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METALATION OF ALKYL ARYL SULFONES: QUALITATIVE AND QUANTITATIVE PRODUCT DETERMINATION

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Summary

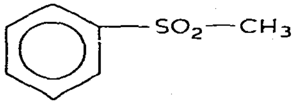
The metalation of methyl phenyl sulfone (I) and methyl naphthyl sulfone (II) was investigated under a variety of conditions. The product species were determined qualitatively and quantitatively after characterization with some electrophilic agents. After the primary metalation at the methyl position, species of various metalation degrees were present simultaneously, including the 1,1,1-trimetalated derivatives. With high LiR/sulfone ratios, in addition to the products of the primary metalation, compounds arising from metalation of the aromatic ring were formed as well as those from reduction, cleavage, etc.

Introduction

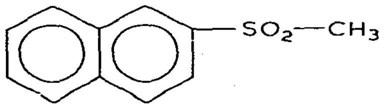
Although there have been many published reports on the metalation of sulfones and the characterization of the products of reaction with various electrophiles [1—8], in only a few reports [9,10] was it pointed out that the process is not selective, and that species involving various degrees of metalation are obtained.

Recent ^{13}C NMR studies [11] on chemical shifts and J(CH) coupling constants have provided information on the structure of the monometalated products, but they are still a matter of controversy [12,13]. Structures probably stabilized by d_π—p_π interaction between the sulfur and carbon atoms have been proposed [4] for the *gem*-dimetalated products, but little, if any information is available concerning the formation of 1,1,1-trimetalated derivatives. Some time ago studies on the preparation of 1,1,1-trilithio derivatives of functionalized active hydrogen compounds were announced [14], but to our knowledge no reports of work on this subject have appeared.

We have investigated the metalation of the alkyl aryl sulfones I and II which, at least in principle, can be completely metalated at the methyl position to give 1,1,1-trimetalated products. The characterisation of the species formed when I



(I)



(II)

and II react with lithium alkyls under various experimental conditions is also described.

Results and discussion

The metalation process is schematized in Fig. 1. The products are the mono-, di- and tri-lithio species, denoted by ML, DL, and TL, respectively, if metalation of the aromatic ring is excluded from consideration. These species were identified and determined quantitatively by analyzing the products of their reactions with alkyl halides. For this purpose pure A, B and C (see Fig. 1), in which R is either a phenyl or a naphthyl group and R′ is a methyl group, were synthesized and their gas chromatographic characteristics were established. As shown in Fig. 2 some of the alkylated products might arise from metalation during reaction with R′X. It is possible, for example, that B is formed both directly from DL and indirectly from ML via the reactions (b) and (c) depicted in Fig. 2. However, the results reported in Table 1 clearly demonstrate the absence of stepwise reactions. This finding agrees with reports [15] that both the equilibrium and kinetic acidity of a sulfone decrease when an alkyl group is introduced at the acidic site. Therefore, metalation of the alkyl derivatives is unlikely.

The mechanism of formation of the metalated species is still unknown; DL and TL can be obtained both from metalation of ML and DL or by disproportionation:

$$2\,\mathrm{ML} \rightarrow \mathrm{S} + \mathrm{DL} \qquad 2\,\mathrm{DL} \rightarrow \mathrm{TL} + \mathrm{ML}$$

