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# METALATION REACTIONS

## VII *. METALATION OF BENZYLALKYL AND β-PHENETHYLALKYL SULFIDES

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## Summary

The products from the reaction between n-butyllithium and benzylalkyl and β-phenethylalkyl sulfides followed by carbonation, have been investigated by GLC/MS analysis. With benzylalkyl sulfides metalation occurs at the benzylic position, and the corresponding carboxylic acid can be isolated, but side products from Wittig like rearrangement, cleavage of the thioether bond, and aliphatic and aromatic substitution are also obtained. No benzylic metalation or Wittig-like rearrangement products are obtained from β-phenethyl sulfides: instead cleavage of the thioether bond and aliphatic and aromatic substitution occur.

## Introduction

Metalation of (methylthio)benzene with n-butyllithium is known to occur at the alkyl group giving yields of 35 or 97% depending on the absence or the presence of 1,4-diazabicyclo [2,2,2] octane [2—4]. In the case of *o*-alkyl- and *o,o'*-dialkyl-substituted (methylthio)benzenes, the lithiation occurs at benzylic, thiomethylic and ring positions with predominant formation of one product when the reaction is carried out in the presence of *N,N,N',N'*-tetramethylethylenediamine [5]. In contrast, in the lithiation of benzyl sulfides, thiacyclophanes and allylbenzyl ethers metalation can be followed by Wittig, Sommelet, or Stevens rearrangements, depending on the temperature and the nature of the solvation of the cation [6—8].

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[*] For Part VI see ref. 1.

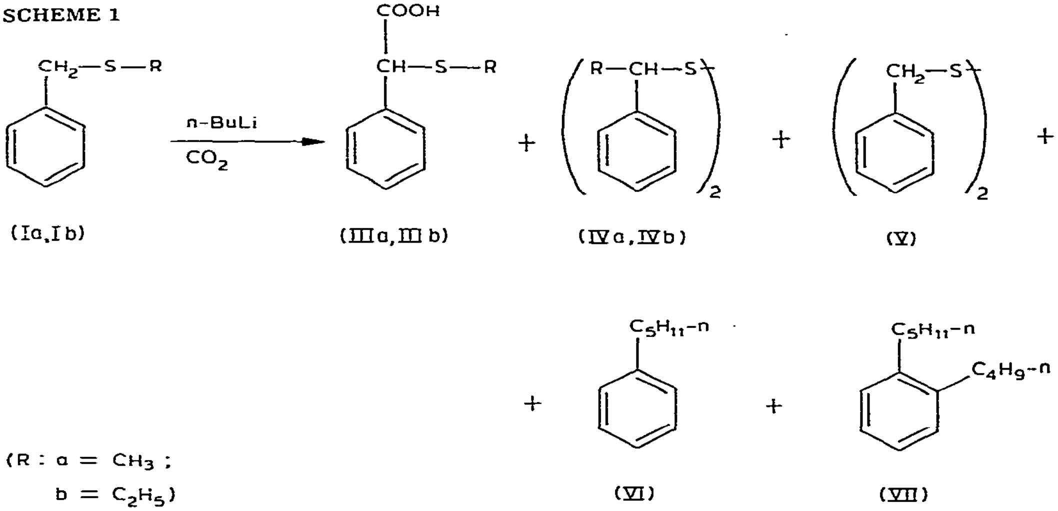
In the light of these results and the lack of data on the lithiation of sulfides in which the sulfur atom is progressively moved away from the aromatic ring, we have extended our studies to alkylbenzylic- (Ia, Ib, Ic) and alkyl-β-phenylethylic sulfides.

## Results

The substrates were treated with equimolar amounts of n-butyllithium and the reaction mixtures were treated with crushed carbon dioxide and the product analyzed by linked GLC-mass spectroscopy. In this way we not only determined the number and the relative percentages of the products, but were also able to suggest structures for them on the basis of the molecular ions and the fragmentations. The structures were then confirmed by synthesizing the postulated products by an unambiguous route and comparing their physical properties. The carboxylic acids were isolated and individually characterized.

The results are listed in Table 1 and can be summarized as follows: (i) When there is only one carbon atom between the ring and the sulfur atom (Ia, Ib) selective metalation occurs at the benzylic position, and the acids IIIa and IIIb are obtained in 55% yield (Scheme 1). The disulfides IVa, IVb and V, and the hydrocarbons VI and VII are also produced, though in very low yields.

