REACTIONS OF ARYLSULFONYL COMPOUNDS WITH EXCESS ORGANOLITHIUM REAGENT

9. t-BUTYL 2,6-DILITHIOPHENYL SULFONE AS A PRECURSOR OF LITHIODEHYDROBENZENE*

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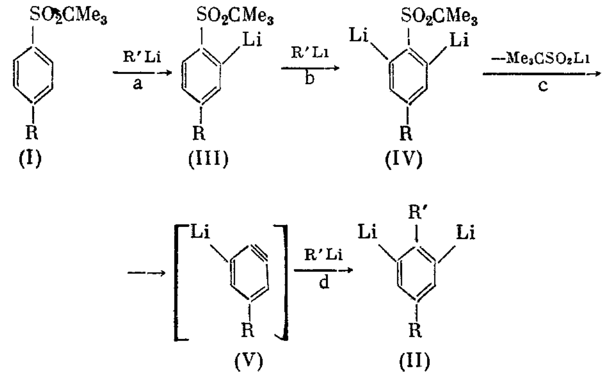
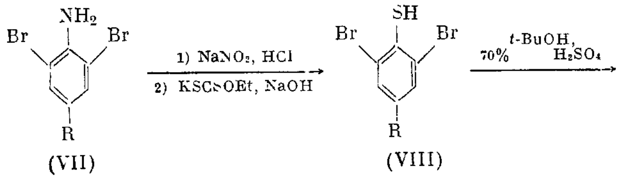
We have shown [2, 3] that t-butyl phenyl sulfone and its substituted derivatives (I) are converted by excess alkyllithium to 2,6-dilithio-1-alkylbenzenes (II). The first step *a* has been found to be metallation of sulfone (I) ortho to the sulfonyl group, forming the monolithio derivative (III). Furthermore, work pertaining to the effect of the para substituent on the rate of formation of p-substituted dilithioalkylbenzenes (II) suggests that these products are formed via a step involving the dilithio derivatives of sulfone (IV), which are unstable under these conditions, and that it is this step b, as the slowest, that determines the overall rate of the process, since steps c and d are far more rapid [3, 4].



R = H (a), CH_3(b)

To confirm the validity of this scheme we had to find conditions that would firstly allow the formation of lithiosulfones (IV) to be detected and that would secondly ensure the instability of the latter, thus facilitating their conversion to lithioalkylbenzenes (II) by reaction with excess R'Li. Conversion of (III) to (II) proceeds efficiently either when refluxed in ether or at −20°C or above in THF. We were unable to detect 2-(t-butylsulfonyl)isophthalic acid after carboxylation, which would imply the presence of compound (IV) in the system. For this reason we used an independent synthesis of these compounds from 2,6-dibromosulfones (VI), in the hope that Br−Li exchange could be brought about at a lower temperature than direct metallation of sulfones (I), thus preserving at least some of the dilithio derivative (IV) from decomposition.

The original 2,6-dibromides (VI) were prepared from the dibromoanilines (VII) by the scheme



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*For Part 8, see [1].

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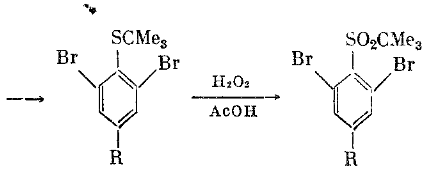


(IX) (VI)

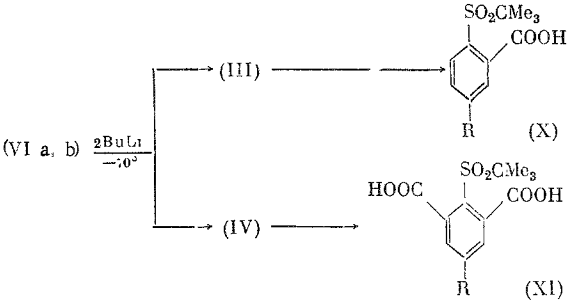
R = H (a), CH$_3$ (b)

The yields and properties of compounds (VI), (VIII), and (IX) appear in Table 1.

