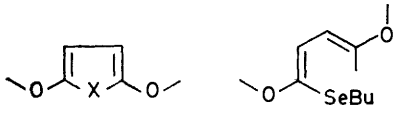
Ring-opening Reactions. Part 16.[1] Ring-opening of 2,5-Dimethoxy-3-thienyl-lithium and Some Related Compounds

By **Anders Hallberg, Torbjörn Frejd,*** and **Salo Gronowitz,** Division of Organic Chemistry 1, Chemical Center, University of Lund, P.O. Box 740, S–220 07 Lund, Sweden

Evidence is presented indicating that 2,5-dimethoxythiophen is metallated in the β-position by butyl-lithium to give 2,5-dimethoxy-3-thienyl-lithium, which subsequently undergoes ring-opening. By the use of 2 equiv. of butyl-lithium followed by dimethyl sulphate, it was possible to isolate 1-methylthio-octa-1,3-diyne as the main product.

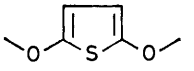
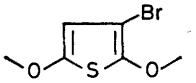
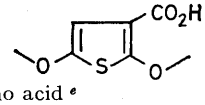
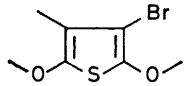
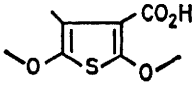
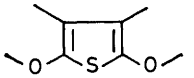
We recently reported that 2,5-dimethoxyselenophen (1; X = Se) was attacked by butyl-lithium to give various ring-opened products, *e.g.* (2), after trapping with



(1) (2)

dimethyl sulphate.[1] The reaction was suggested to take place through attack by butyl-lithium at the selenium atom of (1; X = Se), followed by cleavage of the Se–C-α bond, *i.e.* substitution on selenium. It was therefore of interest to examine also the behaviour of 2,5-dimethoxythiophen (1; X = S) and related compounds towards butyl-lithium, especially since it was previously reported that (1; X = S) gave unidentified products with butyl-lithium at room temperature.[2]

Treatment of methoxy-substituted thiophens with butyl-lithium

Entry	Substrate	BuLi (mol. equiv.)	Conditions	Products
1		1	20 °C, 2 h, DMS [a]	non-acetylenic unidentified prod. + starting material
2		2	20 °C, 2 h, DMS [a]	$H_3CS(C{\equiv}C)_2Bu$ (45%) [b] + starting material (47%) [b]
3		2	20 °C, 4 h, DMS [a]	as entry 2
4		4	20 °C, 4 h, DMS [a]	polymers
5 [d]		1	−70 °C, CO_2	 (60%) [c]
6		1	−70 °C → 20 °C, 2 h, CO_2	polymers; no acid [e]
7		2	−70 °C → 20 °C, 2 h, DMS [a]	$H_3CS(C{\equiv}C)_2Bu$ (67%) [b] + starting material (18%) [b]
8		1	−70 °C, CO_2	 (56%) [c]
9		1	−70 °C → 20 °C, 2 h, CO_2	polymers; no acid [e]
10		2	−70 °C → 20 °C, 2 h, DMS [a]	several unidentified products
11		15	20 °C, 18 h, DMS [a]	starting material (97%) [b]

[a] DMS = dimethyl sulphate. [b] G.l.c.-yields. [c] Isolated yields. [d] Confirmation of the results in ref. 2. [e] As determined by n.m.r. spectroscopy.

