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Metallation reactions. XXV. A re-examination of the metallation reaction of (alkylthio)fluorobenzenes[1]

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Abstract

The metallation of (alkylthio)fluorobenzenes by organolithium compounds, lithium amides and butyllithium/potassium *tert*-butoxide superbasic mixture was re-examined. To avoid the formation of defluorinated compounds all the reactions must be carried out below −80°C. The *para*-substituted **1a** and **1b** showed a regiochemistry directed by the halogen; the *ortho*-derivative **1c** underwent metallation *ortho* to the halogen when treated with lithium tetramethylpiperidide, an α-metallation with butyllithium while *sec*-butyllithium was less selective. Compounds **1a** and **1c** allowed the preparation of disubstituted products. At temperatures higher than −80°C increasing amounts of dehalogenated products are formed, whose formation can be explained through the intermediacy of arynes.

Keywords: Metallation; Organolithium; Superbases; Lithium amides; (Alkylthio)fluoroarenes

1. Introduction

In a previous paper [2] we reported the monometallation reaction of (alkylthio)fluorobenzenes by butyllithium showing that the halogen atom is an *ortho*-directing group stronger than the alkylthio. We also reported that our attempts to bimetallate these molecules were unsuccessful, leading only to defluorinated products. To complete our study on these substrates we examined several metallating reagents; butyllithium (BuLi), *sec*-butyllithium (*sec*-BuLi), lithium diisopropylamide (LDA), lithium tetramethylpiperidide (LITMP), superbasic mixture obtained by mixing BuLi and potassium *tert*-butoxide (LICKOR), in various working conditions. All the metallated intermediates were quenched by iodomethane and examined by GC/MS for identification of products.

2. Results and discussion

(a) 1-Fluoro-4-(methylthio)benzene (**1a**) (Scheme 1, Table 1) in anhydrous tetrahydrofuran (THF) reacted with 1 molar equivalent of BuLi in hexane at −100°C to give, after quenching with iodomethane, the product **2** [2], while the use of two equivalents of BuLi yielded the isomers **2** and **3**, the last one arising from the substitution of a thiomethylic hydrogen. The same reaction at −50°C gave **2**, **3**, **4** and **5** whereas, at −30°C, we found **8** and **9a** and traces of **4**, **5**, **6** and **7**.

The use of 2 molar equivalents of *sec*-BuLi in cyclohexane, at −80°C, gave **2** as main product and small amounts of **3**, **10** and **11**; using 4 molar equivalents of the same reagent we obtained a larger amount of **10** (22%): the main product was **2** with traces of **3**, **11**, **12** and **13** and the dehalogenated **9b** and **14**. Using one equivalent of the LICKOR in hexane at −100°C we obtained **2**, while two equivalents of the same reagent led to **10** as the main product (80%) and to small amounts of **2** and **13**. The use of LDA in THF gave unsatisfactory results in the range of temperatures between −70°C and −25°C, or using several molar ratios of amide (from 2 to 4 molar equivalents): we always recovered the starting material **1a**, a small amount of **2** (never more than 17%) and traces of **3**. On the other hand, LITMP (1.5 molar equivalents) in hexane and THF gave **2** and traces of **12** and **15**, while using three equivalents of this reagent increased the amount of **2** up to 58%.

(b) 1-Fluoro-4-(isopropylthio)benzene (**1b**) (Scheme 2, Table 1) reaction with 1 molar equivalent of BuLi at −100°C confirmed the already reported results [2]: we obtained product **11** arising from the substitution of a

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[1] For Part XXIV, see [1].

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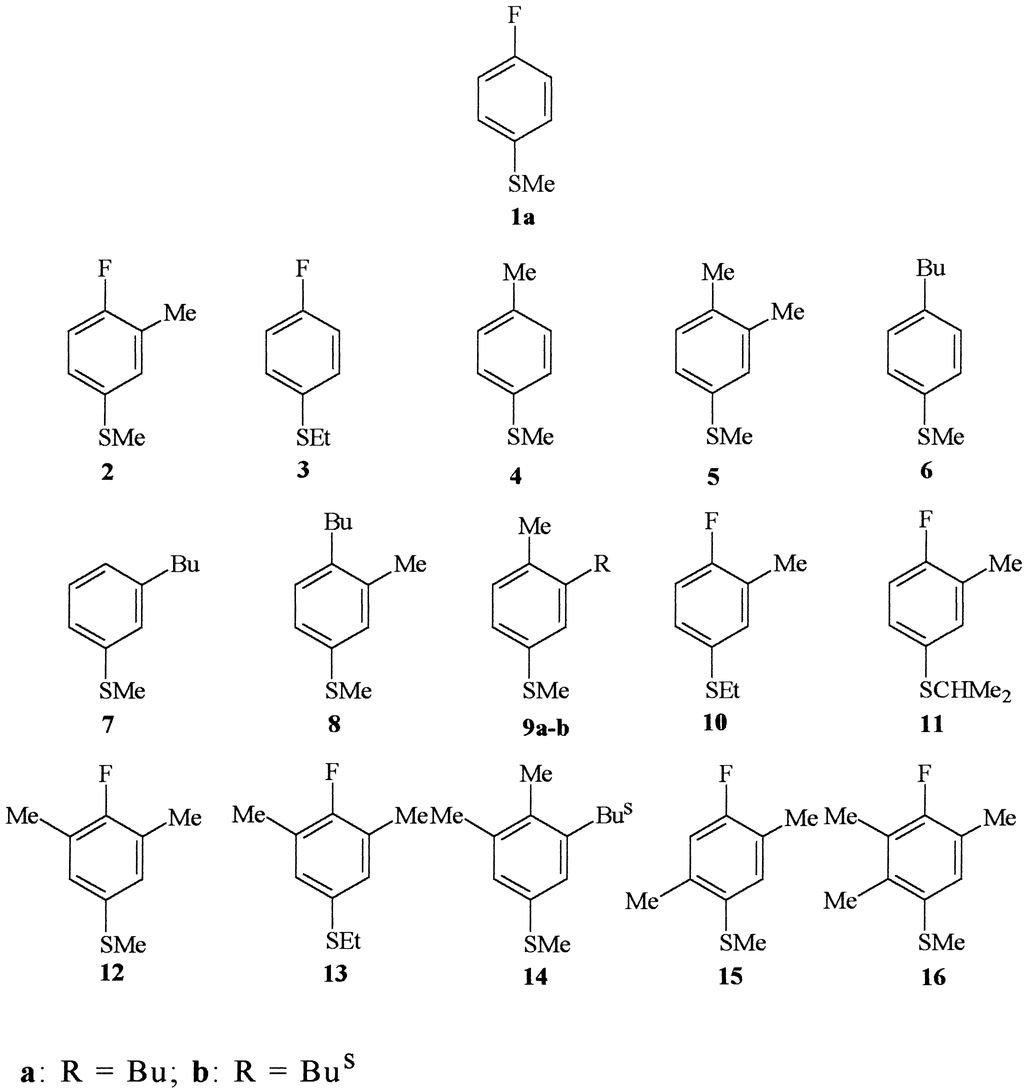


Scheme 1.

hydrogen *ortho* to the fluorine. Using two or more equivalents of BuLi at −100°C or −85°C we obtained **11** and a small amount of **17**. When the reaction was performed at −30°C these products were present only in traces with **18**, **19** and **20** in almost equal amounts. The use of one equivalent of LICKOR led almost exclusively to **11**, while with two or more equivalents, **11** decreased and the main products were the defluorinated **19**, **20** and **21**.

