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Metallation reactions. Part 35: A change of the regiochemistry in the metallation of (alkylthio)arenes

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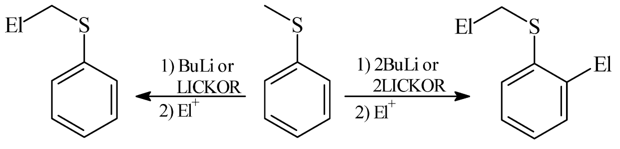
Abstract—The metallation reaction of bromo(alkylthio)benzenes is described. The results show the complementarity of these reactions with the metal–hydrogen exchange reaction. In fact, monometallation of bromo(methylthio)benzenes afforded products substituted in *para* or *meta* or *ortho* to the thioethereal function while bimetallation led to *αS,para*, *αS,meta* and *αS,ortho* disubstituted products. Analogously, the monometallation of 4-bromo-(isopropylthio)benzene afforded *para*-monosubstituted and *ortho*,*para*-disubstituted products.

1. Introduction

The use of organolithium compounds as reaction intermediates is of great interest in synthesis.[1–6] They can be prepared by hydrogen–lithium (this field includes the directed *ortho*-lithiation of aromatic compounds),[1–6] halogen–lithium,[4,6] calcogen–lithium,[7–10] tin–lithium[11] and phosphorus–lithium exchange.[12]

The metallation reaction of aromatic compounds leads to 1,2-disubstituted derivatives: whenever organolithiums with the metal atom *meta* or *para* to the substituent are needed, the method of choice is mainly the halogen–lithium exchange.[13–19]

In our previous work we showed how (methylthio)benzene can be monometallated at the methylthio carbon by butyllithium or by superbases.[20,21] When the reaction was performed with 2 M equiv. of the same reagents, the thioether (Scheme 1) underwent bimetallation on the methylthio carbon and in the *ortho* position.[20,21]



Scheme 1.

In our synthetic studies we sometimes needed (methylthio)arenes bearing a substitutent *para* and *meta* to the thioethereal group, retaining this function unaltered, or in *alpha* and *para* or *meta* to this group. We decided to attempt the metal–halogen exchange reaction for the first set of products, and for the other products a one-step metal–halogen/metal–hydrogen exchange using 4-bromo-(**1a**), and 3-bromo-1-(methylthio)benzene (**1b**). For a full analysis of the synthetic potential of this reaction we also examined 2-bromo-1-(methylthio)benzene (**1c**).

2. Results and Discussion

All reactions were performed by treating ethereal solutions of **1a–c** with 2 or 3 M equiv. of *n*-butyllithium in hexane. The results presented in Scheme 2 shows that 2 M equiv. of organolithium effect the metal–halogen exchange with subsequent functionalization, after electrophilic quenching of the aromatic carbon previously bonded to the halogen. In this way, products **2a–h** were obtained in 75–85% yields.

When the reaction was performed with 3 M equiv. of the same organolithium, we functionalized this aromatic carbon and the methylthio one with the same electrophile in one step. Thus, products **3a–h** were isolated in 63–73% yields. It is also possible to introduce two different electrophiles at these same sites by performing two sequential monometallations/electrophilic quenching. In contrast, the attempt to substitute in one-step the halogen and both hydrogens *alpha* and *ortho* to the methylthio group was unsuccessful. In fact, even using a large excess of organolithium (10–12 M equiv.) the only products isolated

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Keywords: Metallation; Lithiation; Bromo(alkylthio)arenes; Thioethers.

