The Directing Ability of the Methylthio Substituent in Lithiation Reactions of Thiophenes

Edward C. Taylor* and Dennis E. Vogel

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

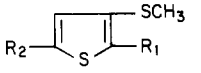
Received July 25, 1984

A method for regiospecific electrophilic substitution of 3-(methylthio)thiophene in either the 2- or 5-position has been developed on the basis of a combination of bromination, metal–halogen exchange, and controlled rearrangement of 2-bromo-5-lithio-3-(methylthio)thiophene to 5-bromo-2-lithio-3-(methylthio)thiophene.

An important method for α-functionalization of thiophenes is lithiation followed by treatment with an electrophile.[1] When a coordinating substituent (i.e., (dimethylamino)methyl) is present in position 3, lithiation is directed to the 2-position,[2] whereas noncoordinating sterically bulky substituents in position 3 (i.e., *tert*-butyl) lead exclusively to 5-lithiation.[3] When the coordinating ability of a 3-substituent does not fully compensate for steric effects, lithiation can occur in both the 2- and 5-positions. For example, lithiation of 3-methoxythiophene leads to a 93:7 ratio of the 2- and 5-lithiated products, respectively,[3] and 3-(methylseleno)thiophene yields a 56:44 ratio of 2- to 5-lithiated products, respectively.[4] We report in this paper on the directing ability of a 3-methylthio substituent, as well as related chemistry which makes possible selective electrophilic substitution in either position 2 or position 5 of 3-(methylthio)thiophene.

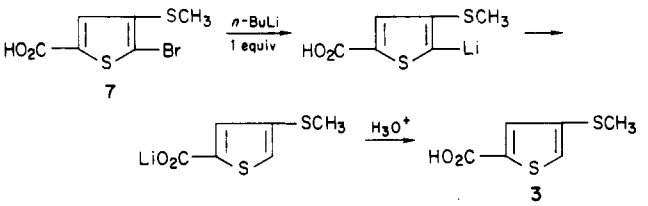
Although Gronowitz has reported[5] that treatment of 3-(methylthio)thiophene (**1**) with 1 equiv of *n*-butyllithium in ether, followed by addition of CO_2, yields 3-(methylthio)thiophene-2-carboxylic acid (**2**) in 60% yield as the major product, we have found that, in ether–hexane, the crude reaction mixture contains a 3:1 mixture of **2** and its regioisomer, 4-(methylthio)thiophene-2-carboxylic acid (**3**). This result was confirmed by quenching the lithiated intermediate(s) with acetaldehyde. Acetylation or methylation of the resulting reaction mixtures gave corresponding mixtures of the 2-(1-acetoxyethyl) and 2-(1-methoxyethyl) derivatives **4b,c** and the isomeric 5-(1-acetoxyethyl) and 5-(1-methoxyethyl) derivatives **5b,c**, respectively. A simple procedure, however, has been developed for the regiospecific synthesis of compounds **2–5** starting with 3-(methylthio)thiophene (**1**). Thus, bromination of **1** with 1 equiv of *N*-bromosuccinimide yields 2-bromo-3-(methylthio)-thiophene (**6**) in almost quantitative yield. Halogen–metal exchange of **6** with *n*-butyllithium leads exclusively to the 2-lithio derivative; carboxylation then gives 3-(methylthio)thiophene-2-carboxylic acid (**2**), while reaction with acetaldehyde leads exclusively to **4a** (methylation of which yields **4c**), with no trace of the 5-substituted regioisomers. It should be noted that lithiation of **4c** with *n*-butyllithium occurs exclusively at position 5, as demonstrated by deuteration (to give **4d**) and by carboxylation to give **4e**. These experiments conclusively demonstrate the greater influence of the ring sulfur atom over the methylthio substituent in directing lithiation.

Table I. 2- and 5-Substituted 3-(Methylthio)thiophenes

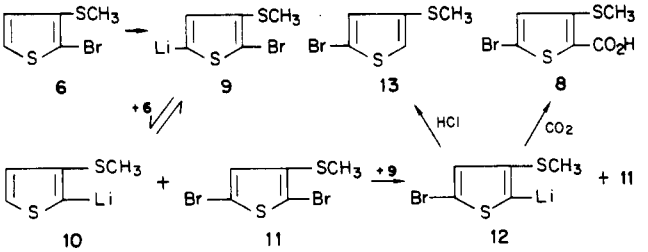


compd	R_1	R_2
1	H	H
2	COOH	H
3	H	COOH
4a	$CH(CH_3)OH$	H
4b	$CH(CH_3)OCOCH_3$	H
4c	$CH(CH_3)OCH_3$	H
4d	$CH(CH_3)OCH_3$	D
4e	$CH(CH_3)OCH_3$	COOH
5a	H	$CH(CH_3)OH$
5b	H	$CH(CH_3)OCOCH_3$
5c	H	$CH(CH_3)OCH_3$
6	Br	H
7	Br	COOH
8	COOH	Br
13	H	Br

