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Metallation reactions

XVIII *. Regioselective metallation of (alkylthio)benzenes by superbases

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Abstract

(Alkylthio)benzenes were monometallated at the *alpha* position by a stoichiometric mixture of butyllithium and potassium t-butoxide and bimetallated at both the *alpha* and the *ortho* positions by two equivalents of the same reagent.

Introduction

The reactivity of organolithium compounds is greatly enhanced by the addition of alkoxides. These reagents are usually called superbases and are very useful in many organic syntheses where weakly acidic hydrogen atoms have to be abstracted [1]. Superbases allow mono- and poly-metallations of benzene, arenes, dienes and acyclic or cyclic trienes [2–6]. It is also possible to metallate benzene and toluene containing alkoxy, fluoro and trifluoromethyl groups [6–11]. On the other hand, very little is reported on the use of superbases with sulphur-containing compounds. It is known that vinyl ethers and vinyl thioethers are both *alpha*-monometallated by superbases [12,13]. Attempts to *ortho*-metallate benzenethiol were unsuccessful, in contrast to the easy *ortho*-metallation of phenol [6,14–16].

It was found that simple lithiating reagents such as butyllithium monometallate (methylthio)benzene regioselectively at the thiomethylic carbon atom, whereas higher (alkylthio)benzenes are monometallated at the ring carbon atom *ortho* to the thioether function [17,18]. An excess of butyllithium does not metallate further the higher (alkylthio)benzenes but it does dimetallate (methylthio)benzene, the second lithium atom replacing an *ortho* ring hydrogen atom [17,18]. It can be

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* For Part XVII see ref. 29.

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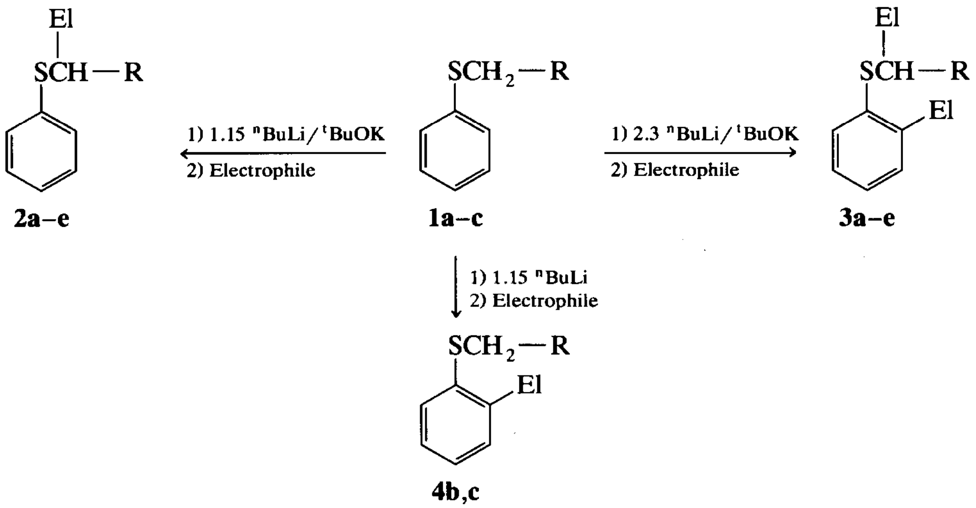

a: R = H, El = Me
b: R = El = Me
c: R = Et, El = Me
d: R = Me, El = CO_2H
e: R = Me, El = $SiMe_3$

Scheme 1.

assumed that alkyl substitution decreases the acidity of the *alpha* hydrogen because of the inductive effect.

The aim of the present work is to investigate superbases to *alpha*-metallate (alkylthio) aromatic ethers.

Results and discussion

All monometallation reactions were performed by treating the (alkylthio)benzenes **1a–b** with an equimolar amount of the superbase mixture of butyllithium and potassium t-butoxide. Dimetallation reactions were carried out with two equivalents of the same reagent. The intermediates were identified after reaction with iodomethane using GC/MS comparison with authentic samples.

The results given in the Scheme [19*] and Table 1 show that an equimolar amount of metallating reagent functionalizes the *alpha*-carbon atom. On the other hand, the use of two moles of metallating reagent allows the one-step functionalization of the *alpha*-carbon atom along with the carbon *ortho* to the thioether group. This was proved by quenching of the lithiated intermediates with iodomethane, which afforded the methyl derivatives **2a–c**, and **3a–c** in 70–78% yield.

The synthetic utility of this route was further proved by reaction of the mono- and di-anion of **1b** with other electrophiles (see Table 1). In this way, the quenching of the lithiated mixture with carbon dioxide gave the mono- **2d** and

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* Reference number with an asterisk indicates a note in the list of references.

