

Directed Metallation of Certain Thiophen Compounds

By D. W. SLOCUM* and P. L. GIERER

(Department of Chemistry, Southern Illinois University, Carbondale, Illinois 62901)

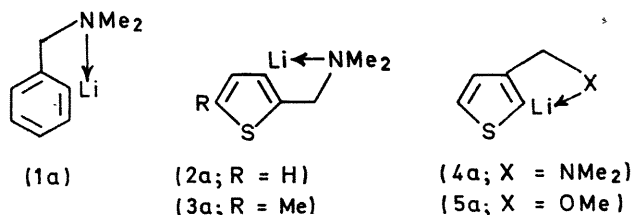
Summary Lithiation of certain thiophen compounds has been found useful as a synthetic tool when the lithium atom can be directed to a specific ring position by the substituent; condensation of the lithiated intermediate with a variety of electrophilic reagents gave a number of specifically substituted thiophens.

A RECENT review has discussed the difficulties involved in the preparation of bi- and tri-functional thiophens.¹ The 2,5-disubstituted compounds are easily synthesised and, recently, routes to 2,4-compounds have been discovered. We report a route to 2,3-disubstituted and 2,3,5-trisubstituted thiophens, a method which may be extendable to other heterocyclic systems.

Directed metallation of *NN*-dimethylbenzylamine,² its ferrocene analogue,³ and a number of related amines followed by condensation with electrophilic reagents has yielded a variety of aromatic amines substituted exclusively in the 2-position. Recently, similar results were reported for the lithiation of methoxymethylferrocene,⁴ thereby establishing that an ether function can direct metallation. We now describe examples of amine- and ether-directed lithiations of certain thiophen derivatives.

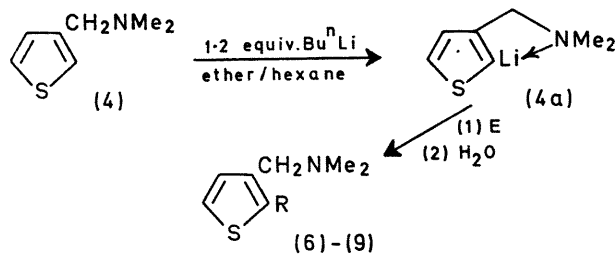
Directed lithiation intermediates have been described using a co-ordinate lithium-nitrogen bond²⁻⁴ as shown in

(1a). Such an intermediate could not be realized for *NN*-dimethyl-2-thenylamine (2) without blocking the 5-position, *i.e.*, stabilization of the lithio-species at the 5-position by the sulphur atom was greater than stabilization of the 3-lithio-intermediate (2a) by nitrogen co-ordination. The ease of metallation of the 2-position in thiophens is well documented.⁵ However, for 5-methyl-*NN*-dimethyl-2-thenylamine, lithiation of the 3-position was easily



effected. Further, the corresponding 3-substituted compounds, *NN*-dimethyl-3-thenylamine and 3-thenyl methyl ether, were found to be exclusively lithiated in the 2-position, presumably *via* lithio-intermediates (4a) and (5a) respectively.

NN-Dimethyl-3-thenylamine was treated with 1.2 equiv. of *n*-butyl-lithium in ether-hexane followed by condensation with D₂O, dimethylformamide, benzophenone, and benzonitrile to give the corresponding 2-substituted derivatives (6)–(9) (Scheme 1, Table) in yields of 80, 75, 66, and 54%, respectively. The n.m.r. spectrum of the deuterated compound (6) exhibited absorption at δ (CDCl₃) 7.26 (1H, d, 5-H), 7.04 (1H, d, 4-H), 3.43 (2H, s, CH₂), and 2.21 p.p.m. (6H, s, 2CH₃). The value of the coupling constants of the ring protons (about 5.0 Hz) substantiated the indicated disposition of the ring protons and hence the ring substituents.⁶ Similarly, the n.m.r. spectra of (7)–(9) supported their assigned structures.



3-Thenyl methyl ether (5) could also be lithiated in the 2-position as shown by condensation of the lithio-intermediate (5a) with dimethylformamide and dimethyl disulphide to produce the corresponding 2-substituted aldehyde (10) and the 2-substituted methyl sulphide (11) in 72 and 61% yields, respectively. The structures assigned to these compounds were based on n.m.r. spectra and elemental analyses.

