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Short Note

Preparation of 5-Bromo-2-naphthol: The Use of a Sulfonic Acid as a Protecting and Activating Group

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Abstract: The preparation of 5-bromo-2-naphthol (**4**) in three steps from 5-amino-2-naphthol (**1**) is described. A sulfonic acid group is introduced at the 1-position as an activating and protecting group for the Sandmeyer reaction. The sulfonate group allows for the use of only water and sulfuric acid as solvents. The sulfonic acid is introduced with three equivalents of sulfuric acid, and it is removed in 20% aq. sulfuric acid.

Keywords: Sandmeyer reaction; protecting group; sulfonation; desulfonation

1. Introduction

Regioselective synthesis of disubstituted naphthalenes can be challenging especially when the substituents are on different rings. We needed 5-bromo-2-naphthol (**4**) as a starting material for a multistep synthesis. This simple derivative is virtually unknown [1,2]. The most direct route to **4** is from 5-amino-2-naphthol (**1**) using the Sandmeyer reaction. Unfortunately, the Sandmeyer reaction fails with **1** because the hydroxyl group is too activating. Even when the hydroxyl group is protected as a methyl ether, the normal solution-phase Sandmeyer reaction employing cuprous salts is still problematic. In their preparation of 5-bromo-2-methoxynaphthalene, Dauben and co-workers resorted to pyrolysis of the diazonium ion double salt with $HgBr_2$, but this procedure gives just a 30% yield of the bromide [3].

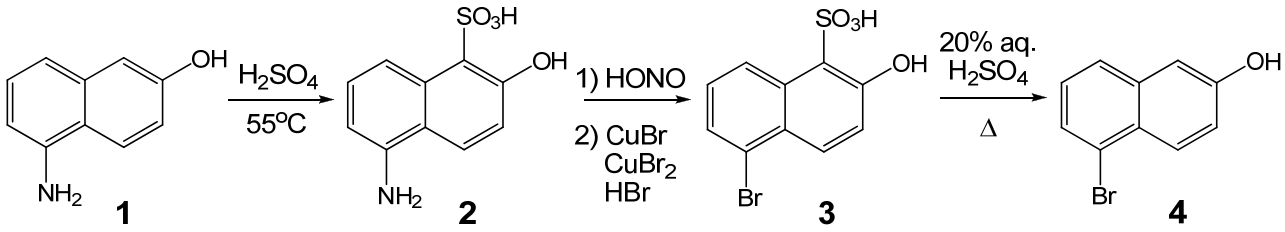
The cuprous salt method is poor because the methoxy group makes the diazonium ion too electron-rich. As a result, the electron transfer from Cu(I), the first step in the mechanism, is slow. Making the naphthalene less electron-rich should make the normal Sandmeyer reaction viable. Bueno and co-workers protected the hydroxyl group of **1** as a triflate [4]. This derivative deactivates the naphthalene sufficiently to allow for iodination and chlorination but not for bromination. They prepared the triflates using *N*-phenyl-bis(trifluoromethanesulfonamide). The high cost of this reagent would be a serious issue with large scale preparations.

In this paper we describe the use of sulfonation as a way to both activate the Sandmeyer reaction while protecting the naphthalene nucleus from further substitution. Both the sulfonation and desulfonation procedures are simple, inexpensive, and avoid the use of organic solvents and exotic reagents. The three step procedure gives access to **4** on a scale sufficient for a multistep synthesis.

2. Results and Discussion

The preparation of **4** is shown in Scheme 1. Sulfonation of **1** is carried out with neat sulfuric acid using slightly less than four equivalents. This amount is just enough to completely dissolve the substrate. When sulfonic acid **2** forms, it precipitates out of solution. Within 15 min the reaction mixture has turned completely solid. Using excess sulfuric acid leads to further sulfonation and diminished yields. Chlorosulfonic acid also works, but yields are smaller. It is also necessary to quench the reaction after just a few minutes to avoid over-sulfonation.