(c) 1-Fluoro-2-(methylthio)benzene (**1c**) (Scheme 3, Table 1) treated with one equivalent of BuLi at −100°C gave the product **22** and a small amount of **23**. The use of two or more equivalents of BuLi, aimed at the preparation of the product **24**, yielded an increased amount of **23**. When the metallating reagent was *sec*-BuLi we obtained the same compounds **22** and **23**, with **23** the main product. Two equivalents of the same reagent gave the disubstituted **24** in an acceptable yield (41%). When we tried to increase this yield using three or four equivalents of *sec*-BuLi we noticed a decrease of the amount of **24** and the formation of four new products **25**, **26b**, **29** and **30**. The LICKOR gave only defluorinated products (**26a**, **27**, **28**, **31**) while LDA did not even react. On the other side, LITMP was shown to be a good reagent to prepare **23** in good yield, but **24** was obtained in small amounts and also disubstituted **32**.

The above results completed those previously reported and showed that the occurrence of defluorinated products was minimised by working at temperatures between −70°C and −100°C. The use of iodomethane as electrophile allowed us to detect even traces of those products through GC/MS. Scheme 4 shows the possible paths leading to the products formed from **1a**.

The formation of **3** can be explained by a substitution of a thiomethylic hydrogen (leading to the intermediate **A**). This reaction is in competition with the main path involving the hydrogen *ortho* to the fluorine atom leading to the intermediate **B**, that can give **2** or, at higher temperatures, react to the aryne **C** by elimination of alkali fluoride. **C** would undergo addition of 1 mol of organolithium (BuLi) to yield

Table 1
Metallation of (alkylthio)fluorobenzenes (**1a–c**)

Entry	RM (equivalent)	*T* (°C)	*t* (min)	St. mat. recov. (%)	α-S (%)	*o*-F (%)	α-S-*o*-F (%)	*o*,-*o*′-F (%)	Defluor. prod. (%)
1a	BuLi (1)	−100	360	9		91			
1a	BuLi (2)	−100	360	<1	30	70			
1a	BuLi (4)	−100	360	<1	25	75			
1a	BuLi (2)	−50	360	<1	13	68			18[a]
1a	BuLi (2)	−30	360	<1					~100[b]
1a	*sec*-BuLi (2)	−80	240	19	4	53	20[c]		
1a	*sec*-BuLi (4)	−80	240	11	6	37	22	5[d]	12[e]
1a	*sec*-BuLi (4)	−70	120	7		50	11		32[e]
1a	LICKOR (1)	−100	360	7		93			
1a	LICKOR (2)	−100	360	5		5	80[f]		
1a	LDA (2)	−25	240	85	2	13			
1a	LDA (4)	−25	240	80	3	17			
1a	LITMP (1.5)	−80	240	50		42		4[g]	
1a	LITMP (3)	−80	240	18		58		11[h]	
1b	BuLi (1)	−100	360	15		85			
1b	BuLi (2)	−100	360	10	8	82			
1b	BuLi (2)	−85	360	<1	10	90			
1b	BuLi (2)	−30	360	<1	Tr	5			95[i]
1b	LICKOR (1)	−100	360	<1		~100			
1b	LICKOR (2)	−100	360			10			90[j]
1c	BuLi (1)	−100	240	12	73	15			
1c	BuLi (2)	−100	240	10	60	30			
1c	BuLi (4)	−100	240	8	52	40			
1c	*sec*-BuLi (1)	−90	240	28	30	42			
1c	*sec*-BuLi (2)	−90	240	12	13	34	41		
1c	*sec*-BuLi (4)	−90	240	12	14	25	30[k]		12[l]
1c	LICKOR (1)	−90	240	~100					
1c	LICKOR (2)	−90	240	28	1	1	9		61[m]
1c	LDA (2)	−80	240	~99	Tr	Tr			
1c	LDA (2)	−25	240	~98	Tr	Tr			
1c	LDA (4)	−25	240	~98	Tr	Tr			
1c	LITMP (1.5)	−80	240	31	3	50	7[n]		
1c	LITMP (3)	−80	240	13	4	67	5[o]		
1c	LITMP (6)	−80	240	9	4	71	5[o]		

[a] The defluorinated products were a mixture of **4** and **5** in the ratio 1 : 2.

[b] The defluorinated products were a mixture of **4**, **5**, **6**, **7**, **8**, **9a** in the ratio 1 : 3 : 3 : 3 : 45 : 45.

[c] About 4% of the product *o*-F-α,α′-S trisubstituted **11** was also detected.

[d] About 5% of the product *o*,*o*′-F-α-S trisubstituted **13** and 2% of **11** were also detected.

[e] The defluorinated products were a mixture of **9b** and **14** in the ratio 1 : 1.

[f] About 10% of the product **13** was also detected.

[g] About 4% of the product **15** was also detected.

[h] About 10% of the product **15** and 3% of **16** were also detected.

[i] The defluorinated products were a mixture of **18**, **19**, **20** in the ratio 32 : 34 : 34.

[j] The defluorinated products were a mixture of **19**, **20**, **21** in the ratio 17 : 39 : 44.

[k] About 7% of the product *o*-F-α,α′-S trisubstituted **25** was also detected.

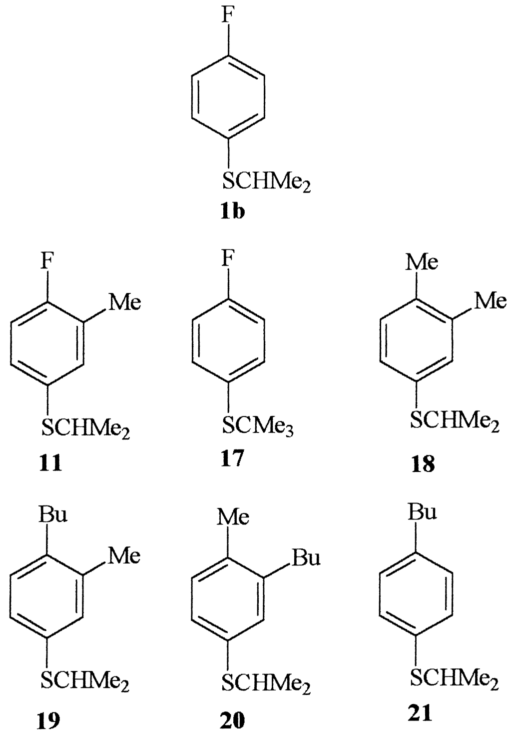
[l] The defluorinated products were a mixture of **26b**, **29**, **30** in the ratio 50 : 37 : 13.

[m] The defluorinated products were a mixture of **26a**, **27**, **28**, **31** in the ratio 24 : 20 : 28 : 28.

