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THE METALATION OF THIOANISOLE AND THIOPHENETOLE WITH n-BUTYLLITHIUM

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SUMMARY

The metalation of thioanisole and thiophenetole with n-butyllithium in ether has been reinvestigated with careful product analysis. Thioanisole metalates initially in the ring with shift of lithium to the methyl group, probably by transmetalation, although the possibility of concurrent initial attack of the methyl group by n-butyllithium was not excluded by the data.

The metalation of thiophenetole occurred at all ring positions with unexpectedly large amounts (compared with phenetole) of *meta* and *para* attack. Also unexpected were large amounts of cleavage of the sulfur-to-phenyl bond leading to phenyllithium. Only small amounts of metalation in the α-position of the ethyl group were indicated by the product composition. It is postulated that initial ring attack is followed by transmetalation of the α-position of the ethyl group, and that this species undergoes a rapid intramolecular cleavage of the sulfur-to-phenyl bond.

INTRODUCTION

Gilman and Webb[1] in 1940 first observed the metalation of methyl phenyl sulfide with n-butyllithium in the methyl group ("lateral metalation"), and this result was in contrast to the ring metalation of many related types. In a subsequent paper[2] these authors examined the metalation of thioanisole under a variety of conditions and with several different metalating agents. They also extended the study to higher alkyl phenyl sulfides and to several other methyl aryl sulfides[2]. In general the higher alkyl phenyl sulfides metalated (n-BuLi) in the ring in rather poor yield (< 20%) and the methyl aryl sulfides metalated (n-BuLi) in the methyl group in yields up to about 40% based on the starting sulfide.

More recent work by Peterson and Hays[3] has demonstrated metalation (n-BuLi and tert-BuLi) of dimethylphenylphosphine and methyldiphenylphosphine in the methyl group in yields up to about 50%.

In a continuing program[4-6] of careful analysis of acidic reaction products from metalation and carbonation of various aromatic substrates, we have re-examined the metalation of thioanisole and thiophenetole, since the earlier work had been done before the advent of vapor phase chromatographic separation methods. We were primarily interested in the degree of selectivity in ring *vs.* methyl group competition in the position of metalation.

RESULTS AND DISCUSSION

Metalations were conducted with 0.15 mole of n-butyllithium and 0.20 mole of alkyl phenyl sulfide in ether. The reaction mixture was carbonated with solid carbon dioxide and the total acidic product treated with diazomethane. The resulting mixture of methyl esters was chromatographed. Identification of components was made by comparison of retention times with known compounds and quantitative determination of the components was made from peak area measurements on known mixtures of approximately the same composition as the unknowns.

It was soon noted that thioanisole, unlike other aromatic substrates investigated previously (*e.g.*, phenetole[5]) showed a different distribution of isomers among the products depending on reaction time. The results are summarized in Table 1. In our analytical system it was not found possible to separate the products from *ortho* and *meta* substitution and these products are listed together.

TABLE I

THIOANISOLE METALATION RESULTS

Reaction time	Yield[a] (%)	Product composition (mole %) resulting from metalation at indicated position		
		Methyl	*Ortho* and *meta*	*Para*
5 min	30	63	37	<0.5 (trace)
1 h	33	90	9	1.3
15 h	42	96	4	<0.5 (trace)

[a] Based on n-butyllithium and total acidic product excluding valeric acid.

It is apparent that as reaction proceeds, the product from metalation in the methyl group increases and that from ring metalation decreases. The results are immediately remindful of those of Benkeser and co-workers[7,8] from the metalation of ethylbenzene and isopropylbenzene with alkylsodium and alkylpotassium reagents, and similar interpretations are applicable to both cases. Ring metalation by n-butyllithium occurs faster than or at about the same rate as methyl group attack (kinetic phase), but in time the aryllithium first formed metalates aryl methyl sulfide in the methyl group (equilibrium phase).
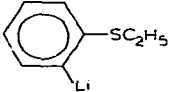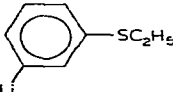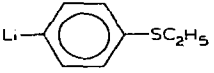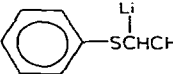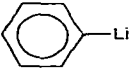

It is of interest to note that Gilman and Webb[1] surmised without any confirming data that the above route may be followed to the methyl group metalated product. They state "There is a possibility that nuclear metalation may have occurred

initially, and that the lithium then migrated to the methyl group. This remains to be established."

The changes in the amount of *para* isomer shown in Table 1, while small are outside the limits of experimental error. The data indicate that the *para* position is metalated more slowly than the *ortho/meta* combination, and further that the *p*-lithiothioanisole metalates thioanisole more slowly than the others.

Several interesting results were obtained from the metalation of thiophenetole. Here it was possible to determine all three ring-substituted products, although there was some overlap of the *ortho* and *meta* isomer peaks. The acidic product mixture from runs at two widely different reaction times were analyzed with the results as shown in Table 2.

TABLE 2

THIOPHENETOLE METALATION RESULTS

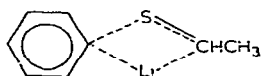| Product	Mole % of product[a]	
	Run 1 (15 h)	Run 2 (140 h)
-SC$_2$H$_5$ (Li ortho)	55	33.5
-SC$_2$H$_5$ (Li meta)	18.5	12
Li- -SC$_2$H$_5$ (para)	5	2.5
-SCHCH$_3$ (Li)	1.5	0.5
-Li	20	51.5

[a] The data are $\pm 0.3\%$ or better.

First it should be pointed out that Gilman and Webb[2] report two 15 h metalation runs with the isolation after carbonation of 7.7 and 5.4% 2-(ethylthio)benzoic acid and in one run 3.3% of benzoic acid based on thiophenetole introduced in the reaction. No metalation in the ethyl group or at ring positions other than *ortho* was reported in these runs or in the metalation of other alkyl phenyl sulfides.

