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METALLATION - SULFIDATION: A CONVENIENT METHOD FOR THE SYNTHESIS OF ARYL ALKYL SULFIDES AND OF UNSYMMETRICAL DIARYL SULFIDES

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A number of procedures have been employed for the synthesis of sulfur-substituted aromatics; e.g., electrophilic substitution with sulfur-containing electrophiles such as sulfenyl halides[1,2], chlorosulfonic acid[3] and sulfoxides[4], nucleophilic substitution of aryl halides with metal mercaptides[5,6], replacement reactions involving diazonium intermediates[7,8], and conversion of phenols to thiophenols via thermal rearrangement of thiocarbamates[9]. Aromatic systems with sulfur-containing substituents have also been prepared by nucleophilic addition to quinones[10,11] or their mono[12] or diketals[13].

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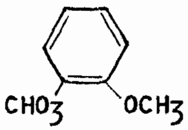
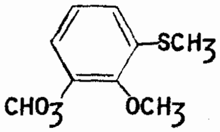
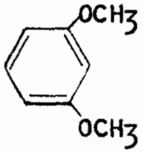
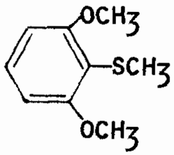
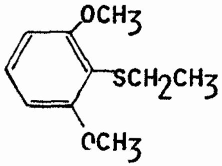
The reaction of aryl lithium compounds with elemental sulfur[14] or dialkyldisulfides[15-18] has also been reported but this approach has not received much attention as a synthetic procedure.

We have found that the metallation of both aromatic and hetero-aromatic compounds **1** with butyllithium tetramethylethylenediamine (TMEDA) complex, followed by reaction with dialkyl or diaryl disulfides, provides the corresponding unsymmetrical sulfides **2** in generally

excellent yields (Table). Since the metallation of aromatic substrates leads, as a rule, to substitution *ortho* to activating substituents[19], the metallation - sulfidation procedure presented here provides a specific route to products not accessible *via* the usual electrophilic reactions.

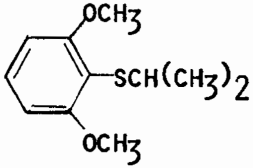
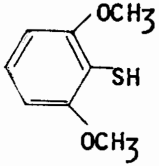
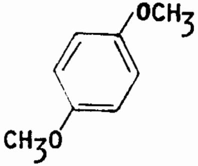
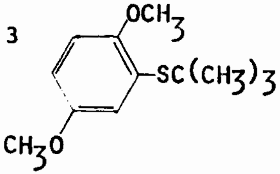
Using dimethyldisulfide as a model disulfide, we have explored the generality of this reaction employing a variety of aromatic systems. The three dimethoxybenzenes, as well as a number of representative aprotic

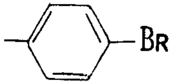
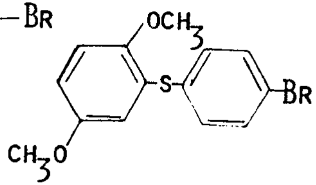
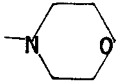
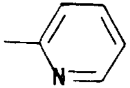
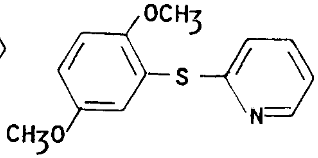
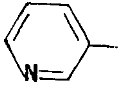
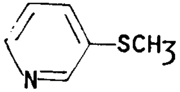
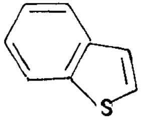
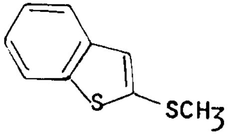
TABLE: Reaction of ArH (1) with BuLi (TMEDA), and RSSR to yield ArSR (2)

Compound	Ar (1)	R	Product (2)	Yield (%)	m.p.°C or b.p.°C/torr	Additional data (a)
2a		$-CH_3$		71	36.5-37	(b)
2b		$-CH_3$		85	81-82	(c)
2c	"	$-CH_2CH_3$		83	45-46 85-96/0.4	NMR: 1.16(t)CH_3(3H); 2.85(q)CH_2(2H); 3.87 (s) OCH_3(6H); 6.56(d) 7.23(t)ArH(3H).