Scheme 1. Preparation of 5-bromo-2-naphthol



The product **2** is an inner salt and, as such, is not soluble in either water or acetone. It is easily isolated by rinsing with these solvents. The water rinse removes unreacted **1** as the hydrogen sulfate salt, while the acetone rinse removes any **1** that remains. Neutralization of the aqueous filtrate affords unreacted **1**. The sulfonation goes in nearly 90% yield based on recovered starting material.

The success of the sulfonation reaction is due to both the amino and hydroxyl groups. The amino group protonates under these conditions rendering it unreactive. Sulfonation of naphthols and other phenolic compounds is known to proceed via a sulfate ester which subsequently decomposes [5]. Support for this mechanism in this case comes from the observation that the methyl ether derivative of **1** does not sulfonate under similar conditions.

The Sandmeyer reaction on **2** is straightforward and efficient. Sulfuric acid is used to generate nitrous acid instead of HCl to avoid incorporation of chloride in the final product **4**. The diazonium sulfonate zwitterion precipitates as it forms. It is isolated by filtration, and excess nitrous acid is

removed by washing with water. The zwitterion is reacted with an aqueous 1:1:1 mixture of CuBr, $CuBr_2$ and HBr. Typically, excess CuBr is used in the Sandmeyer reaction; however, more recent studies have found that an equimolar ratio of CuBr and $CuBr_2$ is more efficacious [6]. We found that the Cu(II) salt also inhibits the formation of the H-atom abstraction byproduct, which gives 2-naphthol after subsequent desulfonation. The product **3** is isolated by salting out the aqueous solution. The filtrate still contains some **3**; however, it is very impure, and desulfonation of this material gives as much 2,5-dibromonaphthalene as **4**. The formation of the dibromonaphthalene byproduct is pronounced if the Sandmeyer reaction is heated above 75 ºC.

The sulfonic acid group affects the Sandmeyer reaction in three ways. Most importantly, it enhances the reaction yield, an effect that has long been noted [7]. In fact, a sulfonic acid group is used for the large scale preparation of 2-bromonaphthalene [8]. In the present case, in contrast to the latter example, we introduce the sulfonate group deliberately. The sulfonic acid group facilitates the electron transfer reaction between CuBr and the diazonium intermediate by making the diazonium compound a better electron acceptor [9]. The sulfonic acid group also serves to block the 1-position from azo coupling, a ubiquitous reaction of 2-naphthols [10,11]. Finally, the use of the sulfonic acid results in the formation of an insoluble diazonium sulfonate zwitterion [12]. Isolation of this salt is a purification step.

The sulfonic acid group is easily removed under relatively mild conditions. By comparison, removing the sulfonic acid in 2-bromonaphthalene-1-sulfonic acid requires refluxing with 50% aq. sulfuric acid solution for 12-16 hrs. With **3** several minutes of refluxing with a 20% solution is sufficient. The reaction is carried out for 20 min only to ensure completion. Other methods of desulfonation work nearly as well. They include vacuum sublimation from a 1:1 mixture of **3** and $KHSO_4$, and refluxing in toluene with Amberlyst-15. The former is useful on small scales because it avoids the use of all solvents, while the latter avoids a solvent extraction. Desulfonation is simply the mechanistic reverse of sulfonation. The hydroxyl group activates electrophilic aromatic substitution, and hence also accelerates desulfonation.

In conclusion, through the use of a sulfonic acid as an activating and protecting group, we have devised a route into 5-bromo-2-naphthol amenable to large scale preparation.

3. Experimental

3.1. General Methods

NMR spectra were recorded on a Varian Mercury 400-Vx system. High resolution ESI-MS were acquired with a Bruker Apex-Qe instrument.

