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Metalation reactions

XV *. Regioselective metalation of (alkylthio)fluorobenzenes

S. Cabiddu, C. Fattuoni, C. Floris, G. Gelli and S. Melis

Dipartimento di Scienze Chimiche, Università, I-09124 Cagliari (Italy)

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Abstract

In reactions of (alkylthio)fluorobenzenes with *n*-butyllithium the compounds 4-RSC₆H₄F (R = Me, ⁱPr) and 2-ⁱPrSC₆H₄F were found to undergo metalation selectively *ortho* to the fluorine atom, whereas 2-MeSC₆H₄F undergoes metalation at the thiomethyl carbon atom.

Introduction

It is well known that substituents with unshared electron pairs facilitate *ortho*-lithiation of aromatic compounds [2,3] and that the *ortho*-directing power depends on the nature of the substituents. These have been classified as strong, medium and weak activators [4], and their influence appears to involve both coordination and inductive effects [5]. Inductive effects seem to dominate in the metalation of fluorobenzene, since *ortho*-metalated intermediates cannot be coordinatively stabilized by fluorine atom [6]; on the other hand, substituents such as the methoxy group *ortho* to the deprotonation site have an effect greater than expected for the inductive effect alone, suggesting that coordination also plays a significant role [5,6]. These observations have been investigated by both experimental and theoretical approaches, such as consideration of ¹³C NMR spectral data and semiempirical MO calculations [7]. A study of the distribution of the electron density for some methoxybenzenes and, consequently, the positions of the energy minima, show that the most probable site for the attack of the organolithium reagent lies next to the more electronegative substituents [7]. In particular, two significant energy minima have been identified for 1-fluoro-2-methoxybenzene, one close to the fluorine atom and the other to the methoxy group, respectively. The calculations predict competitive attack of the organometallic reagent at positions *ortho* to the two substituents,

* For Part XIV see ref. 1.

as shown by Kirk et al. [8]. The attack occurs mainly *ortho* to the methoxy group, and this was explained on the basis of the greater stability of the oxygen-organo-lithium complex with respect to that of the corresponding fluorine-organolithium species, along with a greater net electron density in the first complex than the second [7].

To our knowledge there have been no reports on the competition between sulphur and fluorine in the orientation of metalation and in view of the importance of fluoro and thioether groups in the synthesis of bioactive molecules, we decided to examine the lithiation of the fluorosubstituted (alkylthio)benzenes 1–4.

Results and discussion

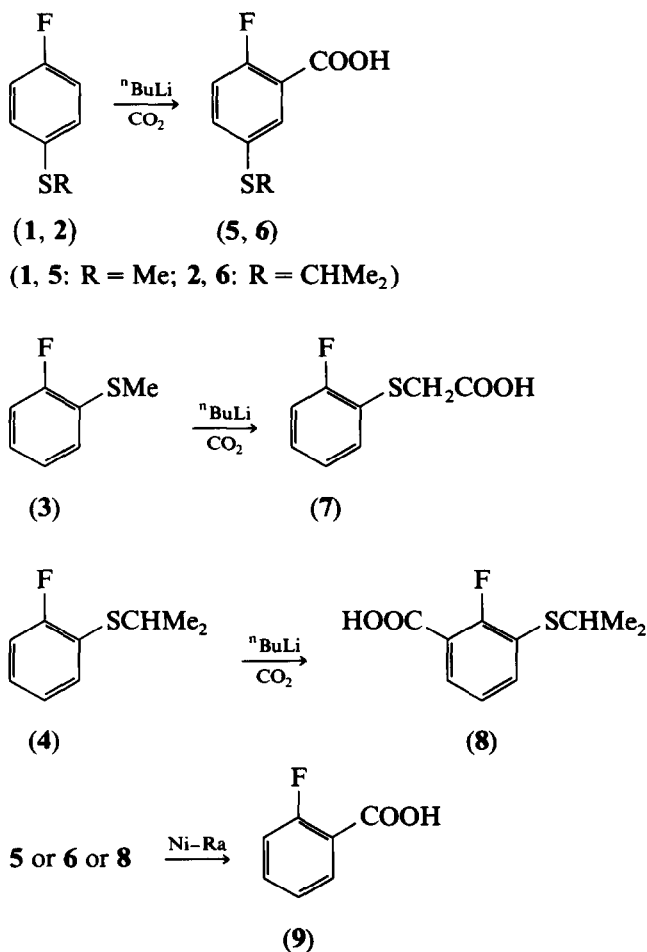
Lithiation of 1-fluoro-4-(methylthio)benzene (1) with an equimolar amount of *n*-butyllithium at -60°C , followed by quenching with solid carbon dioxide, gave only one product detectable by chromatographic (TLC, HPLC) analysis of the crude product mixture. This product was isolated and identified as 2-fluoro-5-(methylthio)benzoic acid (5). The analogous procedure with 4-(isopropylthio) (2), and 2-(isopropylthio)-1-fluorobenzene (4) gave 5-(isopropylthio)- (6) and 3-(isopropylthio)-2-fluorobenzoic acid (8), respectively. However, a similar procedure involving 1-fluoro-2-(methylthio)benzene (3) yielded selectively [(2-fluorophenyl)thio]acetic acid (7) (Scheme 1).

