Metallation Reactions. XXXVI. A Study on the Metallation of (Methylthio)- and (Methylsulfonyl)thiophenes

Claudia Fattuoni,* Michele Usai, Maria G. Cabiddu, Enzo Cadoni, Stefania De Montis, Francesca Sotgiu, Salvatore Cabiddu

Dipartimento di Scienze Chimiche, Università di Cagliari, Cittadella Universitaria di Monserrato, SS. 554,
Bivio per Sestu. I-09042 Monserrato (CA), Italy

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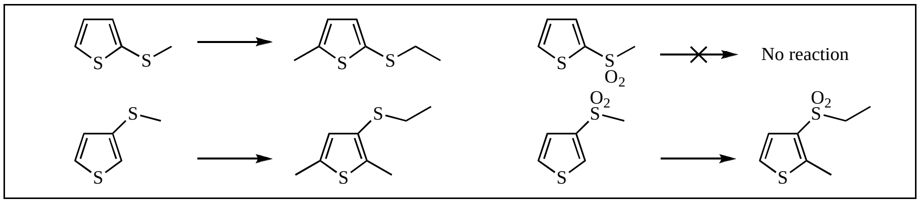

Methylthio- and methylsulfonyl thiophenes were polymetallated by *n*-buthyllithium and superbase (LICKOR) in one-step. 2-(Methylthio)thiophene was bimetallated in 5 and in *alpha* to the methylthio sulfur atom by superbase. 3-(Methylthio)thiophene was bimetallated in both 2 and 5 positions by the organolithium and trimetallated in these two positions and in *alpha* to the thioethereal sulfur atom by superbase. 3-(Methylsulfonyl)thiophene was bimetallated in 2 and in *alpha* to the sulfonyl sulfur atom by the organolithium while the 2-(methylsulfonyl)thiophene underwent degradation in the same conditions.

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INTRODUCTION

Thiophenes and benzothiophenes constitute an important class of molecules for their application as organic optical materials or pharmacologically active products [1-7]. Owing to their various applications it is important to find new synthetic methods for their polyfunctionalization with rapid and high yielding procedures.

The reactivity of thiophene towards organolithiums has been extensively studied and the directing power of a wide range of substituents on the ring has been examined [8-11]; nevertheless, the direct polymetallation of (methylthio)- and (methylsulfonyl)thiophenes on the chain or on the ring has never been reported.

We have previously studied the directing power of the methylthio group on the benzene ring in metallation reactions: the monometallation occurs in the *alpha* position while the one-step bimetallation occurs in *ortho* and *alpha* position either with organolithiums or superbases [12-14]. On the other hand, mono- di- or polymetallation of linear alkyl aryl sulfones usually leads to mono- di- or poly-*alpha*-metallations [15]. The isopropyl phenyl sulfone was monometallated in *alpha* [16], while dimetallation leads to *alpha*,*ortho*-disubstitution [17]. Furthermore, the dimetallation of *tert*-butyl phenyl sulfone leads to di-*ortho*,*ortho*-metallation [18,19].

In connection with these studies, in this work we examined the reaction of 2-(methylthio)-(**1a**), 3-(methylthio)- (**1b**), 3-(methylsulfonyl)- (**1c**) and 2-(methylsulfonyl)-thiophene (**1d**) with *n*-butyllithium and superbases [20,21] with the aim of carrying out a one-step polymetallation in the side chain and in the ring that could allow their polyfunctionalization after electrophilic quenching.

This study should be particularly important as these substrates have been only monolithiated through hydrogen-metal or halogen-metal exchange [9-11, 22-26].

As a matter of fact in 1959 Gol'dfarb first reported the lithiation of **1a** using *n*-butyllithium at 0°C in ether obtaining the 5-carboxylic acid in 86% yield [22]. Barbarella *et al.* reported analogous results (88% yield) working in ether at room temperature [23]. A change of the solvent (dioxane/hexane) and a lowering of the temperature (-10°C) gave a 30% yield of the 5-monolithiated product as reported by Noack et al. [24].

Compound **1b** was first monolithiated with *n*-butyllithium at 0°C in ether by Gronowitz in 1958 giving the 2-carboxylic acid as only product in 70% yield [25]. More recently Taylor and Vogel obtained a 3:1 mixture of 2- and 5–substituted products performing the reaction in ether/hexane at room temperature [26].

The monolithiation of **1c** with *n*-butyllithium at 0°C in ether allowed Gronowitz to prepare the (3-thienylsulfonyl)acetic acid derived from the *alpha*-substitution [25].

