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A Novel Method for the Preparation of 2,6-Disubstituted Benzenesulfonates and Benzenesulfonyl Chlorides Utilizing the Powerful Alkyl Sulfonate Ortho Directing Group.

Lori A. Spangler

Exploratory Agricultural Products Research
Rohm and Haas Co., Springhouse, PA 19477

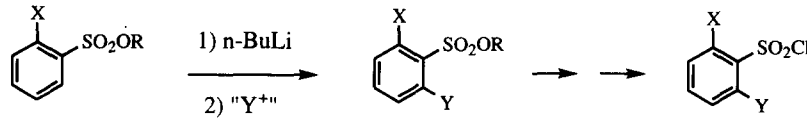
Abstract: Ortho lithiation technology using alkyl benzenesulfonates has been developed to prepare a series of 2,6-disubstituted benzenesulfonates, benzenesulfonic acids and benzenesulfonyl chlorides. By comparison with other ortho directing groups, alkyl sulfonates are very powerful, leading to excellent regioselectivity. Copyright © 1996 Elsevier Science Ltd

Directed ortho lithiation is an effective tool for construction of regiospecifically substituted aromatic rings.[1] A number of sulfur-based ortho directing groups have been reported, including thioethers,[2] mercaptophosphonic acids,[3] lithium thiolates,[3] alkyl sulfones,[4] sulfonic acids,[5] sulfonamides,[6] and alkyl sulfonates.[7]

A series of unsymmetrical 2,6-disubstituted benzenesulfonyl chlorides was required as intermediates for an SAR program. Directed ortho lithiation was investigated as a route to these intermediates using readily available 2-substituted benzenesulfonyl chlorides as starting materials. Attempted ortho lithiation and alkylation of lithium 2-trifluoromethylbenzenesulfonate, **1a**, failed to produce any alkylated product. 2-Substituted alkyl benzenesulfonates were next explored as an entry to the 2,6-disubstituted benzenesulfonyl chlorides. The 2-substituted ethyl and isopropyl benzenesulfonates (**1b-g**) were prepared in high yield from the appropriate benzenesulfonyl chloride, alcohol and a base such as pyridine or sodium hydride at 0°C. Treatment with n-butyllithium and an electrophile led to the formation of 2,6-disubstituted alkyl benzenesulfonates **2b-j** in good yields (53-90%, Table 1).

In order to successfully prepare 2,6-disubstituted alkyl benzenesulfonates from the reaction, rather than a regioisomer, the alkyl sulfonate must be a stronger ortho director than the 2-substituent, X. There is no report in the literature about the effectiveness of alkyl sulfonate groups as ortho directors relative to other known ortho directing groups. The alkyl sulfonate group is both strongly electron-withdrawing and contains heteroatom lone pair electrons available for coordination to lithium, both of which are criteria for an effective director of ortho lithiation.[1] Intramolecular competition[8] studies were performed beginning with 2-trifluoromethyl (**1b**), 2-chloro (**1c**), 2-trifluoromethoxy (**1d**), and 2-fluoro (**1e**) isopropyl benzenensulfonate with n-butyllithium and then an iodoalkane. All of these groups are weak to moderate ortho directors.[1] In all cases but fluoro, the alkylation went exclusively ortho to the alkyl sulfonate group. In the case of **1e**, the product was a 70:30 mixture of the 2-fluoro, 6-methyl benzenesulfonate, **2e**, and the isomeric 2-fluoro, 3-methyl benzenesulfonate. Analysis in all cases was by GC and proton nmr. The proton ortho to the sulfonate group is deshielded relative to the other aromatic protons and its replacement is readily observed.

Table 1. Results of Lithiation / Quench Reactions (**1** to **2**)



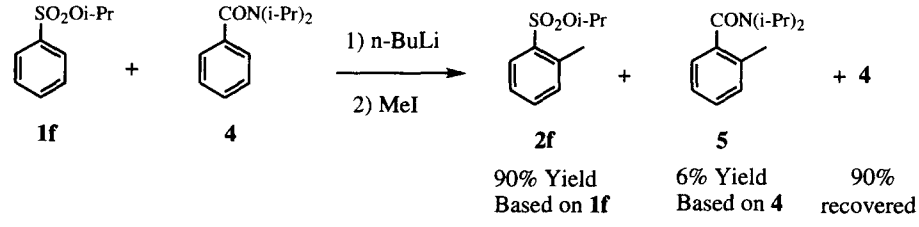
1 a-g **2** b-j **3** b-j

1,2,3	X	R	Electrophile	Y	Yield of 2
a	CF3	Li	MeI	-	0%
b	CF3	i-Pr	MeI	Me	83%
c	Cl	i-Pr	EtI	Et	66%
d	OCF3	i-Pr	MeI	Me	58%
e	F	i-Pr	MeI	Me	70%[a,b]
f	H	i-Pr	MeI	Me	90%
g	CF3	Et	MeI	Me	60%
h	CF3	i-Pr	EtI	Et	53%
i	CF3	i-Pr	F3CCH2I	I	65%
j	CF3	i-Pr	n-PrI	n-Pr	58%[c]

a. 70:30 mixture of isomers, 2e : isopropyl 2-fluoro,3-methylbenzenesulfonate
b. Example run by Bill Zabrodski
c. Example run by Damian Weaver