Slow addition of 2-bromo-3-(methylthio)thiophene (**6**) to an excess of LDA at −78 °C, followed by addition of CO_2, leads exclusively to the formation of 5-bromo-4-(methylthio)thiophene-2-carboxylic acid (**7**). By contrast, however, rapid addition of **6** to 1 equiv of LDA at −78 °C, followed after 1 h by addition of CO_2, yields exclusively 5-bromo-3-(methylthio)thiophene-2-carboxylic acid (**8**), the regioisomer of **7**. The structures of **7** and **8** were readily confirmed by treatment of each with 2 equiv of *n*-butyllithium followed by quenching with dilute hydrochloric acid. This procedure yielded pure 4-(methylthio)-thiophene-2-carboxylic acid (**3**) from **7** and pure 3-(methylthio)thiophene-2-carboxylic acid (**2**) from **8**. Interestingly, the same result is obtained if one treats the bromo acid **7** with 1 equiv of *n*-BuLi followed by dilute HCl. This



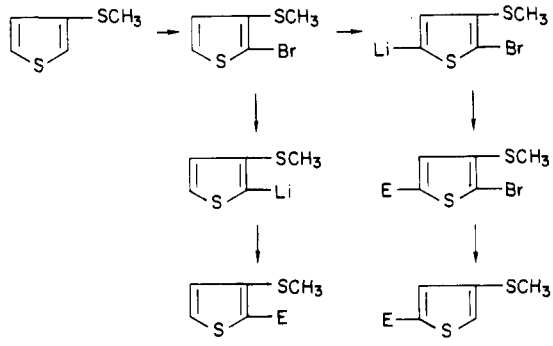
Scheme I



(1) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* (*N.Y.*) **1979**, *26*, Chapter 1.
(2) Slocum, D. W.; Gierer, P. L. *J. Chem. Soc., Chem. Commun.* **1971**, 305. Slocum, D. W.; Gierer, P. L. *J. Org. Chem.* **1976**, *41*, 3668.
(3) Gronowitz, S.; Cederland, B.; Hornfeldt, A. B. *Chem. Scr.* **1974**, *5*, 217.
(4) Gol'dfarb, Ya. L.; Litvinov, V. P.; Sukiasyan, A. N. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1971**, 1296.
(5) Gronowitz, S. *Arkiv. Kemi* **1958**, *13*, 269.

0022-3263/85/1950-1002$01.50/0

Scheme II



experiment demonstrates that metal–halogen exchange is more facile than proton removal. There are other reports in the literature describing similar reactions.[6,7]

We suggest that the regiospecific rearrangement involved in the conversion of **6** to **8** occurs as outlined in Scheme I. LDA, as a strong base but a poor nucleophile, leads only to deprotonation and consequently exclusive 5-lithiation to generate **9**.[8] Rapid addition of **6** to only 1 equiv of LDA, however, apparently results in the formation of **9** in the presence of some unreacted **6**. Metal–halogen exchange would then lead to the thermodynamically more stable 2-lithio derivative **10** and 2,5-dibromo-3-(methylthio)thiophene (**11**). The latter, however, can now act as a catalyst for the conversion of **9** to 2-bromo-5-lithio-4-(methylthio)thiophene (**12**). It should be noted that the conversion of **9** to **12**, catalyzed by **11**, is also a thermodynamically favored rearrangement. Apparently under conditions of slow addition of **6** to an excess of LDA, **9** is formed in the absence of unreacted **6**; under these conditions, the catalyst **11** is not formed, and no arrangement is observed.

The reaction sequence suggested in Scheme I receives support from the observation that deliberate addition of 0.1 equiv of **11** (prepared independently by dibromination of 3-(methylthio)thiophene) to a solution of **9** (generated, as described above, by slow addition of **6** to an excess of LDA) followed after 1 h at −70 °C by addition of CO_2 led exclusively to the rearrangement product **8**. Quenching of the intermediate lithio derivative **12** with dilute hydrochloric acid led exclusively to 2-bromo-4-(methylthio)thiophene (**13**).