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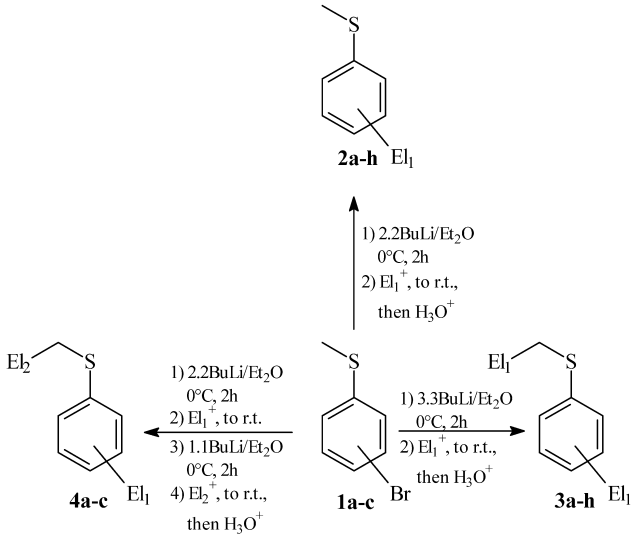
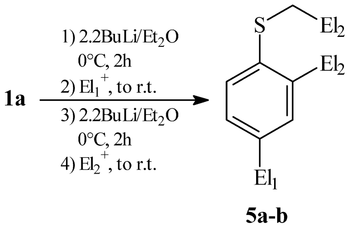


1	Substituents position	2	Yield (%)	3	Yield (%)	4	Yield (%)	El$_1$	El$_2$
a	1,4	**a**	80	**a**	68	**a**	61	Me	CO_2H
a	1,4	**b**	78	**b**	65	**b**	63	Et	CO_2H
a	1,4	**c**	85	**c**	70			CO_2H	
a	1,4	**d**	75	**d**	72			$SiMe_3$	
b	1,3	**e**	77	**e**	69	**c**	65	Me	CO_2H
b	1,3	**f**	81	**f**	73			CO_2H	
c	1,2	**g**	82	**g**	63			Me	
c	1,2	**h**	84	**h**	68			CO_2H	

Scheme 2.



5	Yield (%)	El$_1$	El$_2$
a	64	Me	Me
b	67	Me	CO_2H

Scheme 3.

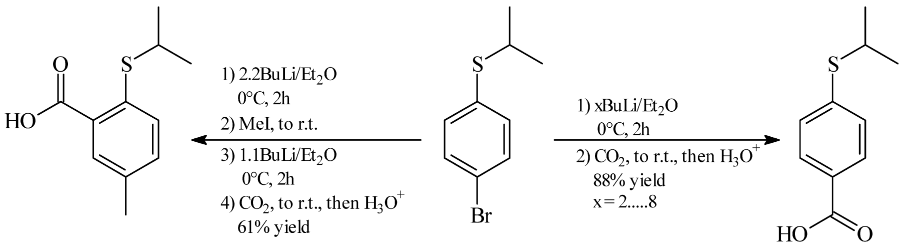
were the ones derived by bromine and *alpha* substitution. The trisubstitution reaction can, however, be achieved through two iterative one-pot metallations (Scheme 3): the first substitutes the halogen atom by a monometallation/electrophilic quenching and the second effects a bimetallation/electrophilic quenching.

With the aim of testing the behaviour of other thioalkyl groups (SR where R≠Me), analogous reactions were performed on 4-bromo-1-(isopropylthio)benzene (**6**) (Scheme 4). The results showed that every molar ratio of organolithium (from two to eight) leads exclusively to the metal–halogen exchange to give a 4-monolithiated intermediate: this was proved by the attainment of **7** alone after carboxylation. Furthermore it is possible to introduce a second electrophile *ortho* to the thioethereal function by a subsequent 'one-pot' metallation, as proved by the attainment of compound **8**. The results obtained are entirely complementary with those obtained with (isopropylthio)benzene.[22] In fact it is possible to prepare from this compound 2-substituted-(alkylthio)benzenes by monometallation and 2,6-disubstituted derivatives by two iterative 'one-pot' monometallations.