Table 1

Metallation of (alkylthio)benzenes **1a–c** with butyllithium [a]

Starting Material	Additive	Reagent equiv.	% of products		
			2	**3**	**4**
1a	^{t}BuOK	1.15	75 [b]	–	–
	^{t}BuOK	2.3	–	74	–
		1.15	80 [b]	–	–
		2.3	–	58	–
1b	^{t}BuOK	1.15	71	–	–
	^{t}BuOK	2.3	–	75	–
		1.15 [c]	–	–	75 [d]
1c	^{t}BuOK	1.15	69	–	–
	^{t}BuOK	2.3	–	78	–
		1.15 [c]	–	–	70

[a] Reaction mixtures were quenched with methyl iodide. [b] This reaction product is identical with **1b**. [c] The same results were obtained employing 2.3 or more equivalents of reagent. [d] This reaction product is identical with **3a**.

di-carboxylic acids **3d** in good yields (60–65%); using chlorotrimethylsilane, the mono- **2e** and di-silylated derivatives **3e** were obtained in nearly 60% yield.

The above results show that although the use of superbases does not change the metallation pattern of (methylthio)benzene [18], the behaviour of the higher (alkylthio)benzenes is changed substantially. This can be explained in terms of acidity of the different hydrogen atoms, the activating effect of the sulphur atom, and the basicity of the metallating agent. The basicity of superbases is such that intramolecular activation by sulphur atom is not necessary for hydrogen abstraction, so that the acidity of the different hydrogen atoms is the controlling factor. The *alpha*-hydrogen atom is more acidic than the aromatic hydrogen. With less basic metallating agents a hydrogen atom can be abstracted only with the intramolecular assistance of the sulphur atom, which stabilizes the intermediate carbanion. This assistance is available only for the substitution of the *ortho* aromatic hydrogen atom. Thus, *ortho* metallation occurs first. Similar regioselective control in the metallation of fluoroanisoles has been recently discussed by Schlosser *et al.* [20].

In the case of the higher (alkylthio)benzenes (see Scheme and Table 1) selection of the normal lithiating agents or of the superbases allows the regioselective introduction of functional groups either in the *ortho* or in the *alpha* positions, respectively.

Experimental

General

IR spectra were recorded on a Perkin-Elmer 1310 grating spectrophotometer. ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer with tetramethylsilane as internal reference. The GC-MS analyses were performed at 70 eV with a Hewlett Packard 5989A GC-MS system with HP 5890 GC fitted with a capillary column (50 m × 0.2 mm) packed with DH 50.2 Petrocol (0.50 μ film thickness). The TLC analyses were carried out on a silica gel 60 F_{254} plates (Merck); spots were located by UV illumination. All flash chromatography was on silica G60 (Merck) columns. Microanalyses were carried out with a Carlo Erba 1106 elemental analyser. Melting points were obtained on a Kofler hot stage microscope and are uncorrected.

Commercially available reagent-grade starting materials and solvents were used. Solutions of butyllithium in hexane were obtained from Aldrich Chemical Company and were analyzed by the Gilman double titration method before use [21].

Starting materials

(Methylthio)- (**1a**) and (ethylthio)-benzene (**1b**) were purchased (Aldrich). (Propylthio)-benzene (**1c**) was prepared as previously described [22].

Authentic samples

[(1-Methylethyl)thio]- (**2b**), [(1-methylpropyl)thio]- (**2c**), 1-(ethylthio)-2-methyl- (**3a**), 2-methyl-1-[(1-methylethyl)thio]- (**3b**) and 2-methyl-1-(propylthio)-benzene (**4c**), 2-(phenylthio)-propanoic acid (**3d**), and [(1-phenylthio)ethyl]trimethylsilane (**3e**) were prepared by published methods [23–28].

2-Methyl-1-[(1-methylpropyl)thio]benzene (3c)

A mixture of 2-methylbenzenethiol (200 mmol), 2-bromobutane (210 mmol), anhydrous potassium carbonate (230 mmol), and dry acetone (60 ml) was heated under reflux for 10 h, and then added to water. The organic product was extracted with diethyl ether, the ethereal layer was separated and dried ($CaCl_2$), the solvent evaporated, and the residue flash-chromatographed using light petroleum as eluent. Yield 82%; b.p. 190–192°C; ^1H NMR ($CDCl_3$): δ 0.87 (t, 3H, CH_3CH_2), 1.15 (d, 3H, CH_3CH), 1.48 (q, 2H, CH_3CH_2), 2.28 (s, 3H, $ArCH_3$), 3.15 (q, 1H, CH_3CH), 7.12 (m, 4H, arom-*H*); MS, m/z 180 (M^+). Elemental analysis: Found: C, 73.20; H, 8.91; S, 17.65. $C_{11}H_{16}S$ (180.3) calcd.: C, 73.27; H, 8.95; S, 17.78%.

