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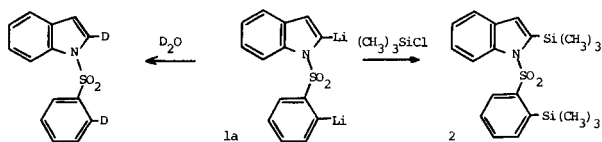
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Benzenesulfonylindole is converted to a dilithio derivative by 2.2 equivalents of lithiating reagent. The dilithio derivative gives rise to sultones on reaction with carbonyl compounds. This reaction proceeds by an intramolecular displacement of the indole group from the bis-adduct. Fair to poor yields of the 2-indolycarbinols can also be isolated. Benzoyl chloride forms a thiazine dioxide ring by addition at both the 2-indolyl and 2'-phenylsulfonyl positions. 3-Methyl-1-benzenesulfonylindole is also easily dilithiated.

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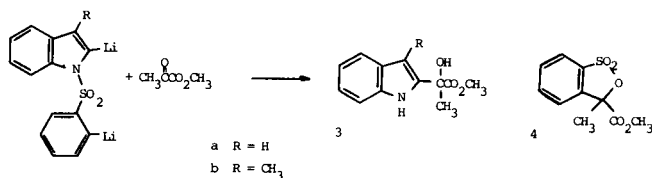
Several years ago the synthetic utility of 2-lithio-1-benzenesulfonylindole was demonstrated (1). This conveniently available reagent has subsequently proven to be a useful intermediate for the preparation of 2-substituted indoles in a number of synthetic contexts (2). We report here that 1-benzenesulfonylindole (1-BSI) undergoes facile dilithiation with 2.2 equivalents of *t*-butyllithium and illustrate certain circumstances in which the dilithiated intermediate is of synthetic utility.

Reaction of 1-BSI with 2.2 equivalents of *t*-butyllithium at $-10-0^\circ$ for 0.5-1.0 hour followed by deuterium oxide quench resulted in recovery of 1-BSI with $>95\%$ of the product dideuterated as determined by mass spectrometric analysis. The mass spectrum further revealed that one deuterium was located in the benzenesulfonyl group. It follows that the dilithiated intermediate must be **1a**. Chemical evidence for dilithiation was obtained by

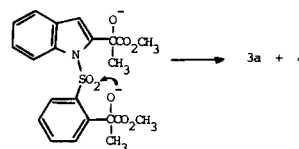


reaction with trimethylsilyl chloride which gave the bis-trimethylsilyl derivative **2**. 1-Benzenesulfonyl-3-methylindole was also dilithiated under these conditions as determined by deuteration and mass spectrometric analysis.

Our main synthetic interest was in preparation of methyl 2-hydroxy-2-(2-indolyl)propionate **3a**. Reaction of intermediate **1a** with 6 equivalents of methyl pyruvate gave **3a** in 35% yield, along with a 55% yield of the

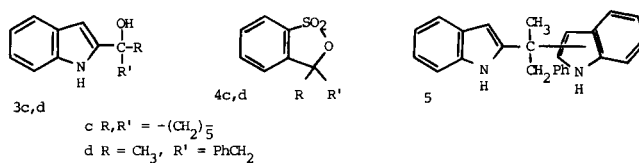


sultone **4**. The course of this reaction evidently involves the breakdown of the intermediate bis-adduct with intramolecular cleavage of the indole sulfonyl substituent.



This intramolecular deprotection is useful for synthesis of **3a**, since the usual hydrolytic removal of the benzenesulfonyl group (1) is inappropriate. The yield of **31** and **41** was improved to 60% and 70%, respectively when the lithiation was carried out with *n*-butyllithium in the presence of tetramethylethylenediamine. The dilithio derivative **1b** prepared by using 2.2 equivalents of *t*-butyllithium reacted similarly to give **3b** in 25% yield and **4** in 40% yield.

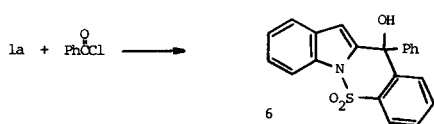
The generality of addition-deprotection reaction sequence was examined using several other carbonyl compound. The sultones **4c** (55%) and **4d** (35%) were isolated after reaction with cyclohexanone and phenylacetone,



respectively. The carbinols derived from the indole were difficult to isolate from the reaction mixture, however. Although carbinol **3c** crystallized directly from the reaction mixture, the yield was only 20%. Phenylacetone gave more of a deprotected 2:1 adduct **5** (22%) than the carbinol **3d** (7%). The structure of **5** is somewhat uncertain. Although the carbon nmr spectrum shows the expected number of aliphatic and aromatic carbons, peaks at 98.7 and 146.1 are somewhat outside the normal range of indole ring carbons (3). The symmetrical bis(2-indolyl) adduct is definitely ruled out by the ¹³C nmr spectrum. At least in part these low yield are probably a result of the known instability of tertiary 2-indolyl carbinols (4).