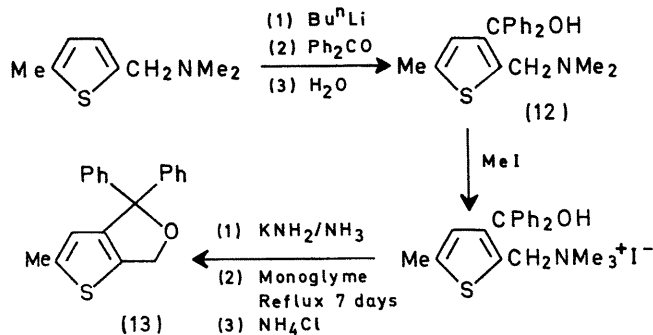
TABLE

Compound	E (electrophile)	R (substituent)
(6)	D ₂ O	D
(7)	HCONMe ₂	CHO
(8)	(Ph) ₂ CO	(Ph) ₂ COH
(9)	PhCN	PhCO

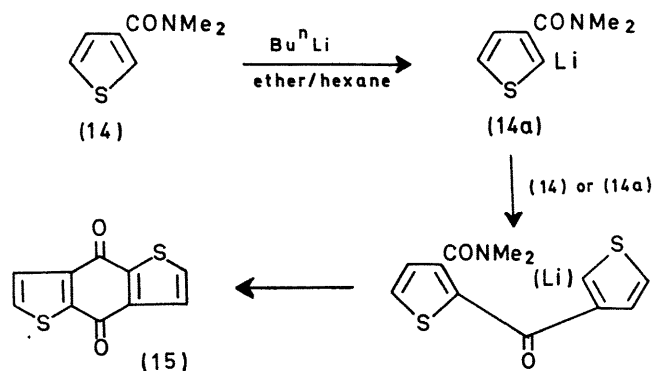
Directed metallation was also demonstrated in 5-methyl-*NN*-dimethyl-2-thenylamine (3). The reaction between this compound and *n*-butyl-lithium followed by condensation of the resulting 3-lithio-intermediate (3a) with benzophenone gave the 3-substituted diphenylmethanol (12) in 65% yield. I.r., n.m.r., and elemental analyses were all in accord with the assigned structure.

Conclusive evidence that the site of metallation in amine (3) was the 3-position was obtained from the cyclization

reaction shown in Scheme 2. (13) had analytical data which supported its assigned structure.



In an attempt to extend these results to thiophenecarboxamides,⁷ *NN*-dimethyl-3-thenylcarboxamide (14) was metallated for 12 h with *n*-butyl-lithium in ether-hexane. Condensation products could not be isolated from this solution. Instead, the lithio-intermediate formed, presumably (14a), condensed with itself or with a molecule of carboxamide (14), to form the unknown quinone (15) (Scheme 3). The product was deduced to have structure (15) based on the following data: ¹H n.m.r. spectrum exhibited two equivalent doublets at δ (C₆D₆) 7.21 and 6.61 p.p.m. (*J*_{2,3} 5 Hz),⁶ *M*⁺ = 220 and elemental analysis.



The configuration shown in (15) is the most likely based on Scheme 3.

(Received, September 16th, 1970; Com. 1581.)

¹ J. L. Gol'dfarb, Ju. B. Volkenstein, and L. J. Belenkij, *Angew. Chem. Internat. Edn.*, 1968, 7, 519.

² F. N. Jones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, 1963, 28, 663; F. N. Jones, R. L. Vaulx, and C. R. Hauser, *ibid.*, p. 3461.

³ D. W. Slocum, B. W. Rockett, and C. R. Hauser, *Chem. and Ind.*, 1964, 1831; D. W. Slocum, B. W. Rockett, and C. R. Hauser, *J. Amer. Chem. Soc.*, 1965, 87, 1241.

⁴ D. W. Slocum and B. P. Koonsvitsky, *Chem. Comm.*, 1969, 846.

⁵ S. Gronowitz, *Adv. Heterocyclic Chem.*, 1963, 1, 73.

⁶ S. Gronowitz, *Arhiv Kemi*, 1960, 16, 563.

⁷ W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, 1964, 29, 853.