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Short Note

3-Hydroxy-2-Iodophenyl-(4-Methylbenzenesulfonate)

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Abstract: 3-hydroxy-2-iodophenyl-(4-methylbenzenesulfonate) was synthesized via a three-step procedure, starting from commercially available resorcinol, with an overall yield of 65%. The structures of the products were determined by ^{1}H and ^{13}C NMR, HRMS and IR.

Keywords: bis(4-methylbenzenesulfonate); selective monohydrolysis; 3-hydroxy-2-iodophenyl-(4-methylbenzenesulfonate)

1. Introduction

Halogenated hydroxyphenyl sulfonate has been considered as an important building block for the construction of functionalized molecules. Based on the difference in cleavage reactivity between C-X and C-S, the halogenated phenyl sulfonate can result in highly selective reactions in transition metal-catalyzed processes [1–4]. Arenes with adjacent halogen and sulfonyloxy groups act as precursor of aryne species in alkalic systems [4,5]. The free phenolic hydroxyl enables various approaches to further conversion [6–8].

In this study, we synthesized 3-hydroxy-2-iodophenyl-4-methylbenzenesulfonate, as a potential precursor for various areas.

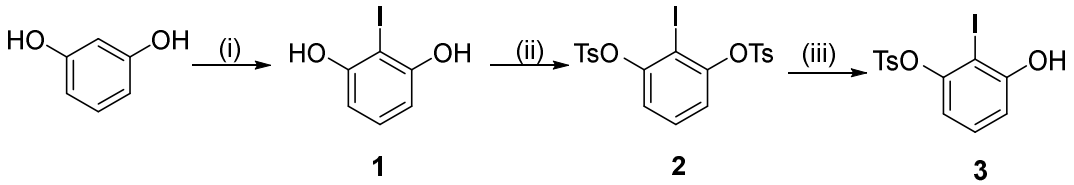
2. Results and Discussion

The target compound was synthesized in three steps using commercially available resorcinol as the starting material. Iodination at position 2 of resorcinol was carried out to produce 2-iodoresorcinol **1** using iodine in water [9]. Sodium bicarbonate ($NaHCO_3$) was used to remove hydroiodic acid produced. The direct monotosylation of compound **1** to **3** failed. Based on the symmetrical structure and the reasonable acidity of the hydrogen of the two hydroxyls in compound **1**, there was no selectivity in monotosylation when using only one equivalent of *p*-toluenesulfonyl chloride, and a mixture of di-, mono- and non-sulfonated compounds was obtained in this case.

On the contrary, the selective hydrolysis of iodophenyl bissulfonate **2** is an effective method for obtaining the target compound **3**. By treatment with cesium carbonate in 1,2-dimethoxyethaneas solvent, 2-iodoresorcinol bis(trifluoromethanesulfonate) was desulfonylated on one side only [10,11]. Clark, Jr. et al. achieved the preparation of 3-hydroxy-5-iodophenyl-(4-methylbenzenesulfonate) via the selective hydrolysis of the symmetric substrate [12]. To our best knowledge, the monodesulfonylation of compound **2** is still unreported to date. In this research, compound **1** was sulfonylated with two equivalents of *p*-toluenesulfonyl chloride in the presence of potassium

carbonate to generate phenyl bissulfonate **2** stoichiometrically. Compound **3** was obtained with an 87% yield by selective hydrolysis with potassium hydroxide in methanol at gradient temperature. It is noteworthy that general workup without further chromatographic purification for the reaction residue could provide satisfactory purity for **3**. The synthetic procedure is shown in Scheme 1.

Therefore, 3-hydroxy-2-iodophenyl-(4-methylbenzenesulfonate) was synthesized in three steps, with an overall yield of 65% the first time.



Scheme 1. Synthesis of 3-hydroxy-2-iodophenyl-(4-methylbenzenesulfonate). (**i**) I_2, $NaHCO_3$ and H_2O, 0 °C to r. t.; (**ii**) *p*-TsCl, K_2CO_3 and acetonitrile, r. t.; (**iii**) KOH and MeOH, 35–45 °C.

3. Materials and Methods

Unless otherwise noted, all the starting materials were commercially available and were used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker DMX400 (400 MHz) or Bruker DMX300 (300 MHz) in $CDCl_3$ solutions and with tetramethylsilane as an internal standard. High-resolution electrospray ionization mass spectra were recorded on a Shimadzu HRMS-EI-TOF. Infrared spectra were obtained on a Nicolet iS5. All the spectra of the products can be found in the Supplementary Materials.