For quantitative determination of the metalated product, reaction with alkyl

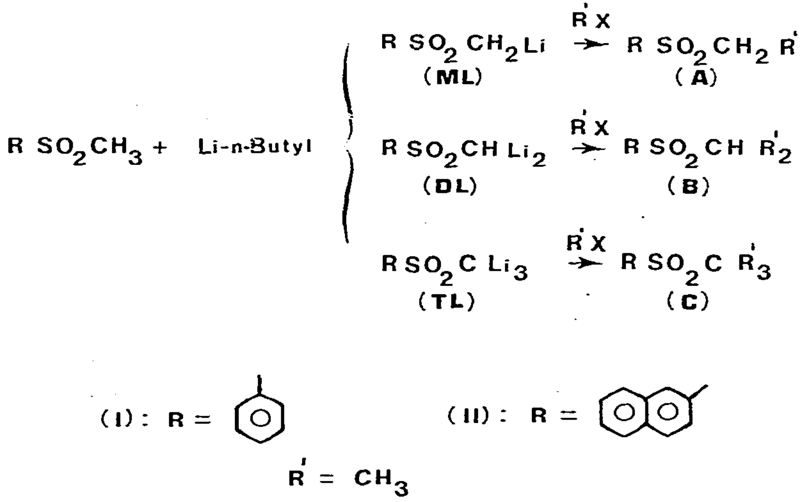
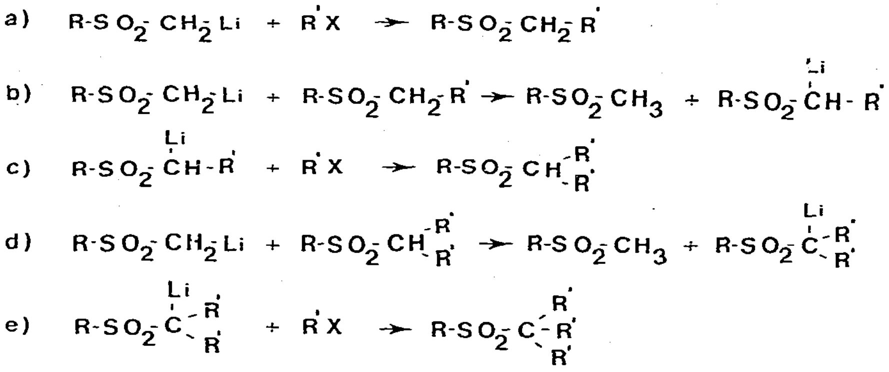


Fig. 1. Metalation scheme and characterization with alkyl halides.



and other similar reactions.

Fig. 2. Scheme of stepwise reactions.

halides might be unsatisfactory because the various species may have different reactivities. Therefore the metalated products were also characterized by treatment with D_2O/DCl (see Fig. 3) and the corresponding derivatives were analyzed by MS. The results with the two different electrophilic agents reported in Table 2 are in very good agreement.

The metalation of I and II was also studied under a variety of experimental conditions (temperature, time and LiR/sulfone ratio) (Table 3). The behaviour of the two sulfones is quite similar: at low temperatures longer reaction times are required, but the products are almost the same. As expected, the LiR/sulfone ratio is the most important factor, strongly affecting the composition of the metalated products.

At ratios higher than those reported in Table 3, these is an increase in species involving an even higher degree of metalation, and secondary reactions occur as shown in Table 4. Furthermore, the results following treatment with CH_3I (GC analyses), are in poor agreement with those following treatment with D_2O/DCl (MS analyses): lower values for the TL species are obtained with CH_3I. As mentioned above the various species formed in the metalation of sulfones I and II

TABLE 1

TESTS FOR STEPWISE REACTIONS

Sample	Procedure [a]	Products (mol%)			
		S	A	B	C
1	Sulfone S [b] is metalated with Li-n-butyl and characterized with CH_3I	10	85	5	—
2	One part of sample 1 before derivatization is added to one part of A and the mixture is characterized with CH_3I.	10	185	5	—
3	One part of sample 1 before derivatization is added to one part of B and the mixture is characterized with CH_3I	10	85	105	—

[a] Other data are reported in the experimental section. [b] S = II.

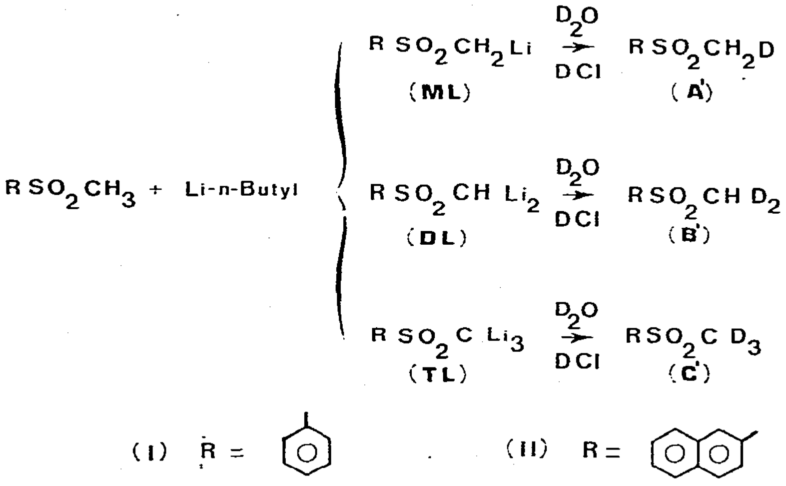


Fig. 3. Metalation scheme and characterization with D_2O/DCl.