The regiochemistry of lithiation was determined by spectroscopic and chemical methods. The ^{13}C NMR signals of compounds 1, 2 and 3 were assigned on the basis of the ^{13}C – ^{19}F coupling constants (Table 1) and comparison of the data with those previously reported [9–11]. The products 5, 6 and 8 were identified by comparing ^1H -coupled and ^1H -decoupled spectra and noting that the ^{13}C signals of the carboxyl group in the ^1H -decoupled spectrum showed a splitting due to the carbon–fluorine coupling. The value of this coupling constant (3.5 Hz) was characteristic of an *ortho*-substituted fluorobenzene [9–11], and so the carboxylic group must be bonded in *ortho* to the fluorine in compounds 5, 6 and 8.

The identities of the acids 5, 6 and 8 were further confirmed by their desulphurization with Ni–Raney to give 2-fluorobenzoic acid (9). The structure of the acid 7 was confirmed by comparison with an authentic sample obtained by treating 2-fluorobenzenethiol with monochloroacetic acid.

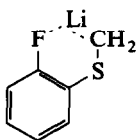
The results show that the metalation usually occurs at the carbon atom *ortho* to the fluorine, the only exception being in the case of compound 3, which was metalated at the thiomethyl carbon atom.

The regiocontrol of the metalation depends on the coordination properties, on the electron density, and on the inductive and mesomeric effects exerted by the substituents on the aromatic ring. A fluorine substituent on the aromatic ring gives rise to the energy minimum for the proton abstraction reaction at the *ortho* position; the thioether group exerts a coordinating effect. The simultaneous presence of both such groups in an aromatic ring could be expected to make the positions *ortho* to both substituents suitable for metalation. The fact that only products of lithiation *ortho* to the fluorine atom were found, with no trace of products from the lithiation *ortho* to the thioalkyl group, indicates that the inductive effect of the fluorine prevails over the weak coordinating power of the thioether group [6].



Scheme 1

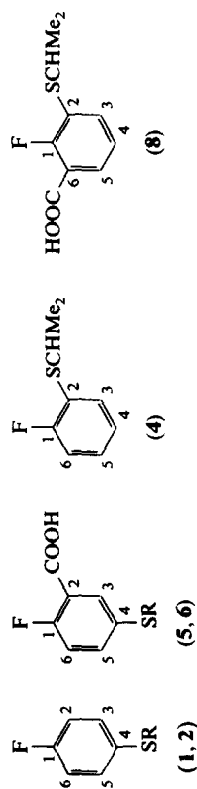
Metalation of **3** at the thiomethyl carbon can be accounted for by stabilization of the thiomethyl carbanion by the adjacent fluorine:



Such an intermediate cannot be formed in the case of **1**.