[n] About 9% of the product **32** was also detected.

[o] About 11% of the product **32** was also detected.

D and **E**, which lead to **8** and **9a** after quenching with iodomethane, or **6** and **7** by abstraction of a hydrogen atom from solvent (THF). The product **2** can give **F** by a metal–halogen exchange, or **12** by further metallation/quenching with iodomethane. From **F** it is possible to obtain either **5** or the aryne **G** by elimination of alkali fluoride. The formation of **G** was confirmed by the presence of **14** through the intermediacy of **H**, obtained by addition of 1 mol of organolithium. Another secondary reaction can be the metal–halogen exchange of **1a** leading to **I** and then **4**. The bimetallation of **1a** can give either **J**, that leads to **10**, or the intermediate **K**, that leads to **15**. This latter, with an excess of metallating mixture, can afford **L** and then **16**. The product **10** can undergo a further metallation *ortho* to the fluorine atom to give **M** and then **13**. **10** can be α-metallated on the thiomethyl group to give **N** and **11**.

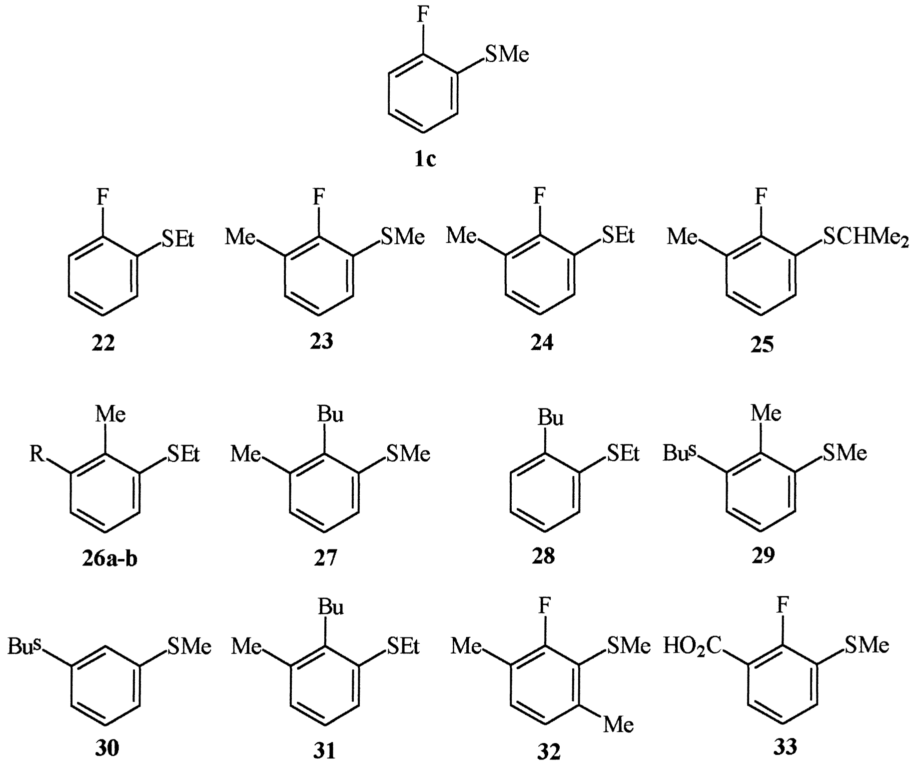


Scheme 2.

Similar considerations can be applied to the reaction pathways of **1b** and **1c**. The reactions reveal the following interesting features:

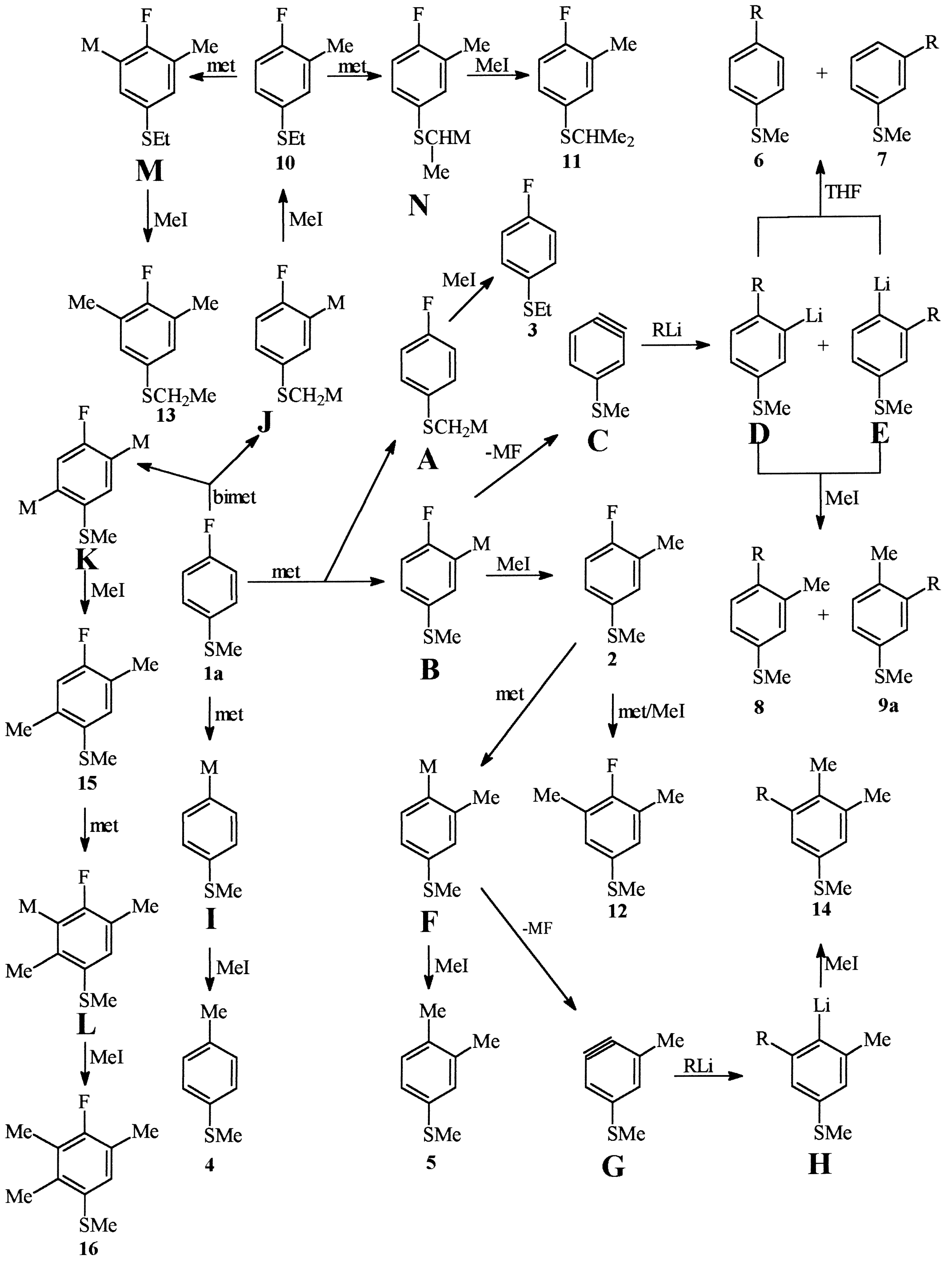
1. From **1a** and 1 molar equivalent of organolithium or superbase or LITMP (Scheme 5) it is possible to substitute the hydrogen atom *ortho* to the fluorine, while with 2 molar equivalents of superbase it is possible to substitute both the hydrogen atom of the thiomethyl group and that *ortho* to the halogen.
2. From **1c** and organolithium compounds it is possible to substitute a thiomethyl hydrogen (Scheme 6), while with LITMP it is possible to substitute the aryl hydrogen *ortho* to the fluorine. In this way these reagents allow the achievement of complementary results. It is also possible to obtain acceptable yields of the disubstituted products by treating **1c** with 2 molar equivalents of *sec*-BuLi.
3. On the contrary, attempts to prepare disubstituted products starting from **1b** were unsuccessful.

