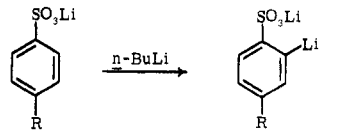
Ortho Lithiations of Arenesulfonic Acids. New Methodology for Electrophilic Aromatic Substitutions

Summary: The directed ortho lithiation of aromatic sulfonic acids occurs in high yield. The ease of desulfonation makes this a useful method for the synthesis of substituted arenes lacking the sulfonic acid function.

Sir: Ortho lithiations with *n*-butyllithium (*n*-BuLi) of benzene derivatives with the substituents NMe_2,[1] CH_2NMe_2,[2] $CH_2CH_2NMe_2$,[3] OMe,[4] $CONR_2$,[5] SO_2NR_2,[6] CF_3,[7] F,[8] SO_2Ar,[9] $C(Ph)_2OCH_3$,[10] and 2-oxazoline[11] have been well-studied.[12] More recently, substituents have been studied which undergo side-chain lithiation prior to ring ortho lithiation to give dilithiated species.[13] We report evidence for the ortho lithiation of the lithium salts of aromatic sulfonic acids to give new members in the family of dilithiated species.

The preparation of derivatives of the type 1 is easily accomplished by the addition of the lithium sulfonate[14,15] to 1.1 equiv of *n*-BuLi in tetrahydrofuran (THF) at 0 °C.

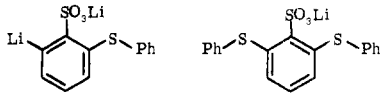


1a (R = H)
1b (R = CH_3)

After 10 min the reaction is complete. Examination of the crude product of a D_2O quench of the dilithiated material shows quantitative ortho lithiation, as evidenced by integrals and by coupling patterns in the 220-MHz ^1H NMR spectra. The dilithiated material (homogeneous for **1a**, heterogeneous for **1b**) can be bottled and stored at −20 °C for up to 3 weeks with a loss of less than 10% of **1**.

Electrophilic substitution reactions are easily carried out by simple direct addition of the electrophile (dissolved in THF when possible) to the dilithiated sulfonic acid mixture. Table I lists several illustrative reactions. In the general procedure the reaction mixture was stirred for 18 h at 25 °C and was then quenched with 15% aqueous HCl. The aqueous fraction was extracted with ether and the water was removed in vacuo to leave a mixture of the desired product and the starting lithium sulfonate. The quoted conversion to the desired product was calculated from NMR peak ratios. Separation of the desired products from the starting sulfonate was usually difficult. Recrystallization of the *S*-benzylthiuronium salt prepared from **4b** gave the sulfonate,[16] mp 178–179 °C. The preparations of sulfide **2b**, disulfide **3b**, and iodo compound **4b** all proceed with excellent conversions. Bromide **5b** and tertiary alcohol product **7b** were obtained in lower but still useful conversions. Optically active sulfoxide **6b** ($[\alpha]^{27}_D$ −103° (CH_3OH))[17] was obtained in 67% conversion from menthyl (*S*)-benzenesulfinate ($[\alpha]^{21}_D$ −202° (acetone)).[18]

When sulfide **2a** is treated with excess *n*-BuLi, addition of D_2O shows by ^1H NMR that lithiation at the other position ortho to the sulfonate group occurs to give **8**. For **2b**, R = CH_3, there is competing side-chain lithiation when an excess of *n*-BuLi is used. Compound **8** can be treated again with diphenyl disulfide to give the di-ortho-substituted species **9** in ~40% conversion.



8 **9**

The use of aromatic sulfonic acid groups as directing and/or blocking substituents, followed by desulfonation to synthesize substituted aromatic systems otherwise very

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(14) The lithium sulfonate is made first as a way of purification of the very crude commercially available (from Aldrich Chemical Company) sulfonic acids by treatment with LiOH and heating in vacuo to obtain the white solid salt, which is then recrystallized from toluene–ethanol.

(15) The sodium sulfonate salts do not undergo the lithiation reaction under these conditions. This may be a solubility effect.

(16) ^1H NMR for the *S*-benzylthiuronium salt of **4b** (CD_3OD, 220 MHz): δ 7.93 (AB pattern, 1, J_{AB} = 8 Hz, H ortho to SO_3^-), 7.85 (s, 1, H ortho to I and CH_3), 7.35 (m, 5, Ph), 7.20 (AB pattern, 1, J_{AB} = 8 Hz, H ortho to CH_3), 4.41 (s, 2, CH_2), 2.30 (s, 4, NH). Anal. Calcd for $C_{15}H_{17}IN_2O_3S$: C, 38.80; H, 3.67; N, 6.03. Found: C, 39.25; H, 3.48; N, 5.82.

(17) The optical rotation obtained on the product mixture consisting of 67% sulfoxide and 33% starting lithium sulfonate was −69°. Assuming linear correlation of rotation with sample purity, pure sulfoxide **6b** would have a rotation of −103°. Thus far all attempts to determine the enantiomeric purity of the material by NMR using Pirkle's method have failed. (See W. H. Pirkle and S. D. Beare, *J. Am. Chem. Soc.*, **90**, 6250 (1968).) There was no evidence by NMR of any contamination of the sample with the starting menthyl sulfinate.