3.2. 5-Amino-2-hydroxynaphthalene-1-sulfonic acid

Sulfonation. 5-Amino-2-naphthol (**1**, 16.7 g, 104 mmol) is ground to a fine powder and heated to 55°C under a stream of N_2. Sulfuric acid (21.6 mL, 389 mmol) is added in one portion and mixed rapidly with the solid. Stirring is continued until the mixture becomes too viscous. The heat is removed, the reaction is covered and allowed to stand overnight. The solid is taken up in water (ca. 500 mL) and collected by suction filtration. The solid is then taken up in acetone (ca. 300 mL) and

collected by suction filtration. It is washed with more acetone and air-dried giving 5-amino-2-hydroxynaphthalene-1-sulfonic acid (20.90 g, 84%) as a white solid. Unreacted **1** (0.84 g, 5.3 mmol) is recovered from the first aqueous filtrate after neutralization and suction filtration (88% based on 100% conversion).

M.p. 288-290ºC (dec). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.17 (s, 1H), 8.63 (d, *J*=8.8 Hz, 1H), 7.86 (d, *J*=9.2 Hz, 1H), 7.47 (dd, *J*=8.8, 7.4 Hz, 1H), 7.28 (d, *J*=7.4 Hz, 1H), 7.22 (d, *J*=9.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.95. 131.65, 128.07, 126.05, 126.00, 124.75, 121.91, 121.06, 120.55, 117.21.

Found $[M+Na]^+$ 262.01430. $C_{10}H_9NO_4SNa$ requires 262.01454.

3.3. 5-Bromo-2-naphthol

Sandmeyer Reaction. Sulfonic acid **2** (11.11 g, 46.5 mmol), NaOH (1.90 g, 48.0 mmol) and $NaNO_2$ (3.20 g, 46.4 mmol) are dissolved in water (80 mL). This solution is added dropwise to a solution of H_2SO_4 (8.2 mL) in H_2O (20 mL) at such a rate that the internal temperature never exceeds 5 ºC. The yellow diazonium sulfate precipitate is collected by suction filtration and washed several times with ice-water. The moist filter cake is transferred to a mixture of CuBr (6.70 g, 46.7 mmol), $CuBr_2$ (10.40 g, 46.6 mmol), HBr (5.2 mL) and H_2O (ca. 200 mL). The mixture is warmed to 70ºC for 1 hr then filtered by gravity. The filtrate is saturated with NaCl (90 g), and the solution is stirred overnight. The precipitate is collected by suction filtration. The solid is air-dried, giving crude 5-bromo-2-hydroxynaphthalene-1-sulfonic acid (**3**, 11.11 g, 36.7 mmol, 79%), which is used without further purification.

Desulfonation. Crude **3** (11.11 g, 36.7 mmol) is mixed with 20% aq. H_2SO_4 (250 mL). The slurry is heated to reflux for 20 min. After the reaction cools, it is extracted with Et_2O (3 × 200 mL). The ether layers are combined, washed with H_2O (2 × 50 mL), dried over Na_2SO_4 and conc. *in vacuo*. The residue is sublimed under vacuum (180 ºC, 0.5 torr) giving 5-bromo-2-naphthol (**4**, 4.59 g, 20.6 mmol, 56%) as a white solid.

M.p. 110-111ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J*=8.1 Hz, 1H), 7.64 (d, *J*=9.2 Hz, 1H), 7.61 (d, *J*=7.6 Hz, 1H), 7.26 (dd, *J*=8.1, 7.6 Hz, 1H), 7.20 (dd, *J*=9.2, 2.4 Hz, 1H), 7.15 (d, *J*=2.4 Hz, 1H), 5.05 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.13, 136.05, 129.62, 127.98, 127.73, 127.23, 126.68, 123.01, 119.24, 110.18. IR (Nujol, cm^{-1}): 3200, 1503, 1464, 1378, 861, 812, 771, 740.

Found $[M-H]^-$ 220.96077. $C_{10}H_6BrO$ requires 220.96020.

Acknowledgements

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