SCHEME 1



In contrast, no detectable amount of carboxylic acid was found in the case of Ic (Scheme 2) but only the disulfides IVa and IVc together with the hydrocarbons VIII, IX, X, XI.

(ii) When there are two carbon atoms between the ring and the sulfur atom (IIa, IIb), no detectable amounts of carboxylic acids are found. The characterized products (Scheme 3) are the disulfide XII and the hydrocarbons IX, X, XI. In the case of IIb the arene XIII was also found.

## Discussion

To rationalize the results it is necessary to postulate the occurrence of both consecutive and competitive reactions. In the case of Ia and Ib the benzylic

(continued on p. 153)

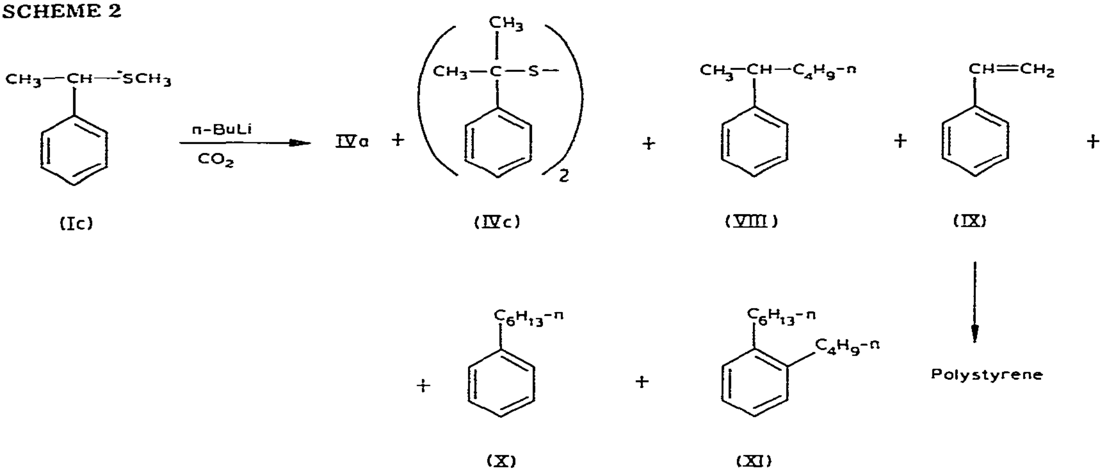
TABLE 1

REACTION OF n-BUTYLLITHIUM WITH SULFIDES (I AND II) [a]

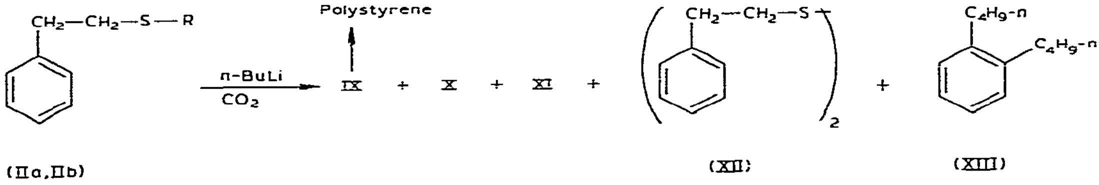
| Starting material | Products after carbonation | Fraction (%) | Material balance (%) |
|---|---|---|---|
| [(Methylthio)methyl] benzene (Ia) | [α-(Methylthio)] benzeneacetic acid (IIIa) | 61 | 68 |
| | Bis(1-phenylethyl)disulfide (IVa) | 13 | |
| | Bis(phenylmethyl)disulfide (V) | 9 | |
| | Pentylbenzene (VI) | 10 | |
| | 1-Butyl-2-pentylbenzene (VII) | 8 | |
| [(Ethylthio)methyl]benzene (Ib) | [α-(Ethylthio)benzeneacetic]acid (IIIb) | 62 | 65 |
| | Bis(1-phenylpropyl)disulfide (IVb) | 10 | |
| | Bis(phenylmethyl)disulfide (V) | 7 | |
| | Pentylbenzene (VI) | 15 | |
| | 1-Butyl-2-pentylbenzene (VII) | 6 | |
| [(1-Methylthio)ethyl] benzene (Ic) | Bis(1-phenylethyl)disulfide (IVa) | 15 | 53 |
| | Bis(1-methyl-1-phenylethyl)disulfide (IVc) | 33 | |
| | (1-Methylpentyl)benzene (VIII) | 13 | |
| | Styrene (IX) | 18 | |
| | Hexylbenzene (X) | 16 | |
| | 1-Butyl-2-hexylbenzene (XI) | 5 | |
| [2-(Methylthio)ethyl] benzene (IIa) | Styrene | 28 | 38 |
| | Hexylbenzene (X) | 26 | |
| | 1-Butyl-2-hexylbenzene (XI) | 16 | |
| | Bis(2-phenylethyl)disulfide (XII) | 30 | |
| [2-(Ethylthio)ethyl]benzene (IIb) | Styrene (IX) | 31 | 33 |
| | Hexylbenzene (X) | 21 | |
| | 1-Butyl-2-hexylbenzene (XI) | 9 | |
| | Bis(2-phenylethyl)disulfide (XII) | 28 | |
| | 1,2-Dibutylbenzene (XIII) | 11 | |