(18) For similar reactions generating optically active sulfoxides, see (a) K. K. Andersen, *Tetrahedron Lett.*, 93 (1962); (b) P. Bickart, M. Axelrod, J. Jacobus, and K. Mislow, *J. Am. Chem. Soc.*, **89**, 697 (1967); (c) paper by Martin and Balthazor in ref 13a.

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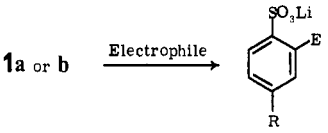
Table I. Reaction of 1a and 1b with Electrophiles

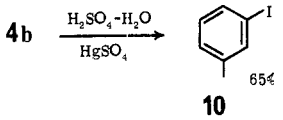


2a, 6a (R = H)
2-7b (R = CH_3)

electrophile	product	E	% conversion
PhSSPh	2a	SPh	*a*
PhSSPh	2b	SPh	83
S_8	3b	S-S-*o*-$(SO_3Li)C_6H_3$-*m*-CH_3	85
I_2	4b	I	80
Br_2	5b	Br	40
p-$CH_3C_6H_4S(O)OEt$	6a	$S(O)C_6H_4$-*p*-CH_3	55
p-$CH_3C_6H_4S(O)O$-menthyl ($[\alpha]^{21}_D$ −202°)	6b	$S(O)C_6H_4$-*p*-CH_3 ($[\alpha]^{27}_D$ −103°)	67
acetone	7b	$C(CH_3)_2OH$	33

[a] The absence of a convenient NMR probe for 2a made it impractical to determine the percent conversion. The crude product was used in the preparation of 9 (see text).

difficult to obtain, is a well-known synthetic stratagem.[19] Our method allows easy access to such materials as meta-substituted toluenes through an easy desulfonation procedure. For instance, when ortho-iodo derivative **4b** (1 g) is boiled for 2 days with 100 mL of aqueous H_2SO_4 (50%) and $HgSO_4$ (10% based on moles of sulfonate)[20] in an apparatus (available from Aldrich Chemical Company) which allows continuous steam distillation with continuous extraction of products into CH_2Cl_2, *m*-iodotoluene (**10**)[21] is obtained in 65% isolated yield.[22] By the same process 3,3′-dimethyldiphenyl disulfide (**11**)[23] is obtained (53%)[22] from the desulfonation of **3b**.



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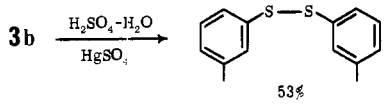

11

The ortho lithiation of aromatic sulfonic acids makes it possible to introduce electrophilic substituents ortho to a sulfonate group. Acid hydrolysis of the sulfonic acid group provides a way to replace it by hydrogen, thus providing overall a new directing group which can be removed after it performs its directing function in a multistep synthesis of a substituted aromatic compound. Further work is currently being done to explore the full synthetic potential of this method.

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(20) For the use of $HgSO_4$ as a desulfonation catalyst, see G. Travagli, *Gazz. Chim. Ital.*, 81, 668 (1951).
(21) ^1H NMR for **10** ($CDCl_3$, 90 MHz): δ 7.72 (m, 2), 7.21 (m, 2), 2.40 (s, 3, CH_3). Mass spectrum: 218 (M^+·, 96%), 91 (M^+· − I, 100%).
(22) Since the starting material for the desulfonation is always a mixture of desired sulfonate, starting sulfonate, and LiCl, yields were calculated from the actual amount of desired sulfonate present, which was determined by NMR peak ratios in D_2O with acetone as an internal standard.
(23) Column chromatography on silica gel with hexane gave the pure disulfide. ^1H NMR for **11** ($CDCl_3$, 90 MHz): δ 7.20 (m, 4), 2.32 (s, 3, CH_3). Mass spectrum: 246 (M^+·, 100%), 123 (M^+· − $CH_3C_6H_4S$, 28%). Anal. Calcd for $C_{14}H_{14}S_2$: C, H, S.

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Novel Synthesis of (±)-Velbanamine and (±)-Isovelbanamine

Summary: Reaction of the allyl lactams **6** (3α-H and 3β-H) with iodine in aqueous THF produced the iodo lactones **8** (3α-H and 3β-H), which were converted into (±)-velbanamine (**1**) and (±)-isovelbanamine (**2**), respectively.

Sir: We have developed[1] a new route for the synthesis of the nine-membered indole alkaloids related to the cleavamine-type alkaloids,[2] employing the thio-Claisen rearrangement[3] as a key step. However, its application has been limited to a saturated system. The syntheses of cleavamine[4] itself and its hydrated congeners, velbanamine[5-10] (**1**) and isovelbanamine[8-10] (**2**), which are potentially important for the syntheses of their parent alkaloids, oncolytic agents vinblastine[6] and vincristine,[6] and the *pandaca* alkaloids pandoline[11,12] and isopandoline[11,12] have not been accomplished. We now report here a synthesis of (±)-velbanamine (**1**) and (±)-isovelbanamine (**2**), which both are synthetic precursors[9] of cleavamine, from

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