RESULTS AND DISCUSSION

The starting compounds (**1a-d**) were treated with different metallating reagents: *n*-butyllithium (BuLi) and the superbasic mixture *n*-butyllithium/potassium *tert*-butoxide (LICKOR). All metallated compounds were quenched with iodomethane and analysed by GC/MS.

It was already known that **1a** can be monometallated by one molar equivalent of *n*-butyllithium in the thiophene 5-position to give the monolithiated intermediate **2** [9,22-24]. All attempts to substitute other hydrogen atoms using two or more (even six) molar equivalents of *n*-butyllithium led to the same result (Scheme 1, Table 1), as proven by the isolation of **3** as the sole product, after quenching of **2** with iodomethane.

Scheme 1

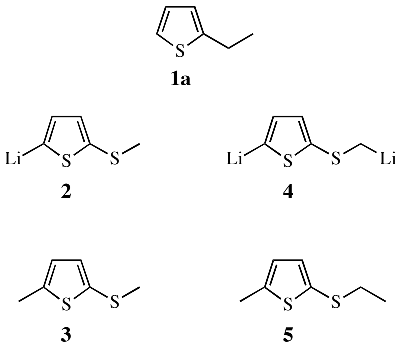


Table 1

Metallation of 2-(methylthio)thiophene (**1a**)

RM (equivalents)	SM recovered (%) [a]	Metallated positions (%) [a]	
		5	5,α*S*
BuLi (1)	32	68 [b]	
BuLi (2)	tr	>99	tr
BuLi (3)	tr	>99	tr
BuLi (4)	tr	>99	tr
BuLi (6)	tr	>99	tr
LICKOR (1)	tr	97	tr
LICKOR (2)	tr	98	tr
LICKOR (3)	tr		70 [c]
LICKOR (4)	tr		90 [d]
LICKOR (5)	tr		56 [e]
LICKOR (6)	tr		6 [f]

[a] Ratio in crude product determined by GC/MS. [b] In agreement with literature data, see ref. [22] reporting the quenching with carbon dioxide. [c] Unidentified degradation products have been detected in 30% total amount. [d] Degradation products have been detected in 10% total amount. [e] Degradation products have been detected in 44% total amount. [f] Degradation products have been detected in 94% total amount.

When the reaction was performed with one or two molar equivalents of LICKOR only **3** was obtained. On the other hand, three molar equivalents of LICKOR led to the bimetallated intermediate **4** deriving from the substitution of one hydrogen of the methylthio group and of the 5-hydrogen atom of the ring. This intermediate gave, after quenching with iodomethane, the product **5** in 70% yield. In this reaction the GC/MS analysis also revealed the presence of degradation products. Using four molar equivalents of LICKOR **5** was obtained in 90% yield. All attempts to substitute other hydrogen atoms using five or six molar equivalents of superbase were unsuccessful: in fact only **5** was isolated but the amount of degradation products increased. It is noteworthy that the superbase always required short reaction times (about 15') because longer times gave resinous products probably deriving from ring opening [27,28].

Then we examined the compound **1b** (Scheme 2, Table 2). It was already known that its reaction with one molar equivalent of *n*-butyllithium gives two isomeric 2-lithiated (**6**) and 5-lithiated (**7**) intermediates as proven by the isolation of **8** and **9** after quenching with iodomethane [26].

Table 2

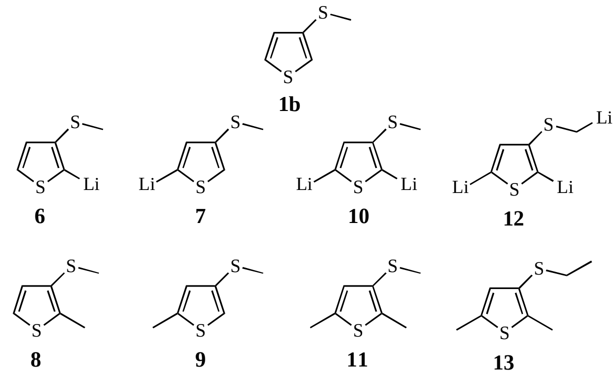
Metallation of 3-(methylthio)thiophene (**1b**)

RM (equivalents)	SM recovered (%) [a]	Metallated positions (%) [a]			
		2	5	2,5	2,5,α*S*
BuLi (1)	tr	69 [b]	30 [b]		
BuLi (2)	tr	26	20	54	
BuLi (3)	tr			>98	
BuLi (4)	tr			>99	
BuLi (6)	tr			>99	
LICKOR (1)	40	40	15	5	
LICKOR (2)	tr	63	20	17	
LICKOR (3)	tr			92	8
LICKOR (4)	tr			45	55
LICKOR (5)	tr			18	82
LICKOR (6)	tr				>99

[a] Ratio in crude product determined by GC/MS. [b] In agreement with literature data, see ref. [26] reporting the quenching with carbon dioxide.