TABLE 2

CHARACTERIZATION WITH VARIOUS ELECTROPHILES

Sulfone	LiR/sulfone (mol)	Electrophile	Characterization products (mol.%)						
			S	A	A'	B	B'	C	C'
I	1.0	CH_3I	13.4	77.6		9.0		traces	
		D_2O/DCl	13.6		76.6		8.8		1.0
II	1.0	CH_3I	11.0	79.5		9.5		traces	
		D_2O/DCl	10.0		80.0		9.0		1.0

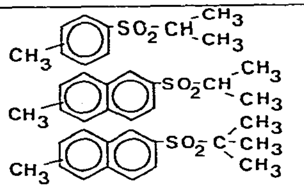
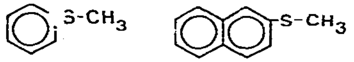
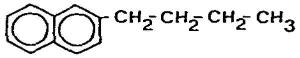
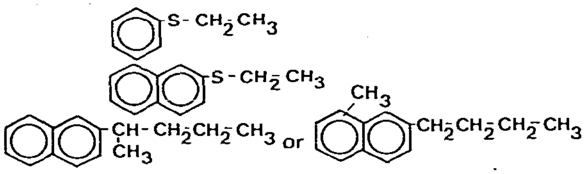
TABLE 3

METALATION OF I AND II UNDER VARIOUS EXPERIMENTAL CONDITIONS

Sulfone	Li-n-butyl/ sulfone (mol)	Temp. (°C)	Time (min)	Products (mol.%)				
				S	A'	B'	C'	No. D/mol
I	1.00	—78	60	20.2	69.2	6.3	1.3	0.91
	1.00	—78	240	13.2	77.0	7.2	1.6	0.96
	1.00	—78	300	7.2	80.3	8.8	1.7	1.03
	0.85	25	15	19.3	78.0	2.2	0.5	0.84
	0.93	25	15	12.6	83.6	3.1	0.7	0.92
	1.00	25	15	11.0	81.0	7.5	0.5	0.98
	1.07	25	15	8.0	79.0	11.0	2.0	1.07
	1.22	25	15	7.0	62.0	28.0	3.0	1.27
II	0.93	25	15	10.6	86.8	2.1	0.5	0.93
	1.00	25	15	10.0	80.0	9.0	1.0	1.01
	1.00	25	15	10.0	81.0	8.0	1.0	1.00
	1.10	25	15	7.2	76.2	13.5	3.1	1.12
	1.30	25	15	6.8	61.6	28.4	3.4	1.29

TABLE 4

SECONDARY REACTIONS AND PRODUCTS

Reactions	Characterization products with CH_3I [a]
– Secondary metalation on aromatic ring	
– Reduction	
–Cleavage	
–Other type of secondary metalation	

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[a] For D_2O/DCl characterization, only some of the products corresponding to those reported here were found: see the Experimental section.

could have different reactivities toward different electrophiles, and so the TL species might be more readily characterized with D_2O/DCl than with CH_3I, while this might not be true for the ML and DL derivatives. The GC and MS data for the products characterized with D_2O/DCl afford semiquantitative values for primary metalation at the CH_3 position as well as for secondary metalation at the aromatic ring and other secondary reactions. From the GC analyses the total amount of variously deuterated sulfones I and II with respect to all products formed from reduction, cleavage and other types of secondary metalation can be determined. Furthermore, from MS data for the molecular ions, the distribution of deuterated species can be obtained, while the data for the $(M - CH_3)^+$ ions give the primary and the secondary metalation ratios. Results of the metalation of I and II at high LiR/sulfone ratio and the characterization with D_2O/DCl are reported in Table 5. When II was metalated at a still higher

TABLE 5

METALATION [a] OF I AND II AT HIGH LiR/SULFONE RATIOS

Sulfone	LiR/sulfone (mol)	Reaction products characterized with D_2O/DCl (mol.%)				
		Primary metalation			Secondary metalation of the aromatic ring	Cleavage, reduction and other reactions
		A'	B'	C'		
I	3.0	7	39	32	12	10
II	2.5	4	65	19	12	10

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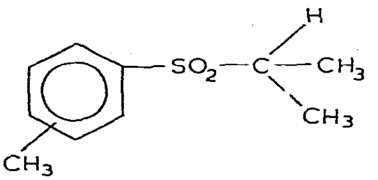
[a] Additional data are reported in the experimental section.

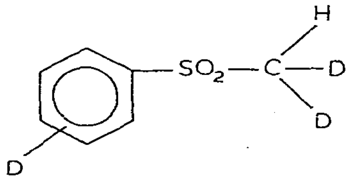
ratio (3.0), secondary reactions became very competitive. This probably accounts for the low yield of 1,1,1-trimetalated products from I and II.

