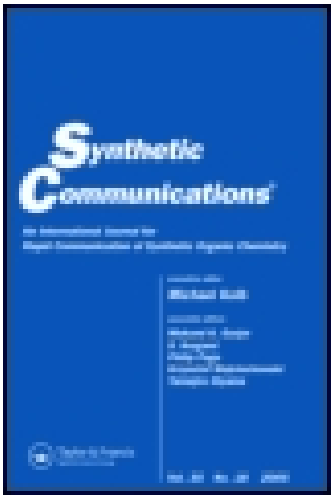

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Convenient Synthesis of 2-Hydroxybenzenesulfonamide

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Published online: 23 Sep 2006.

To cite this article: Peter F. Drygala, Andrew F. Kirbya & Keith G. Watson (1994) A Convenient Synthesis of 2-Hydroxybenzenesulfonamide, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:5, 671-675, DOI: 10.1080/00397919408012644

To link to this article: http://dx.doi.org/10.1080/00397919408012644

SYNTHETIC COMMUNICATIONS, 24(5), 671-675 (1994)

A CONVENIENT SYNTHESIS OF 2-HYDROXYBENZENESULFONAMIDE

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Abstract: Chlorosulfonation of 4-*t*-butylanisole and formation of the sulfonamide **2,** followed by removal of the t-butyl and O-methyl groups with aluminium chloride provides a simple, novel synthesis of 2-hydroxybenzenesulfonamide **3.**

2-Hydroxybenzenesulfonamide **3** has been used as the key precursor to several very active sulfonylurea herbicides[1,2], but otherwise there are remarkably few references to this simple compound. As part of our exploration into novel bicyclic sulfonylureas[3] we required reasonable quantities of compound **3** and we have devised a new synthesis which is both higher yielding and easier to carry out than the two previously reported methods. We hope that this simple approach will lead to greater investigation into the chemistry of this neglected compound.

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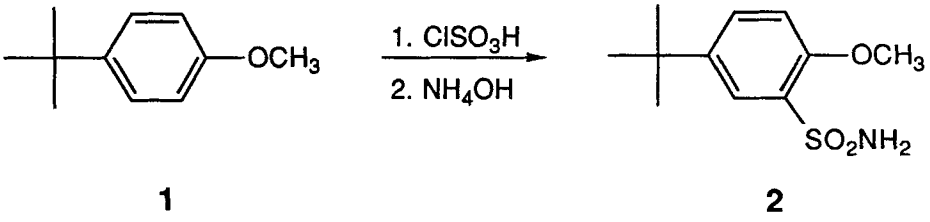
The synthesis of **3** was first achieved in 1958 utilizing a low-yielding 6-step reaction sequence starting with 2-nitrophenol.[4] Later workers improved upon this method but still only obtained an overall yield of 14%.[5] More recently a 3-stage preparation of **3** was described in the patent literature which gives impure material, and involves the dehalogenation of 3,5-dichloro-2-hydroxy-benzenesulfonamide by high-pressure hydrogenation.[6] We now describe a simple 3-step preparation of **3** which proceeds in 54-66% overall yield starting from 4-*t*-butylanisole **1**.

To allow the direct introduction of a sulfonyl group exclusively in the ortho position of a phenol derivative we have explored the use of *t*-butyl as a positional protecting group on the benzene ring.[7] Any attempt to carry out the direct chlorosulfonation of 4-*t*-butylphenol would be complicated by the ease of disulfonation and also dimerization of the product.[8] Therefore we used 4-*t*-butylanisole **1** which reacts cleanly with chlorosulfonic acid in methylene chloride at ice temperature to give the crude sulfonylchloride which was converted using standard conditions[9] to the sulfonamide **2** in an overall yield of 60-70%. The 2-methoxybenzenesulfonamide **2** was then treated with four equivalents of aluminium chloride in warm meta-xylene to effect both demethylation and removal of the *t*-butyl protecting group from the benzene ring. We found that meta-xylene gave a slightly better yield than toluene which is the most commonly used solvent for deprotective trans-alkylations.[7] We believe that this represents the first reported use of a *t*-butyl positional-protecting group in the presence of a sulfonamide.