All the results can be explained by considering that the regiocontrol of metallation reactions depends on the coordinating properties, on the electron density and on the inductive and mesomeric effects exerted by the substituents on the aromatic ring [2–11]. The reaction of *para*-derivatives **1a** and **1b** involves mainly the position *ortho* to the

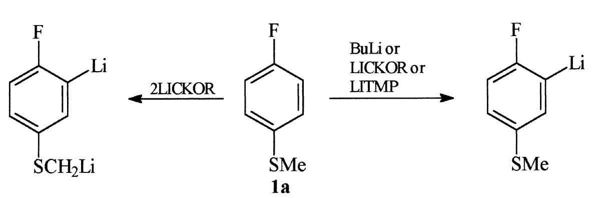


a: R = Bu; **b**: R = Bu^S

Scheme 3.

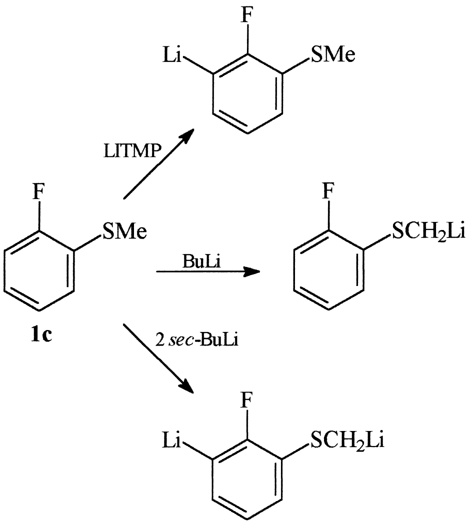


Scheme 4.



Scheme 5.

fluorine atom because its strong inductive effect prevails over the weak coordinating power of the sulphur atom of the alkylthio group. On the other hand, the *ortho*-derivative **1c** shows a different regioselectivity depending on the metallating reagent used: this can be justified by noting that BuLi acts in a coordinative way through a cyclic intermediate involving the fluorine and the sulphur atom [2] leading to α-substitution. On the contrary, the more basic LITMP attacks the aromatic hydrogen inductively activated by the adjacent



Scheme 6.

fluorine. With *sec*-BuLi, which is even more basic than BuLi, competition between the positions *ortho* to the fluorine and *alpha* to the sulphur is brought into play.

All products were identified by comparison with authentic samples (**3**, **4**, **5** and **18**) or by analysis of their mass spectra, assuming that metallations lead to carbanions *ortho* to the heteroatom or *alpha* in the chain bonded to the heteroatom [4–12]. In the defluorinated products the butyl and the methyl groups obviously occupy the same position as the fluorine or the site *ortho* to this. The value of the molecular ion allows determination of many low methyl groups are in the substrate, the presence of the halogen atom or the butyl group. The occurrence of ethyl or isopropyl groups linked to the sulphur is proved by the loss of ethyl, ethylene or propylene, respectively, in **10**, **13**, **22**, **24**, **26a–b**, **28**, **31**, **11**, **18**, **19**, **20**, **21**, **25**. The presence of the methyl group *ortho* to the SCH_3 or to the SC_2H_5 is shown by the high abundance of the peak ($M^+ - CH_3$) for the first and ($M^+ - C_2H_5$) more abundant than ($M^+ - C_2H_4$) for the second [13]. The value of the abundance ratio of peaks ($M^+ - C_3H_7$) and ($M^+ - C_3H_6$) allows to determine the position of the butyl group relative to the SR group in **6**, **7**, **8**, **9a**, **26a**, **27**, **28**, **31**. A high value of this ratio shows that the two groups are *ortho* or *para* to each other, while a low value suggests a *meta* relation. This can be explained considering that the loss of a propyl moiety in *ortho* or *para* isomers leads to ions more stabilised than *meta*. Moreover, **26a** but not **27**, **28**, **31**, shows three peaks (M^+ – SR), 147, 105 and 91 with a high abundance confirming the poor double bond character of the C_{arom}–S bond.

Compounds **19**, **20** and **21** show a similar behaviour though the presence of the isopropyl group linked to the sulphur leads to an increase of the peak $M^+ - C_3H_6$, as in **18**. Compound **17** is identified through the loss of $C(CH_3)_3$ and the presence of the peak $^+C(CH_3)_3$.

The attribution of structure to **9b**, **14**, **26b**, **29** and **30** needs a more accurate analysis. These substances show some fragmentations ($M^+ - C_2H_5 - CH_3$ and $M^+ - C_2H_5 - C_2H_5$) contradicting the even-electron rule, which can be justified only when much conjugation is present [14,15]. This could suggest that **9b**, **14**, **26b**, **29** and **30** bear a *sec*-butyl and a SR group *ortho* or *para* each other. The comparison of such spectra with those of other defluorinated products obtained only in traces (and not reported in this paper) reveals that **9b**, **14**, **26b**, **29** and **30** have discrete peaks at $m/e = 104$ and 105 or at $m/e = 119$, 117 and 115 due to the loss of SCH_3 or SC_2H_5. These data suggest that **9b**, **14**, **26b**, **29** and **30** have a lower double bond character in the C_{arom}–S bond. Finally, the formation of odd-electron ions from even-electron ones, present in similar quantity in these compounds, can be explained from the fact that the ion formed by the loss of C_2H_5 from *sec*-butyl can transpose to tropylium [16] causing an increase of conjugation even when the *sec*-butyl and the sulphur are *meta* to each other. These results, in accord with the defluorination proposed, are also supported by the fact that *sec*-butyl, bulkier than the *n*-butyl, would enter the less hindered position.

3. Experimental

3.1. General

^1H and ^{13}C 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 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 μm film thickness). 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 BuLi in hexane were obtained from Aldrich and were analysed by the Gilman double titration method before use [17].

3.2. Starting materials

1-(Methylthio)- (**1a**) and 1-[(1-methylethyl)thio]-4-fluorobenzene (**1b**) and 1-(methylthio)-2-fluorobenzene (**1c**) were prepared by published methods [18–20].