Two molar equivalents of *n*-butyllithium gave three products: **8**, **9** and **11**, the last one deriving from the 2,5-dilithiated intermediate **10**, in the relative percentage of 26%, 20% and 54%.

Scheme 2



Three molar equivalents of *n*-butyllithium gave almost quantitatively the disubstituted product **11**. The same result was obtained performing the metallation with four, five or six molar equivalents of the same reagent. The reaction with one molar equivalent of LICKOR afforded products **8**, **9** and **11** in the relative percentage of 40%, 15%, 5% beside 40% of the starting material. Using two molar equivalents of superbase we obtained **8**, **9** and **11** in the percentage of 63%, 20%, 17% and traces of the starting material. We did not find any monosubstituted product using three molar equivalents of superbase: in fact we obtained the disubstituted compound **11** together with a small amount of **13** deriving from the 2,5,α*S*-trimetallated intermediate **12**, in the ratio of 92:8. Four equivalents of LICKOR gave a greater amount of **13**: the ratio **13**:**11** was 55:45. Performing the reaction with five molar equivalents of superbase the ratio **13:11** was 82:18. The compound **13** was isolated as the only product when six molar equivalents of LICKOR were used.

This study has been extended to the sulfonyl derivatives **1c** and **1d**. It was known that 3-(methylsulfonyl)-thiophene (**1c**) can be monolithiated *alpha* to the methylsulfonyl group [25]. Two molar equivalents of *n*-butyllithium (Scheme 3, Table 3) gave two products: **14** derived from an *alpha-S* lithiation and **15** derived from bimetallation in *alpha-S* and in 2, as proven by the isolation of **16** and **17** in the ratio of 10:90 after quenching with iodomethane. The use of three or more molar equivalents of *n*-butyllithium led only to **17**. Attempts to replace other hydrogen atoms using the superbasic mixture were unsuccessful. In fact two molar equivalents of LICKOR gave a mixture of **16** and **17** in the ratio of 12:88, while four equivalents gave the same products in the ratio of 8:92; six equivalents gave **17** as the only product. Degradation products were formed in all reactions lowering the global yield of target compounds.

Table 3

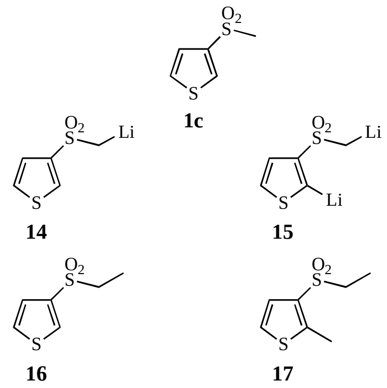
Metallation of 3-(methylsulfonyl)thiophene (**1c**)

RM (equivalents)	SM recovered (%) [a]	Metallated positions (%) [a]	
		α*S*	2,α*S*
BuLi (1)	12	88 [b]	
BuLi (2)	tr	10	90
BuLi (3)	tr		>98
BuLi (6)	tr		>99
LICKOR (2) [c]	tr	12	88
LICKOR (4) [c]	tr	8	92
LICKOR (6) [c]	tr		>99

[a] Ratio in crude product determined by GC/MS. [b] In agreement with literature data, see ref. [25] reporting the quenching with CO_2. [c] In the reactions with LICKOR degradation products were always formed lowering the desired products yields, see Experimental.

The different behaviour of **1c** compared with the analogous (methylsulfonyl)benzene must be evidenced: the benzene derivative undergoes substitution of the hydrogen atom *alpha* to the sulfonyl group [15], whereas the thiophene derivative is metallated at the 2 annular position and *alpha* to the sulfonyl group. In the thiophene derivative the heterocyclic sulfur clearly plays a fundamental role in stabilizing the neighbouring carbanion.

Scheme 3



3-(Methylsulfonyl)thiophene (**1d**) showed a great instability towards the metallating reagent employed (both *n*-butyllithium, with or without TMEDA, and LICKOR) at any temperature and reaction time. In fact, even when the reaction was performed adding the substrate to a mixture of the metallating reagent and the electrophile, only degradation products were obtained.