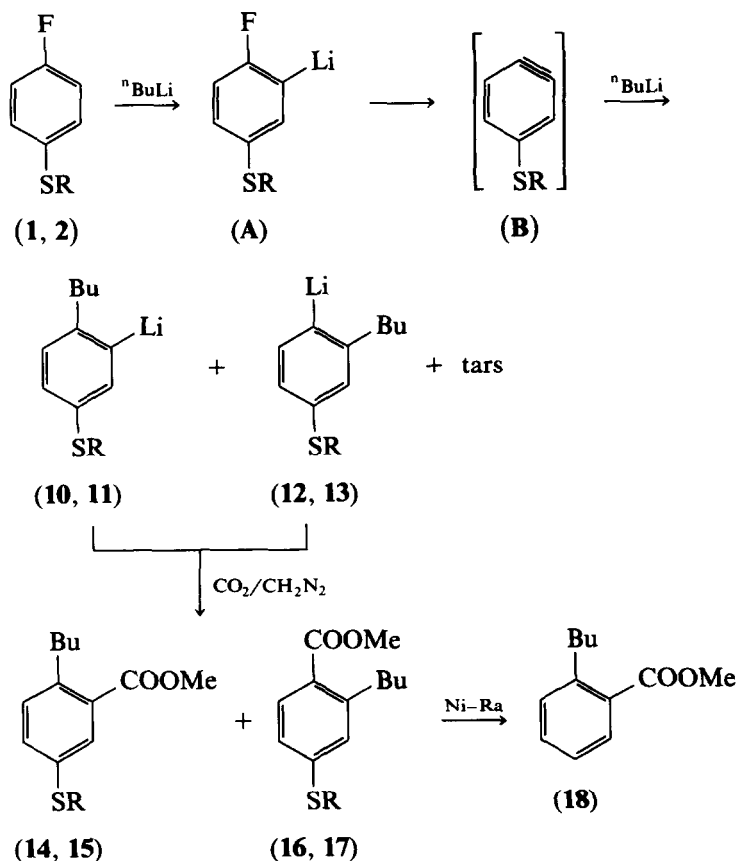
Dimetalation was also attempted using two mole equivalents of organolithium reagent. After 5 h, the usual reaction time for metalation, only the monometalation product was obtained. When reaction was allowed to proceed for a longer time (30 h) other products were formed. In all cases mixtures of products were obtained, mostly intractable tars. It was possible to isolate and characterize two isomeric carboxylic acids for each substrate only in the case of reactions of **1** and **2**. When the reaction mixture after metalation of **1** was treated with diazomethane, analysis

Table 1

 ^{13}C NMR data ^a for compounds 1, 2, 4, 5, 6, 8

	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	R	COOH
1	160.1 (241.5)	115.6 (22.6)	128.5 (7.5)	133.2 (4.5)	128.5 (7.5)	115.6 (22.6)	16.2(CH ₃)	
5	160.5 (261.0)	117.9 (9.6)	130.3 (-)	134.2 (4.1)	134.0 (9.1)	117.6 (23.7)	16.5(CH ₃)	169.1 (3.5)
2	162.0 (226.0)	115.2 (22.6)	134.5 (7.5)	130.0 (5.0)	134.5 (7.5)	115.2 (22.6)	38.0(CH)	23.0(CH ₃)
6	161.6 (262.9)	117.8 (9.8)	136.2 (6.8)	131.2 (3.8)	139.5 (9.1)	117.6 (23.2)	38.9(CH)	169.3 (3.5)
4	162.0 (245.2)	122.2 (15.0)	134.6 (1.9)	124.2 (3.8)	129.0 (7.5)	115.5 (22.6)	37.8(CH)	23.1(CH ₃)
8	161.5 (261.4)	124.8 (19.1)	139.5 (2.6)	123.9 (4.5)	131.5 (-)	118.0 (10.6)	37.7(CH)	169.9 (3.5)

^a In CDCl₃; chemical shifts δ with respect to Me₄Si. Coupling constants $^nJ(^{13}\text{C}-^{19}\text{F})$ are given in brackets. Carbon atoms in 5, 6 and 8 have been numbered analogously to 1, 2 and 4 for quick reference.



(1, 10, 12, 14, 16: R = Me; 2, 11, 13, 15, 17: R = CHMe_2)

Scheme 2

by GC-MS showed that two products were present, in almost equal amounts, giving the same molecular ion $[M]^+$ 238. Similar treatment of the mixture obtained by dimetalation of **2**, gave two products showing the molecular ion $[M]^+$ 266, in almost equal amounts. Both mixtures, after desulphurisation with Ni-Raney, gave the same product, which was identified as the methyl ester of the butylbenzoic acid (**18**) by GC comparison with an authentic sample. These results suggested that the two products obtained from **1** were the methyl esters of the 5-(methylthio)- (**14**) and 4-(methylthio)-2-butylbenzoic acid (**16**), whilst those derived from **2** were the methyl esters of the 5-(isopropylthio)- (**15**) and 4-(isopropylthio)-2-butylbenzoic acid (**17**) (Scheme 2).

Formation of compounds **14–17** may result from the aryne intermediate **B**, formed by elimination of lithium fluoride from the monometalation intermediate **A** [2]. The intermediate **B** would undergo addition of one mole of organolithium to yield the lithiated compounds **10** and **12** from the reaction of **1**, and **11** and **13** from **2**. Formation of an aryne intermediate was attributed to the high concentration of organolithium reagent [12]. This was confirmed by the fact that the monometalation reaction of the same substrates (**1** and **2**) yielded the expected monometalation product even after much longer reaction times.