3.3. Authentic samples

1-(Ethylthio)-4-fluorobenzene (**3**), 1-methyl- (**4**), and 1,2-dimethyl-4-(methylthio)benzene (**5**) were prepared by published methods [21–23]. The following compounds were obtained as previously described.

3.3.1. 1-(Ethylthio)-2-fluorobenzene (**1c**)

Yield 83%; n_D^{30} 1.5400; ^{1}H NMR ($CDCl_3$) δ: 1.27 (t, 3H, CH_3CH_2), 2.89 (q, 2H, CH_2CH_3), 7.03 (m, 2H, Ar–H), 7.15 (m, 1H, Ar–H), 7.33 (m, 1H, Ar–H); EI–MS: *m/e* = 156 (100%, M^+), 141 (48.9%, $M^+ - CH_3$), 128 (99.4%, $M^+ - C_2H_4$), 127 (15.2%, $M^+ - C_2H_5$), 109 (13.1%, $C_6H_5S^+$), 108 (51.9%, $C_6H_4S^+$), 84 (47.4%, $C_5H_5F^+$), 83 (52.5%, $C_5H_4F^+$), 75 (14.4%, C_2FS^+), 69 (34.5%, $C_4H_2F^+$), 57 (33.3%, $C_3H_2F^+$), 45 (91.9%, CHS^+). Elemental analysis: Found: C, 61.40; H, 5.74; S, 20.35. C_8H_9FS (156.2); calc.: C, 61.51; H, 5.81; S, 20.52%.

3.3.2. 3,4-Dimethyl-1-[(methylethyl)thio]benzene (**19**)

Yield 74%; n_D^{30} 1.5340; ^{1}H NMR ($CDCl_3$) δ: 1.29 (d, 6H, $(CH_3)_2CH$), 2.55 (s, 6H, Ar–CH_3), 3.32 (m, 1H, SCH), 7.08 (d, 1H, Ar–H), 7.18 (d, 1H, Ar–H), 7.23 (s, 1H, Ar–H); EI–MS: *m/e* = 180 (79.8%, M^+), 165 (4.4%, $M^+ - CH_3$), 138 (100%, $M^+ - CH_3CHCH_2$), 123 (8.0%, $M^+ - CH_3CHCH_2 - CH_3$), 105 (92.3, $C_8H_9^+$), 91 (15.3%, $C_7H_7^+$), 77 (19.9%, $C_6H_5^+$), 41 (19.8%, $C_3H_5^+$). Elemental analysis: Found: C, 73.19; H, 8.91; S, 17.69. $C_{11}H_{16}S$ (180.31); calc.: C, 73.28; H, 8.94; S, 17.78%.

3.4. Metallation of **1a**

3.4.1. Method A

To a vigorously stirred solution of **1a** (2.5 mmol) and anhydrous THF (5 ml) cooled to −100°C, a 1.2 M solution of BuLi in hexane (2.6 mmol) was gradually added under argon, and stirring was continued at the same temperature for ca. 3 h. The resulting mixture was then treated with iodomethane (2.6 mmol), left at room temperature for 3 h and poured into water. The organic layer was separated, the aqueous layer extracted with diethyl ether and the organic solutions combined and dried (Na_2SO_4) were analysed by GC/MS. These (see Table 1), exhibited the presence of product **2** (91%). If the reaction was performed with 2 molar equivalents of BuLi, the GC/MS analyses exhibited two products (**2**, **3**) in the ratio of 7 : 3, respectively. If the reaction was performed with 4 molar equivalents of BuLi, the GC/MS analyses exhibited two products (**2**, **3**) in the ratio 7.5 : 2.5.

If the reaction was performed at −50°C, four products (**2**, **3**, **4**, **5**) were detected in the ratio 68 : 13 : 6 : 12.

When the reaction was performed at −30°C, the GC/MS exhibited six products (**4**, **5**, **6**, **7**, **8**, **9a**) in the ratio 1 : 3 : 3 : 3 : 45 : 45.

2: EI–MS: *m/e* = 156 (100%, M^+), 141 (44%, $M^+ - CH_3$), 123 (12.1%, $M^+ - HS$), 110 (16.2%, $C_7H_7F^+$), 109 (21.5%, $C_7H_6F^+$), 97 (11.9%, $C_5H_5S^+$), 45 (34.2%, CHS^+).

3: EI–MS: *m/e* = 156 (100%, M^+), 141 (51.2%, $M^+ - CH_3$), 128 (61.1%, $M^+ - C_2H_4$), 108 (27%, $M^+ - C_2H_4 - HF$), 84 (13.7%, $C_4H_4S^+$), 83 (33.5%, $C_4H_3S^+$), 69 (10.5%, $C_5H_9^+$), 57 (15.9%, $C_4H_9^+$), 45 (40.6%, CHS^+).

4: EI–MS: *m/e* = 138 (100%, M^+), 137 (14.7%, $M^+ - H$), 123 (27.8%, $M^+ - CH_3$), 105 (6.5%, $M^+ - HS$) 91 (83.6%, $C_7H_7^+$), 65 (10.6%, $C_5H_5^+$).

5: EI–MS: *m/e* = 152 (100%, M^+), 137 (34.1%, $M^+ - CH_3$), 105 (81%, $M^+ - SCH_3$), 77 (28.1%, $C_6H_5^+$), 45 (45.1%, CHS^+).

6: EI–MS: *m/e* = 180 (24.3%, M^+), 137 (100%, $M^+ - C_3H_7$), 91 (7.6%, $C_7H_7^+$), 45 (4.4%, CHS^+).

7: EI–MS: *m/e* = 180 (48.7%, M^+), 138 (57.1%, $M^+ - C_3H_6$), 137 (25.8%, $M^+ - C_3H_7$), 91 (100%, $C_7H_7^+$), 45 (24.5%, CHS^+).

8: EI–MS: *m/e* = 194 (25.8%, M^+), 152 (9.7%, $M^+ - C_3H_6$) 151 (100%, $M^+ - C_3H_7$), 105 (1%, $C_8H_9^+$), 91 (1.2%, $C_7H_7^+$).

9a: EI–MS: *m/e* = 194 (82.5%, M^+), 152 (37.3%, $M^+ - C_3H_6$), 151 (83.2, $M^+ - C_3H_7$), 105 (100%, $C_8H_9^+$), 91 (19.4%, $C_7H_7^+$), 45 (16.9%, CHS^+).

3.4.2. Method B

To a vigorously stirred solution of **1a** (2 mmol) and anhydrous THF (5 ml) cooled to −80°C, a 1.2 M solution of *sec*-BuLi in cyclohexane (4.8 mmol, 4 ml) was gradually added under argon. After 4 h, an excess of iodomethane (4 mmol) was added, the cooling bath removed and the reaction completed by stirring overnight at room temperature. The reaction mixture was poured into water, worked up as described above and analysed. The GC/MS analyses (see Table 1) exhibited four products **2**, **3**, **10** and **11** in the ratio of 65 : 5 : 25 : 5. The starting material remaining was 19%.

If the reaction was performed at the same temperature with 4 molar equivalents of organolithium eight products (**2**, **3**, **10**, **11**, **12**, **13**, **9b**, **14**) were detected in the ratio 40 : 7 : 25 : 6 : 6 : 2 : 7 : 7. The remaining starting material was 11%.