The results obtained, together with those derived from the literature, allow to selectively prepare mono- or bimetallated intermediates starting from **1a** and **1c**, and mono-, bi- or trimetallated species starting from **1b** by careful choice of the proper conditions. In fact:

i) In the case of **1a**, the best experimental conditions to substitute the hydrogen atom at 5 required two molar equivalents of *n*-butyllithium. To substitute both the 5-hydrogen and the one *alpha* to the thioethereal group, four molar equivalents of superbase should be used (Table 1 and Scheme 1).

ii) In the case of **1b**, the substitution of the hydrogen atom at 2 is achievable using one molar equivalent of *n*-butyllithium while both the annular hydrogen atoms at 3 and 5 can be substituted simultaneously using four molar equivalents of superbase. Finally, the substitution of three hydrogen atoms 2, 5 and *alpha* to the thioethereal group, requires the use of six molar equivalents of superbase (Table 2 and Scheme 2).

iii) In the case of **1c**, the hydrogen atom *alpha* to the sulfonyl group can be substituted using one molar equivalent of *n*-butyllithium [25]. Three molar equivalents of *n*-butyllithium allow substitution of both the 2-hydrogen atom and the hydrogen atom *alpha* to the sulfonyl group (Table 3 and Scheme 3).

EXPERIMENTAL

The ir spectra were recorded with a Perkin-Elmer 1310 grating spectrophotometer. Nmr spectra were recorded on a Varian VXR-300 spectrometer operating at 300 MHz for ^{1}H nmr and 75 MHz for ^{13}C nmr spectra. Chemical shifts are reported in ppm relative to tetramethylsilane and *J* values in Hz. The mass spectral data were recorded 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). Microanalyses were carried out on a Carlo Erba 1106 element analyzer.

Reagent-grade reagents and solvents were used. All reagents were purchased from Aldrich Chemical Co. Solutions of *n*-butyllithium in hexane were purchased from Aldrich Chemical Company and were analysed before use [29]. All solvents were dried and purified using standard techniques. 2-(Methylthio)- (**1a**) and 3-(methylthio)thiophene (**1b**), 3-(methylsulfonyl)- (**1c**) and 2-(methylsulfonyl)thiophene (**1d**) were prepared by published methods [9, 25, 30].

Authentic samples

3-(Ethylsulfonyl)thiophene (**16**). To a vigorously stirred 1.6 *M* solution of *n*-butyllithium in hexane (5.5 mL, 8.5 mmol) **1c** (1 g, 7.7 mmol) in dry THF (20 mL) was added dropwise at 0 °C under argon. After 1 hour, a solution of iodomethane (1.21 g, 8.5 mmol) in dry THF (10 mL) was added dropwise and the reaction was completed by stirring for 20 minutes at the same temperature. The cooling bath was removed, the reaction mixture was hydrolysed with water and the pH adjusted to 4-5 by addition of 10% aqueous hydrochloric acid. The organic layer was separated, the aqueous layer extracted with diethyl ether and the organic solutions combined, dried (sodium sulfate) and evaporated. The crude product was flash-chromatographed on silica gel using 1:1 light petroleum/diethyl ether as eluent to give a brown oil, 0.89 g (71%); ir (neat): 2970, 2940, 1490, 1450, 1400, 1300, 1260, 1220, 1200, 1130, 1100, 1045, 900, 860, 820, 780, 720 cm^{-1}; ^{1}H nmr (deuterochloroform): δ 1.27 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 3.11 (q, *J* = 7.5 Hz, 2H, CH_2CH_3), 7.35 (dd, *J* = 1.2 Hz and *J* = 5.1 Hz, 1H, H-4), 7.45 (dd, *J* = 3.0 Hz and *J* = 5.1 Hz, 1H, H-5), 8.05 (dd, *J* = 1.2 Hz and *J* = 3.3 Hz, 1H, H-2); ^{13}C nmr (deuterochloroform): δ 7.36 (CH_3), 50.76 (CH_2), 125.93 (CH-4), 128.26 (CH-5), 132.61 (CH-2), 138.93 (C-3); ms: m/z 176 (M^+, 47), 147 ($C_4H_3O_2S_2^+$, 40), 131 ($C_4H_3OS_2^+$, 26), 100 ($C_4H_4OS^+$, 35), 84 ($C_4H_4S^+$, 54), 57 (C_2HS^+, 25), 45 (CHS^+, 58), 39 ($C_3H_3^+$, 100). *Anal.* Calcd. for $C_6H_8O_2S_2$: C, 40.89; H, 4.57; S, 36.39. Found: C, 40.97; H, 4.63; S, 36.27.

