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METALATIONS OF ALKOXYALKYLTHIOBENZENES

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Summary

Metalation of *o*-, *m*- and *p*-alkoxyalkylthiobenzenes with n-butyllithium is examined. The analysis of the products shows that in the *o*-compound only a thiomethyl hydrogen is replaced, while in the other compounds studied a ring hydrogen *ortho* to the alkoxylic group is replaced The metalation has a low steric requirement.

Introduction

In metalation of aromatic substrates by organolithium reagents the metal atom usually replaces a hydrogen atom *ortho* to an electron-withdrawing group [1—4].

However, some *o*-alkoxy-substituted alkylbenzene derivatives show competition between ring and side-chain metalation [3,4], while the thioanisole is metalated exclusively in the side chain [5,6]

We previously showed that treatment of some organometallic compounds of magnesium, mercury and calcium with ether or thioether derivatives caused cleavage of the ether and/or thioether bond [7—10] We have now extended these studies to reactions of n-butyllithium with aromatic substrates containing both ether and thioether bonds, in order to examine the possibility of a competition between oxygen and sulfur in the orientation of the metalation, and to obtain information about the steric requirements of these substrates

Results and discussion

We have examined the *ortho*-, *meta*- and *para*-alkoxyalkylthiobenzene derivatives (Ia, Ib; IIa, IIb, IIIa, IIIb, IIIc) The reactions were carried out by treating the ether solution of the substrate with an equimolar amount of n-butyllithium in hexane. The aryllithium compounds were carbonated In the case of IVa (Scheme 1) the acid was identified by comparison with the acid obtained by

TABLE 1

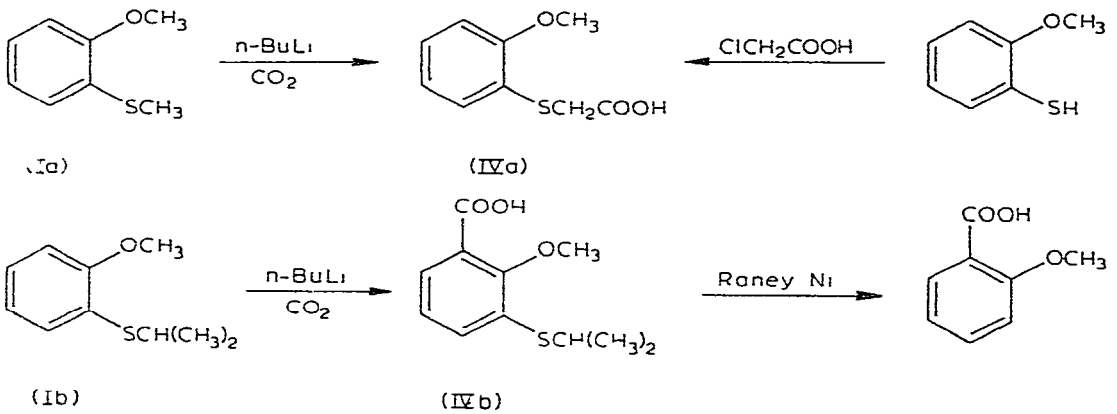
METALATION OF ALKOXYALKYLTHIOBENZENES (I, II AND III)

Starting material	Products after carbonation	Yield (%)
1-Methoxy-2-(methylthio)benzene (Ia)	(2-Methoxyphenyl)thioacetic acid (IVa)	65
1-Methoxy-2-(isopropylthio)benzene (Ib)	2-Methoxy-3-(isopropylthio)benzoic acid (IVb)	45
1-Methoxy-3-(methylthio)benzene (IIa)	2-Methoxy-6-(methylthio)benzoic acid (Va)	46
1-Methoxy-3-(isopropylthio)benzene (IIb)	2-Methoxy-6-(isopropylthio)benzoic acid (Vb)	43
1-Methoxy-4-(methylthio)benzene (IIIa)	2-Methoxy-5-(methylthio)benzoic acid (VIa)	45
1-Methoxy-4-(isopropylthio)benzene (IIIb)	2-Methoxy-5-(isopropylthio)benzoic acid (VIb)	50
1-Isopropoxy-4-(methylthio)benzene (IIIc)	2-Isopropoxy-5-(methylthio)benzoic acid (VIc)	38

reaction of 2-methoxybenzenethiol with monochloroacetic acid. All the other acids (Scheme 1—3) were identified from their spectra and by comparison of their desulfuration products with authentic samples.