Reports by Moses and Gronowitz,[9] Turner et al.,[10] and Kano et al.[11] describe similar metal–halogen exchange reactions which probably also involve catalytic dihalo and trihalo intermediates, respectively. Analogous mechanisms have been proposed for the "Halogen Dance" reaction of aryl halides.[12]

Thus, despite the fact that 3-(methylthio)thiophene gives a mixture of 2- and 5-lithio derivatives by direct lithiation, we have shown that a combination of bromination with metal–halogen exchange makes possible regiospecific electrophilic substitution in either position 2 or position 5 (see Scheme II). We suggest that this general methodology may be useful in other systems where direct lithiation is not sufficiently regiospecific.

Experimental Section

2-(1-Acetoxyethyl)-3-(methylthio)thiophene (4b). To a solution of 3-(methylthio)thiophene (**1**) in 16 mL of anhydrous ether at 25 °C was added 11.0 mL (17.6 mmol) of 1.6 N *n*-BuLi, followed by heating to reflux for 1 h. This mixture was cooled to 0 °C and 0.8 g (18 mmol) of freshly distilled acetaldehyde was added dropwise at such a rate that the reaction temperature remained below 0 °C. This mixture was stirred for 4 h and quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted with ether and the ether layer dried and concentrated to give the crude hydroxyethyl derivative. This material without further purification was stirred with 1.6 mL of acetic anhydride in 2.0 mL of pyridine for 14 h, poured into ice-cold 6 N H_2SO_4, and extracted with ether. The ether layer was washed with 10% aqueous Na_2CO_3 until the aqueous layer remained basic. The ether layer was dried ($MgSO_4$) and concentrated, and the residue was distilled to give 0.70 g (3.2 mmol, 20%) of **4b**: bp 72–73 °C (0.15 torr); IR (neat) 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.59 (3 H, d, J = 7.0 Hz), 2.07 (3 H, s), 2.42 (3 H, s), 6.48 (1 H, q, J = 7.0 Hz), 7.06 (1 H, d, J = 5.5 Hz), 7.33 (1 H, d, J = 5.5 Hz).

Anal. Calcd for $C_9H_{12}O_2S_2$: C, 49.97; H, 5.59; S, 29.64. Found: C, 49.79; H, 5.32; S, 29.37.

2-Bromo-3-(methylthio)thiophene (6). To a stirred solution of 97.9 g (750 mmol) of 3-(methylthio)thiophene (**1**) in 400 mL of acetic acid cooled to 15 °C was added 133.5 g (750 mmol) of *N*-bromosuccinimide at such a rate that the reaction temperature remained between 15 °C and 17 °C. The resulting mixture was stirred for $2^1/_2$ h as it warmed to 25 °C, poured into water, and extracted with ether. The ether layer was washed with water and a saturated solution of $NaHCO_3$, dried, and concentrated. The residue (151 g) was distilled to give 136.5 g (650 mmol, 87%) of **6**: bp 67–71 °C (0.1 torr); NMR ($CDCl_3$) δ 2.41 (3 H, s), 6.84 (1 H, d, J = 6.0 Hz), 7.21 (1 H, d, J = 6.0 Hz).

Anal. Calcd for $C_5H_5BrS_2$: C, 28.72; H, 2.41; Br, 38.21; S, 30.66. Found: C, 28.75; H, 2.40; Br 38.11; S, 30.37.

2-(1-Methoxyethyl)-3-(methylthio)thiophene (4c). Method A. The procedure for **4b** was followed with 10.0 g (76.9 mmol) of 3-(methylthio)thiophene (**1**), 150 mL of anhydrous ether, 29.8 mL (71.5 mmol) of 2.4 M *n*-BuLi, and 3.4 g (77 mmol) of acetaldehyde to give the crude hydroxyethyl derivative. Without further purification, this material was dissolved in 100 mL of methanol with 3.5 mL of concentrated H_2SO_4. This mixture was stirred for 5 min and poured over ice water, extracted with ether, dried ($MgSO_4$), and concentrated. Fractional distillation gave 5.38 g (28.6 mmol, 37%) of **4c**: bp 55–56 °C (0.25 torr); NMR ($CDCl_3$) δ 1.47 (3 H, d, J = 7.0 Hz), 2.37 (3 H, s), 3.25 (3 H, s), 4.89 (1 H, q, J = 7.0 Hz), 6.96 (1 H, d, J = 5.0 Hz), 7.25 (1 H, d, J = 5.0 Hz).