When the reaction was performed at −70°C, the GC/MS exhibited four products (**2**, **10**, **9b**, **14**) in the ratio of 54 : 12 : 17 : 17. The remaining starting material was 7%.

9b: EI–MS: *m/e* = 194 (33.3%, M^+), 165 (100%, $M^+ - C_2H_5$), 150 (21.1%, $M^+ - C_2H_5 - CH_3$), 131 (5.2%, $M^+ - C_2H_5 - H_2S$), 118 (11.6%, $C_9H_{10}^+$), 117 (16.6%, $C_9H_9^+$), 105 (4.9%, $C_8H_9^+$), 91 (7.3%, $C_7H_7^+$), 65 (4.6%, $C_7H_7^+$).

10: EI–MS: *m/e* = 170 (100%, M^+), 155 (52.4%, $M^+ - CH_3$), 142 (37.7%, $M^+ - C_2H_4$), 109 (78.6%, $C_7H_6F^+$), 83 (11.4%, $C_4H_3S^+$), 45 (96.7%, CHS^+).

13: EI–MS: *m/e* = 184 (100%, M^+), 169 (44.4%, $M^+ - CH_3$), 156 (31.7%, $M^+ - C_2H_4$), 123 (87.3%, $M^+ - C_2H_5S$), 109 (23.8%, $C_6H_5S^+$), 45 (85.7%, CHS^+).

11: EI–MS: *m/e* = 184 (51.1%, M^+), 142 (100%, $M^+ - C_3H_6$), 141 (11.5%, $M^+ - C_3H_7$), 109 (81.9%, $C_7H_6F^+$), 97 (8.1%, $C_5H_5S^+$), 83 (16.1%, $C_5H_4F^+$), 45 (27.8%, CHS^+), 43 (2.7%, $C_3H_7^+$).

14: EI–MS: *m/e* = 208 (33.8%, M^+), 179 (100%, $M^+ - C_2H_5$), 164 (9.8%, $M^+ - C_2H_5 - CH_3$), 149 (6.6%, $M^+ - C_2H_5 - C_2H_6$), 132 (9.3%, $M^+ - C_2H_5 - SCH_3$), 117 (8.4%, $M^+ - C_2H_5 - SCH_3 - CH_3$), 91 (5.4%, $C_7H_5^+$), 77 (6.1%, $C_6H_5^+$).

3.4.3. Method C

A solution of BuLi in hexane (2.7 mmol) was cooled to −100°C under argon and a solution of **1a** (2.5 mmol) in hexane (10 ml) was added. Finely powdered potassium *tert*-butoxide (2.7 mmol) was added. After 4 h, an excess of iodomethane (4 mmol) was added, the cooling bath removed and the reaction completed by stirring overnight at room temperature. The reaction mixture was poured into water, worked up as described above and analysed. The GC/MS analyses (see Table 1) exhibited only the product **2** (93%).

When 2 molar equivalents of superbase were used, the reaction mixture exhibited three products (**2**, **10**, **13**) in the ratio 5 : 80 : 10. Analogous results were obtained performing the reaction with 3 or more molar equivalents of the same reactant.

3.4.4. Method D

A solution of diisopropylamine (8.8 mmol) in THF (10 ml) was cooled to −70°C under argon and a solution of BuLi in hexane (8.8 mmol, 6.2 ml), was added dropwise. After 15 min a solution of **1a** (3.5 mmol) in THF (5 ml) was added. After 4 h, an excess of iodomethane (9 mmol) was added, the cooling bath removed and the reaction completed by stirring overnight at room temperature. The reaction mixture was poured into water, worked up as described above and analysed. GC/MS analyses (see Table 1) exhibited small amounts (15%) of two products (**2**, **3** in the ratio of 6 : 1, respectively); the remainder was starting material.

The same results were obtained performing the reaction with 4 molar equivalents of LDA.

3.4.5. Method E

A solution of BuLi in hexane (15 mmol, 10 ml) and THF (10 ml) was cooled to −80°C and 2,2,6,6-tetramethylpiperidine (15 mmol) under argon was added dropwise. Then a solution of **1a** (10 mmol) in THF (5 ml) was added. After 4 h, an excess of iodomethane (15 mmol) was added, the cooling bath removed and the reaction completed by stirring overnight at room temperature. The reaction mixture was poured into water, worked up as described above and analysed by GC/MS that exhibited (see Table 1) **2** (42%) with traces of **12** and **15**; the remainder was starting material.

When the reaction was performed with 3 molar equivalents of metallating mixture, **2** was obtained in 58% yield. The GC/MS analyses exhibited the presence of minor amounts of **12**, **15** and **16**.

12: EI–MS: *m/e* = 170 (100%, M^+), 155 (43.2%, $M^+ - CH_3$), 137 (21.5%, $M^+ - HS$), 124 (18.0%, $M^+ - CH_2S$), 123 (17.9%, $M^+ - SCH_3$), 109 (34.5%, $C_7H_6F^+$), 77 (9.7%, $C_6H_5^+$), 45 (44.1%, CHS^+).

15: EI–MS: *m/e* = 170 (100%, M^+), 155 (83.2%, $M^+ - CH_3$), 154 (6.4%, $M^+ - CH_4$), 153 (4.8%, $M^+ - CH_4 - H$), 140 (8.1%, $M^+ - C_2H_6$), 139 (7.1%, $M^+ - C_2H_6 - H$), 123 (29.0%, $M^+ - SCH_3$), 122 (12.9%, $M^+ - CH_3SH$), 109 (32.2%, $C_7H_6F^+$), 103 (16.1%, $C_8H_7^+$), 96 (19.3%, $C_5H_4S^+$), 77 (11.3%, $C_6H_5^+$), 45 (35.5%, CHS^+).

16: EI–MS: *m/e* = 184 (100%, M^+), 169 (74.2, $M^+ - CH_3$), 168 (4.8%, $M^+ - CH_4$), 154 (6.7%, $M^+ - C_2H_6$), 153 (7.5%, $M^+ - C_2H_6 - H$), 151 (6.4%, $M^+ - SH$), 137 (20.9%, $M^+ - CH_3S$), 123 (19.7%, $M^+ - CH_3 - CH_2S$), 109 (17.1%, $C_7H_6F^+$), 96 (6.2%, $C_5H_4S^+$), 45 (25.5%, CHS^+).

3.5. Metallation of **1b**

3.5.1. Method A

The same procedure described above was followed. When 1 molar equivalent of BuLi was used GC/MS analysis showed, beside the starting material (15%), the product **11** in 85% yield. When 2 molar equivalents of organolithium were used at −100°C, the reaction mixture showed **11** and **17** in the ratio of 91 : 9 with 10% of starting material. The same two products **11** and **17** in a 90 : 10 ratio were obtained performing the reaction at −85°C; only traces of the starting material were detected. When the reaction was performed at −30°C, the reaction mixture showed **11**, **17**, **18**, **19**, **20** in the ratio of 5:1:30:32:32; the starting material was <1%.