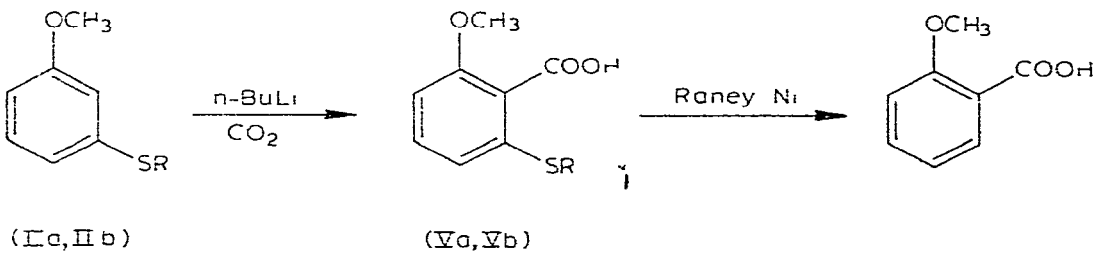
The results, listed in Table 1, show that: (i) metalation of *o*-disubstituted compounds (Ia, Ib) gives two different types of results (Scheme 1). Ia gives IVa

SCHEME 1



by substitution of a thiomethyl hydrogen, while Ib gives IVb by substitution of a ring hydrogen *ortho* to the methoxy group, (ii) metalation of *m*-disubstituted compounds (IIa, IIb) occurs between the two functional groups giving Va, Vb (Scheme 2). No metalation of the thiomethyl group was observed, (iii) in the

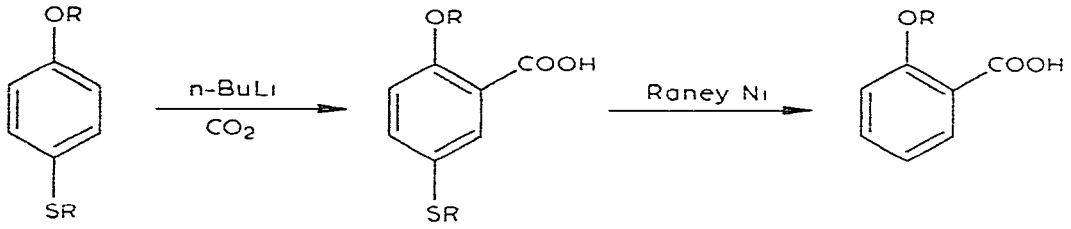
SCHEME 2



R = CH_3, $CH(CH_3)_2$

p-disubstituted compounds (IIIa—IIIc) (Scheme 3) the metalation occurs *ortho* to the alkoxyl group, giving the compounds VIa—VIc Again no metalation of the thiomethyl group (compound IIIa) was observed.

SCHEME 3



(III a–III c) (VI a–VI c)

R = CH_3 , $CH(CH_3)_2$

The metalation of the sidechain in Ia can be attributed to the acidity of the thioalkyl group, probably increased by the presence, in the *ortho*-position, of a methoxy group, which can stabilize the thioalkylic carbanion through its inductive effect [1—7]. This hypothesis is supported by the fact that in the metalation of Ib the metalation takes place *ortho* to the methoxy group in this case the carbanion from the thioalkyl chain would be greatly destabilized by the presence of two methyl groups [11] With the *meta*- and *para*-disubstituted substrates (IIa, IIb and IIIa—IIIc) the metal atom enters *ortho* to the alkoxy group even when this is more sterically hindered (compound IIIc), showing that the alkoxy group has a stronger orientating effect than the thioalkyl group