Metallation of 1a. Method A. To a vigorously stirred 1.6 *M* solution of *n*-butyllithium in hexane (6.5 mL, 10.2 mmol) **1a** (1 g, 7.7 mmol) in dry THF (20 mL) was added dropwise at –78 °C under argon. After fifteen minutes, a solution of iodomethane (1.77 g, 12.5 mmol) in dry THF (10 mL) was added dropwise and the reaction was completed by stirring for twenty minutes at the same temperature. The cooling bath was removed, the reaction mixture was hydrolysed with water and the pH adjusted to 4-5 by addition of 10% aqueous hydrochloric acid. The organic layer was separated, the aqueous layer extracted with diethyl ether and the organic solutions, combined and dried (sodium sulfate) were analysed by GC/MS showing the product **3** (68%) (see Table 1) while the remaining starting material was 32%.

When two or three or four or six molar equivalents of *n*-butyllithium were used the GC/MS analyses exhibited only **3** with traces of **5** and starting material.

Metallation of 1a. Method B. To a vigorously stirred solution of potassium *tert*-butoxide (1.14 g, 10.2 mmol) and dry THF (20 mL) a 1.4 *M* solution of *n*-butyllithium in hexane (6.5 mL, 10.2 mmol) was added under argon at –78 °C. After fifteen minutes a solution of **1a** (1 g, 7.7 mmol) in dry THF (10 mL) was added and stirring was continued for 15 min at –78 °C. The mixture was then treated dropwise with an excess of iodomethane (2.61 g, 18.4 mmol) in dry THF (10 mL). After twenty minutes the cooling bath was removed, the reaction mixture was treated with 10% aqueous hydrochloric acid, poured into water, the organic layer separated and the aqueous layer extracted with diethyl ether. The combined organic extracts were dried (sodium sulfate), concentrated and analysed by GC/MS. The analyses (see Table 1) showed the presence of **3** (97%) and traces of **5**. The starting material remaining was about 3%.

Similar result was obtained performing the reaction with two molar equivalents of the superbasic mixture.

When three molar equivalents of LICKOR were used the GC/MS analyses (see Table 1) exhibited the presence of **5** (70%), various unidentified products (30%) and traces of starting material.

When four molar equivalents of LICKOR were used the GC/MS analyses (see Table 1) exhibited the presence of **5** (90%), various unidentified products (10%) and traces of starting material.

Analogous results were obtained performing the reaction with five molar equivalents of LICKOR (see Table 1) but the yield of **5** lowered to 56% and the yield of unidentified products became 44%.

When the reaction was performed with six molar equivalents of LICKOR the GC/MS analyses showed **5** in 6% yield. Various unidentified products were also formed in 94% yield.

In this manner, the following compounds were isolated and characterised:

5-Methyl-2-(methylthio)thiophene (**3**). This compound was obtained from **1a** and two molar equivalents of *n*-butyllithium. The crude product was flash-chromatographed on silica gel using light petroleum as eluent to give a pale yellow oil, 0.90 g (81%), bp 82-83° (10 mm) [lit. [31], bp 90-92° (20 mm)]; ir (neat) 2960, 2920, 1460, 1380, 1310, 1260, 1220, 800, 730 cm^{-1}; ^{1}H nmr (deuterochloroform): δ 2.47 (s, 3H, CH_3), 2.48 (s, 3H, SCH_3), 6.63 (d, *J* = 3.6 Hz, 1H, H-4 or H-3), 6.64 (d, *J* = 3.6 Hz, 1H, H-3 or H-4); ^{13}C nmr (deuterochloroform): δ 15.41 (CH_3), 22.45 (SCH_3), 125.37 (CH-3), 131.81 (CH-4), 133.80 (C-2), 142.83 C-5); ms: m/z 144 (M^+, 100), 129 ($C_5H_5S_2^+$, 97), 85 ($C_4H_5S^+$, 45), 45 (CHS^+, 38). This product was also identified by comparison with an authentic sample prepared by literature methods [31].