In conclusion, from the results obtained, the difference with analogous oxygen or nitrogen compounds is evident:[6] (methylthio)bromobenzenes can successfully undergo a direct bimetallation reaction. This is a further confirmation of the thioether group's capability to promote both annular and side-chain metallations. Moreover, the above results emphasize the synthetic potential both of dilithiation in the preparation of polyfunctionalized aromatics, either in a single or in two successive 'one-pot' monolithiations, and of trilithiations through a combination of 'one-step' and 'one-pot' processes. In particular, comparing the results here obtained with those previously reported,[20–22] it can be deduced that:

(a) starting from (methylthio)benzene it is possible to prepare:[22]
- αS-substituted benzene derivatives through a direct monometallation/electrophilic quenching;
- αS,*ortho*-substituted benzene derivatives through a 'one-step' direct bimetallation/electrophilic quenching;

(b) starting from 2-bromo-1-(methylthio)benzene it is possible to obtain 2-substituted (methylthio)benzenes through metal–halogen exchange/electrophilic quenching. This result demonstrates that the monometallations performed on (methylthio)benzene and on



8 **6** **7**

Scheme 4.

2-bromo-1-(methylthio)benzene give complementary results as they allow selective preparation of α*S*-substituted or *ortho*-substituted products;

(c) starting from 3- and 4-bromo-substituted (methylthio)benzenes it is possible to obtain:
- *meta*- and *para*-substituted (methylthio)benzenes through metal–halogen exchange/electrophilic quenching;
- *meta*- or *para*,α*S*-disubstituted benzenes through a simultaneous 'one-step' metal–halogen and metal–hydrogen exchange followed by electrophilic quenching;

(d) starting from 4-bromo-1-(isopropylthio)benzene it is possible to obtain:
- 4-substituted-(alkylthio)benzenes derived by substitution of the halogen with the electrophile;
- 2,4-disubstituted-(alkylthio)benzenes through two subsequent 'one-pot' metallation/electrophilic quenching procedures.

3. Experimental

3.1. General

NMR spectra were recorded on a Varian VXR-300 spectrometer with tetramethylsilane as internal reference. IR spectra were recorded on a Perkin–Elmer 1310 grating spectrophotometer. The GC–MS analyses were performed 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 μm film thickness). All flash chromatographies were performed 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. All yields reported are mass yields of purified products.

Commercially available reagent-grade starting materials and solvents were used. Solutions of butyllithium in hexane were obtained from Aldrich Chemical Company and were analysed by the Gilman double titration method before use.[23] 4-Bromobenzenethiol, 4-bromo-(**1a**)-, 3-bromo-(**1b**) and 2-bromo-1-(methylthio)benzene (**1c**) were purchased (Aldrich).

3.1.1. 4-Bromo-1-(isopropylthio)benzene (6). A mixture of 4-bromobenzenethiol (12.5 g, 66.0 mmol), 2-bromopropane (6.15 mL, 66.0 mmol) anhydrous potassium carbonate (13.0 g, 94.0 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, dried ($CaCl_2$) and the solvent evaporated. The crude product was purified by distillation to give the title compound **6** (13.90 g, 60.16 mmol, 91%) as a pale yellow oil, bp 108–109 °C/5 mm Hg (Lit.[24] bp 125–126 °C/18 mm Hg). Spectroscopic data identical to those reported in the literature.[24]

3.2. General procedure for monometallation

A vigorously stirred solution of starting material (5 mmol) in anhydrous diethyl ether (25 mL) was treated with a 1.4 M solution of *n*-butyllithium in hexane (7.9 mL, 11 mmol) at 0 °C under argon. After 2 h, a solution of the appropriate electrophile (5 mmol) in anhydrous diethyl ether (10 mL) was added, the cooling bath removed and the reaction completed by stirring overnight at room temperature. The reaction mixture was poured into water and the pH adjusted to 4–5 by addition of 10% aqueous hydrochloric acid. The organic layer was separated and the aqueous layer extracted with diethyl ether (3×20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated.