Conclusions

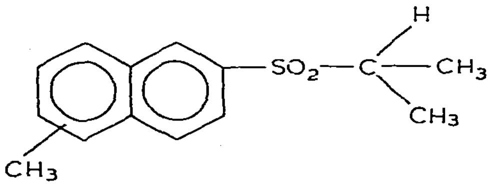
As already reported for sulfolane [9], species with various metalation degrees are formed simultaneously in the metalation of the alkyl aryl sulfones I and II, and the formation of the mono, *gem*-di and 1,1,1-trimetalated species has been demonstrated. In addition, products of aromatic ring metalation were also obtained, in particular C″(I), C‴(I), C″(II) and C‴(II). The presence of C″ and C‴ together with C and C′ suggests the following possible reactions (eq. 1). The stabilizing effect proposed for the *gem*-dimetalated species [4] could play an important role in this case.



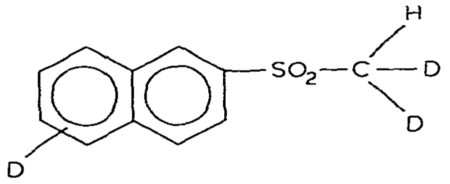
C″(I)



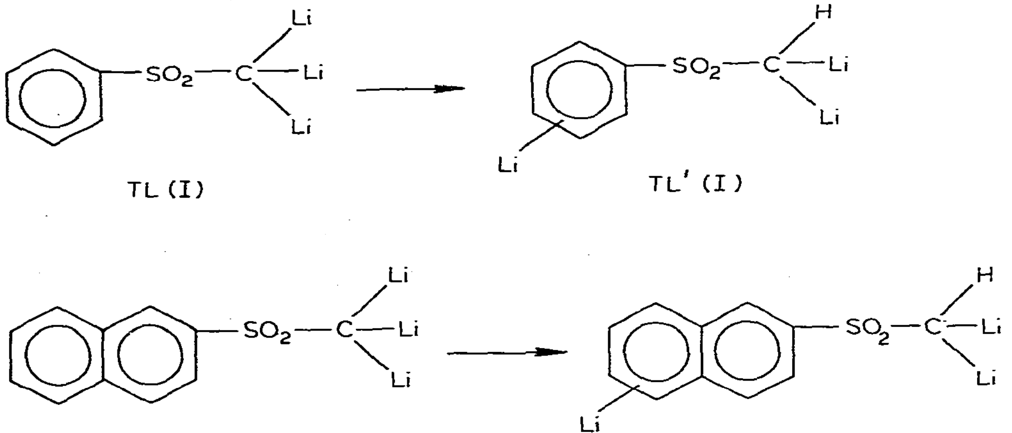
C‴(I)



C″(II)



C‴(II)



TL(I)

TL′(I)

TL(II)

TL′(II)

(1)

Experimental

Materials

Li-n-butyl was used as a 2 molar hexane solution. THF (tetrahydrofuran) was freshly distilled from $LiAlH_4$ prior to use. $PhSO_2CH_3$ was purchased from K&K. $NpSO_2CH_3$ (Np = 1-naphtyl) [16], $NpSO_2CH_2CH_3$, $NpSO_2CH(CH_3)_2$, $PhSO_2CH_2CH_3$ and $PhSO_2CH(CH_3)_2$ were prepared by standard oxidations of the corresponding sulfides. $NpSO_2C(CH_3)_3$ and $PhSO_2C(CH_3)_3$ were prepared from $NpSO_2CH(CH_3)_2$ and $PhSO_2CH(CH_3)_2$, respectively, by metalating with Li-n-butyl and reacting the product with CH_3I.