Our data also indicate that the process has a low steric requirement [3] since in the reactions with compounds IIa and IIb the lithium atom replaces the hydrogen lying between the two substituents This hydrogen is, of course, activated by the presence of two adjacent electron-withdrawing groups

Experimental

General

Solutions of n-butyllithium in hexane were obtained from EGA-Chemie Infrared spectra were recorded on a Perkin—Elmer Model 325 instrument NMR spectra were recorded on a JEOL C-60 HL spectrometer with hexamethyldisiloxane as internal reference Microanalyses for C and H were carried out on a Perkin—Elmer model 240 Elemental Analyzer, analyses for S were performed by a published procedure [12,13] Boiling and melting points are uncorrected, the latter were determined on a Tottoli apparatus All compounds were shown to be pure by GLC analysis.

Starting materials

1-Methoxy-2-(methylthio)- (Ia), 1-methoxy-4-(methylthio)- (IIIa) and 1-methoxy-4-(isopropylthio)-benzene (IIIb) were prepared by published methods [14—16]

1-Methoxy-3-(methylthio)benzene (IIa) To a solution of 3-methoxybenzene-

thiol [17] (0 1 mol), sodium hydroxide (0 15 mol) and water (60 ml), dimethyl sulphate (0.12 ml) was added dropwise under nitrogen with stirring The mixture was heated under reflux for 2 hours, cooled, and poured into water. After extraction with diethyl ether, the ethereal solution was dried ($CaCl_2$), the solvent was evaporated, and the residue distilled Yield 91%, b p 118—119°C/10 mmHg, n_D^{18} 1 5800 (lit [8] b p 125—127°C/16 mmHg).

1-Methoxy-2-(isopropylthio)benzene (Ib) To a stirred solution of sodium ethoxide (0 14 mol, prepared from 3 4 g of sodium) in absolute ethanol (100 ml) 2-methoxybenzenethiol [3] (0 13 mol) was added dropwise under nitrogen After 3 h of reflux the solvent was removed in a rotary evaporator, and the residue was poured into water and extracted with diethyl ether The ethereal solution was dried with calcium chloride, the solvent evaporated, and the residue distilled Yield 83%, b p 113—114°C/6 mmHg, n_D^{18} 1 5620. (Found C, 65 74, H, 7 74, S, 17 32 $C_{10}H_{14}OS$ calcd C, 65 89; H, 7.74, S, 17 59%) ^{1}H NMR (CCl_4), δ 6 90 (m, 4H arom), 3 55 (s, 3H, —OCH_3), 3.30 (m, 1H, CH_3—C<u>H</u>—CH_3) and 1 15 ppm (d, 6H, C<u>H</u>$_3$—CH—C<u>H</u>$_3$)

Similarly starting from 3-methoxybenzenethiol and 4-(methylthio)phenol [19], respectively, the following compounds IIb and IIIc were obtained.

1-Methoxy-3-(isopropylthio)benzene (IIb) Yield 88%, b p 115—116°C/6 mmHg, n_D^{18} 1 5560 (Found: C, 65 52, H, 7 71, S, 17.38 $C_{10}H_{14}OS$ calcd C, 65 89, H, 7.74; S, 17 59%.) ^{1}H NMR (CCl_4) δ 6.75 (m, 4H arom), 3 60 (s, 3H, —OCH_3), 3.25 (m, 1H, CH_3—C<u>H</u>—CH_3) and 1 20 ppm (d, 6H, C<u>H</u>$_3$—CH—C<u>H</u>$_3$).