As expected, exchange of the Br atoms in the dibromosulfones (VIa, VIb) on treatment with n-BuLi proceeded smoothly between −65°C and −70°C in ether over a period of 1 h and even faster in THF−ether. The rate and completeness of exchange were easily checked by hydrolysis of samples removed from the reaction mixture and quantitative GLC analysis of the resulting sulfones (Ia, Ib) using an internal standard. The yields of sulfones (I) for various reaction times and solvents appear in Table 2.

It is important that treatment of dibromosulfone (VIb) with an equimolar quantity of BuLi gave after hydrolysis a mixture of sulfone (Ib) with t-butyl 2-bromo-4-tolyl sulfone in the ratio 1.6 : 1 (GLC), which indicates a higher rate of exchange of the second Br than the first.

The yields of sulfones (I) would seem to imply the exclusive formation of dilithio derivatives (IV) in the reaction of sulfones (VI) with BuLi. However carboxylation of the reaction mixture after Br− Li exchange showed that in addition to the 2,6-dilithio derivatives (IV) the reaction mixture contained monolithio derivatives (III).



R = H (a), CH$_3$ (b)

The quantitative distributions of (III) and (IV), determined in terms of the monocarboxylic and dicarboxylic acids (X) and (XI)* formed in carboxylation, depended on the nature of the solvent, the substituent R, and even the concentration of the solution (Table 3).

In THF−ether sulfone (VIa) formed a mixture of (IVa) and (IIIa) in the ratio 1.1 : 1, while in ether alone the quantity of dilithio derivative (IVa) rose to a ratio of 1.7 : 1; sulfone (VIb) in ether yielded primarily the dilithio derivative [(IVb) : (IIIb) = 4 : 1] with a slight change in total yield, which was 76-80%. Reduction of the con-

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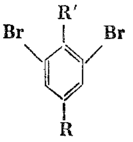
*We attempted to determine the ratio (III) : (IV) by deuterolysis of the reaction mixture and determination of the ratio of monodeutero to dideutero derivatives by mass spectrometry and PMR. However we concluded from the results that extremely rapid deuterium exchange takes place, the reasons for which remain unclear.

TABLE 1. Dibromo Derivatives



Compound	R′	R	Yield, %	mp, °C or bp, °C (p, mm Hg)	Found, %				Empirical formula	Calculated, %			
					C	H	S	Br		C	H	S	Br
(VIIIa)	SH	H	50	66—68									
(VIIIb)	SH	CH$_3$	61	50—51	29,81	2,17	11,37	56,70	$C_7H_6Br_2S$	29,81	2,14	11,37	56,68
(IXa)	SCMe$_3$	H	80	121—124* (0,5)	37,26	3,85	9,86	49,13	$C_{10}H_{12}Br_2S$	37,06	3,75	9,89	49,32
(IXb)	SCMe$_3$	CH$_3$	93	79—80	38,69	3,95	9,55	47,59	$C_{11}H_{14}Br_2S$	39,08	4,17	9,49	47,27
(VIa)	SO$_2$CMe$_3$	H	83	139—140	33,81	3,51	9,06	45,18	$C_{10}H_{12}Br_2O_2S$	33,73	3,40	9,00	44,88
(VIb)	SO$_2$CMe$_3$	CH$_3$	80	172—173	35,79	3,64	8,66	43,17	$C_{11}H_{14}Br_2O_2S$	35,70	3,81	8,66	43,18

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*n_D^{20} 1.6072.

TABLE 2. Yields of Sulfones (I) from Br–Li Exchange in Dibromides (VI) and Hydrolysis

$$(VIa, b) + 2BuLi \xrightarrow[H_2O]{-70^\circ} (Ia, b)$$

Original sulfone	Solvent	Reaction time from start of addition, min	Yield of (I), %*	
			GLC data	isolated
(VIa)	THE–ether	19	87	77
		29	83	
		62	82	
(VIb)	Ether	19	61	78
		29	65	
		62	91	
(VIb)	THF–ether	19	82	—
		29	90	
		62	91	

*See experimental section for the conditions used for isolation of products and quantitative GLC analysis.

centration of sulfone (VI) in ether was accompanied by a sharp reduction in the quantity of dilithio derivative (IV). The hitherto unknown dicarboxylic acids (XI) were isolated and characterized, and the monocarboxylic acids (X) were identified by comparison with authentic samples.