2-(Ethylthio)-5-methylthiophene (**5**). This compound was obtained from **1a** and four molar equivalents of LICKOR. The crude product was flash-chromatographed on silica gel using light petroleum as eluent to give a pale yellow oil, 0.91 g (75%), bp 64-65° (2 mm) [lit. [32] bp 61-62° (2 mm)]; ir (neat) 2960, 2920, 1460, 1380, 1310, 1260, 1220, 1160, 970, 950, 800 cm^{-1}; ^{1}H nmr (deuterochloroform): δ 1.31 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 2.48 (s, 3H, CH_3), 2.79 (q, *J* = 7.5 Hz, 2H, CH_2CH_3), 6.66 (d, *J* = 3.6 Hz, 1H, H-4), 6.96 (d, *J* = 3.6 Hz, 1H, H-3); ^{13}C nmr (deuterochloroform): δ 14.03 (CH_3), 14.70 (CH_3), 22.68 (CH_2), 125.50 (CH-3), 131.31 (CH-4), 134.16 (C-2), 143.87 (C-5); ms: m/z 158 (M^+, 77), 143 ($C_6H_7S_2^+$, 9), 129 ($C_5H_5S_2^+$, 100), 114 ($C_4H_2S_2^+$, 11), 85 ($C_4H_5S^+$, 76), 45 (CHS^+, 73). This product was also identified by comparison with an authentic sample prepared by literature methods [32].

Metallation of 1b. Method A. To a vigorously stirred 1.6 *M* solution of *n*-butyllithium in hexane (6.5 mL, 10.2 mmol) **1b** (1 g, 7.7 mmol) in dry THF (20 mL) was added dropwise at –78 °C under argon. After two hours a solution of iodomethane (1.77 g, 12.5 mmol) in dry THF (10 mL) was added dropwise. After one hour the resulting solution was worked up in the same manner above described. The GC/MS analyses (see Table 2) exhibited the presence of **8** (69%), **9** (30%) and traces of the starting material.

When two molar equivalents of *n*-butyllithium were used the GC/MS analyses (see Table 2) exhibited the presence of **8** (26%), **9** (20%), **11** (54%) and traces of the starting material.

When three molar equivalents of *n*-butyllithium were used the GC/MS analyses (see Table 2) exhibited only the product **11** (>98%) and traces of the starting material.

When 4 molar equivalents of *n*-butyllithium were used the GC/MS analyses (see Table 2) exhibited only the product **11** (>99%) and traces of the starting material.

When 6 molar equivalents of *n*-butyllithium were used the GC/MS analyses (see Table 2) exhibited only the product **11** (>99%) and traces of the starting material.

Metallation of 1b. Method B. To a vigorously stirred solution of potassium *tert*-butoxide (1.14 g, 10.2 mmol) and dry THF (20 mL) a 1.4 *M* solution of *n*-butyllithium in hexane (6.5 mL, 10.2 mmol) was added under argon at –78 °C. After fifteen minutes a solution of **1b** (1 g, 7.7 mmol) in dry THF (10 mL) was added and stirring was continued for two hours at –78 °C. The mixture was then treated dropwise with an excess of iodomethane (2.61 g, 18.4 mmol) in dry THF (10 mL). After one hour the mixture was worked up in the same manner above described. The GC/MS analyses (see Table 2) showed the presence of **8** (40%), **9** (15%), **11** (5%). The remaining starting material was 40%. The ratio between **8**, **9**, **11** was 67:25:8.

When two molar equivalents of LICKOR were used the GC/MS analyses (see Table 2) exhibited the presence of **8** (63%), **9** (20%), **11** (17%) and traces of the starting material.

When three molar equivalents of LICKOR were used the GC/MS analyses (see Table 2) exhibited the presence of **11** (92%), **13** (8%) and traces of the starting material.

When four molar equivalents of LICKOR were used the GC/MS analyses (see Table 2) exhibited the presence of **11** (45%), **13** (55%) and traces of the starting material.

When five molar equivalents of LICKOR were used the GC/MS analyses (see Table 2) exhibited the presence of **11** (18%), **13** (82%) and traces of the starting material.

When six molar equivalents of LICKOR were used the GC/MS analyses (see Table 2) exhibited only the product **13** and traces of the starting material.

In this manner, the following compounds were isolated and characterised:

2-Methyl-3-(methylthio)thiophene (**8**) and **2-methyl-4-(methylthio)thiophene** (**9**). These compounds were obtained from **1b** and one molar equivalent of *n*-butyllithium. The crude product was flash-chromatographed on silica gel using light petroleum as eluent. The first fraction was **8** as a yellow oil, 0.74 g (67%); ir (neat) 3070, 2935, 2925, 1430, 1320, 1245, 1110, 850 cm^{-1}; ^{1}H nmr (deuterochloroform): δ 2.43 (s, 3H, SCH_3), 2.55 (s, 3H, CH_3), 7.04 (d, J = 5.1 Hz, 1H, H-4), 7.14 (d, J = 5.1 Hz, 1H, H-5); ^{13}C nmr (deuterochloroform): δ 16.46 (CH_3), 17.87 (CH_3), 125.84 (CH-4), 132.65 (C-2), 137.89 (CH-5), 141.33 (C-4); ms: m/z 144 (M^+, 83), 129 ($C_5H_5S_2^+$, 100), 97 ($C_5H_5S^+$, 14), 85 ($C_4H_5S^+$, 14), 69 (C_3HS^+, 34), 45 (CHS^+, 52). *Anal.* Calcd. for $C_6H_8S_2$: C, 49.95; H, 5.59; S, 44.46. Found: C, 50.04; H, 5.53; S, 44.33.