1-Isopropoxy-4-(methylthio)benzene (IIIc) Yield 78%, b p 122—124°C/2 mmHg, m p 32—33°C (Found C, 65 60, H, 7 68, S, 17 65 $C_{10}H_{14}OS$ calcd C, 65.89, H, 7.74, S, 17.59%) ^{1}H NMR ($CDCl_3$): δ 7 10 (m, 4H arom), 4 60 (m, 1H, CH_3—C<u>H</u>—CH_3), 2 50 (s, 3H, —SCH_3) and 1 35 ppm (d, 6H, C<u>H</u>$_3$—CH—C<u>H</u>$_3$)

Authentic samples

[(2-Methoxyphenyl)thio]acetic acid (IVa) and 2-isopropoxybenzoic acid were prepared by published procedures [20,21] 2-Methoxy-, 3-methoxy- and 4-methoxy-benzoic acid were commercial products (EGA-Chemie)

Metalation procedure

A stirred solution of starting material (0 03 ml) in anhydrous diethyl ether (50 ml) was blanketed with nitrogen and then treated dropwise at room temperature with 1.6 *M* n-butyllithium in hexane (0.035 mol, 22 ml) When the addition was complete the mixture was stirred under reflux for 4 hours After cooling, the mixture was poured onto ca 100 g of crushed solid carbon dioxide and allowed to stand for 24 hours The residue was treated successively with 10% aqueous sodium bicarbonate and diethyl ether (100 ml) The alkali layer was separated, washed with diethyl ether and then acidified with cold concentrated hydrochloric acid The acidified layer was then extracted with chloroform The combined extracts were dried with sodium sulphate, filtered and concentrated in vacuo. The crude product was chromatographed on a silica gel column, using benzene/diethyl ether (1/2) as eluent.

In this manner, starting from Ia, Ib, IIa, IIb and IIIa—IIIc, respectively, the following compounds were obtained.

[(2-Methoxyphenyl)thio]acetic acid (IVa) Yield 65%, m p 119—121°C, (lit [20]: m p. 121—122°C).

2-Methoxy-3-(isopropylthio)benzoic acid (IVb) Yield 41%, m p 67—68°C (Found C, 58.25; H, 6.31; S, 14 01. $C_{11}H_{14}O_3S$ calcd · C, 58.38; H, 6 24, S, 14.17%) ^{1}H NMR ($CDCl_3$) δ 10 20 (s, 1H, COOH, D_2O exchanged), 7 25 (m, 3H arom), 3 80 (s, 3H, —OCH_3), 3 30 (m, 1H, CH_3—C<u>H</u>—CH_3) and 1 10 ppm (d, 6H, C<u>H</u>$_3$—CH—C<u>H</u>$_3$) IR (KBr): 3300 (OH), 1700 (C=O), 750 cm^{-1} (1,2,3-trisubstituted benzene).

2-Methoxy-6-(methylthio)benzoic acid (Va) Yield 46%, m p. 184—185°C (Found: C, 54.41; H, 5.04. S, 16 01. $C_9H_{10}O_3S$ calcd C, 54 53, H, 5 08, S, 16 17%) ^{1}H NMR ($CDCl_3$) δ 9.35 (s, 1H, COOH, D_2O exchanged), 6 95 (m, 3H arom), 3 90 (s, 3H, —OCH_3) and 2 40 ppm (s, 3H, —SCH_3) IR (KBr) 3200 (OH), 1690 (C=O), 760 cm^{-1} (1,2,3-trisubstituted benzene)

2-Methoxy-6-(isopropylthio)benzoic acid (Vb) Yield 43%, m p 109—110°C (Found. C, 58 24, H, 6 31, S, 13 99 $C_{11}H_{14}O_3S$ calcd C, 58 38, H, 6.24, S, 14.17%) ^{1}H NMR ($CDCl_3$). δ 10 50 (s, 1H, COOH, D_2O exchanged), 6 90 (m, 3H arom), 3 80 (s, 3H, —OCH_3), 3 40 (m, 1H, CH_3—C<u>H</u>—CH_3) and 1 30 ppm (d, 3H, C<u>H</u>$_3$—CH—C<u>H</u>$_3$) IR (KBr) 3200 (OH), 1710 (C=O), 760 cm^{-1} (1,2,3-trisubstituted benzene)