(continued)

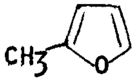
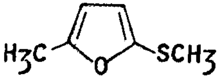
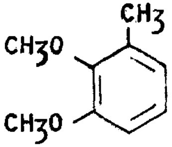
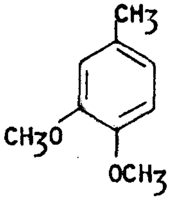
TABLE, cont.

2d	"	$-CH(CH_3)_2$		83	37-38 90-98/0.4	NMR: 2.10,2.19(d) $(C\underline{H}_3)_2CH$(6H);4.41(m) CH(1H);3.86(s)OCH_3 (6H);6.54(d)7.19(t) ArH(3H).
2e	"	$-C(CH_3)_3$	(d)			
2f	"	(e)		5	85.5-87.5	IR: SH 2575 cm^{-1}; 1029, 939, 768. 713.
2g		$-C(CH_3)_3$		81	95-105/0.5	NMR: 1.30(s)(CH_3) 9H;3.70,3.75(2s) $(OCH_3)_2$(6H);6.72, -7.03(m)ArH 3H.

2h	"			84	72-73 150-170/0.5	NMR: 3.68,3.79(2s) $(OCH_3)_2$ (6H); 6.68-7.46(m)ArH(7H)
2i	"		(f)			
2j	"			61	66-67.5 135-150/0.4	NMR: 3.77(s)$(OCH_3)_2$ (6H); ArH,$PyH_{3,4,5}$(m) 6.82-7.55(6H);PyH_6 (m)8.37-8.46(1H).
2k		$-CH_3$		88	110-120/30	·HCl 162-164° (g) ·Picrate 132.5-134.
2l		"		80	28-29	(h)

(continued)

TABLE, cont.

2m		"		56	66-68/25	(i)
2n		"	(j)			
2o		"	(j)			

(a) All microanalyses (C,H) were ± 0.4% of the theoretical values.
(b) See: P. Jacob III and A. T. Shulgin, J.Med.Chem., IN PRESS.
(c) Lit. value 80° (A. J. Birch et al., Aust.J.Chem. 24 2179 (1971).
(d) No product isolated.
(e) Elemental sulfur.
(f) Only recovered starting material isolated.
(g) Lit. value 156-158° (A. Albert and G. B. Barlin, J.Chem.Soc. 2384 (1959).
(h) Lit. value 28-29; 153-154/9 (R. P. Dickinson and B. Iddon, J.Chem.Soc. 182 (1971).
(i) Nine of the 10 major absorption peaks in the 600-1400 cm^{-1} IR region lie within 2 cm^{-1} of the published values, in: M. Stoll et al. Helv.Chim.Acta 50 628 (1967). Lit. b.p. 80/45-50.
(j) Mixture of products; see experimental section.

heterocyclics, all reacted in good yields to give unique products. The lithiated intermediates were also prepared by lithium halogen exchange. Examples wherein lithiation would be expected to give a mixture of lithiated products[20] gave a corresponding mixture of sulfides. The versatility with regard to the disulfide was established using 1,4-dimethoxybenzene as a model aromatic. A wide range of disulfides underwent successful reaction, including the sterically hindred di-_t_-butyldisulfide, and disulfides containing hetero-atoms.

The determination of the steric limitations of this reaction was carried out using 2-lithio-1,3-dimethoxybenzene and dialkyldisulfides of varying steric bulk. Methyl, ethyl, and isopropyldisulfide reacted smoothly between the adjacent methoxyl groups, but t-butyldisulfide gave a complex mixture of products which was unresolved. Using the same aryl lithium, the reaction with elemental sulfur produced a mixture of the thiophenol and the aryl disulfide.

It appears that this metallation - sulfidation procedure is a general and efficient method for the introduction of alkylthio and arylthio groups into aromatic nuclei. The experimental procedure is simple, and the reactions are complete within an hour at, or below, room temperature. Since a wide range of aromatic compounds can be converted into lithio derivatives either by metallation[19,21] or metal-halogen exchange[22], the method should find broad application.