In this manner, the following compounds were prepared:

3.2.1. 4-Methyl-1-(methylthio)benzene (2a). This compound was obtained from the reaction of the monometallated **1a** and iodomethane and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 4-methylbenzenethiolate with iodomethane. The crude product was purified by distillation to give the title compound **2a** (0.55 g, 4.0 mmol, 80%) as a pale yellow oil, bp 91–92 °C/10 mm Hg (Lit.[25] bp 104–105 °C/20 mm Hg).

3.2.2. 4-Ethyl-1-(methylthio)benzene (2b). This compound was obtained from the reaction of the monometallated **1a** and iodoethane and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 4-ethylbenzenethiolate with iodomethane. The crude product was purified by distillation to give the title compound **2b** (0.59 g, 3.87 mmol, 78%) as a pale yellow oil, bp 100–102 °C/10 mm Hg (Lit.[26] bp 212 °C).

3.2.3. 4-(Methylthio)benzoic acid (2c). The monometallated mixture of **1a** was poured onto ca. 100 g of crushed solid carbon dioxide. After 24 h the residue was treated with 10% aqueous sodium bicarbonate (20 mL) and then with diethyl ether (20 mL). The alkaline layer was separated, washed with diethyl ether (3×10 mL), and then acidified with cold concentrated hydrochloric acid, extracted with diethyl ether (3×10 mL), dried (Na_2SO_4), and concentrated. The crude product was crystallised from 1:1 aqueous ethanol to give the title compound **2c** (0.71 g, 4.23 mmol, 85%) as pale yellow crystals, mp 195–196 °C (Lit.[27] mp 196–197 °C). This compound was identical to the commercial product **2c**.

3.2.4. Phenyl(trimethylsilyl)methyl sulfide(2d). This compound was obtained from the reaction of the monometallated **1a** and trimethylchlorosilane. The crude product was flash-chromatographed on silica gel using light petroleum as eluent to give the title compound **2d** (0.73 g, 3.73 mmol, 75%). Spectroscopic data identical to those reported in the literature.[28]

3.2.5. 3-Methyl-1-(methylthio)benzene (2e). This compound was obtained from the reaction of the monometallated **1b** and iodomethane and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 3-methylbenzenethiolate with iodomethane. The crude product was purified by distillation to give the title compound **2d** (0.53 g, 3.83 mmol, 77%) as a pale yellow oil, bp 91–94 °C/15 mm Hg (Lit.[29] bp 101–103 °C/28 mm Hg).

3.2.6. 3-(Methylthio)benzoic acid (2f). This compound was obtained from the reaction of the monometallated **1b** and carbon dioxide. The crude product was crystallised from 1:1 aqueous ethanol to give the title compound **2f** (0.68 g, 4.03 mmol, 81%) as pale yellow crystals, mp 123–124 °C (Lit.[30] mp 122–123 °C). This compound was identical to the commercial product **2f**.

3.2.7. 2-Methyl-1-(methylthio)benzene (2g). This compound was obtained from the reaction of the monometallated **1c** and iodomethane and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 2-methylbenzenethiolate with iodomethane. The crude product was purified by distillation to give the title compound **2g** (0.57 g, 4.12 mmol, 82%) as a pale yellow oil, bp 104–105 °C/25 mm Hg (Lit.[31] bp 96 °C/16 mm Hg).

3.2.8. 2-(Methylthio)benzoic acid (2h). This compound was obtained from the reaction of the monometallated **1c** and carbon dioxide. The crude product was crystallised from 1:1 aqueous ethanol to give the title compound **2h** (0.71 g, 4.19 mmol, 84%) as pale yellow crystals, mp 125–126 °C (Lit.[32] mp 126–127 °C). This compound was identical to the commercial product **2h**.