2-Methoxy-5-(methylthio)benzoic acid (VIa) Yield 45%, m p 69—70°C (Found. C, 54.35, H, 4 98, S, 16 02 $C_9H_{10}O_3S$ calcd . C, 54 53, H, 5.08, S, 16 17%.) ^{1}H NMR ($CDCl_3$)· δ 9 85 (s, 1H, COOH, D_2O exchanged), 7 30 (m, 3H arom), 3 95 (s, 3H, —OCH_3) and 2 40 ppm (s, 3H, —SCH_3) IR (KBr) 3100 (OH), 1700 (C=O), 820 cm^{-1} (1,2,4-trisubstituted benzene)

2-Methoxy-5-(isopropylthio)benzoic acid (VIb) Yield 50%, n_D^{18} 1 5700 (Found: C, 58 21, H, 6 16, S, 14 05 $C_{11}H_{14}O_3S$ calcd C, 58 38, H, 6 24, S, 14.17%) ^{1}H NMR ($CDCl_3$). δ 9 00 (s, 1H, COOH, D_2O exchanged), 7 50 (m, 3H arom), 3 95 (s, 3H, —OCH_3), 3 20 (m, 1H, CH_3—C<u>H</u>—CH_3) and 1 20 ppm (d, 6H, C<u>H</u>$_3$—CH—C<u>H</u>$_3$) IR (neat) 3300 (OH), 1730 (C=O), 810 cm^{-1} (1,2,4-trisubstituted benzene)

2-Isopropoxy-5-(methylthio)benzoic acid (VIc) Yield 38%, n_D^{28} 1 5240 (Found C, 58 15, H, 6 20, S, 14 03 $C_{11}H_{14}O_3S$ calcd C, 58 38, H, 6 24, S, 14 17%) ^{1}H NMR ($CDCl_3$). δ 8 75 (s, 1H, COOH, D_2O exchanged), 7 50 (m, 3H arom), 4 85 (m, 1H, CH_3—C<u>H</u>—CH_3), 2 50 (s, 3H, —SCH_3) and 1 50 ppm (d, 6H, C<u>H</u>$_3$—CH—C<u>H</u>$_3$) IR (neat) 3200 (OH), 1710 (C=O), 820 cm^{-1} (1,2,4-trisubstituted benzene)

TABLE 2

ACTION OF RANEY NICKEL ON BENZOIC ACIDS (IV V AND VI)

Benzoic acids	Products	Yield (%)
2-Methoxy-3-(isopropylthio)benzoic acid (IVb)	2-Methoxybenzoic acid	68
2-Methoxy-6-(methylthio)benzoic acid (Va)	2-Methoxybenzoic acid	63
2-Methoxy-6-(isopropylthio)benzoic acid (Vb)	2-Methoxybenzoic acid	71
2-Methoxy-5-(methylthio)benzoic acid (VIa)	2-Methoxybenzoic acid	60
2-Methoxy-5-(isopropylthio)benzoic acid (VIb)	2-Methoxybenzoic acid	75
2-Isopropoxy-5-(methylthio)benzoic acid (VIc)	2-Isopropoxybenzoic acid	58

General method for desulfuration of acids IV, V and VI

A solution of acids (IV, V and VI) (0 01 mol) in 10 ml of 95% ethanol was refluxed 2 hours with about 2 g of Raney nickel [22] The mixture was filtered and evaporated. The residue was treated with warm concentrated sulfuric acid, poured into water and extracted with chloroform After drying (Na_2SO_4), the solvent was evaporated, and the residue identified by comparison with an authentic sample The results are listed in Table 2.

Acknowledgement

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