IR spectra were recorded on a Beckman Acculab-2 grating spectrophotometer; NMR spectra were recorded on a Varian FT-80 instrument, in $CDCl_3$ with internal TMS; and GC analyses were performed on a Hewlett Packard 5750. Microanalyses were carried out by Galbraith Laboratories, Knoxville, Tenn. Satisfactory microanalyses ($\pm$ 0.4%) were obtained for all new compounds reported. Variations from the general procedure reported in the table, are detailed separate entries.

General Procedure for Metallation - Sulfidation. Preparation of 2,6-Dimethoxythiophenetole (2c):

A magnetically stirred solution of m-dimethoxybenzene (13.8 g, 100 mM) and TMEDA (12.1 g, 105 mM) in 30-60° b.p. pet. ether (200 ml) was cooled, under nitrogen, with an external ice-water bath. Butyllithium (66 ml of 1.6 M solution in hexane, 105 mM) was added over 10 minutes, resulting in the formation of a granular, easily stirred, precipitate. There was then added diethyldisulfide (12.2 g, 100 mM) over a few minutes, leading to an exothermic reaction with the change of the precipitate character to a thick, creamy texture. The reaction was brought to room temperature, stirred an additional 30 min., then poured into dilute H_2SO_4 (500 ml). The organic layer was separated and the aqueous phase extracted with ether (200 ml). The organic phases were combined, the solvent removed in vacuo, and the resulting oil distilled (Kugelrohr oven, 0.4 mm). A forerun (0.8 g, 75-85°) was discarded, and the main fraction (85-96°) solidified in the receiver (16.4 g, yield 83%). An analytical sample from hexane had a m.p. 45-46°.

2,6-Dimethoxythiophenol. **2f**. The general procedure was modified in that the sulfur was added as a solid, and the reaction mixture was quenched with water. The white flocculant solids that resulted (insoluble in either phase) were removed by filtration. The aqueous layer was separated and the organic layer extracted twice with 5% NaOH. The pooled aqueous portions were acidified (HCl) and the resulting oil extracted with methylene chloride. The solvent was removed in vacuo and the resulting solids sublimed (0.5 mm, 90°). The final analytical sample was crystallized from methanol, m.p. 85.5-87.5°. The insoluble solids above, upon recrystallization from toluene, yielded di-(2,6-dimethoxyphenyl)-disulfide as white crystals, m.p. 206-209°. Reduction of the disulfide (Zn, HOAc) yielded the thiophenol 2f as shown by TLC (Silica gel, $CHCl_3$; Rf of ArSSAr, 0.30; Rf of ArSH, 0.85).

3-Methylthiopyridine. 2k. A solution of buyllithium in hexane (6.3 ml, 1.6 M,10 mM) was added under a nitrogen atmosphere to a stirred solution of 3-bromopyridine (1.0 ml, 1.64 g, 10.4 mM) in 20 ml ether cooled with external dry ice acetone. There was immediate formation of a light yellow precipitate. The reaction mixture was stirred for 5 minutes, and then dimethyl disulfide (1.0 ml, 1.0 g., 11 mM) was added. The reaction was worked up as described in the general procedure.

Methylsulfidation of Lithiated 2,3-Dimethoxytoluene and Lithiated 3,4-Dimethoxytoluene (Attempts to prepare 2n and 2o): The final isolate from 2,3-dimethoxytoluene distilled at 80-120° (0.3 mm) and showed two major peaks by GC, in a ratio of 3:1. As o-methoxytoluene is known to lithiate to give minor lithiation on the $ArCH_3$ group[23], the products may be assumed to be a mixture of 2,3-dimethoxy-4-methylthiotoluene (2n) and 2,3-dimethoxy-alpha-methylthiotoluene. The final isolate from 3,4-dimethoxytoluene distilled at 77-84°/0.05 mm and showed again two major peaks by GC in a ratio of 3:2. As 3-methoxy toluene is known to lithiate in both the 2- and the 4-positions[20], the products may be assumed to be 2-

methylthio-3,4-dimethoxytoluene and 5-methylthio-3,4-dimethoxytoluene. In neither case were the products isolated or characterized.

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