17: EI–MS: *m/e* = 184 (25.8%, M^+), 155 (1.3%, $M^+ - C_2H_6 - H$), 147 (3.8%, $M^+ - (CH_3)_3$), 57 (100%, $^+C(CH_3)_3$), 41 (61.3%, $C_3H_5^+$).

18: Identified by comparison with an authentic sample.

19: EI–MS: *m/e* = 222 (27.5%, M^+), 180 (20.0%, $M^+ - C_3H_6$), 179 (24.8%, $M^+ - C_3H_7$), 138 (9.6%, $M^+ - C_3H_6 - C_3H_6$), 137 (100%, $M^+ - C_3H_7 - C_3H_6$), 105 (4.8%, $C_8H_9^+$), 91 (7.2%, $C_7H_7^+$), 45 (10.2%, CHS^+), 43 (13.1%, $C_3H_7^+$).

20: EI–MS: *m/e* = 222 (30.1%, M^+), 180 (35.2%, $M^+ - C_3H_6$), 179 (8.5%, $M^+ - C_3H_7$), 138 (10.1%, $M^+ - C_3H_6 - C_3H_6$), 137 (100%, $M^+ - C_3H_7 - C_3H_6$), 105 (8.2%, $C_8H_9^+$), 91 (8.1%, $C_7H_7^+$), 45 (8.3%, CHS^+), 43 (10.1%, $C_3H_7^+$).

3.5.2. Method C

The same procedure described above was followed operating at −100°C. When 1 molar equivalent of superbasic mixture was used GC/MS analysis showed product **11** at about 100%. When 2 molar equivalents of the same reactant were used, the reaction mixture showed **11**, **19**, **20**, **21** in the ratio of 10 : 15 : 35 : 40; the starting material was <1%. Similar results were obtained performing the reaction with more equivalents of the same superbasic mixture.

21: EI–MS: *m/e* = 208 (28.4%, M^+), 193 (1.6%, $M^+ - CH_3$), 166 (32.2%, $M^+ - C_3H_6$), 165 (9.7%, $M^+ - C_3H_7$), 123 (100%, $M^+ - C_3H_6 - C_3H_7$), 109 (2.3%, $C_6H_5S^+$), 91 (7.1%, $C_7H_7^+$), 45 (8.2%, CHS^+), 43 (12.9%, $C_3H_7^+$).

3.6. Metallation of **1c**

3.6.1. Method A

The same procedure described above was followed. When 1 molar equivalent of BuLi was used at −100°C, GC/MS analysis showed, beside the starting material (12%), the products **22** and **23** in the ratio of 83 : 17. When 2 molar equivalents of the same reactant were used, the reaction mixture showed the same products **22** and **23** in the ratio of 67 : 33; the starting material was 10%. **22** and **23** were also obtained in the ratio of 56 : 44 operating with 4 molar equivalents of BuLi; the starting material was 8%.

22: Identified by comparison with an authentic sample.

23: EI–MS: *m/e* = 156 (100%, M^+), 141 (23.9%, $M^+ - CH_3$), 123 (30.4%, $M^+ - SH$), 110 (18.2%, $C_7H_7F^+$), 109 (35.9%, $C_7H_6F^+$), 97 (11.1%, $C_5H_4S^+$), 96 (7.6%, $C_5H_3S^+$), 83 (8.1%, $C_5H_4F^+$), 57 (7.3%, $C_3H_2F^+$), 45 (40.4%, CHS^+).

3.6.2. Method B

The same procedure described above was followed. When 1 molar equivalent of *sec*-BuLi at −90°C was used, GC/MS analysis showed, beside the starting material (28%), the products **22** and **23** in the ratio of 42 : 58. When 2 molar equivalents of the same reactant were used, the reaction mixture showed three products, **22**, **23** and **24**, in the ratio of 15 : 39 : 46; the starting material was 12%. When 4 molar equivalents of *sec*-BuLi were used, the reaction mixture showed seven products, **22**, **23**, **24**, **25**, **26b**, **29** and **30** in the ratio 16 : 28 : 34 : 4 : 4 : 3 : 1; the starting material was 13%.

24: EI–MS: *m/e* = 170 (94.2%, M^+), 155 (43.8%, $M^+ - CH_3$), 142 (59.3%, $M^+ - C_2H_4$), 141 (12.7%, $M^+ - C_2H_5$), 121 (15.6%, $M^+ - C_2H_5 - HF$), 109 (100%, $M^+ - SC_2H_5$), 97 (11.6%, $C_5H_4S^+$), 96 (10.7%, $C_5H_3S^+$), 83 (12.5%, $C_4H_5F^+$, 69 (9.3%, $C_4H_2F^+$), 57 (10.9%, $C_3H_2F^+$), 45 (96.6%, CHS^+).

25: EI–MS: *m/e* = 184 (43.5, M^+), 169 (3.2%, $M^+ - CH_3$), 142 (100%, $M^+ - C_3H_6$), 141 (9.7%, $M^+ - C_3H_7$), 121 (9.2%, $M^+ - C_3H_7 - HF$), 109 (62.9%, $C_7H_6F^+$), 97 (5.6%, $C_5H_4S^+$), 96 (4.0%, $C_5H_3S^+$), 83 (6.4%, $C_5H_4F^+$), 77 (8.0%, $C_6H_5^+$), 69 (4.1%, $C_4H_2F^+$), 57 (3.9%, $C_3H_2F^+$), 45 (17.7 CHS^+), 43 (24.2%, $C_3H_7^+$).

26b: EI–MS: *m/e* = 208 (62.7%, M^+), 193 (6.7%, $M^+ - CH_3$), 179 (100%, $M^+ - C_2H_5$), 151 (26.8%, $M^+ - C_2H_5 - C_2H_4$), 150 (13.9%, $M^+ - C_2H_5 - CH_5$) 149 (10.8%, $M^+ - C_2H_5 - CH_5 - H$), 119 (14.2%, $C_9H_{11}^+$), 117 (13.5%, $C_9H_9^+$) 115 (15.4%, $C_9H_7^+$), 105 (9.7%, $C_8H_9^+$), 91 (15.4%, $C_7H_7^+$), 77 (6.5%, $C_6H_5^+$), 45 (8.4%, CHS^+).

29: EI–MS: *m/e* = 194 (56.8%, M^+), 179 (2.8%, $M^+ - CH_3$), 165 (100%, $M^+ - C_2H_5$), 150 (46.9%, $M^+ - C_2H_5 - CH_3$), 149 (4.5%, $M^+ - C_2H_5 - CH_4$), 119 (9.1%, $C_9H_{11}^+$), 118 (12.0%, $C_9H_{10}^+$) 117 (17.3%, $C_9H_9^+$) 115 (15.9%, $C_9H_7^+$), 91 (14.0%, $C_7H_7^+$), 77 (6.5%, $C_6H_5^+$), 45 (9.9%, CHS^+).

30: EI–MS: *m/e* = 180 (63.3%, M^+), 151 (100%, $M^+ - C_2H_5$), 136 (56.7%, $M^+ - C_2H_5 - CH_3$), 135 (23.9%, $M^+ - C_2H_5 - CH_4$), 117 (7.8%, $C_9H_9^+$), 105 (9.1%, $C_8H_9^+$),104 (14.4%, $C_8H_8^+$), 91 (19.1%, $C_7H_7^+$),77 (10.4%, $C_6H_5^+$) 45 (7.3%, CHS^+).

