Directed Metallation of Certain Thiophen Compounds

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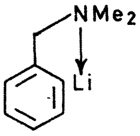
Summary Lithiation of certain thiophen compounds has been found useful as a synthetic tool when the lithium atom can be directed to a specific ring position by the substituent; condensation of the lithiated intermediate with a variety of electrophilic reagents gave a number of specifically substituted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

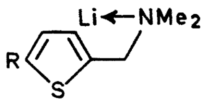
A RECENT review has discussed the difficulties involved in the preparation of bi- and tri-functional thiophens.[1] The 2,5-disubstituted compounds are easily synthesised and, recently, routes to 2,4-compounds have been discovered. We report a route to 2,3-disubstituted and 2,3,5-trisubstituted thiophens,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

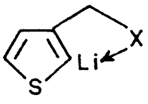
Directed lithiation intermediates have been described using a co-ordinate lithium–nitrogen bond[2–4] as shown in (**1a**). Such an intermediate could not be realized for *NN*-dimethyl-2-thenylamine (**2**) without blocking the 5-position, *i.e.*, stabilization of the lithio-species at the 5-position 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.



(1a)

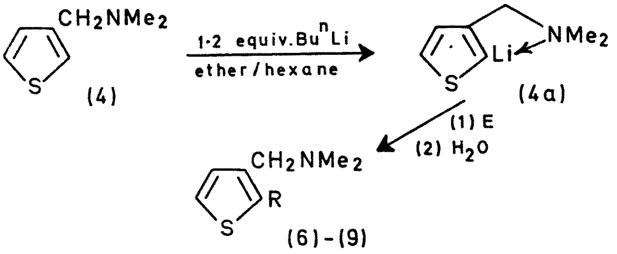


(2a; R = H)
(3a; R = Me)



(4a; X = NMe2)
(5a; X = OMe)

NN-Dimethyl-3-thenylamine was treated with 1·2 equiv. of n-butyl-lithium in ether–hexane followed by condensation with D_2O, 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 deuteriated compound (**6**) exhibited absorption at δ ($CDCl_3$) 7·26 (1H, d, 5-H), 7·04 (1H, d, 4-H), 3·43 (2H, s, CH_2), and 2·21 p.p.m. (6H, s, $2CH_3$). 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.



SCHEME 1

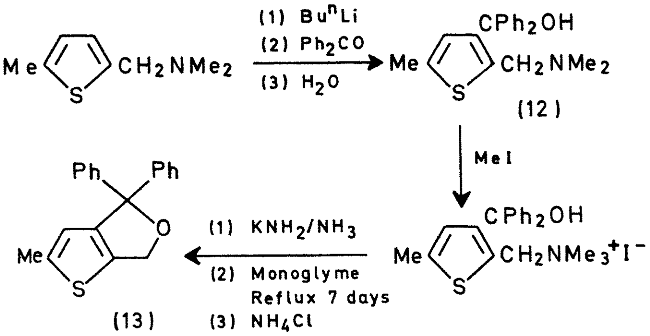
3-Thenyl methyl ether (**5**) could also be lithiated in the 2-position as shown by condensation of the lithio-intermediate (**5a**) with dimethylformamide and dimethyl disulphide to produce the corresponding 2-substituted aldehyde (**10**) and the 2-substituted methyl sulphide (**11**) in 72 and 61% 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_2O	D
(**7**)	$HCONMe_2$	CHO
(**8**)	$(Ph)_2CO$	$(Ph)_2COH$
(**9**)	PhCN	PhCO

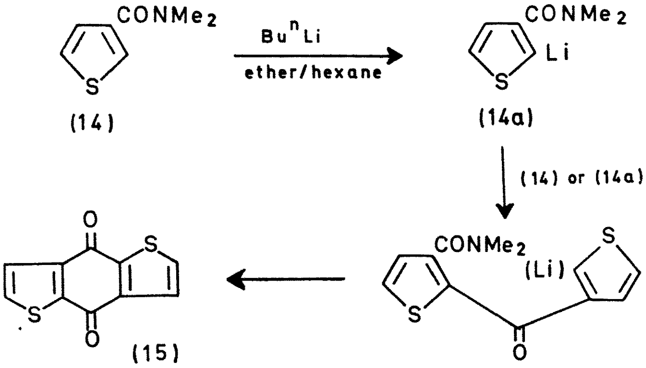
Directed metallation was also demonstrated in 5-methyl-*NN*-dimethyl-2-thenylamine (**3**). The reaction between this compound and n-butyl-lithium followed by condensation of the resulting 3-lithio-intermediate (**3a**) with benzophenone gave the 3-substituted diphenylmethanol (**12**) in 65% yield.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



SCHEME 2

In an attempt to extend these results to thiophen carboxamides,[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 (C_6D_6) 7·21 and 6·61 p.p.m. ($J_{2,3}$ 5 Hz),[6] $M^+ = 220$ and elemental analysis.



SCHEME 3

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

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

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