Reaction of **1** with benzoyl chloride gave an 85% yield of the 1:1 adduct **6**. The structure is readily accounted for by rapid elimination of chloride ion from an initial adduct

followed by an intramolecular addition step. *N,N*-Dimethylbenzamide, which is formally capable of a similar



cyclization but much less reactive, gave only 2-benzoylindole.

These results demonstrate that the dilithio derivative of 1-benzenesulfonylindole can be prepared easily and illustrate some circumstances in which this may be a useful intermediate for synthesis.

EXPERIMENTAL

Dilithiation of 1-Benzenesulfonylindole.

A solution of 5 mmole of benzenesulfonylindole in THF (20 cc) was treated with 2.2 equivalents of *t*-butyllithium at -5° . Stirring was continued for 45 minutes at this temperature. After quenching with deuterium oxide, the mass spectrum and nmr confirmed that dilithiation had occurred.

Dilithiation of 1-Benzenesulfonyl-3-methylindole.

A solution of 2.5 mmoles of 1-benzenesulfonyl-3-methylindole in 15 ml of THF was treated with 5.4 mmoles of *t*-butyllithium at -10° . Stirring was continued for 45 minutes before addition of the appropriate reagent.

Reactions of 1a.

A. Trimethylsilyl Chloride.

The lithiated solution was treated a -5° with a solution of 1.7 ml of trimethylsilyl chloride in THF (15 ml). Thin layer chromatography indicated formation of a single major product, a very minor product, and recovery of a very small amount of benzenesulfonylindole. A pure sample of the major product was isolated by preparative layer chromatography on silica gel. It was soluble in hexane and could not be induced to crystallize from other solvents. Removal of solvent gave a viscous gum showing two sharp singlets at 0.31 and 0.54 ppm, in addition to the aromatic signals.

Anal. Calcd. for $C_{20}H_{17}NO_2SSi_2$: C, 59.8; H, 6.8; Found: C, 59.2; H, 6.7.

B. Methyl Pyruvate.

The dilithiated solution was added to an excess (6 equivalents) of methyl pyruvate in THF at -78° . After 15 minutes the reaction mixture was quenched with methanolic acetic acid and the products isolated by hydrolysis and extraction. Separation was achieved by chromatography on silica using 2:1:1 hexane ether-chloroform, the sultone **4** being eluted first from the column. Several runs under these conditions gave yields of **3a** and **4** averaging 35% and 55%, respectively. In a run in which *n*-butyllithium and tetramethylethylenediamine was used for lithiation the yields increased to 60 and 70%, respectively.

Compound 4.

This compound was recrystallized from ether-hexane, mp $97-98^{\circ}$.

Anal. Calcd. for $C_{10}H_{10}SO_5$: C, 49.58; H, 4.16. Found: C, 49.52; H, 4.20.

Compound 3a.

This compound was recrystallized from benzene-hexane, mp $100-102^{\circ}$.

Anal. Calcd. for $C_{12}H_{10}NO_3$: C, 65.74; H, 5.98. Found: C, 65.65; H, 6.04.

C. Cyclohexane.

Cyclohexanone (3 equivalents) was added at -5° , stirred for 1 hour quenched with aqueous ammonium chloride and products extracted with ether. Some of the carbinol **3c** crystallized directly from the reaction mixture and an additional amount obtained by chromatography gave a total yield of **3c** of 20%. Chromatography also gave the sultone **4c** (55%). Enolization and self-condensation of cyclohexanone was evidenced by isolation of considerable amounts of 2-(1-hydroxycyclohexyl)cyclohexanone.

Compound 3c.

This compound was recrystallized from toluene, mp $179-180^{\circ}$.

Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96. Found: D, 78.07; H, 7.98.

Compound 4c.

This compound was recrystallized from ether-hexane, mp $118-119^{\circ}$.

Anal. Calcd. for $C_{12}H_{14}SO_3$: C, 60.51; H, 5.88. Found: C, 60.51; H, 5.95.

D. Phenylacetone.

Phenylacetone (2.6 equivalents) was added as a solution in THF to **1a**. After one hour the reaction mixture was hydrolyzed in the usual manner and extracted into chloroform. After drying and evaporating the chloroform, crystallization from toluene-hexane gave the sultone **4d** in 35% yield.