Experimental

General

^1H NMR spectra were recorded on a Varian 60A spectrometer with tetramethylsilane as internal reference. Natural abundance ^{13}C FT NMR spectra were recorded at the probe temperature (20°C) on a Varian VXR-300 spectrometer at the operating frequency of 75.429 Hz, using 10 mm sample tubes. The ^1H -decoupled spectra were obtained by means of square wave modulation of the decoupler carrier, centered in the proton field, using 20 KHz spectral width (10.0 μsec pulse width) and an average over 600–800 f.i.d. signals depending on the solubility of the compound. The coupled spectra were recorded with Overhauser enhancement in the gated decoupling mode using 10.0 μs pulse width, 1 s pulse delay and averaging over 800–1000 f.i.d. signals. IR spectra were recorded on a Perkin–Elmer 1310 grating spectrophotometer. Analyses by HPLC were carried out with a Waters 600 apparatus equipped with an ODS column (4.6 $\times$ 250 mm) and an UV detector. Analyses by GC were carried out with a Carlo Erba Fractovap 4200 Gas Chromatograph equipped with a flame ionization detector, and a 5 m Apiezon L capillary column. The TLC analyses were carried out on a silica gel 60 F₂₅₄ plates (Merck); the spots was located by illumination with an UV lamp. Flash-chromatography was performed on silica G60 (Merck) columns. The GC-MS analyses were performed with a Finnigan 1020 GC-MS instrument fitted with a capillary column. 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 *n*-butyllithium in hexane were obtained from Aldrich Chemical Company and were analyzed by the Gilman double titration method before use [12]. Tetrahydrofuran was dried by distillation from sodium benzophenone ketyl.

Starting materials

4-(Methylthio)- (1), 4-(isopropylthio)- (2) and 2-(methylthio)-1-fluorobenzene (3) were prepared by published methods [14–16].

1-Fluoro-2-(isopropylthio)benzene (4)

A mixture of 2-fluorobenzenethiol [14] (200 mmol), 2-bromopropane (210 mmol), anhydrous potassium carbonate (230 mmol), and dry acetone (60 ml) was refluxed for 10 h 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 distilled. Yield 78%, b.p. 61–63°C/1 mmHg; n_{D}^{18} 1.5260; ^1H NMR (CDCl_3): δ 1.25 (d, 6H, CH_3); 3.98 (m, 1H, CH); 7.25 (m, 4H, arom-*H*). Elemental analysis: Found: C, 63.28; H, 6.42; S, 18.65. $\text{C}_9\text{H}_{11}\text{FS}$ (170.24) calcd.: C, 63.49; H, 6.51; S, 18.83%.

Authentic samples

2-Butylbenzoic acid (18) was prepared as previously described [17]. 2-Fluorobenzoic acid (9) was purchased from the Aldrich Chemical Company.

[(2-Fluorophenyl)thio]acetic acid (7)

A solution of 2-fluorobenzenethiol (36 mmol), chloroacetic acid (36 mmol), and sodium hydroxide (90 mmol) in water (35 ml) was stirred under reflux for 3 h then

allowed to cool and acidified with 10% aqueous hydrochloric acid. Extraction with diethyl ether was followed by drying of the extract (Na_2SO_4), filtration, and concentration *in vacuo*. The product was purified by flash-chromatography with chloroform as eluent. Yield 85%, m.p. 80°C . IR (CHCl_3): 3050 (OH), 1710 cm^{-1} ($\text{C}=\text{O}$). $^1\text{H NMR}$ (CDCl_3): δ 2.65 (s, 2H, CH_2); 7.30 (m, 4H, arom-H); 9.15 (s, 1H, COOH, D_2O exchanged). Elemental analysis: Found: C, 51.49; H, 3.71; S, 17.12. $\text{C}_8\text{H}_7\text{FO}_2\text{S}$ (186.2) calcd.: C, 51.60; H, 3.79; S, 17.22%.

Monometallation procedure

A solution of the starting material (28 mmol) in dry tetrahydrofuran (30 ml) was blanketed with dry nitrogen and then treated dropwise at -60°C with *n*-butyllithium in hexane (28 mmol, 24 ml). When the addition was complete the mixture was stirred for ca. 5 h at the same temperature and then poured onto ca. 100 g of crushed solid carbon dioxide. After 15 h the residue was treated with 10% aqueous sodium bicarbonate and then with diethyl ether. The aqueous layer was separated, washed with diethyl ether, acidified with cold concentrated hydrochloric acid, and extracted with chloroform. The combined chloroform extracts were dried over anhydrous sodium sulphate, and TLC and HPLC analyses of the extract showed the presence of one significant product. The solvent evaporation *in vacuo* gave a residue, which was purified by flash-chromatography with chloroform as eluent.

