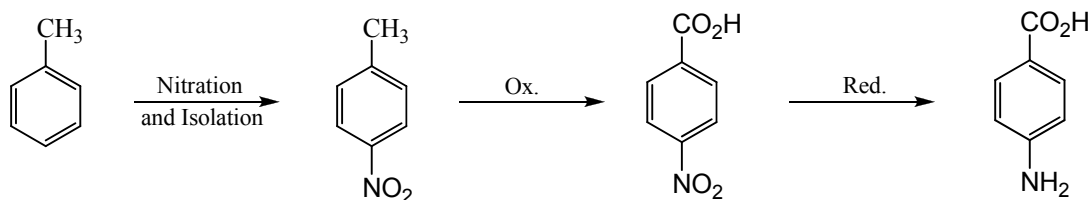


Figure 3. Synthesis of PABA (2) (Old process).

Column chromatography was done with silica gel 60 (70-230 mesh ASTM) from E. Merck mostly by gravity. Initiator 400 W microwave oven was used to perform the reaction.

2.2. Synthesis

PABA (2) : To a solution of **1** (100g, 0.610 mol) in methylene chloride (500 mL) was slowly introduced chlorine gas at room temperature under atmospheric pressure through gauge with 100 cc/min rate. After 4 hours, the resulting mixture was diluted with additional methylene chloride (200 mL) and cooled down to 0 °C. Then ammonia gas was slowly added with 100 cc/min rate. In the beginning, reaction temperature elevated to 50.0 °C and down to room temperature. After 4 hours addition, vigorous stirring was continued for 1 hour. After checking TLC, the reaction mixture was concentrated under reduced pressure. Aqueous NaOH solution (500 mL, 1.68 mol) was added at 0 °C. A solution of Ca(OCl)₂ (79.8 g, 0.363 mol) and NaOH (45 g, 1.13 mol) in H₂O (200 mL) was added to reaction mixture below 5 °C for 2 hours. This resulting mixture was heated to 60 °C for 1 hour. After cooling to RT, all impurities were removed by filtration. **2** was isolated from filtrate by adding aqueous HCl and adjusted pH 4.0. Filtration and dry gave pure 75.2 g (90%) of PABA (**2**) as a white solid : m.p.187-189 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 7.59 (d, J = 8.5 Hz, 2H), 6.51 (d, J = 8.8 Hz, 2H), 5.87 (s, 2H); ¹³C NMR (75 MHz, DMSO-d₆) δ 166.4, 153.0, 131.5, 118.2, 112.4. IR (KBr) : ν = 3463, 3364 cm⁻¹ (NH₂), 3200 - 2300 cm⁻¹ (O-H), 1670 cm⁻¹ (C=O).

3. Results and discussion

In our method, PABA (**2**) was prepared from MFB (**1**) by Hofmann degradation method[7,8]. Therefore MFB (**1**) was treated with chlorine gas under atmospheric pressure to obtain acid chloride **3** by known oxidation-chlorination sequence[9]. Chlorine was added to a methylene chloride solution of MFB (**1**) at room temperature under atmospheric pressure for 4 hours in which resulting acid further reacted with chlorine to give acid chloride **3**. The progress of this reaction was easily monitored by the TLC. In order to optimize the yield, oxidation and chlorination of MFB (**1**) with chlorine were tested in a variety of solvents. Among the employed solvents, methylene chloride resulted in best yield. It is noted that very strong polar solvents such as DMSO, DMF and acetonitrile gave relative poor yields (Figure 4).

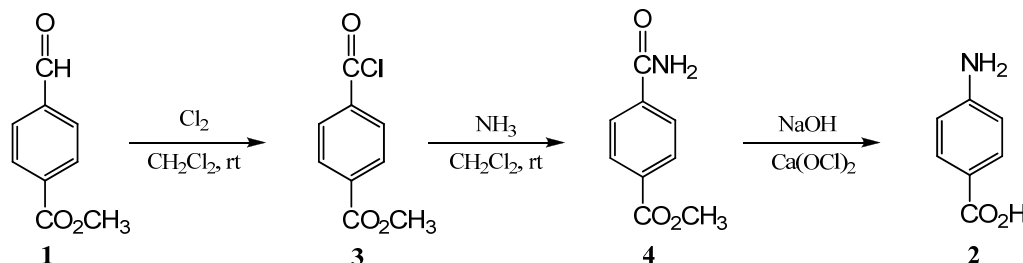


Figure 4. Synthetic scheme of PABA (2) (New process).

With these interesting results, we have moved on to address issues associated with whole synthesis done in one-pot reaction. Therefore NH_3 gas was slowly bubbled to reaction mixture under atmospheric pressure to obtain amide **4**. Although in the beginning reaction temperature elevated up to 50°C for 2 hours owing to neutralization between HCl and NH_3 , amide **4** was finally obtained within 2 hour without any side products. After evaporation of reaction solvent methylene chloride under reduced pressure, this crude amide **4** was treated with aqueous NaOH and $\text{Ca}(\text{OCl})_2$ and heated to reflux for 1 hour to furnish target PABA (**2**). After filtration of impurity solids, isolation of PABA (**2**) was accomplished by adding HCl to aqueous solution and adjusting pH around 4.0. The ^1H and ^{13}C NMR spectra of the isolated PABA (**2**) were identical to literature spectra[10].

In conclusion, we have demonstrated that MFB (**1**) can be readily converted into PABA (**2**) in three steps, a yield of 90% by oxidation of aldehyde in methylene chloride and chlorination of resulting acid, followed by Hofmann degradation of the subsequent amide with basic $\text{Ca}(\text{OCl})_2$. This facile one-pot process does not involve any expensive materials and should offer an attractive alternative to PABA (**2**) production. The future works including commercial conversion of MFB (**1**) into PABA (**2**) are under investigation in our laboratory.

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