We find it difficult to regard the presence of the monolithio compounds (III) among the products of the reaction of dibromides (VI) with BuLi as resulting from partial hydrolysis of dilithio derivatives (IV) by water introduced with the solvent. According to the analytical data, the moisture content of the THF was not more than 0.01 mole/liter, and that of the ether was not more than 0.005 mole/liter. Even assuming that only the dilithio derivative (IV) was hydrolyzed forming (III), then the quantity of the latter should still have been several times less. The formation of (III), in all probability, involves reaction of the dilithio derivative (IV) with the solvent, toward which dilithiosulfones (IV) function as metallating agents. Parham and Sayed [5], for example, have discussed this phenomenon.

Thus we can consider it established that exchange of both atoms of Br for Li in dibromides (VI) is sufficiently rapid and complete at −70°C that up to 66% of the dilithio derivatives (IV) together with a more or less considerable quantity of the monolithio derivatives (III) are formed. If the temperature was raised to 0°C, then even after 10 min dilithio derivative (IV) disappeared, which was obvious from the absence of sulfone (I) in the hydrolyzate. Simultaneously t-butylsulfinic acid appeared in the reaction mixture. In the presence of excess BuLi dilithio derivatives (II) were formed; these on carboxylation gave good yields (Table 4) of the 2-n-butylisophthalic acids (XIIa, XIIb) previously described in [3].

The dilithio derivatives (II) are the end products of the reaction of sulfones (I) with dilithiumalkyls [3]. They are formed as a result of the addition of R'Li to lithiodehydrobenzene (V) (stage d). We consider the formation of (V) as adequately substantiated on the basis of our earlier experimental confirmation [4, 6, 7] of the existence of (V) as an intermediate in the reaction, together with the results of quantum-chemical calculations, which account for the directional nature of the attack on the nucleophile [8], and also other data.* The experimental evidence cited above implies that lithiodehydrobenzene (V) is generated directly from dilithiosulfone (IV) as a result of the elimination of t-butylsulfinate when the temperature is increased.

The significant reduction in the quantity of dilithio derivatives (IV) and the increase in the quantity of (II) ensued above a temperature between −22°C and −26°C. This we established by removing samples containing an added internal standard from the reaction mixture, followed by carboxylation and quantitative determination (GLC) of the resulting acids.

A kinetic study of this reaction ran into serious experimental difficulties involving not only heterogeneity of the reaction mixture, maintenance of stable subzero temperatures, etc., but also particularly the existence of side reactions, the most important of which are the formation of monolithio derivative (III) in the reaction of dilithio derivative (IV) with solvent and metallation of (III) with excess BuLi to (IV). Nevertheless we cannot

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*At present, we have available evidence that implies the addition to lithiodehydrobenzene (V) of relatively weak nucleophiles such as RO^-, Ph_2N^-, etc.

TABLE 3. Yields of Acids (X) and (XI) from Treatment of Sulfones (VIa and VIb) with BuLi (3 moles) at −70°C and Carboxylation

Original sulfone	Solvent	Concn. of (VI), mole/liter	Reaction time from start of addition, min	Yield of (X), %		Yield of (XI), %		Molar ratio (XI):(X)
				GLC data	isolated	GLC data	isolated	
(VIa)	THF−ether	0,2	20	38	18	41	27	1,1 : 1
	Ether	0,12	60	29	—	49	—	1,7 : 1
	»	0,06	60	22	—	15,5	—	0,7 : 1
(VIb)	»	0,08	60	16	—	66	45	4 : 1
	»	0,06	60	19,5	—	36	—	1,8 : 1

TABLE 4. Yields of 2-n-Butylisophthalic Acid (XIIa) and 2-n-Butyl-5-methylisophthalic Acid (XIIb) from a BuLi : (VI) Ratio of 7 : 1

Original sulfone	Solvent	Reaction product	Yield, %	
			GLC data	isolated
(VIa)	THF−ether	(XIIa)	57	—
	Ether	(XIIa)	57	46
(VIb)	»	(XIIb)	65	51

doubt that the lithium-substituted sulfone (IV) is the precursor of lithiodehydrobenzene (V) not only when it is prepared from dibromide (VI) but also in the metallation of sulfone (I). This is confirmed by recent observations. Among the carboxylation products from metallation of sulfone (I) at −70°C with the stronger metallating agent t-butyllithium, we detected 2-(t-butylsulfonyl)isophthalic acid (XI).