3.2.9. 4-(Isopropylthio)benzoic acid (7). This compound was obtained from the reaction of the monometallated **6** and carbon dioxide. The crude product was crystallised from methanol to give the title compound **7** (0.86 g, 4.40 mmol, 88%) as pale yellow crystals, mp 154–155 °C (Lit.[33] mp 155–156 °C); [Found: C, 61.09; H, 6.10; S, 16.21. $C_{10}H_{12}O_2S$ requires: C, 61.20; H, 6.16; S, 16.34%]; ν_{max} (KBr) 3100, 2990, 1675, 1595, 1430, 1300, 1195, 1140, 1100, 1055, 960, 850, 770 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.01 (2H, d, *J*=8.4 Hz, Ar*H*), 7.39 (2H, d, *J*=8.4 Hz, Ar*H*), 3.59 (1H, m, C*H*Me), 1.40 (6H, d, *J*=6.7 Hz, CH*Me*); δ_C (75.4 MHz, $CDCl_3$) 171.9, 144.8, 130.5, 128.1, 126.1, 36.6, 22.9; *m*/*z* (EI) 196 (41, M$^+$), 154 (24), 136 (100), 108 (23), 97 (7), 69 (15%).

3.3. General procedure for bimetallation

A vigorously stirred solution of starting material (5 mmol) in anhydrous diethyl ether (25 mL) was treated with a 1.4 M solution of *n*-butyllithium in hexane (12 mL, 16.5 mmol) at 0 °C under argon. After 2 h, a solution of the appropriate electrophile (10 mmol) in anhydrous diethyl ether (15 mL) was added, the cooling bath removed and the reaction completed by stirring overnight at room temperature. The resulting mixture was worked up in the same manner above described.

In this manner the following products were prepared:

3.3.1. 1-(Ethylthio)-4-methylbenzene (3a). This compound was obtained from the reaction of the bimetallated **1a** and iodomethane and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 4-methylbenzenethiolate with iodoethane. The crude product was purified by distillation to give the title compound **3a** (0.51 g, 3.38 mmol, 68%) as a pale yellow oil, bp 115–117 °C/10 mm Hg (Lit.[34] bp 101–103 °C/2 mm Hg).

3.3.2. 4-Ethyl-1-(propylthio)benzene (3b). This compound was obtained from the reaction of the bimetallated **1a** and iodoethane and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of potassium 4-ethylbenzenethiolate with 1-bromopropane. The crude product was purified by distillation to give the title compound **3b** (0.58 g, 3.23 mmol, 65%) as a pale yellow oil, bp 118–120 °C/10 mm Hg (Lit.[35] bp 105–106/3 mm Hg).

3.3.3. 4-[(Carboxymethyl)thio]benzoic acid (3c). This compound was obtained from the reaction of the bimetallated **1a** and carbon dioxide; the crude product was crystallised from 1:1 aqueous ethanol to give the title compound **3c** (0.74 g, 3.48 mmol, 70%) as pale yellow crystals, mp >250 °C (Lit.[36] mp >250 °C); [Found: C, 50.81; H, 3.71; S, 14.99. $C_9H_8O_4S$ requires: C, 50.94; H, 3.80; S, 15.11%]; ν_{max} (KBr) 3400, 3100, 2990, 1690, 1590, 1500, 1420, 1325, 1300, 1280, 1190, 1120, 1090, 1015, 900, 850, 810, 760 cm^{-1}; δ_H (300 MHz, DMSO) 13.00 (2H, broad, CO_2*H*, D_2O exchangeable), 7.95 (2H, d, *J*=8.2 Hz, Ar*H*), 7.50 (2H, d, *J*=8.2 Hz, Ar*H*), 4.04 (2H, s, C*H*$_2$); δ_C (75.4 MHz, DMSO) 170.2, 167.0, 142.5, 129.8, 127.6, 126.1, 33.9; *m*/*z* (EI) 212 (100, M$^+$), 195 (8), 167 (76), 149 (14), 137 (24), 123 (14.5), 105 (1), 77 (2%).