Anal. Calcd for $C_8H_{12}OS_2$: C, 51.02; H, 6.43; S, 34.05. Found: C, 51.02; H, 6.30; S, 33.94.

Method B. A solution of 12.0 g (57.4 mmol) of 2-bromo-3-(methylthio)thiophene (**6**) in 30 mL of anhydrous ether was stirred at −70 °C, to which was added 24.4 mL (58.6 mmol) of 2.4 M *n*-BuLi in hexane. The solution was stirred at −70 °C for 15 min, at which point 2.6 g (59 mmol) of freshly distilled acetaldehyde was added. External cooling was discontinued and the solution allowed to warm for $^1/_2$ h. A saturated aqueous solution of NH_4Cl was added, and the mixture was extracted with ether. The ether layer was washed with water, dried, and concentrated to give the crude alcohol which was converted to the methyl ether **4c** as described in method A; yield 7.28 g (38.7 mmol, 67%)

5-(1-Methoxyethyl)-4-(methylthio)thiophene-2-carboxylic Acid (4e). To a solution of 31.2 g (166 mmol) of **4c** in anhydrous THF was added 75.7 mL (174 mmol) of 2.3 M *n*-BuLi in hexane at such a rate that the temperature never exceeded 35 °C. After 15 min the reaction mixture was cooled to −35 °C and dry CO_2 gas was passed through the solution until substantial frothing occurred (no more CO_2 absorption). The solution was concentrated in vacuo and the residue dissolved in water and filtered. The filtrate was acidified with 6 N HCl to pH ~1 and extracted with ether. The ether layer was dried and concentrated to give 35.1 g (151 mmol, 91%) of **4e**, mp 109–110 °C. An analytical sample, mp 111–112 °C, was obtained by recrystallization from isopropyl alcohol–water: IR (KBr) 3000–2300, 1660 cm^{-1}; NMR

(6) Boatman, R. J.; Whitlock, B. J.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1977**, *99*, 4822.
(7) Stein, C. A.; Morton T. H. *Tetrahedron Lett.* **1973**, 4933.
(8) See, for example: Davies, G. M.; Davies, P. S. *Tetrahedron Lett.* **1972**, 3507.
(9) Moses, P.; Gronowitz, S. *Arkiv. Kemi* **1961**, *18*, 119.
(10) Guildford, A. J.; Tometzki, M. A.; Turner, R. W. *Synthesis* **1983**, 987.
(11) Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *Heterocycles* **1983**, *20*, 2035.
(12) (a) Bunnett, J. F. *Acc. Chem. Res.* **1972**, *5*, 139. (b) Gronowitz, S.; Holm, B. *Acta Chem. Scand.* **1969**, *23*, 2207.

($CDCl_3$) δ 1.55 (3 H, d, J = 7.0 Hz), 2.47 (3 H, s), 3.38 (3 H, s), 4.89 (1 H, q, J = 7.0 Hz), 7.82 (1 H, s), 11.23 (1 H, s).

Anal. Calcd for $C_9H_{12}O_3S_2$: C, 46.53; H, 5.21; S, 27.60. Found: C, 46.59; H, 5.01; S, 27.84.

5-Bromo-4-(methylthio)thiophene-2-carboxylic Acid (7). A solution of LDA in 100 mL of THF was prepared at −70 °C from 1.45 g (14.3 mmol) of diisopropylamine and 5.8 mL (13.4 mmol) of 2.3 M *n*-BuLi in hexane. A solution of 2.0 g (9.57 mmol) of **6** in 20 mL of THF was added slowly (30 min) to the cooled solution of LDA. After the addition was complete, the solution was stirred for 10 min and purged with a stream of dry CO_2 until the solution no longer absorbed the gas. The mixture was concentrated in vacuo and dissolved in water. The aqueous solution was washed with ether and acidified with 6 N HCl to pH ~1. The precipitate was collected and dried to give 1.95 g (7.71 mmol, 80%) of **7**, mp 164–168 °C. An analytical sample was obtained by recrystallization from benzene: mp 172–173 °C; IR (KBr) 3200–2300, 1660 cm^{-1}; NMR ($CDCl_3$–Me_2SO-d_6, 20:1) δ 2.47 (3 H, s), 7.53 (1 H, s).