Monometallation procedure with superbases

A solution of butyllithium in hexane (35 ml, 50 mmol) was cooled to −60°C under nitrogen and a solution of the starting material (43 mmol) in hexane (20 ml) added. Finely powdered potassium t-butoxide (5.6 g, 50 mmol) was added and the temperature allowed to rise to −20°C. The mixture was kept for 1 h at −20°C, after which the temperature was allowed to rise to −10°C. After 3 h, an excess of iodomethane (12.8 g, 90 mmol) was added slowly, the cooling bath removed and the reaction completed by stirring overnight at room temperature. The reaction mixture was poured into water, the organic layer separated and the aqueous layer extracted with ether. The combined organic extracts were dried, filtered and evaporated. The products were distilled and identified by GC/MS comparison with authentic samples.

In this manner, starting from **1a**, **1b** and **1c**, respectively, the following compounds were obtained; (ethylthio)benzene (**2a**) [19], yield 75%; [(1-methylethyl)thio]benzene (**2b**), yield 71%; [(1-methylpropyl)thio]benzene (**2c**), yield 69%.

If solid crushed carbon dioxide or chlorotrimethylsilane were used as electrophiles in the reaction with **1b**, the following compounds were obtained.

*2-(Phenylthio)propanoic acid (**2d**).* Yield 65%, b.p. 140–145°C/1 mmHg. IR (liquid film): 3090 (OH), 1720 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.52 (d, 3H, CH_3), 3.80 (q, 1H, CH), 7.41 (m, 5H, arom-H), 9.80 (s, 1H, COOH, D_2O exchanged). The product was also identified by comparison with an authentic sample.

*1-[(Phenylthio)ethyl]trimethylsilane (**2e**).* Yield 63%, b.p. 93–94°C/2 mmHg. ^{1}H NMR ($CDCl_3$): 0.13 (s, 9H, SiCH_3), 1.24 (d, 3H, CH_3CH), 2.42 (q, 1H, CH_3CH), 7.15 (m, 5H, arom-H). The product was also identified by comparison with an authentic sample.

Bimetallation procedure with superbases

A solution of butyllithium in hexane (70 ml, 100 mmol) was cooled to −60°C under nitrogen, then a solution of the starting thioether (43 mmol) in hexane (20 ml), and, successively, finely powdered potassium t-butoxide (11.2 g, 100 mmol) was added. After the usual work-up, an excess of iodomethane (25.6 g, 180 mmol) was added slowly and the mixture worked up as described above. The products were distilled and identified by GC/MS comparison with authentic samples.

In this manner, starting from **1a**, **1b** and **1c**, respectively, the following compounds were obtained; 1-(ethylthio)-2-methylbenzene (**3a**), yield 74%; 2-methyl-1-[(1-methylethyl)thio]benzene (**3b**), yield 75%; 2-methyl-1-[(1-methylpropyl)thio] benzene (**3c**), yield 78%.

If solid crushed carbon dioxide or chlorotrimethylsilane were used as electrophiles in the reaction with **1b**, the following compounds were obtained.

*2-[(2-Carboxyphenyl)thio]propanoic acid (**3d**).* Yield 61%; crystallized from diisopropyl ether, m.p. 189–190°C. IR (Nujol): 3080 (OH), 1715 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6): δ 1.43 (d, 3H, CH_3), 4.10 (q, 1H, CH), 7.55 (m, 4H, arom-H), 9.92 (s, 1H, COOH, D_2O exchanged). MS, m/z (226) (M^+). Elemental analysis: Found: C, 53.01; H, 4.40; S, 10.03. $C_{10}H_{10}O_4S$ (226.24) calcd.: C, 53.08; H, 4.46; S, 14.17%.

*Trimethyl[1-[(2-trimethylsilylphenyl)thio]ethyl]silane (**3e**).* Yield 58%; viscous oil. ^{1}H NMR ($CDCl_3$): δ 0.11 (s, 18H, SiCH_3), 1.30 (d, 3H, CH_3CH), 2.55 (q, 1H, CH_3CH), 7.38 (m, 4H, arom-H). MS, m/z 282 (M^+). Elemental analysis: Found: C, 59.38; H, 9.23; S, 11.23. $C_{14}H_{26}SSi_2$ (282.53) calcd.: C, 59.51; H, 9.28; S, 19.86%.

Metallation procedure with butyllithium alone

These reactions were carried out as previously described [18], using iodomethane as electrophile. The products were distilled and identified by GC/MS comparison with authentic samples.

In this manner, starting from **1a**, **1b** and **1c**, respectively, and using one mole of organolithium compound per mole of thioether the following compounds were obtained; (ethylthio)benzene (**2a**) [19], Yield 80%; 1-(ethylthio)-2-methylbenzene (**4b**) [19], Yield 75%; 2-methyl-1-(propylthio)benzene (**4c**), Yield 70%.

Using two or more moles of organolithium compound per mole of thioether, only **4b** and **4c** were obtained starting from **1b** and **1c**, respectively, while only **3a** was obtained from **1a**, in 58% yield [19].

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