[a] Analyses were by GC/MS; material balance = percentage of reacted starting material.

SCHEME 2

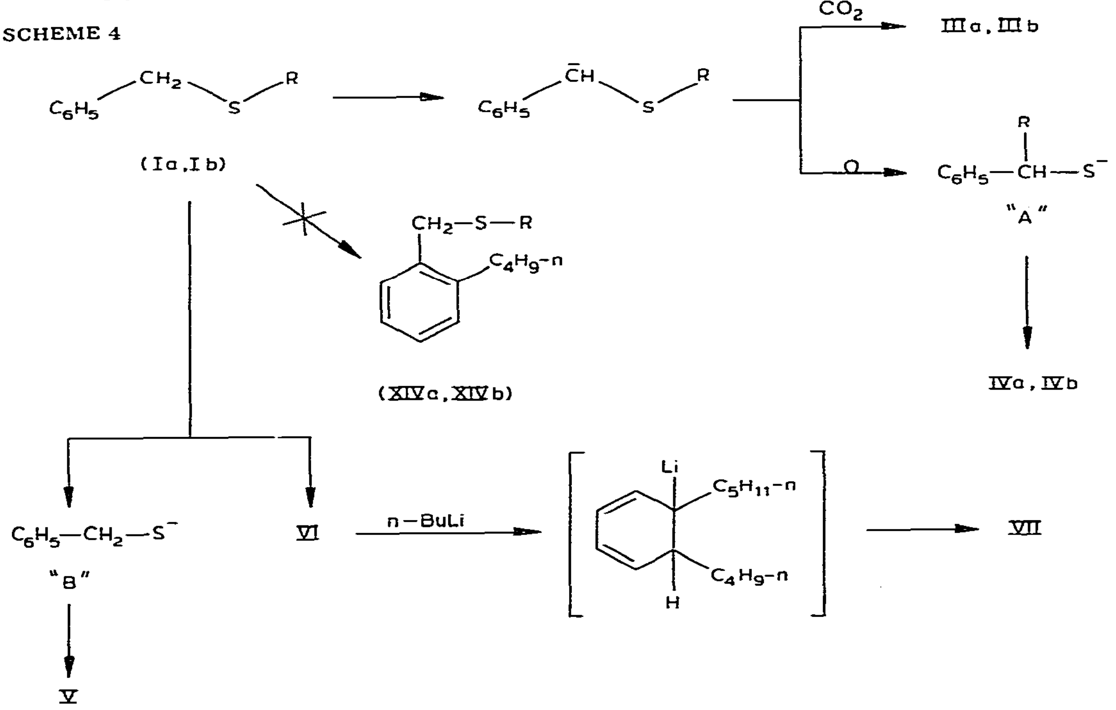


SCHEME 3



(R: a = $CH_3$;
b = $C_2H_5$)

SCHEME 4

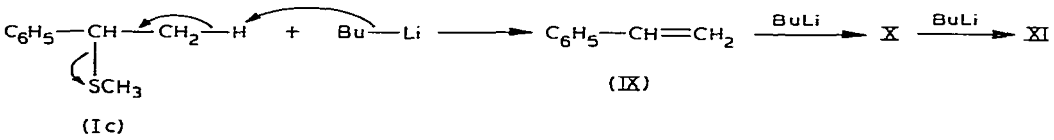


carbon is preferentially attacked because of the simultaneous stabilization of the carbanion by the adjacent ring and the *d* interaction with the sulfur atom. The carbanion produced (Scheme 4) after treatment with carbon dioxide will mainly afford the acids IIIa or IIIb (and this fact can be used for synthetic purposes) and to a less extent undergoes a Wittig transposition, as occurs with benzylic ethers [9,10], thiacyclophanes [7] and allylic-sulfides [11]. The anion "A" thus formed can undergo oxidation to the disulfide IVa or IVb.