RESULTS

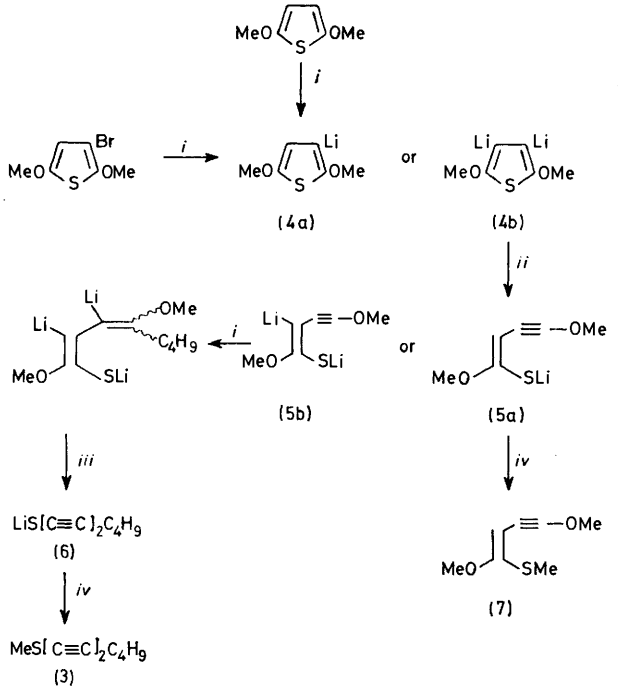
The outcome of the reactions of some different methoxy-substituted thiophens and butyl-lithium is summarized in the Table. It is immediately apparent that the results with (1; X = S) (entries 1—4) are critically dependent on the amount of butyl-lithium used. Thus, (1; X = S) gave a 45% yield of 1-methylthio-octa-1,3-diyne (3) with 2 equiv. of the reagent, while this product could barely be traced when 1 or 4 equivalents of butyl-lithium were used.

Concerning the reaction of 3-bromo-2,5-dimethoxythiophen and butyl-lithium, we have confirmed the earlier result of Barker *et al.*[2] However, the absence of 2,5-methoxythiophen-3-carboxylic acid when the reaction mixture was kept at room temperature prior to carboxylation (entry 6) indicated the instability of 2,5-dimethoxy-3-thienyl-lithium (4a), and by the use of 2 equivalents of butyl-thienyl-lithium followed by dimethyl sulphate, (3) was generated (67%, entry 7). 3-Bromo-2,5-dimethoxy-4-methylthiophen showed similar behaviour (entries 8—10), except that no ring-opened product could be identified. It is noteworthy that 2,5-dimethoxy-3,4-dimethylthiophen apparently did not react with butyl-lithium to any appreciable extent (entry 11), despite a prolonged reaction time and a large excess of the reagent.

DISCUSSION

Since 3-bromo-2,5-dimethoxythiophen gave a fair yield of (3) with 2 equivalents of butyl-lithium after trapping with dimethyl sulphate (entry 7), it seems highly

probable that the intermediate (4a) ring-opens in a way similar to 2,5-dimethyl-3-thienyl-lithium.[3] The evidence that (4a) is the intermediate for this ring-opening reaction is that 3-bromo-2,5-dimethoxythiophen gave a good yield of 2,5-dimethoxythiophen-3-carboxylic acid with butyl-lithium followed by carboxylation, provided the reaction was performed at −70 °C (entry 5). If, however, the reaction mixture was allowed to reach room temperature before treatment with solid carbon dioxide, no acid was formed (entry 6). Thus, the enyne thiolate (5) (Scheme) is suggested as a primary ring-opened product. The conversion (5) ⟶ (6) is then likely to proceed through



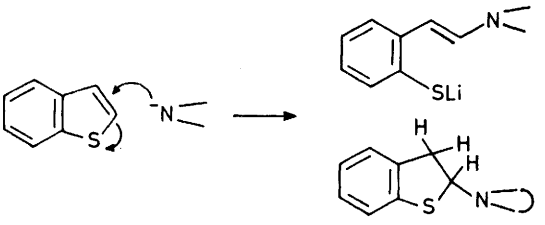
SCHEME *Reagents*: *i*, BuLi; *ii*, room temperature; *iii*, $-2CH_3OLi$; *iv*, dimethyl sulphate

addition of a second equivalent of butyl-lithium to the acetylenic bond of (5) followed by base-induced elimination of methoxide and methanol to give the diyne thiolate (6), which is finally trapped by dimethyl sulphate to give (3).

In support of this route is the previously reported facile replacement of an acetylenic methoxy-group with different organic groups by the use of the corresponding organolithium reagents.[4]

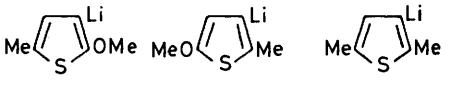
With only one equivalent of butyl-lithium, the acetylenic ether (7) would result. This substance could, however, not be detected, which may be due to instability towards the basic work-up conditions, but this point remains to be clarified.