A final intermolecular competition[4,9] was performed, comparing alkyl sulfonate to the N,N-diisopropyl carboxamide directing group, one of the strongest ortho directing groups[10], which is lithiated under the same reaction conditions as the alkyl sulfonate. As illustrated in Scheme 1, an equimolar mixture of N,N-diisopropyl benzenecarboxamide, **4**, and isopropyl benzenesulfonate, **1f**, was treated with one equivalent of n-butyllithium and an excess of iodomethane. Following reaction work-up, GC showed no **1f**, and a good recovery of **4**. Two new products were observed. Column chromatography confirmed the absence of **1f**, and 90% of starting **4** was recovered. There was a 90% yield of **2f** (based on **1f**) and a 6% yield of **5** (based on **4**). The alkyl sulfonate is a very strong ortho director, more powerful than the N,N-dialkylcarboxamide, and comparable to the sulfone and sulfonamide directing groups.[1,6]

Scheme 1



1f **4** **2f** **5**

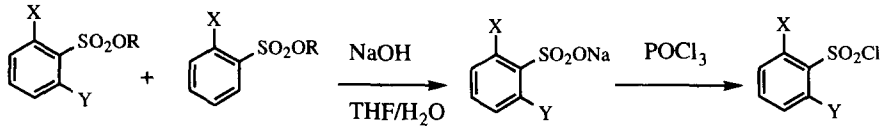
90% Yield Based on **1f** | 6% Yield Based on **4** | 90% recovered

Higher yields were obtained when using the isopropyl sulfonate group as an ortho director than the ethyl

sulfonate. In the case of the ethyl sulfonate **1g**, up to a 13% yield of the n-butylsulfone was isolated which results from the addition of n-butyllithium to the alkyl sulfonate. Less than 3% yield of this material was obtained with **1b**, the corresponding isopropyl sulfonate directing group. The polarity of the solvent also is important to the yield of the reaction. The reaction is run in THF using n-butyllithium in hexane. If the amount of THF is 24 ml / g of starting material, the isolated ratio of alkylated product: starting material was 3:1. If the amount of THF was reduced to 10 ml / g of starting material, the ratio was 9:1, dramatically increasing the yield of the reaction.

An advantage of the alkyl sulfonate as an ortho directing group is the ease of hydrolysis and conversion to other sulfur containing functional groups. Following an alkylation with iodomethane, the 2,6-disubstituted alkyl benzene sulfonate **2** exists as a mixture containing up to 10% of unalkylated 2-substituted alkyl benzenesulfonate starting material. A non-chromatographic purification of the crude reaction mixture has been developed, based on the hydrolysis of the alkyl sulfonate. The 2,6-disubstituted alkyl sulfonate **2** hydrolyzes much more rapidly in a mixture of sodium hydroxide, THF, and water, than the unreacted 2-substituted alkyl benzenesulfonate. The hydrolysis reaction is monitored by GC and stopped after all the **2** has reacted, then partitioned between water and an organic solvent. The sodium salt of the 2,6-disubstituted benzenesulfonic acid, **6**, dissolves in the water and is of >95% purity, while the unreacted **1** is washed out into the organic phase. After removal of water, the sodium benzenesulfonate can be converted cleanly to the sulfonyl chloride by heating to reflux in phosphorus oxychloride for 4-6 hours (Scheme 2).

Scheme 2



2 b-j **1** b-j **6** b-j water soluble

In conclusion, methodology has been developed for the conversion of 2-substituted benzenesulfonyl chlorides to 2,6-disubstituted alkyl benzenesulfonates, benzenesulfonic acids, and benzenesulfonyl chlorides, using isopropyl sulfonate or ethyl sulfonate as an ortho director for lithiation. The alkyl sulfonate is a powerful ortho director relative to other known ortho directing groups, as established by intramolecular and intermolecular competition studies.

Representative Experimental Procedure for Lithiation/Quench of Alkyl Benzenesulfonates. A 100g (0.37 mol) sample of **1b** was placed in an oven-dried flask and dissolved in 1 L of dry THF under a static nitrogen atmosphere. The solution was cooled to -78°C and treated with 257 mL (0.41 mol) of a 1.6 molar solution of n-butyllithium in hexane at a rate to keep the internal temperature <-70°C. The orange or brown solution was stirred 2 hours at -78°C, then treated with 46 mL (0.74 mol) of iodomethane. The reaction mixture was allowed to warm to 0°C, stirred for 2 h and poured into cold saturated aqueous ammonium chloride and ether. The layers were separated, the aqueous extracted with ether, and the combined organic layers washed with water and brine and dried with sodium sulfate. Removal of solvent yielded 93 g of crude oil, 90% desired **2b** by

nmr and GC, which was carried into the hydrolysis step without further purification. Alternatively, the product can be purified by flash silica gel chromatography using 10% ether/hexane. ^{1}H nmr ($CDCl_3$, 200 MHz): δ 7.8 (m, 1H), 7.6 (m, 2H), 5.0 (m, 1H), 2.8 (s, 3H), 1.3 (d, 6H).

Representative Experimental Procedure for Hydrolytic Purification.
To a solution of 83 g (0.29 mol) of **2b** in 300 mL of THF was added a solution of 24.8g (0.31 mol) of 50% aqueous sodium hydroxide in 150 ml of water. The mixture heated to reflux for 4 h. The reaction was monitored for the disappearance of **2b** by GC. THF was removed by rotary evaporation, and 100 ml of water was added. The aqueous phase was washed with 2X200 mL hexane, then stripped to yield **6b** as 71g of a white solid which was >95% pure by proton nmr. ^{1}H nmr (D_2O, 200 MHz): δ 7.6 (m, 1H), 7.3 (m, 2H), 2.4 (s, 3H).

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