EXPERIMENTAL

Melting points were determined on a Boetius microscopic hot-stage. The PMR spectra were recorded with a DA-60-IL instrument (60 MHz) with hexamethyldisilane as internal standard. Chemical shifts in ppm are referred to the δ scale relative to TMS. Gas−liquid chromatography was carried out with an LKhM-8MD-5 instrument equipped with a flame-ionization detector and stainless-steel columns. Column A: (2.25 m × 3 mm) with 1% Silicone GE SE-30 (Werner Günther) on glass beads, 60-80 mesh (Varian Aerograph, USA), efficiency 650 theoretical plates. Column B: (1.9 m × 3 mm) with 7% PFMS-4 on Chromosorb G-AW, 60-80 mesh. Carrier gas was argon or nitrogen, flow rate 40 ml/min. Quantitative GLC analysis was carried out using internal standards and preliminary calibration with synthetic mixtures. The column temperature, retention indices, and internal standards for the quantitative determination are stated below.

2,6-Dibromothiophenol (VIIIa). After adding a mixture of concentrated HCl (20 ml) and ice (20 g) to a stirred solution of 2,6-dibromoaniline (25.1 g) [9], a cooled solution of $NaNO_2$ (7.4 g) in water (18 ml) was gradually added to the resulting suspension. After stirring for 2 h at 4°C, the resulting solution was added over a period of 1 h to a solution of calcium ethylxanthonate (19 g) in water (24 ml), maintained at 50°C; the reaction mixture was held at this temperature for a further 0.5 h and then left overnight. Using the method of [10], steam-distillation, extraction with $CHCl_3$, and reprecipitation from alkaline solution with acid gave thiol (VIIIa) (14.2 g, 53%), mp 66-68°C (from alcohol).

Reprecipitation or dissolution in ether of (VIIIa) led to the isolation of small quantities of bis(2,6-dibromophenyl) disulfide, mp 238-240°C (from benzene). Found: C 26.95; H 1.13; Br 59.93; S 12.02%. $C_{12}H_6Br_4S_2$. Calculated: C 26.99; H 1.13; Br 59.86; S 12.01%.

2,6-Dibromo-4-thiocresol (VIIIb) was prepared in the same way as (VIIIa) (Table 1).

t-Butyl 2,6-Dibromophenyl Sulfide (IXa). The method described in [11] for t-butyl 2-naphthyl sulfide gave (IXa) from (VIIIa) (16.3 g) in ether (150 ml), t-butyl alcohol (23.8 g), concentrated H_2SO_4 (105 ml), and water (60 ml) after stirring for 18 h.

t-Butyl 2,6-Dibromo-4-tolyl Sulfide (IXb) was prepared in the same way as (IXa). The yields, physical constants, and analyses of sulfides (IX) appear in Table 1.

t-Butyl 2,6-Dibromophenyl Sulfone (VIa). Sulfide (IXa) (14.4 g) in glacial AcOH (350 ml) was mixed with 24% H_2O_2 (75 ml) in glacial AcOH (100 ml) and the reaction mixture was left for 14 days at 20°C, whereupon it was cautiously concentrated to half volume under vacuum and diluted with water. We obtained sulfone (VIa) (13.9 g, 83%), mp 138-140°C (from aqueous alcohol). (Under normal oxidation conditions [11] we observed the formation of a water-soluble product, which we did not investigate further.)

The PMR spectrum (in CH_2Cl_2): 1.45 c (t-Bu); 7.20 and 7.80 (seven lines, A_2B spectrum, identical with the calculated spectrum [12], $H_{3(5)}$ and H_4); $J_{3(5),4} = 8.0$ Hz. Intensity ratio 3:1.

t-Butyl 2,4-Dibromo-4-tolyl Sulfone (VIb) was prepared from sulfide (IXb) in the same way as (VIa). PMR spectrum (in CH_2Cl_2): 1.43 c (t-Bu); 2.29 c (CH_3); 7.72 c ($H_{3(5)}$; intensity ratio: 9:3:2.