3.3.4. (Trimethylsilyl)methyl 4-(trimethylsilyl)phenyl sulfide (3d). This compound was obtained from the reaction of the bimetallated **1a** and chlorotrimethylsilane. The crude product was purified by flash-chromatography (light petroleum) to give the title compound **3d** (0.96 g, 3.58 mmol, 72%) as a pale yellow oil, n_D^{25}=1.540; [Found: C, 58.05; H, 8.93; S, 11.83. $C_{13}H_{24}SSi_2$ requires: C, 58.14; H, 9.01; S, 11.94%]; ν_{max} (neat) 2970, 2940, 2875, 1580, 1480, 1440, 1255, 1180, 850, 745, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.43 (2H, d, *J*=8.1 Hz, Ar*H*), 7.28 (2H, d, *J*=8.1 Hz, Ar*H*), 2.20 (2H, s, SC*H*$_2$), 0.27 (9H, s, *Me*SiAr), 0.20 (9H, s, *Me*SiCH$_2$); δ_C (75.4 MHz, $CDCl_3$) 141.4, 135.9, 133.5, 128.6, 29.7, −1.1, −1.6; *m*/*z* (EI) 268 (17, M$^+$), 253 (9), 180 (8), 165 (11), 151 (2), 135 (2), 73 (100%).

3.3.5. 1-(Ethylthio)-3-methylbenzene (3e). This compound was obtained from the reaction of the bimetallated **1b** and iodomethane and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 3-methylbenzenethiolate with iodoethane. The crude product was purified by distillation to give the title compound **3e** (0.52 g, 2.91 mmol, 69%) as a pale yellow oil, bp 112–113 °C/10 mm Hg (Lit.[37] bp 80–82 °C/1 mm Hg).

3.3.6. 3-[(Carboxymethyl)thio]benzoic acid (3f). This compound was obtained from the reaction of the bimetallated **1b** and carbon dioxide and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of 3-mercaptobenzoic acid and chloroacetic acid in potassium carbonate/acetone. The crude product was crystallised from aqueous ethanol to give the title compound **3f** (0.77 g, 3.62 mmol, 73%) as white crystals, mp 196–197 °C (Lit.[36] mp 198 °C).

3.3.7. 1-(Ethylthio)-2-methylbenzene (3g).

This compound was obtained from the reaction of the bimetallated **1c** and iodomethane and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 2-methylbenzenethiolate with iodoethane. The crude product was purified by distillation to give the title compound **3g** (0.48 g, 3.14 mmol, 63%) as a pale yellow oil, bp 115–117 °C/10 mm Hg (Lit.[22] bp 120–122 °C/15 mm Hg).

3.3.8. 2-[(Carboxymethyl)thio]benzoic acid (3h).

This compound was obtained from the reaction of the bimetallated **1c** and carbon dioxide and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from bimetallation/treatment with carbon dioxide of (methylthio)benzene.[20] The crude product was crystallised from aqueous ethanol to give the title compound **3h** (0.72 g, 3.38 mmol, 68%) as pale yellow crystals, mp 119–120 °C (Lit.[20] mp 118–120 °C).

3.4. Sequential, one-pot, introduction of two different electrophiles on 1a–b

A vigorously stirred solution of starting material (5 mmol) in anhydrous diethyl ether (25 mL) was treated with a 1.4 M solution of *n*-butyllithium in hexane (7.9 mL, 11 mmol) at 0 °C under argon. After 2 h, a solution of the appropriate electrophile (5 mmol) in anhydrous diethyl ether (15 mL) was added, the cooling bath removed and the reaction completed by stirring overnight at room temperature. The resulting mixture was then cooled to 0 °C and treated dropwise with *n*-butyllithium in hexane (3.9 mL, 5.5 mmol). After the usual work-up, the resulting solution was poured onto ca. 100 g of crushed solid carbon dioxide and worked up in the same manner above described.