Table I

NMR Data

Compounds	Chemical Shifts in ppm
2	0.31 (s, 9H), 0.54 (s, 9H), 6.34 (d, J = 7 Hz, 1H), 7.0-7.9 (m, 8H)
3a	1.78 (s, 3H), 3.68 (s, 3H), 4.05 (s, 1H), 6.42 (s, 1H), 6.9-7.5 (m, 4H), 8.65 (s, 1H)
3b	1.9 (s, 3H), 2.3 (s, 3H), 3.75 (s, 3H), 4.15 (s, 1H), 7.0-7.8 (m, 4H), 8.6 (s, 1H)
3c	1.0-2.0 (m, 10H), 4.80 (s, 1H), 6.05 (s, 1H), 6.8-7.0 (m, 2H), 7.2-7.4 (m, 2H)
3d	1.45 (s, 3H), 2.15 (s, 1H), 3.0 (s, 2H), 6.20 (s, 1H), 6.8-7.5 (m, 9H), 8.36 (s, 1H)
4a	2.0 (s, 3H), 3.75 (s, 3H), 7.5-1.8 (m, 4H)
4c	1.6-2.2 (m, 10H), 7.1-1.9 (m, 4H).
4d	1.70 (s, 3H), 3.19 (ABq, 2H), 7.2-7.4 (m, 6H), 7.5-7.8 (m, 3H)
5	1.65 (s, 3H), 3.60 (ABq, 2H), 6.5-8.0 (m, 15H).
(carbon nmr)	26.74, 39.94 (a), 45.67, 98.72, 110.51, 111.05, 119.21, 119.54, 119.93, 120.49 (a), 120.61, 120.81, 121.87, 122.21, 125.81 (a), 126.90, 127.12, 128.38 (a), 130.41, 135.61 (a), 130.60 (a), 137.40 (a), 146.14 (a)
6	3.65 (s, 1H, exchanged by deuterium oxide); 6.51 (s, 1H), 7.1-7.6 (m, 11H), 7.9-8.1 (m, 2H)

(a) These peaks were determined by low power decoupling to be non-protonated carbons.

The mother liquors were subjected to chromatography on Activity II-III alumina using first 10% ether in toluene and then 3:1:1 toluene-ether-chloroform for elution. The former solvent eluted a product (260 mg, 22%) which was identified as compound **5**. The former solvent eluted **3d** (90 mg, 7%). Attempts at crystallization of **3d** were unsuccessful but the nmr provided unambiguous structural identification.

Further confirmation of the structure of **3d** was obtained by hydrolysis of the *N*-benzenesulfonyl derivative of **3d** made in the routine way from *N*-benzenesulfonylindole and phenylacetone. Overnight reflux in methanol containing 20% by volume of 10% NaOH solution gave **3d** in 50% yield as an oil accompanied by a 20% yield of the corresponding methyl ether. Compound **4d**, mp 117-118°, was recrystallized from toluene-hexane.

Anal. Calcd. for $C_{15}H_{13}SO_3$: C, 65.68; H, 5.15. Found: C, 65.67; H, 5.16.

E. Benzoyl Chloride.

A solution of benzoyl chloride (1 equivalent) in THF was added at -78°. A precipitate formed. The reaction mixture was hydrolyzed with cold dilute hydrochloric acid and the mixture extracted with chloroform. The residue was essentially pure product by tlc and was crystallized from dichloromethane-benzene in 90% yield, mp 143-145°.

Anal. Calcd. for $C_{21}H_{15}NO_3S$: C, 69.80; H, 4.18; N, 3.87. Found: C, 69.70; H, 4.18; N, 3.84.

F. *N,N*-Dimethylbenzamide.

One equivalent of *N,N*-dimethylbenzamide was added to the THF solution of **1a** and the solution stirred for 3 hours. The reaction mixture was processed by ammonium chloride hydrolysis and extraction gave

2-benzoylindole (20%) identified by comparison with an authentic sample.

Reaction of **1b** with Methyl Pyruvate.

The dilithiated intermediate (5mmoles) was transferred by syringe to a solution of methyl pyruvate (3 ml) in THF cooled to -78°. After 0.5 hour at -78° the solution was quenched with 10% methanolic acetic acid (10 ml) and poured into methylene chloride. The product mixture was separated by chromatography on silica using 2:1:1 hexane-ether-chloroform. The first fractions contained sultone **4** (40%). The indolic product **3b** was obtained in 25% yield, mp 130-132° after recrystallization from benzene-hexane.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48. Found: C, 66.86; H, 6.53.

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