Bromine-Lithium Exchange in Dibromides (VI)

a) t-Butyl Phenyl Sulfone (Ia) from (VIa). A solution of dibromide (VIa) (5 μmole) in THF (15 ml) was cooled to −70°C and, at a temperature maintained between −70°C and −65°C, n-BuLi (15 μmole) in ether (here and subsequently as a 1.5 N solution) was stirred in over a period of 7-10 min. The resulting greenish-yellow, mobile, opaque mass after 15 min stirring was poured into water and extracted with ether; the ethereal extract was washed, dried over $MgSO_4$, and evaporated under vacuum. We obtained sulfone (Ia) (0.76 g), mp 98-99°C (from hexane), identical to an authentic sample (mixed melting point, GLC, and TLC). The variation in the yield of sulfone (Ia), determined by GLC analysis, as a function of reaction time appears in Table 2.

After reaction of BuLi (5 μmole) and sulfone (VIa) (5 μmole) in a stirred ethereal solution (30 ml) at −70°C for 1 h, quenching with water and treatment as before gave a mixture (1.11 g) of sulfone (Ia) with t-butyl 2-bromophenyl sulfone in a molar ratio of 1.6:1 (GLC, column B, 233°C, internal standard t-butyl 4-t-butylphenyl sulfone).

b) t-Butyl 4-Tolyl Sulfone (Ib) from (VIb). After addition of n-BuLi (15 μmole) over a period of 10 min to a stirred suspension of dibromosulfone (VIb) (5 μmole) in absolute ether (30 ml), at a temperature maintained at ~−70°C, the reaction mixture was stirred for 1 h and then poured into water and extracted with ether. We obtained sulfone (Ib) (0.83 g, 78%), mp 118-120°C (from hexane), identical to an authentic sample (mixed melting point, TLC, and GLC). The yields of (Ib) for various reaction times and different solvents appear in Table 2. For quantitative analysis accurate weighed quantities of sulfones (VI) and of the internal standard − t-butyl 4-t-butylphenyl sulfone − were treated with BuLi under the conditions specified above; samples were removed from the reaction mixture and quenched as described above. The analysis of (Ia) was carried out with column A at 206°C, and that of sulfone (Ib) with column B at 230°C.

c) 2-(t-Butylsulfonyl)isophthalic Acid (XIa). After addition of BuLi (1.79 g) in ether over 15 min to a solution of sulfone (VIa) (3.3 g) in absolute THF (26 ml) at −70°C, the reaction mixture was stirred for 5 min at this temperature and poured onto dry ice in ether. When the temperature had reached ~20°C, it was evaporated to dryness in a rotary evaporator; the residue was treated with ether (100 ml) and filtered. The dry precipitate from the filter was gradually added to a mixture of concentrated HCl (10 ml) and ether (80 ml). The layers were separated; the aqueous layer was extracted several times with ether and the combined ethereal extracts were dried over $CaCl_2$ and concentrated under vacuum. The residue (3.84 g) was treated several times with $CHCl_3$ under reflux and the insoluble residue was filtered off. Recrystallization from $CHCl_3$−ether gave acid (XIa) (0.72 g, 27%), mp 184.5-185.5°C (dec.). Found: C 50.19; H 4.92; S 11.01%. $C_{12}H_{14}O_6S$. Calculated: C 50.34; H 4.93; S 11.20%.

The dimethyl ester [by CH_2N_2 treatment of acid (XIa)] had mp 138-139°C (from heptane). Found: C 53.37; H 5.83; S 10.14%. $C_{14}H_{18}O_6S$. Calculated: C 53.49; H 5.76; S 10.20%. PMR spectrum [in $(CD_3)_2CO$]: 1.38 c (t-Bu); 3.85 c ($COOCH_3$); 7.63 ($H_{4(6)}$); 7.80 (H_5) (seven lines A_2B spectrum, identical to the calculated spectrum [12]); $J_{4(6),5} = 7.8$ Hz; intensity ratio 3:2:1.