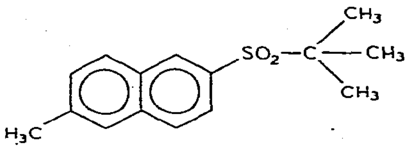
The ^1H NMR spectra for all these sulfones were as expected. The eight most abundant peaks in the mass spectra of the above sulfones are: $PhSO_2CH_3$: *m/e* (rel. int.); 77(100), 51(36), 94(30), 156($M^{+\cdot}$23), 141(22), 50(20), 65(15), 15(11). $PhSO_2CH_2CH_3$: *m/e* (rel. int.): 77(100), 78(90), 94(60), 51(60), 170($M^{+\cdot}$42), 141(30), 29(29), 142(24). $PhSO_2CH(CH_3)_2$: *m/e* (rel. int.): 78(100), 142(72), 43(56), 77(53), 51(30), 41(27), 143(20), 94(15), 184($M^{+\cdot}$ 7). $PhSO_2C(CH_3)_3$: *m/e* (rel. int.): 57(100), 41(30), 29(18), 77(16), 78(14), 51(14), 39(9), 143(6), 198($M^{+\cdot}$ 0.3). $NpSO_2CH_3$: *m/e* (rel. int.): 127(100), 206($M^{+\cdot}$ 56), 128(20) 115(20), 191(16), 143(12), 126(12), 77(12). $NpSO_2CH_2CH_3$: *m/e* (rel. int.): 127(100), 220($M^{+\cdot}$50), 128(43), 175(42), 115(23), 126(20), 176(18), 191(17). $NpSO_2CH(CH_3)_2$: *m/e* (rel. int.): 192(100), 128(90), 127(82), 234($M^{+\cdot}$ 74), 43(40), 144(36), 176(20), 126(20). $NpSO_2C(CH_3)_3$: *m/e* (rel. int.): 57(100), 192(82), 128(56), 127(44), 29(16), 193(14), 41(13), 115(12), 248($M^{+\cdot}$ 10).

Reactions

(1) Metalation. The procedure has been described previously [17].

(2) Tests for lithiation during the characterization procedure. Sulfone (II) (3 mmol) was metalated with Li-n-butyl (3 mmol) in THF/hexane solution (30 ml) at room temperature for 15 min, and the solution was divided into three equal aliquots. The first or test sample was treated with CH_3I for 15 min and analyzed by GC. The second aliquot was treated with an equimolar amount of $Ph_2SO_2CH_2CH_3$ for 15 min at room temperature, with stirring. After characterization with CH_3I the product was analyzed by GC. Finally, $Ph_2SO_2CH(CH_3)_2$ was added to the third portion (equimolar amount) and the product mixture was treated as described above for the second portion. The results are reported in Table 1.

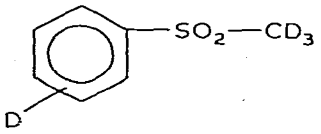
(3) Reaction at high LiR/sulfone ratio. Metalation is performed at Li-n-butyl/sulfone ratios of 2.5—3.0. The products of reaction with CH_3I were analyzed by GC—MS. In addition to compounds methylated at the CH_3 position (A, B and C) products of methylation in the aromatic rings like C″(I), C″(II) and III



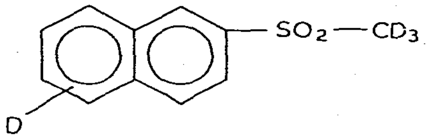
(III)

were also found. These compounds were easily identified by comparison of their mass spectra with those of the derivatives with no aromatic ring methylation. The ions resulting from the alkyl portion have the same *m/e* values while those containing the aryl group are 14 m.u. higher. The other compounds reported in Table 4 were identified by means of GC—MS by comparison or analogy with literature data.

When the characterization was performed with D_2O/DCl, compounds deuterated in the CH_3 position (A′, B′ and C′) and products deuterated in the aromatic ring, such as C‴(I), C‴(II), IV and V were found. Among the products of other secondary reactions, one compound, whose mass spectrum showed a molecular ion at *m/e* 185 and the most abundant fragment at *m/e* 142, was consistent with a n-butylnaphthalene, monodeuterated either in the aromatic ring or on the alkyl chain in the position α to the aromatic ring.



(IV)



(V)

It must be noted that the methyl derivatives are more readily characterized by MS than the deutero derivatives, since mono- (A), di- (B) and even trimethyl derivative isomers (C and C″) give separate GC peaks allowing the MS of the single component to be recorded. This is not possible for the deutero-derivatives, which show a single GC peak.

Analyses

^{1}H NMR spectra were recorded on a Varian HA-100 spectrometer. Mass spectra were obtained with a LKB 9000 instrument at 70 eV with an ion source temperature of 290°C. For both sulfones the percentage of each deuterated species was determined by MS using the molecular ions and that of the secondary metalation at the aromatic ring was determined by use of $M - \mathrm{CH(D)}_3$ ions. Corrections were made for the natural content of ^{13}C, ^{2}H, ^{17}O, ^{33}S and ^{34}S. The results reported represent the average of five determinations.

GC analyses were carried out with a C. Erba Fractovap Model C instrument, using a column (l 3—5 m) packed with SE 30 (5%) on Chromosorb W (60—80 mesh) (T_c 150—200°C; T_{ev} = 200—250°C; He carrier gas, flow rate 1 ml/s).

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