Anal. Calcd for $C_6H_5BrO_2S_2$: C, 28.47; H, 1.99; Br, 31.57; S, 25.33. Found: C, 28.66; H, 2.03; Br, 31.82; S, 24.94.

5-Bromo-3-(methylthio)thiophene-2-carboxylic Acid (8). A solution of LDA in 5 mL of THF was prepared at −70 °C from 97 mg (0.96 mmol) of diisopropylamine and 0.42 mL (0.96 mmol) of 2.3 M *n*-BuLi in hexane. A solution of 0.20 g (0.96 mmol) of **6** in 2 mL of THF was added rapidly (5 min) to the cooled solution of LDA and the mixture was stirred at −70 °C for 1 h, purged with dry CO_2 gas, and allowed to warm. The mixture was concentrated in vacuo and dissolved in water, and the aqueous solution was washed with ether and acidified to pH ~1. The precipitate was collected and dried to give 0.10 g (0.39 mmol, 41%) of **8**, mp 206 °C dec. The analytical sample, mp 211–212 °C dec, was obtained by recrystallization from ethanol: IR (KBr) 3200–2200, 1655 cm^{-1}; NMR ($CDCl_3$–Me_2SO-d_6, 20:1) δ 2.49 (3 H, s), 6.93 (1 H, s).

Anal. Calcd for $C_6H_5BrO_2S_2$: C, 28.47; H, 1.99; Br, 31.57; S, 25.33. Found: C, 28.36; H, 1.82; Br, 31.63; S, 25.18.

2,5-Dibromo-3-(methylthio)thiophene (11). A solution of 1.0 g (7.7 mmol) of **1** in 10 mL of CH_2Cl_2 was stirred at 25 °C while 2.74 g (15.4 mmol) of *N*-bromosuccinimide was added portionwise, and the mixture was allowed to stir for 12 h. The mixture was filtered and concentrated in vacuo, extracted with ether, and filtered again. The ether solution was concentrated and the residue distilled to give 1.18 g (4.10 mmol, 53%) of **11**: bp 115–120 °C (0.5 torr); NMR ($CDCl_3$) δ 2.43 (3 H, s), 6.88 (1 H, s).

Anal. Calcd for $C_5H_4Br_2S_2$: C, 20.85; H, 1.40; Br, 55.49; S, 22.26. Found: C, 21.19; H, 1.40; Br, 55.48; S, 22.08.

2-Bromo-4-(methylthio)thiophene (13). The procedure for **8** was followed with 0.36 g (3.58 mmol) of diisopropylamine, 1.52 mL (3.34 mmol) of 2.2 M *n*-BuLi in hexane (for the preparation of LDA in 10 mL of THF), and 0.70 g (3.35 mmol) of 2-bromo-3-(methylthio)thiophene (**6**) in 7 mL of THF. The rearranged material was quenched with 0.1 M HCl, poured into water, and extracted with ether. The ether layer was dried and concentrated and the residue distilled to give 0.23 g (1.10 mmol, 33%) of **13**: bp 68–70 °C (0.5 torr); NMR (Me_2CO-d_6) δ 2.48 (3 H, s), 7.04 (1 H, d, J = 2.0 Hz), 7.10 (1 H, d, J = 2.0 Hz).

Anal. Calcd for $C_5H_5BrS_2$: C, 28.72; H, 2.41; Br, 38.21; S, 30.66. Found: C, 29.00; H, 2.64; Br, 38.26; S, 30.36.

4-(Methylthio)thiophene-2-carboxylic Acid (3). Method A. A solution of 0.20 g (0.79 mmol) of **7** in 5 mL of anhydrous THF was cooled to −70 °C and 0.75 mL (1.65 mmol) of 2.2 M *n*-BuLi in hexane was added. The solution was stirred at −70 °C for $^1/_2$ h and quenched with 1 N HCl. The mixture was dissolved in water with the aid of $NaHCO_3$, and the aqueous solution was extracted with ether, acidified with 6 N HCl to pH ~1, and extracted with ether. The ether layer was dried and concentrated and the residue recrystallized from $CHCl_3$ to give 0.05 g (0.29 mmol, 36%) of **3**: mp 115 °C; IR (KBr) 3200–2200, 1660 cm^{-1}; NMR (Me_2CO-d_6) δ 2.54 (3 H, s), 7.46 (1 H, d, J = 1.6 Hz), 7.65 (1 H, d, J = 1.6 Hz).

Anal. Calcd for $C_6H_6O_2S_2$: C, 41.36; H, 3.47; S, 36.80. Found: C, 41.28; H, 3.37; S, 36.58.