In our experiments, run 1 (15 h) showed approximately a 27% conversion of the thiophenetole introduced to mixed carboxylic acids. The corresponding figure for the 140 h run was 22%. The rather large amounts of *meta* and *para* metalation are surprising in view of the small (*ca.* 1%) observed in the metalation of phenetole[5]. These results seem to weaken further[4] the strong mechanistic case, made repeatedly

in the past, for the predominate role of a cyclic transition state, derived from a complex between RLi and the basic center on the aromatic substrate, in picking off a proton from an adjacent *ortho* position.

We were able to find evidence for some metalation in the α-position of the ethyl group, but the amount is surprisingly low compared with the thioanisole case. Also surprising is the large amount of phenyllithium in the product. This must have arisen from cleavage of the sulfur-to-phenyl bond by some organolithium species. The data in Table 2 show a large increase in phenyllithium from the 15 h run to the 140 h run with corresponding decreases in the ring metalated products. At the same time the total amount of carboxylic acid mixture containing the components of Table 2 was no greater in the 140 h run than in the 15 h run. This seems to indicate that the cleavage of the sulfur-to-phenyl bond occurred via one of the primary metalation products rather than by direct participation of n-butyllithium in the cleavage reaction. We postulate that nuclear metalation occurred first followed by metalation in the α-position of the ethyl group as in thioanisole. Then α-lithioethyl phenyl sulfide could undergo a relatively rapid and likely intramolecular cleavage of the sulfur-to-phenyl bond. This could drain off the α-metalated product about as rapidly as it was formed leaving the low concentrations observed. The transition state for the cleavage reaction could be four-centered as shown below. The bonds being broken and formed are indicated by dashed lines.

It is not clear why thioanisole did not show some of the cleavage reaction.

The aryl alkyl sulfides are probably worthy of further and more detailed study than has hitherto been reported.

EXPERIMENTAL

General

    Solutions of n-butyllithium in n-hexane were obtained from Foote Mineral Co., and organometallic content was determined by titration of a 1.00 ml sample of the clear solution with standard aqueous hydrochloric acid. Vapor phase chromatographic analyses were performed on a Wilkins Model A-700 "Autoprep" with a $20' \times \frac{3}{8}''$ column packed with 30% silicone SE-30 on 45/60 mesh Chromosorb P. The thioanisole products were chromatographed at a column temperature of 195°, the injector block at 230° and the detector at 260°. The thiophenetole system was analyzed with a column temperature of 200°. In all analyses the helium pressure on the column was 30 psi and the detector filament current was 150 mA.

The metalation reactions were performed essentially as described earlier[5] except that after carbonation, extraction and acidification of the aqueous layer, an oil was precipitated which was taken up in ether. The ether solution was dried and heated on a steam bath until the ether and valeric acid were removed. The remaining acidic residue was then treated with diazomethane for chromatographic analysis as described before[5].

Analysis of the mixed esters from thioanisole metalation

Vapor phase chromatography of the mixture showed three peaks of the following retention times: (a) 6.6 min, (b) 7.8 min and (c) 8.6 min. Peak (a) was methyl (phenylthio)acetate, peak (b) was either or both of methyl *o*- and *m*-(methylthio)-benzoate, and peak (c) was methyl *p*-(methylthio)benzoate. Methyl benzoate was clearly absent since it would have come through much earlier than peak (a).

Methyl *o*-(methylthio)benzoate was prepared via reduction of dithiosalicylic acid[9,10] followed by methylation of the mercapto group with dimethyl sulfate and conversion of the carboxylic acid to the methyl ester with diazomethane.

Methyl *m*-(methylthio)benzoate[11,12] and methyl *p*-(methylthio)benzoate[13] were prepared by the same route.

Methyl (phenylthio)acetate[14] was prepared from sodium thiophenoxide and chloroacetic acid and the carboxylic acid esterified with diazomethane.

Analysis of the mixed esters from thiophenetole metalation

The mixture showed five peaks in the vapor phase chromatograms as follows: (a) 3.2 min, (b) 6.2 min, (c) 7.9 min, (d) 8.2 min and (e) 9.4 min. Peaks (c) and (d) were partially overlapped but adequate peak area estimates could be made particularly with the use of mixtures of the known compounds. The peaks were identified as follows: (a) methyl benzoate, (b) methyl α-(phenylthio)propionate, (c) methyl *o*-(ethylthio)benzoate (d), methyl *m*-(ethylthio)benzoate and (d) methyl *p*-(ethylthio)-benzoate.

Methyl α-(phenylthio)propionate was prepared[15] via sodium thiophenoxide and α-bromopropionic acid. The acid was converted to the methyl ester, b.p. 120°/3 mm. The ester has not been reported. (Found: C, 61.07; H, 6.30. $C_{10}H_{12}O_2S$ calcd.: C, 61.20; H, 6.16%.)

The methyl esters of *o*-, *m*- and *p*-(ethylthio)benzoic acids were synthesized by the routes indicated above for the methyl homologs except that diethyl sulfate was used in place of dimethyl sulfate. All the acids are known[9]. Methyl *p*-(ethylthio)-benzoate has been reported[16]. Methyl *o*-(ethylthio)benzoate boils at 118°/0.9 mm. (Found: C, 61.33; H, 6.33. $C_{10}H_{12}O_2S$ calcd.: C, 61.20; H, 6.16%.) Methyl *m*-(ethylthio)benzoate boils at 113°/0.9 mm. (Found: C, 61.31; H, 6.31. $C_{10}H_{12}O_2S$ calcd.: C, 61.20; H, 6.16%.)

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