These arguments, together with the well-known fact that aromatic methoxy-groups direct metallation to their *ortho*-position,[5] strongly indicate that (1; X = S) ring-opens by way of 2,5-dimethoxy-3-thienyl-lithium (4a) or perhaps, although less likely,* *via* 3,4-dilithio-2,5-dimethoxythiophen (4b), and *not* by attack of butyl-lithium on the sulphur atom (absence of –SBu-containing compounds) or the α-carbon atoms. This is also supported by the result with 2,5-dimethoxy-3,4-dimethyl-thiophen (both β-positions blocked), which gave essentially no reaction (entry 11). Benzo[*b*]thiophen is reported to ring-open *via* α-carbon attack by lithium dimethylamide to give an enamine.[7] However, there



are also some conflicting results showing no ring-opening in a similar case. Instead, the addition product was isolated.[8] The methoxythiophens apparently did not give rise to analogous compounds.

Our previous results concerning the ring-opening of methoxy- and methyl-substituted 3-thienyl-lithium derivatives showed that (9) and (10) also ring-opened,[3,9]



but (8) did not[9] even after several hours at room temperature. However, if the methoxy-group of (8) were replaced by a methylthio-group, ring-opening did take place.[9] These results indicated some kind of stabilizing property of an *ortho*-methoxy-group, but the results presented in this paper show that this property is counterbalanced by another methoxy-group in the *meta* position.

EXPERIMENTAL

N.m.r. spectra were recorded with a Varian A-60 n.m.r. spectrometer, mass spectra with an LKB 9000 mass spectrometer, and gas chromatograms with a Varian 1400 gas chromatograph equipped with a flame-ionization detector. $MgSO_4$ was used as drying agent throughout.

Treatment of Dimethoxythiophens with Butyl-lithium.—To a solution of the appropriate dimethoxythiophen derivative in diethyl ether (*ca.* 10 mmol per 100 ml of ether), butyl-lithium in hexane was added (amounts according to the Table) under nitrogen. For entries 1—4 and 11 the butyl-lithium was added to an ice-cooled solution and then the reaction mixtures were kept at 20 °C, as shown in the Table. The reaction mixtures were quenched at −70 °C by either (i) an excess of freshly distilled dimethyl sulphate or (ii) solid carbon dioxide, and then allowed to reach room temperature. The work-up for case (i) involved destruction of the

* It has previously been suggested,[6] although not rigorously proven, that 3,4-dilithio-thiophens were intermediates in ring-opening reactions to give butadiynes. In these cases the lithium atoms were introduced through halogen–metal exchanges between the iodothiophens and butyl-lithium. However, in the present case, it is necessary to invoke hydrogen–metal exchanges, which generally are much slower than halogen–metal exchanges. Therefore, we believe it less likely that (4b) is an intermediate.

excess of dimethyl sulphate with aqueous ammonia, extraction with ether, washing with water, drying with $MgSO_4$, and analysis by g.l.c.–mass spectrometry. (In cases where g.l.c. yields are given, calibration was made by adding known amounts of authentic material to the sample being analysed.) For case (ii), water was added, the ethereal layer was separated, and the aqueous layer washed with a small volume of ether. After acidification of the aqueous phase with ice-cold 0.2N-HCl, it was extracted with ether several times; the collected ethereal portions were washed once with water, dried, and evaporated. The residues were analysed by n.m.r. spectroscopy, and for entries 5 and 8 subjected to recrystallization from ethanol–water. The results are presented in the Table. *2,5-Dimethoxy-4-methylthiophen-3-carboxylic acid*, m.p. 150 °C (decomp.), had $\nu_{max.}$ (KBr) 3 600—2 000 (OH) and 1 670 (CO) cm^{-1}; δ ([$^2H_6$]acetone) 3.97 (3 H, s, OMe), 3.83 (3 H, s, OMe), and 2.13 (3 H, s, Me); *m/e* 202 (M^+) (Found: C, 47.5; H, 5.01; S, 15.9. $C_8H_{10}O_4S$ requires C, 47.5; H, 4.98; S, 15.9%).