3.6.3. Method C

The same procedure described above was followed. Using 2 molar equivalents of superbase, the GC/MS analysis showed **22**, **23**, **24**, **26a, 27, 28**, **31** in the ratio 1 : 1 : 9 : 15 : 12 : 17 : 17; the starting material was 28%.

26a: EI–MS: *m/e* = 208 (100%, M^+), 207 (50.0%, $M^+ - H$), 179 (46.7%, $M^+ - C_2H_5$), 166 (32.2%, $M^+ - C_3H_6$), 165 (58.0%, $M^+ - C_3H_7$), 151 (25.8%, $M^+ - C_2H_5 - C_2H_4$), 147 (90.3%, $M^+ - SC_2H_5$), 138 (25.8%, $M^+ - C_3H_6 - C_2H_4$), 137 (45.1%, $M^+ - C_3H_7 - C_2H_4$), 123 (22.6%, $C_7H_7S^+$), 109 (31.9%, $C_6H_5S^+$), 105 (82.2%, $C_8H_9^+$), 91 (25.7%, $C_7H_7^+$), 77 (32.2%, $C_6H_5^+$), 71 (27.4%, $C_3H_3S^+$), 65 (27.7%, $C_5H_5^+$), 45 (58.1%, CHS^+), 43 (32.4%, $C_3H_7^+$), 42 (71.6%, $C_3H_6^+$).

27: EI–MS: *m/e* = 194 (19.5%, M^+), 151 (100%, $M^+ - C_3H_7$), 136 (5.4%, $M^+ - C_3H_7 - CH_3$), 135 (3.2%, $M^+ - C_3H_7 - CH_4$), 105 (7.0%, $C_8H_9^+$), 91 (12.9%, $C_7H_7^+$), 71 (35.4%, $C_3H_3S^+$), 45 (16.1%, CHS^+), 43 (11.2%, $C_3H_7^+$).

28: EI–MS: *m/e* = 194 (29.0%, M^+), 151 (100%, $M^+ - C_3H_7$), 123 (29.6%, $M^+ - C_3H_7 - C_2H_4$), 109 (1.2%, $C_6H_5S^+$), 91 (10.3%, $C_7H_7^+$), 45 (17.7%, CHS^+), 43 (4.2%, $C_3H_7^+$).

31: EI–MS: *m/e* = 208 (25.8%, M^+), 179 (1.0%, $M^+ - C_2H_5$), 165 (100%, $M^+ - C_3H_7$), 137 (19.3%, $M^+ - C_3H_7 - C_2H_4$), 105 (3.5%, $C_8H_9^+$), 91 (9.3%, $C_7H_7^+$), 77 (8.4%, $C_6H_5^+$), 45 (12.9%, CHS^+).

3.6.4. Method D

The same procedure described above was followed. When 2 molar equivalents of LDA at −80°C were used, the GC/MS analyses showed traces of two products (**22**, **23**); the remainder was starting material. The same results were obtained performing the reaction at −25°C with 2 and 4 molar equivalents of the same reactant.

3.6.5. Method E

The same procedure described above was followed. When 1.5 molar equivalents of LITMP at $-80°C$ were used, the GC/MS analyses showed four products, **22, 23, 24, 32** in the ratio 73 : 4 : 13 : 10; the starting material was 31%. When 3 molar equivalents of the same reactant were used, the reaction mixture showed the same products in the ratio of 77 : 4 : 13 : 6; the starting material was 13%. When 6 molar equivalents of LITMP were used, the reaction mixture showed the same products in the ratio of 78 : 4 : 12 : 6; the starting material was 9%.

32: EI–MS: *m/e* = 170 (100%, M^+), 155 (93.8%, $M^+ - CH_3$), 140 (8.3%, $M^+ - CH_3 - CH_3$), 139 (9.0%, $M^+ - CH_3 - CH_3 - H$), 123 (30.4%, $M^+ - SCH_3$), 109 (18.3%, $C_7H_6F^+$), 103 (16.6%, $C_8H_7^+$), 96 (20.3%, $C_5H_3S^+$), 91 (10.8%, $C_7H_7^+$), 83 (9.5%, $C_4H_5F^+$), 69 (8.2%, $C_4H_2F^+$), 57 (8.1%, $C_3H_2F^+$), 45 (26.3%, CHS^+).

The metallated mixture, obtained by reaction of **1c** with 3 molar equivalents of LITMP, was poured onto ca. 100 g of crushed solid carbon dioxide. After 24 h the residue was treated successively with 10% aqueous sodium bicarbonate and then with ether. The alkali layer was separated, washed with ether, and then acidified with cold concentrated hydrochloric acid, extracted with chloroform and dried (Na_2SO_4). The solvent was evaporated and the residue, which was identified as 2-fluoro-3-(methylthio)benzoic acid (**33**), was crystallised from 1 : 1 aqueous ethanol. Yield 70%, m.p. 148–150°C. IR (nujol): 2900 (OH), 1689 cm^{-1} (C=O); ^1H NMR (CD_3COCD_3) δ: 2.52 (s, 3H, SCH_3), 7.27 (t, 1H, H-5), 7.55 (dt, 1H, H-6), 7.71 (dt, 1H, H-4); ^{13}C NMR (CD_3COCD_3) δ: 14.12 (d, SCH_3, $^4J_{CF} = 2.17$ Hz), 119.27 (d, C-1, $^2J_{CF} = 10.95$ Hz), 124.63 (d, C-6, $^3J_{CF} = 4.35$ Hz), 128.22 (d, C-3, $^2J_{CF} = 18.0$ Hz), 128.55 (s, C-5), 131.63 (d, C-4, $^3J_{CF} = 3.82$ Hz), 158.66 (d, C-2, $^1J_{CF} = 267.52$ Hz), 164.52 (d, CO_2H, $^3J_{CF} = 2.70$ Hz); EI–MS: *m/e* = 186 (100%, M^+), 171 (5.3%, $M^+ - CH_3$), 169 (15.8%, $M^+ - OH$), 153 (10.1%, $M^+ - SH$), 141 (6.8%, $M^+ - CO_2H$), 140 (3.6%, $M^+ - CH_2S$), 139 (3.1%, $M^+ - CH_3S$), 133 (3.9%, M^+ - HS-HF), 123 (6.6%, $C_7H_7S^+$), 109 (3.2%, $C_6H_5S^+$), 105 (2.9%, $C_8H_9^+$), 96 (1.74%, $C_6H_5F^+$), 95 (2.9%, $C_6H_4F^+$), 83 (8.1%, $C_5H_4F^+$), 69 (2.8%, $C_4H_2F^+$), 57 (3.1%. $C_3H_2F^+$). Elemental analysis. Found: C, 51.49; H, 3.74; S, 17.11. $C_8H_7FO_2S$ (186.01); calc.; C, 51.60; H, 3.79; S, 17.22%.

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