In this manner, the following compounds were prepared:

3.4.1. 2-[(4-Methylphenyl)thio]acetic acid (4a).

This compound was obtained from **1a** using iodomethane as first electrophile and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 4-methylbenzenethiolate with monochloroacetic acid. The crude product was crystallised from 1:1 chloroform/petroleum ether to give the title compound **4a** (0.55 g, 3.03 mmol, 61%) as white crystals, mp 93–95 °C (Lit.[38] mp 94–94.4 °C).

3.4.2. 2-[(4-Ethylphenyl)thio]acetic acid (4b).

This compound was obtained from **1a** and iodoethane as first electrophile and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 4-ethylbenzenethiolate with monochloroacetic acid. The crude product was crystallised from 1:1 chloroform/petroleum ether to give the title compound **4b** (0.61 g, 3.13 mmol, 63%) as white crystals, mp 60–62 °C (Lit.[39] mp 62–63 °C).

3.4.3. 2-[(3-Methylphenyl)thio]acetic acid (4c).

This compound was obtained from **1b** using iodomethane as first electrophile and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 3-methylbenzenethiolate with monochloroacetic acid. The crude product was crystallised from aqueous ethanol to give the title compound **4c** (0.59 g, 3.23 mmol, 65%) as white crystals, mp 67–68 °C (Lit.[38] mp 66.8–67.4 °C).

3.5. Sequential, one-pot, introduction of three electrophiles on 1a

A vigorously stirred solution of **1a** (1.0 g, 5 mmol) in anhydrous diethyl ether (25 mL) was treated with a 1.4 M solution of *n*-butyllithium in hexane (7.5 mL, 11 mmol) at 0 °C under argon. After 2 h, a solution of iodomethane (0.3 mL, 5 mmol) in anhydrous diethyl ether (15 mL) was added, the cooling bath removed and the reaction completed by stirring overnight at room temperature. The resulting mixture was then cooled to 0 °C and treated dropwise with *n*-butyllithium in hexane (7.5 mL, 11 mmol). After 2 h, the solution was treated either with iodomethane (0.6 mL, 10 mmol) in anhydrous diethyl ether (15 mL) or poured onto ca. 100 g of carbon dioxide and worked up in the same manner above described.

In this manner the following products were prepared:

3.5.1. 2,4-Dimethyl-1-(ethylthio)benzene (5a).

This compound was obtained using iodomethane as second electrophile and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 2,4-dimethylbenzenethiolate with iodoethane. The crude product was purified by distillation to give the title compound **5a** (0.53 g, 3.18 mmol, 64%) as a pale yellow oil, bp 73–74 °C/2 mm Hg (Lit.[20] 68–70 °C/1 mm Hg).

3.5.2. 2-[(Carboxymethyl)thio]-5-methylbenzoic acid (5b).

This compound was obtained using carbon dioxide as second electrophile and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from bimetallation/treatment with carbon dioxide of 4-methyl-1-(methylthio)benzene.[20] The crude product was crystallised from chloroform to give the title compound **5b** (0.75 g, 3.33 mmol, 67%) as white crystals, mp 198–199 °C (Lit.[20] mp 197–198 °C).

3.6. Sequential, one-pot, introduction of two electrophiles on 6

Following the above procedure, when **6** was treated with 2.2 M equiv. of *n*-butyllithium followed by treatment with iodomethane and then with 1.1 M equiv. of the same organolithium followed by quenching with carbon dioxide, the following compound was obtained:

3.6.1. 2-(Isopropylthio)-5-methylbenzoic acid (8).

This compound was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from metallation/treatment with carbon dioxide of 1-(isopropylthio)-4-methylbenzene.[22] The crude product was crystallised from aqueous ethanol to give the title compound **8** (0.64 g, 3.04 mmol, 61%) as white crystals, mp 108–109 °C (Lit.[22] mp 106–108 °C).

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