*3.1. 2-Iodoresorcinol (**1**)*

Iodine (27.69 g, 109 mmol) was dispersed in an aqueous solution (80 mL) of resorcinol (11.00 g, 100 mol) in a round-bottom flask open to the atmosphere. The flask was placed in an ice-water bath, and sodium bicarbonate (9.24 g, 110 mmol) was added in portions with a spatula over 10 min at 0 °C. Vigorous gas emission from and jellying of the mixture were observed during the addition. It was of crucial importance to ensure effective stirring. If necessary, increasing the amount of water was helpful. The ice bath was removed, and the mixture was warmed to room temperature, followed by an additional 10 min of stirring at ambient temperature. The slurry was extracted three times with ethyl acetate. The combined organic layer was successively washed with 10% aqueous sodium thiosulfate solution and brine, dried over anhydrous sodium sulfate, filtered, and concentrated with a rotary evaporator. The dark brown residue was triturated in cold chloroform (–10 °C, 30 mL) for 10 min, filtered, and washed with chloroform at the same temperature to provide 2-iodoresorcinol (**1**) as a cream-colored solid (17.70 g, 75%). M.p. = 99–101 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.11 (t, *J* = 8.1 Hz, 1H), 6.54 (d, *J* = 8.1 Hz, 2H), 5.43 (s, 2H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.7 (2C), 130.3, 107.3 (2C), 77.5. The NMR was consistent with the data previously reported [9].

*3.2. 2-Iodo-1,3-Phenylene Bis(4-Methylbenzenesulfonate) (**2**)*

A mixture of 2-iodoresorcinol **1** (4.72 g, 20 mmol), *p*-toluenesulfonyl chloride (9.15 g, 48 mmol) and potassium carbonate (11.04 g, 80 mmol) in acetonitrile (100 mL) was stirred at room temperature. While 2-iodoresorcinol **1** was invisible upon TLC, the inorganic precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted with dichloromethane. The combined organic solution was washed successively with water and saturated brine, dried over anhydrous magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel with petroleum–ethyl acetate (4:1) as an eluent to produce **2** as a white solid (10.8 g, >99%). M.p. 161–162 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 4H), 7.36–7.30 (m, 5H), 7.26–7.23 (m, 2H), 2.46 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4 (2C), 146.0 (2C), 132. 6

(2C), 129.9 (4C), 129.8, 128.8 (4C), 121.1 (2C), 89.0, 21.8 (2C); HRMS $C_{20}H_{17}IO_6S_2$ (543.9511) found 543.9515; IR (cm^{-1}): 1595, 1445, 1356, 1175.

*3.3. 3-Hydroxy-2-Iodophenyl-(4-Methylbenzenesulfonate) (**3**)*

To a suspension of 2-iodo-1,3-phenylene bis(4-methylbenzenesulfonate) **2** (21.77 g, 40 mmol) in methanol (100 mL) was added, dropwise, a solution of potassium hydroxide (4.66 g, 83.2 mmol) in water (2.3 mL) and methanol (210 mL) at 35 °C in a 1 L Erlenmeyer flask. After the addition, the mixture was continuously stirred for about 3 h until compound **2** faded away upon TLC. The above mixture was heated to 45 °C for an additional 20 min, cooled to room temperature and diluted to 800 mL with distilled water. After filtration, the liquid layer was neutralized with hydrochloric acid (5%) and stored at 4 °C for 48 h. The precipitate was filtered, dissolved in diethyl ether and extracted in aqueous sodium hydroxide (10%). A yellow oil formed under the aqueous layer, which was separated, washed with diethyl ether and neutralized with hydrochloric acid (5%). A large amount of white suspension was observed and extracted twice with diethyl ether. The combined organic solution was dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum to yield **3** as a white solid (13.57 g, 87%). M.p. = 97–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.23 (t, *J* = 7.9 Hz, 1H), 6.93–6.87 (m, 2H), 5.47 (br, 1H, OH), 2.49 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.6, 150.3, 145.8, 132.7, 130.1, 129.8 (2C), 128.8 (2C), 114.7, 113.3, 83.1, 21.8; HRMS (EI) calcd. for $C_{13}H_{11}IO_4S$ 389.9423, found 389.9425; IR (cm^{-1}): 3405 (br), 1590, 1448, 1358, 1171.

4. Conclusions

Novel 3-hydroxy-2-iodophenyl-(4-methylbenzenesulfonate) was obtained in three steps, starting from commercially available resorcinol, and isolated easily with a good yield. The target compound could be useful for various applications in organic chemistry, pharmaceutical synthesis, etc.

Supplementary Materials: The following are available online. The NMR, HRMS and IR spectra of the unknown compounds and MOL files are available online. Figure S1: ^{1}H NMR spectrum of compound 2, 2-iodo-1,3-phenylene bis(4-methylbenzenesulfonate); Figure S2: ^{13}C NMR spectrum of compound 2; Figure S3: HRMS of spectrum compound 2; Figure S4: IR spectrum of compound 2; Figure S5: ^{1}H NMR spectrum of compound 3, 3-hydroxy-2-iodophenyl-(4-methylbenzenesulfonate); Figure S6: ^{13}C NMR spectrum of compound 3; Figure S7: HRMS spectrum of compound 3; Figure S8: IR spectrum of compound 3.

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