Another route involves cleavage of the thioether bond [12]. In the case of cleavage of the alkyl-sulfur bond the thiobenzylic anion "B" is formed, and this can give the disulfide V by oxidation. But if the benzyl—sulfur bond is cleaved to give VI, this is likely to undergo nucleophilic aromatic substitution to give VII [13]. We cannot exclude the possibility that VII is formed by a nucleophilic aromatic substitution on the sulfide Ia, Ib, followed by replacement of the alkylthio group. The fact that we did not detect XIVa or XIVb in the products favours the first hypothesis.

In the case of Ic, the benzylic carbanion is destabilized by the adjacent methyl group [14]. This is why we did not detect any trace of the carboxylic acid analogous to IIIa, but only the product IV from a Wittig transposition. The simultaneous presence of IV and VIII can be accounted for the way suggested for Ia and Ib. The formation of styrene (IX) and of the arenes X and XI can be explained (Scheme 5) in terms of an elimination from Ic [13] followed by an addition of the organolithium to form X [15] and then by a nucleophilic aromatic substitution giving XI.

SCHEME 5



In compounds IIa and IIb, in which the sulfur atom is two carbon atoms removed from the aromatic ring, stabilization of the carbanion by the interaction of *d* orbitals of sulfur and $\pi$ orbitals of benzene is no longer possible, and so under our conditions, no products from either benzylic or thiomethylenic substitution are observed. With these substrates the reaction with n-butyllithium led to IX, X, XI, probably by the route proposed for conversion of Ic and of XII and by a similar pathway to that depicted in Scheme 1. In the case of X, we cannot rule out that, in addition to an elimination-addition process, it may also be formed by attack of the organolithium reagent at the sulfur atom in a process formally analogous to a nucleophilic substitution.

Research in progress is described towards accounting for the formation of the arene XIII.

## Experimental

### *Analyses*

$^1$H NMR spectra were recorded on a Varian CFT 80A spectrometer with tetramethylsilane as internal reference. Infrared spectra were recorded on a Perkin—

Elmer 157G spectrophotometer using potassium bromide mulls or neat liquids between sodium chloride plates. Analyses by GLC were carried out with a Carlo Erba Fractovap 4200 Gas Chromatograph equipped with a flame ionization detector, and a 3% SE 52 on Chromosorb W (80—100 mesh) column, using nitrogen as the carrier gas. The composition of various samples was identified by means of a Hewlett-Packard 5992B Gas-chromatograph-Mass spectrometer. Elemental analyses were carried out with a Carlo Erba model 1106 Elemental Analyzer.

*Starting materials*

n-Butyllithium was used as a 1.64 molar hexane solution. Diethyl ether was freshly distilled from $LiAlH_4$ before use. [(Methylthio)methyl] benzene (Ia) was commercial product (Aldrich Chemical Company). [(Ethylthio)methyl]- (Ib), [1-(methylthio)ethyl]- (Ic), [2-(methylthio)ethyl]- (IIa) and [2-(ethylthio)-ethyl]-benzene (IIb) were prepared by published methods [16—19].

*Authentic samples*

Bis(phenylmethyl)disulfide (V), pentyl- (VI), hexyl- (X) and 1,2-dibutyl-benzene (XIII), and styrene (IX) were commercial products (Aldrich Chemical Company, or Fluka AG, or K & K Labs). Bis(1-phenylethyl)- (IVa), bis(1-phenylpropyl)- (IVb), bis(1-methyl-1-phenylethyl)- (IVc) and bis(2-phenyl-ethyl)-disulfide (XII), 2-pentyl- (VII) and 2-hexyl-1-butylbenzene (XI), and (1-methylpentyl)benzene (VIII) were prepared by published methods [20—25].