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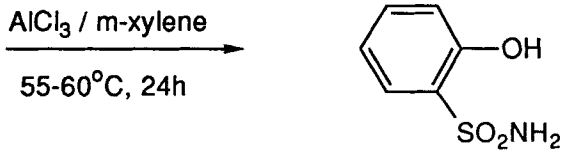

3

The isolation of pure 2-hydroxybenzenesulfonamide **3** in 90-95% yield is facilitated by the fact that the compound has significant solubility in water, but is insoluble in hydrocarbon solvents. Thus the work-up of the final stage of the synthesis was carried out by quenching the deprotection reaction in water, removing all impurities in the organic layer and isolating **3** by extracting the aqueous phase with ether.

EXPERIMENTAL

Melting points were determined with a hotplate microscope and are uncorrected. NMR spectra were recorded with a Bruker AC200 spectrometer. 4-*t*-Butylanisole **1** was prepared by methylation of *t*-butylphenol using standard conditions and it is also commercially available. Other reagents and solvents were used as purchased.

2-Methoxy-5-*t*-butylbenzenesulfonamide 2

A solution of chlorosulfonic acid (11.5 mL, 170 mmol) in methylene chloride (12 mL) was added dropwise to an ice-cold solution of 4-*t*-butylanisole **1** (8.2 g, 50 mmol) in methylene chloride (20 mL). The solution was stirred at 0-5°C for 1h and then allowed to warm to r.t. and stirred for a further h. The solution was poured into ice-water (200 mL) and the organic layer was quickly separated, washed with cold water (100 mL), dried ($MgSO_4$) and evaporated to give crude 2-methoxy-5-*t*-butyl-benzenesulfonylchloride as a low-melting point solid. The crude sulfonylchloride (8.8g) was dissolved in acetonitrile (20 mL) and the solution was stirred with ice-cooling while aqueous ammonia (8 ml of 25% soln) was added. After 16 h at r.t. the mixture was poured into ice-water, neutralized with conc HCl and filtered to give **2** as a pale brown crystalline solid (7.32 g, 60%), mp 159-161°C (Lit.[10] 156-158°C). ^{1}H NMR ($CDCl_3$): d = 1.31 (s, 9H), 3.99 (s, 3H), 5.1 (br s, 2H), 6.98 (d, 1H, J = 8.4 Hz), 7.54 (dd, 1H, J = 8.4, 2.5 Hz), 7.90 (d, 1H, J = 2.5 Hz).

2-Hydroxybenzenesulfonamide 3

Powdered aluminium chloride (11.0 g, 83 mmol) was added to a stirred suspension of sulfonamide **2** (4.85 g, 20.0 mmol) in meta-xylene (60 mL) and the mixture was stirred and heated at 55-60°C for 24 h. The dark reaction mixture was poured with vigorous stirring into ice-water (200 mL). n-Hexane (80 mL) was used to rinse the reaction flask and then the combined organic and aqueous phases were thoroughly shaken in a separating funnel. The aqueous layer was separated and saturated with salt. Extraction with diethyl ether (3 x 200 mL), followed

by drying ($MgSO_4$) and evaporation of the combined ether layers gave **3** as colourless crystals (3.25 g, 95%), mp 139-141°C (Lit.[4] 139-141°C). ^1H NMR (DMSO-d_6): d = 6.8-7.0 (br s), 6.90 (m, 1H), 6.98 (dd, 1H, J = 7.3 and 1.2 Hz), 7.40 (m, 1H), 7.64 (dd, 1H, J = 7.8 and 1.7 Hz), 10.6 (br s, 1H). ^{13}C NMR (DMSO-d_6): d = 116.85, 118.37, 127.37, 129.35, 133.39, 154.48.

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(Received in the UK 05 July 1993)