The ethereal solution was washed with water, and dried (Na_2SO_4). GC examination showed one peak with a retention time identical to that of the starting material.

In this manner, starting from **1**, **2**, **3** and **4**, respectively, the following compounds were obtained:

2-Fluoro-5-(methylthio)benzoic acid (5). Yield 76%, m.p. $105\text{--}106^\circ\text{C}$. IR (CHCl_3): 3080 (OH), 1750 cm^{-1} ($\text{C}=\text{O}$). $^1\text{H NMR}$ (CDCl_3): δ 2.50 (s, 3H, CH_3); 7.50 (m, 3H, arom-H); 9.65 (s, 1H, COOH, D_2O exchanged). Elemental analysis: Found: C, 51.54; H, 3.73; S, 17.09. $\text{C}_8\text{H}_7\text{FO}_2\text{S}$ (186.2) calcd.: C, 51.60; H, 3.79; S, 17.22%.

A solution of **5** (3 mmol) in 95% ethanol (5 ml) was refluxed for 1 h with Raney nickel [18] (1 g). The solution was filtered and evaporated. The residue was diluted with diethyl ether and treated with diazomethane. GC showed one peak with retention time identical with that of methyl ester of **9**.

2-Fluoro-5-(isopropylthio)benzoic acid (6). Yield 74%, m.p. $84\text{--}85^\circ\text{C}$. IR (CHCl_3): 3090 (OH), 1710 cm^{-1} ($\text{C}=\text{O}$). $^1\text{H NMR}$ (CDCl_3): δ 1.30 (d, 6H, CH_3); 3.30 (m, 1H, CH); 7.50 (m, 3H, arom-H); 10.50 (s, 1H, COOH, D_2O exchanged). Elemental analysis: Found: C, 55.98; H, 5.13; S, 14.83. $\text{C}_{10}\text{H}_{11}\text{FO}_2\text{S}$ (214.25) calcd.: C, 56.06; H, 5.18; S, 14.96%.

GC examination of the reaction mixture after the treatment of **6** with Raney nickel and diazomethane showed one peak with a retention time identical to that of methyl ester of **9**.

[(2-Fluorophenyl)thio]acetic acid (7). Yield 65%, m.p. $79\text{--}80^\circ\text{C}$. The product was identified by comparison with an authentic sample.

2-fluoro-3-(isopropylthio)benzoic acid (8). Yield 71%, m.p. $85\text{--}86^\circ\text{C}$. IR (CHCl_3): 3080 (OH), 1700 cm^{-1} ($\text{C}=\text{O}$). $^1\text{H NMR}$ (CDCl_3): δ 1.30 (d, 6H, CH_3); 3.45 (m, 1H, CH); 7.55 (m, 3H, arom-H); 10.65 (s, 1H, COOH, D_2O exchanged). Elemental analysis: Found: C, 55.91; H, 5.15; S, 14.88. $\text{C}_{10}\text{H}_{11}\text{FO}_2\text{S}$ (214.25) calcd.: C, 56.06; H, 5.18; S, 14.96%.

GC examination of the mixture after treatment of **8** with Raney nickel and diazomethane showed one peak, with a retention time identical to that of methyl ester of **9**.

Bimetalation procedure

A solution of the starting material (28 mmol) in dry tetrahydrofuran (30 ml) was blanketed with dry nitrogen and then treated dropwise at -60°C with *n*-butyllithium in hexane (60 mmol, 51 ml). The mixture was stirred for ca. 5 h at the same temperature and then worked up as described above. The aqueous bicarbonate layer from **1** gave only **5** in 78% yield; only **6** was obtained from **2** in 75% yield; only **7** was obtained from **3** in 70% yield; only **8** was obtained from **4** in 65% yield.

Only a small amount of the starting material was obtained from the ethereal layer in all cases.

When the reaction mixture was allowed to proceed for 30 h intractable tars were obtained from **3** and **4** as starting materials. In the case of **1**, a mixture of intractable tars was obtained from the ethereal layer. A very small amount of a mixture was obtained from the bicarbonate layer and GC examination showed two peaks with almost equal areas. GC-MS showed that the two products gave the same molecular ion $[M]^+$ at m/z 238. GC examination of the mixture after desulphurisation showed one peak with a retention time identical to that of **18**.

Similarly, starting from **2**, a mixture of intractable tars was obtained from the ethereal layer, and a very small amount of a mixture from the bicarbonate layer. GC examination of this showed two peaks in almost equal amounts. GC-MS showed that the two products gave the same molecular ion $[M]^+$ at m/z 266. GC analysis of the mixture after desulphurisation showed one peak, with a retention time identical to that of **18**.

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