The chloroform extracts after removal of acid (XIa) were combined and evaporated; the residue was recrystallized from water and then treated with CH_2N_2. We isolated methyl 2-(t-butylsulfonyl)benzoate (Xa) (0.4 g, 18%), mp 138-142°C, which was identical to an authentic sample.

d) 2-(t-Butylsulfonyl)-5-methylisophthalic Acid (XIb). After addition of BuLi (30 μmole) over 10 min to sulfone (VIb) (10 μmole) in ether (100 ml) at −70°C, the reaction mixture was stirred at this temperature for 1 h and then poured onto dry ice in ether. When the temperature had reached ~20°C, water (50 ml) was added; the ethereal layer was separated; the aqueous layer was concentrated under vacuum, acidified with concentrated HCl, and extracted with ether. The ethereal extract was dried over $CaCl_2$, and evaporated under vacuum; residual water was removed by distillation with benzene. The solid product was treated with $CHCl_3$ (3 × 25 ml) under reflux. The insoluble precipitate (1.53 g) contained acid (XIb) (88%, GLC). After repeated treatment with $CHCl_3$

under reflux acid (XIb) had mp 203-205°C (dec.) and still contained up to 8% of monocarboxylic acid (Xb) as an impurity.

The dimethyl ester had mp 143-144°C (from heptane). Found: C 54.84; H 6.04; S 9.76%. $C_{15}H_{20}O_6S$. Calculated: C 54.86; H 6.14; S 9.76%. PMR spectrum [in $(CD_3)_2CO$]: 1.38 c (t-Bu); 2.45 c (CH_3); 3.85 c ($COOCH_3$); 7.45 c ($H_{4(6)}$); intensity ratio 9:3:6:2.

e) 2-n-Butylisophthalic Acid (XIIa) from Dibromosulfone (VIa). After addition of n-BuLi (2.24 g) to a solution of sulfone (VIa) (1.78 g) in ether (30 ml) at −70°C over a period of 10 min, the reaction mixture was stirred for 1 h, whereupon the temperature was allowed to rise to 0°C and after 2 h stirring the reaction mixture was poured onto dry ice in ether. When the temperature had reached ~20°C water was added; the aqueous layer was separated, washed with water, and acidified. We obtained acid (XIIa) (0.51 g, 46%), mp 204-207°C (from CH_3CN). The acid was identical to an authentic sample (mixed melting point and chromatographic properties).

f) 2-n-Butyl-5-methylisophthalic Acid (XIIb) from Sulfone (VIb). Sulfone (VIb) (1.85 g) in ether (50 ml) and n-BuLi (2.24 g) under the conditions described for acid (XIIa) gave acid (XIIb) (0.6 g), mp 212.5-214°C (from CH_3CN), identical to an authentic sample.

The yields of acids (X)-(XII), determined by quantitative GLC analysis, for various combinations of the initial concentration of sulfones (VI) and reaction times appear in Tables 3 and 4.

For quantitative analysis accurate weight quantities of sulfone (VI) and of the internal standard − tricosane ($C_{23}H_{48}$) − were treated with BuLi under the conditions specified above (see also Tables 3 and 4). Samples removed from the reaction mixture were carboxylated, acidified, and extracted with ether; the ethereal extract was treated with CH_2N_2 and analyzed with column A at 208°C and with column B at 252°C. Retention indices: 1700, 2090 (XIIa); 1840, 2135 (XIIb); 1840, 2260 (Xa); 1945, 2355 (Xb), 2070, − (did not emerge) (XIa); 2170, − (XIb). t-Butylsulfinic acid was determined as described in [1].

CONCLUSIONS

1. t-Butyl 2,6-dilithiophenyl sulfone, originating from the reaction of the corresponding dibromo derivative with BuLi at −70°C and stable at this temperature, decomposes above −25°C forming 3-lithio-1,2-dehydrobenzene. The existence of the latter was confirmed by the formation of 2,6-dilithio-1-n-butylbenzene, its adduct with butyllithium.

2. Conversion of t-butyl phenyl sulfone to lithiodehydrobenzene with organolithium reagents goes via a step involving formation of the 2,6-dilithio derivative of the sulfone.

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