1-Methylthio-octa-1,3-diyne (3).—This compound was synthesized according to the method for 1-methylthiopenta-1,3-diyne [10] from 1,4-dichlorobut-2-yne (67% yield), b.p. 96—97° at 11 mmHg; $\nu_{max.}$ (film) 2 220 (C≡C cm^{-1}; δ ([$^2H_6$]acetone) 2.41 (3 H, s, SMe), 2.32 (2 H, t, *J* 6.5 Hz, CH_2), 1.40 (4 H, m, CH_2CH_2), and 0.88 (3 H, t, *J* 6.5 Hz, Me); *m/e* 152 (M^+) (Found: C, 70.8; H, 7.9; S, 21.0. $C_9H_{12}S$ requires C, 71.0; H, 7.95; S, 21.0%).

2,5-Di-iodo-3-methylthiophen.—A mixture of 3-methylthiophen (98 g, 1.0 mol), acetic acid (640 ml), water (240 ml), carbon tetrachloride (160 ml), concentrated sulphuric acid (11 ml), iodine (163 g), and iodic acid (65.6 g) was refluxed for 4 h with stirring. The decolourized mixture was poured onto ice–water and the organic layer washed with aqueous sodium thiosulphate and water, dried, and the solvent evaporated. The residue was distilled to give 224 g (64%) of the title compound, b.p. 137—140° at 2.5 mmHg (lit.,[11] 120.8—121° at 2.5 mmHg); δ ([$^2H_6$]acetone) 7.02 (1 H, s, ArH) and 2.19 (3 H, s, Me); *m/e* 350 (M^+) (Found: C, 17.2; H, 1.1. $C_5H_4I_2S$ requires C, 17.2; H, 1.15%).

2,5-Dimethoxy-3-methylthiophen.—To a solution of sodium methoxide [3.40 mol (from 76 g of sodium)] in methanol (600 ml) in the presence of cupric oxide (38 g, 0.43 mol), 2,5-di-iodo-3-methylthiophen (105 g, 0.300 mol) was added. The mixture was refluxed for 4 days, filtered, and poured into water–ether. The organic layer was separated and the aqueous layer extracted with ether. The ethereal phases were washed with water and dried, and the solvent evaporated. Combined g.l.c.–mass spectrometric analysis of the crude product showed that an iodomethoxy-3-methylthiophen was present to a minor extent. This contaminant was removed by treating the crude product with a calculated amount of butyl-lithium at −70 °C followed by solid carbon dioxide. Thus, the iodomethoxy-3-methylthiophen derivative was converted into a carboxylic acid and was removed by washing the hydrolysed reaction mixture with aqueous K_2CO_3. The resulting organic neutral phase was washed with water, dried, and evaporated. The residue was distilled in the presence of a few grains of K_2CO_3 to give *2,5-dimethoxy-3-methylthiophen* (15.8 g, 30%), b.p. 105° at 22 mmHg; δ ([$^2H_6$]acetone) 5.74 (1 H, s, ArH), 3.78 (3 H, s, OMe), 3.75 (3 H, s, OMe), and 1.94 (3 H, s, Me); *m/e* 158 (M^+) (Found: C, 52.9; H, 6.34; S, 19.5. $C_7H_{10}O_2S$ requires C, 53.1; H, 6.37; S, 20.3%).

3-Bromo-2,5-dimethoxy-4-methylthiophen.—To 2,5-dimethoxy-3-methylthiophen (3.16 g, 0.020 0 mol) in CCl_4 (200 ml) was added *N*-bromosuccinimide (3.56 g, 0.020 0 mol) at room temperature. After 18 h, the mixture was filtered, washed with water, dried, and evaporated to give the title compound (4.26 g, 89%) as a light yellow oil, which according to combined g.l.c.–mass spectrometric analysis was pure. The compound is unstable under ordinary conditions and could not be distilled. Instead, it was immediately dissolved in ether and this solution was used as soon as possible; δ ([$^2H_6$]acetone) 3.87 (3 H, s, OMe), 3.82 (3 H, s, OMe), and 1.96 (3 H, s, Me); *m/e* (%) 238/236 (43/43%, M^+) and 223/221 (100/98, $M^+ - 15$).

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