Method B. A solution of 0.040 g (0.16 mmol) of **7** in 1 mL of anhydrous THF was cooled to −78 °C in an atmosphere of argon and 0.073 mL (0.16 mmol) of 2.2 M *n*-BuLi in hexane was added. The solution was stirred at −70 °C for 0.5 h and quenched with aqueous 1 N hydrochloric acid. The mixture was dissolved in water with the aid of sodium bicarbonate. The aqueous solution was extracted with ether and acidified with aqueous 6 N hydrochloric acid to pH 1. The aqueous layer was extracted with ether, and the ether layer was dried ($MgSO_4$) and concentrated in vacuo to give 0.02 g (0.1 mmol, 70%) of **3**, identical with material prepared by method A.

3-(Methylthio)thiophene-2-carboxylic Acid (2). The procedure for **3** was followed using 0.1 g (0.395 mmol) of **8** in 5 mL of anhydrous THF and 0.36 mL (0.79 mmol) of 2.2 M *n*-BuLi in hexane. Recrystallization of the crude product from EtOH–H_2O gave 0.04 g (0.23 mmol, 58%) of **2**: mp 185 °C dec; IR (KBr) 3200–2300, 1645 cm^{-1} (identical with lit.[5]); NMR (Me_2CO-d_6) δ 2.56 (3 H, s), 7.16 (1 H, d, J = 6.0 Hz), 7.78 (1 H, d, J = 6.0 Hz).

CO_2 Quench of Lithiated 3-(Methylthio)thiophene. A solution of 0.50 g (3.9 mmol) of 3-(methylthio)thiophene (**1**) in 4 mL of anhydrous ether was stirred at 25 °C while 1.75 mL (3.85 mmol) of 2.2 M *n*-BuLi in hexane was added. The mixture was stirred for $^1/_2$ h, poured over CO_2, allowed to warm, dissolved in water, and washed with ether. The aqueous solution was acidified with 6 N HCl and extracted with ether. The ether layer was dried and concentrated to give a 3:1 mixture of **2** and **3**, respectively, as determined by NMR integration.

D_2O Quench of Lithiated 4c. A solution of 0.15 g (0.80 mmol) of 2-(1-methoxyethyl)-3-(methylthio)thiophene (**4c**) in 2 mL of anhydrous ether was stirred at 25 °C while 0.58 mL (0.90 mmol) of 1.55 M *n*-BuLi in hexane was added slowly. After 15 min the mixture was quenched with D_2O, extracted with ether, dried, and concentrated to give **5-deuterio-2-(1-methoxyethyl)-3-(methylthio)thiophene (4d)**: NMR ($CDCl_3$) δ 1.49 (3 H, d, 6.0 Hz), 2.39 (3 H, s), 3.29 (3 H, s), 4.92 (1 H, q, J = 6.0 Hz), 7.03 (1 H, s).

Rearrangement of 9 to 12. Following the above procedure for the preparation of **7**, the lithio species **9** was prepared from 0.50 g (2.4 mmol) of 2-bromo-3-(methylthio)thiophene (**6**) in 5 mL of THF and 3.35 mmol of LDA (from 0.36 g, 3.58 mmol, of diisopropylamine and 1.52 mL, 3.35 mmol, of 2.2 M *n*-BuLi/hexane in 10 mL of THF). The resulting solution of **9** was maintained at −70 °C for 24 h, quenched with CO_2, and worked up in the usual manner; only **7** was formed, as determined by examination of the ^1H NMR spectrum of the reaction mixture. However, after addition of 0.1 g (0.035 mmol) of 2,5-dibromo-3-(methylthio)thiophene (**11**) to the above solution of **9** and stirring at −70 °C for 1 h, only **12** was then present in solution, as determined by carboxylation. Under these conditions, only **8**, and no **7**, could be detected in the reaction mixture.

Registry No. **1**, 20731-74-2; **2**, 60166-80-5; **3**, 94781-31-4; **4a**, 94781-32-5; **4b**, 94781-33-6; **4c**, 94781-34-7; **4d**, 94781-35-8; **4e**, 94781-36-9; **5b**, 94781-37-0; **5c**, 94781-38-1; **6**, 94781-39-2; **7**, 94781-40-5; **8**, 94781-41-6; **11**, 94781-42-7; **13**, 95191-79-0; *n*-BuLi, 109-72-8; acetaldehyde, 75-07-0.