The second fraction was **9** as a pale yellow oil, 0.11 g (10%); ir (neat) 3080, 2925, 2915, 1420, 1330, 1245, 1115, 840 cm^{-1}; ^{1}H nmr (deuterochloroform): δ 2.34 (s, 3H, SCH_3), 2.45 (s, 3H, CH_3), 6.40 (s, 1H, H-3), 6.72 (s, 1H, H-5); ^{13}C nmr (deuterochloroform): δ 15.93, (CH_3), 16.62 (CH_3), 122.41 (CH-3), 143.24 (CH-5), 133.12 (C-4), 138.42 (C-2); ms: m/z 144 (M^+, 100), 129 ($C_5H_5S_2^+$, 42), 111 ($C_6H_7S^+$, 42), 97 ($C_5H_5S^+$, 31), 69 (C_3HS^+, 30), 45 (CHS^+, 58). *Anal.* Calcd. for $C_6H_8S_2$: C, 49.95; H, 5.59; S, 44.46. Found: C, 49.87; H, 5.50; S, 44.36.

2,5-Dimethyl-3-(methylthio)thiophene (**11**). This compound was obtained from **1b** and three molar equivalents of *n*-butyllithium. The crude product was flash-chromatographed on silica gel using light petroleum as eluent to give **11** as a pale yellow oil, 1.03 g (85%); ir (neat) 3085, 2915, 2950, 1420, 1360, 1245, 1130, 840 cm^{-1}; ^{1}H nmr (deuterochloroform): δ 2.40 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 6.59 (s, 1H, H-4); ^{13}C nmr (deuterochloroform): δ 15.99 (CH_3), 16.34 (CH_3), 17.87 (CH_3), 124.64 (CH-4), 132.69 (C-2), 137.55 (C-3), 140.87 (C-5); ms: m/z 158 (M^+, 79), 143 ($C_6H_7S_2^+$, 100), 111 ($C_6H_7S^+$, 14), 59 ($C_2H_3S^+$, 49), 45 (CHS^+, 40). This product was also identified by comparison with an authentic sample prepared by literature methods [33].

3-(Ethylthio)-2,5-dimethylthiophene (**13**). This compound was obtained from **1b** and six molar equivalents of LICKOR. The crude product was flash-chromatographed on silica gel using light petroleum as eluent to give **13** as a pale yellow oil, 1.11 g (84%); ir (neat) 2980, 2930, 1540, 1460, 1380, 1260, 1190, 910, 830, 740 cm^{-1}; ^{1}H nmr (deuterochloroform): δ 1.11 (t, J = 7.5 Hz, 3H, CH_2CH_3), 2.28 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.61 (q, J = 7.5 Hz, 2H, CH_2CH_3), 6.50 (s, 1H, H-4); ^{13}C nmr (deuterochloroform): δ 13.79 (CH_3), 14.05 (CH_3), 15.02 (CH_3), 15.10 (CH_2), 126.52 (CH-4), 129.27 (C-2), 135.32 (C-3), 138.13 (C-5); ms: m/z 172 (M^+, 59), 143 ($C_6H_7S_2^+$, 100), 111 ($C_6H_7^+$, 31), 59 ($C_2H_3S^+$, 63,8), 45 (CHS^+, 26). This product was also identified by comparison with an authentic sample prepared by literature methods [32].

Metallation of 1c. Method A. To a vigorously stirred 1.6 *M* solution of *n*-butyllithium in hexane (12 mL, 18.4 mmol) **1c** (1.25 g, 7.7 mmol) in dry THF (40 mL) was added dropwise at –78 °C under argon. After one hour a solution of iodomethane (3.55 g, 25 mmol) in dry THF (20 mL) was added dropwise. After forty-five minutes the resulting solution was worked up in the same manner above described. The GC/MS analyses (see Table 3) exhibited the presence of **16** (10%) (identified by comparison with an authentic sample) and **17** (90%).