*Metalation of [(methylthio)methyl] benzene (Ia)*

A solution of Ia (36 mmol) in dry diethyl ether (25 ml) was blanketed with dry nitrogen then treated dropwise at room temperature with n-butyllithium in hexane (25 ml). After the addition was complete, the mixture was stirred under reflux for 4 h. After cooling, the mixture was added to ca. 100 g of crushed solid carbon dioxide. After 15 hours most of the residue was treated successively with 10% aqueous sodium bicarbonate and diethyl ether. The alkali layer was separated, washed with diethyl ether, acidified with cold concentrated hydrochloric acid, and extracted with chloroform. The combined extracts were dried over sodium sulphate, filtered, and concentrated in vacuo. The crude product was chromatographed on a silica gel column, using petroleum ether (40—70°)/ diethyl ether (1/1) as eluent and identified as IIIa. Yield 55%, m.p. 81°C. *m/e* 182 ($M^+$). (Found: C, 59.21; H, 5.45; S, 17.53. $C_9H_{10}O_2S$ calcd.: C, 59.31; H, 5.53; S, 17.59%). $^1H$ NMR ($CDCl_3$): $\delta$ 8.60 ppm (s, 1H, COOH, $D_2O$ exchanged), 7.30 (m, 5H, Ar—H), 4.50 (s, 1H, Ar—$CH$) and 2.12 ppm (s, 3H, S—$CH_3$). IR: 3100 (OH), 1695 $cm^{-1}$ (C=O).

The remaining residue was treated with 10% aqueous hydrochloric acid and diethyl ether. The ether solution was dried ($Na_2SO_4$) and analyzed by GC/MS. Beside the compound IIIa and the starting material, products IVa, V, VI and VII were also found. These compounds were easily identified by comparison of their mass spectra with those of authentic samples.

*Metalation of [(ethylthio)methyl] benzene (Ib)*

A solution of Ib (36 mmol) in dry diethyl ether (25 ml) was treated dropwise at room temperature with n-butyllithium in hexane (25 ml). The mixture was worked up as described for Ia.

From the bicarbonate solution the acid IIIb was obtained and was purified by chromatography on a silica gel column, using petroleum ether (40—70°)/ diethyl ether (1/1) as eluent. Yield 57%, $n_D^{27}$ 1.5694. *m/e* 196 ($M^+$). (Found: C, 61.14; H, 6.12; S, 16.26. $C_{10}H_{12}O_2S$ calcd.: C, 61.20; H, 6.16; S, 16.34%). $^1H$ NMR ($CDCl_3$): $\delta$ 8.55 (s, 1H, COOH, $D_2O$ exchanged), 7.30 (m, 5H, Ar—H), 4.52 (s, 1H, Ar—$CH$), 2.50 (q, 2H, $CH_2$—$CH_3$) and 1.16 ppm (t, 3H, $CH_2$—$CH_3$). IR: 3400 (OH), 1700 $cm^{-1}$ (C=O).

The GC/MS analysis of the overall mixture revealed, in addition to IIIb and the starting material products IVb, V, VI and VII. These latter compounds were identified by comparison of their mass spectra with those of authentic samples.

### *Metalation of [1-(methylthio)ethyl]benzene (Ic)*

A solution of Ic (40 mmol) in dry diethyl ether (28 ml) was treated dropwise at room temperature with n-butyllithium in hexane (28 ml). The mixture was stirred under reflux for 4 h and then worked up as described above. From the bicarbonate solution no acidic products were obtained. Treatment of the liquid neutral products with ethanol gave a white solid, which had an infrared spectrum nearly identical with that of an authentic polystyrene film.

The GC/MS analyses of the products solution revealed, in addition to the styrene (IX) and the starting material, the compounds IVa, IVc, VIII, X, XI. These compounds were identified by GC/MS comparison with authentic samples.

### *Metalation of [2-(methylthio)ethyl]benzene (IIa)*

IIa (40 mmol) in dry diethyl ether (28 ml) was metalated with a solution of n-butyllithium in hexane (28 ml). The mixture was worked up as described for Ic. No acidic products were obtained from the bicarbonate layer. Polystyrene was precipitated from the neutral products. The compounds X, XI, XII beside IX and the starting material were detected by GC/MS analysis and identified by comparison with authentic samples.

### *Metalation of [2-(ethylthio)ethyl]benzene (IIb)*

The same procedure as for IIa was employed. The product XIII beside IX, X, XI, XII and the starting meterial was detected by GC/MS.

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