When three molar equivalents of *n*-butyllithium were used the GC/MS analyses (see Table 3) exhibited only the product **17** (>98%).

When six molar equivalents of *n*-butyllithium were used the GC/MS analyses (see Table 3) exhibited only the product **17** (>99%).

Metallation of 1c. Method B. To a vigorously stirred solution of potassium *tert*-butoxide (2.07 g, 18.5 mmol) and dry THF (40 mL) a 1.4 *M* solution of *n*-butyllithium in hexane (11.8 mL, 18.5 mmol) was added under argon at –78 °C. After 15 minutes a solution of **1c** (1.25 g, 7.7 mmol) in dry THF (20 mL) was added and stirring was continued for one hour at –78 °C. The mixture was then treated dropwise with an excess of iodomethane (4.74 g, 33.4 mmol) in dry THF (30 mL). After forty-five minutes the mixture was worked up in the same manner above described. The GC/MS analyses (see Table 3) showed the presence of **16** and **17** in the ratio of 12:88 and traces of starting material. In this reaction the GC/MS analysis revealed many degradation products lowering the products global yield to 40%.

When four molar equivalents of LICKOR were used the GC/MS analyses (see Table 3) exhibited only the presence of **16** and **17** in the ratio of 8:92 and traces of starting material. In this reaction the GC/MS analysis revealed many degradation products lowering the products global yield to 35%.

When six molar equivalents of LICKOR were used the GC/MS analyses (see Table 3) exhibited only the product **17** and traces of starting material. In this reaction the GC/MS analysis revealed many degradation products lowering the products global yield to 18%.

In this manner, the following compound was isolated and characterised:

3-(Ethylsulfonyl)-2-methylthiophene (17). This compound was obtained from **1c** and three molar equivalents of *n*-butyllithium. The crude product was flash-chromatographed on silica gel using 1/1 light petroleum/diethyl ether as eluent to give **17** as a yellow oil, 0.99 g (68%); ir (neat) 3115, 2970, 2228, 1470, 1315, 1270, 1150, 1105, 1175, 920, 740, 710 cm^{-1}; ^{1}H nmr (deuterochloroform): δ 1.20 (t, J = 7.2 Hz, 3H, CH_2CH_3), 2.17 (s, 3H, CH_3), 3.48 (q, J = 7.2 Hz, 2H, CH_3CH_2), 7.38 (d, J = 5.1 Hz, 1H, H-4), 7.48 (d, J = 5.1 Hz, 1H, H-5); ^{13}C nmr (deuterochloroform): δ 15.18 (CH_3), 15.64 (CH_3), 22.61 (CH_2), 126.78 (CH-4 or CH-5), 127.83 (CH-5 or CH-4), 133.29 (C-2 or C-3), 137.43 (C-3 or C-2); ms: m/z 190 (M^+, 7), 131 ($C_4H_3OS_2^+$, 11), 100 ($C_4H_4OS^+$, 24), 84 ($C_4H_4S^+$, 33), 39 ($C_3H_3^+$, 100). *Anal.* Calcd. for $C_7H_{10}O_2S_2$: C, 44.18; H, 5.30; S, 33.70. Found: C, 44.10; H, 5.24; S, 33.58.

Metallation of 1d. Method A. To a vigorously stirred 1.6 *M* solution of *n*-butyllithium in hexane (6.5 mL, 10.2 mmol) **1c** (1.25 g, 7.7 mmol) in dry THF (20 mL) was added dropwise at –78 °C under argon. After fifteen minutes, a solution of iodomethane (1.77 g, 12.5 mmol) in dry THF (10 mL) was added dropwise. After twenty minutes at the same temperature, the resulting solution was worked up in the same manner above described. The GC/MS analyses exhibited only the presence of degradation products.

The same results were obtained performing the reaction with two or more equivalents of *n*-butyllithium even with TMEDA, or performing the metallation in the presence of the electrophile.

Metallation of 1d. Method B. To a vigorously stirred solution of potassium *tert*-butoxide (1.14 g, 10.2 mmol) and dry THF (20 mL) a 1.4 *M* solution of *n*-butyllithium in hexane (6.5 mL, 10.2 mmol) was added under argon at –78 °C. After fifteen minutes a solution of **1c** (1.25 g, 7.7 mmol) in dry THF (10 mL) was added and stirring was continued for fifteen minutes at –78 °C. The mixture was then treated dropwise with an excess of iodomethane (2.61 g, 18.4 mmol) in dry THF (10 mL). After twenty minutes the mixture was worked up in the same manner above described. The GC/MS analyses exhibited only the presence of degradation products.

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