(5) (a) D. A. Shirley, J. R. Johnson, Jr., and J. P. Hendrix, *J. Organomet. Chem.*, **11**, 209 (1968); (b) *ibid.*, **11**, 217 (1968); (c) T. E. Harmon and D. A. Shirley, *J. Org. Chem.*, **39**, 3164 (1974).
(6) R. A. Finnegan and J. W. Altschuld, *J. Organomet. Chem.*, **9**, 193 (1967).
(7) D. W. Slocum, B. P. Koonsvitsky, and C. R. Ernst, *J. Organomet. Chem.*, **38**, 125 (1972).
(8) (a) B. M. Graybill and D. A. Shirley, *J. Organomet. Chem.*, **31**, 443 (1968); (b) D. A. Shirley and C. F. Cheng, *ibid.*, **20**, 251 (1970); (c) H. Gilman, C. E. Arntzen, and F. J. Webb, *J. Org. Chem.*, **10**, 374 (1945); (d) S. V. Sunthankar and H. Gilman, *ibid.*, **16**, 8 (1951).
(9) D. W. Slocum and B. P. Koonsvitsky, *J. Org. Chem.*, **38**, 1675 (1973).
(10) S. I. Goldberg, L. H. Keith, and T. S. Prokopov, *J. Org. Chem.*, **28**, 850 (1963).
(11) (a) D. W. Slocum, B. W. Rockett, and C. R. Hauser, *J. Am. Chem. Soc.*, **87**, 1241 (1965); (b) D. W. Slocum, C. A. Jennings, T. R. Engelmann, B. W. Rockett, and C. R. Hauser, *J. Org. Chem.*, **36**, 377 (1971).
(12) D. W. Slocum and F. E. Stonemark, *J. Org. Chem.*, **38**, 1677 (1973).
(13) D. W. Slocum and B. P. Koonsvitsky, *Chem. Commun.*, 846 (1969).
(14) B. P. Valkovich, G. W. Gokel, and I. K. Ugi, *Tetrahedron Lett.*, 2947 (1973).
(15) P. Smith, J. J. McLesky, III, and D. W. Slocum, *J. Org. Chem.*, **30**, 4359 (1965).
(16) M. Rosenblum, Ph.D. Thesis, Harvard University, 1953; M. Rosenblum, *Chem. Ind. (London)*, 953 (1958).
(17) For a related example, cf. D. W. Slocum and T. R. Engelmann, *J. Organomet. Chem.*, **24**, 753 (1970).
(18) Yu. A. Ustynyuk, E. G. Perevalova, and A. N. Nesmeyanou, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1**, 70 (1964).
(19) For further discussion of this point, cf. ref 3d, pp 389–390.
(20) D. W. Slocum, B. Silverman, B. W. Rockett, and C. R. Hauser, *J. Org. Chem.*, **30**, 4356 (1965).
(21) Mention must be made here that Valkovitch et al.[14] also metalated ether **6** with *n*-butyllithium and have reported isolation of significant yields of all three possible ring metalated derivatives upon condensation with benzophenone. Such discrepancy in yields from the same metalated intermediate is not as unusual as it may seem. We are prompted to report here some unpublished studies[22] involving carbonation of commercial phenyllithium (Ventron Corp.). Repeated attempts to effect this carbonation, either by bubbling CO_2 through the phenyllithium or by pouring the phenyllithium solution over dry ice/ether, afforded only low yields of benzoic acid (<20%). On the other hand, condensation of this same phenyllithium solution with benzophenone under various conditions brought routinely yields of 60–70% of triphenylcarbinol. A similar study by Gilman and co-workers[23] has been published.
(22) W. Achermann, S. Ulrich, and D. W. Slocum, unpublished results.
(23) R. C. Edmondson, A. E. Jukes, and H. Gilman, *J. Organomet. Chem.*, **25**, 273 (1970).
(24) D. W. Slocum and W. Jones, *J. Organomet. Chem.*, **15**, 262 (1968).
(25) W. P. Fitzgerald, Jr., *Diss. Abstr.*, **24**, 2687 (1964).

Directed Metalation Reactions. 8.[1] Directed Metalation of 3-Mono- and 2,5-Disubstituted Thiophenes

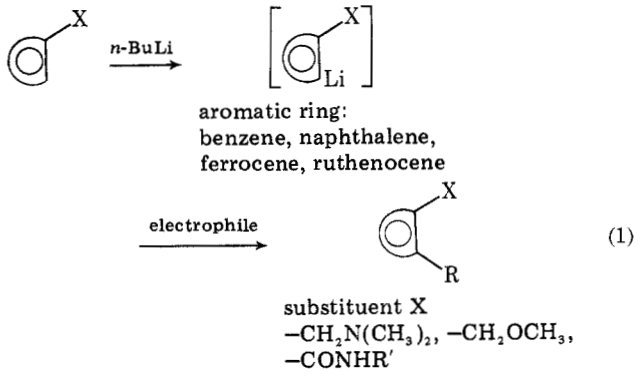
D. W. Slocum*[2] and P. L. Gierer

Neckers Laboratory, Southern Illinois University, Carbondale, Illinois 62901

Received August 13, 1974

Regiospecific 2 metalation of thiophene has long been known. In this study we have examined the metalation with *n*-butyllithium of thiophenes containing a substituent that directs metalation such that a competition between the directing properties of the sulfur and the substituted group was set up. Results were as follows: (1) 2-Substituted thiophenes were lithiated in the 5 position, i.e., the sulfur atom controlled the site of metalation; (2) if the 5 position was blocked, 3 lithiation was observed; (3) 3-substituted thiophenes were lithiated in the 2 position, a site common to the directing properties of both the substituent and the sulfur moiety. Each of these metalations was surprisingly regiospecific. These lithiation pathways were explored via a number of derivatization and cyclization experiments and can be utilized in the synthesis of a wide variety of 2,3-disubstituted thiophenes. An intriguing dimerization of *N,N*-dimethyl-3-thiophenecarboxamide (**5**) in the presence of *n*-butyllithium to 4,8-dehydrobenzo[1,2-*b*:4,5-*b*′]dithiophene-4,8-dione (**5a**) was discovered.

Directed metalation of *N,N*-dimethylbenzylamine,[3] its ferrocene analogue,[4] and a number of related amines with subsequent treatment with electrophilic reagents has provided a general route to a variety of aromatic amines substituted exclusively in the 2 position.[5] In the preceding paper of this series[1] similar results are recorded for the directed lithiation of methoxymethylferrocene, thereby establishing unequivocally that the ether analogue of the dimethylaminomethyl group can also direct metalation. The 2-metalating ability of the N-substituted carboxamide group on benzene[6] and ferrocene[7] has also been reported. A generalized picture of these transformations is summarized in eq 1.



(1)

The ability of the directed metalation reaction to produce ortho-disubstituted products uncontaminated by other isomers would possess significant synthetic potential for other aromatic systems, notably heterocycles. In this study the utility of this method for the preparation of specific di- and trisubstituted thiophenes is described. These results can be contrasted to those for the electrophilic substitution of thiophenes. Generally for 2-substituted thiophenes, varying amounts of 2,5- or 2,4-disubstituted compounds are obtained depending on the competitive directing influence of the ring sulfur and the 2 substituent.[8] The yield of 2,3-disubstituted thiophenes is improved somewhat for 3-substituted compounds containing ±I + M substituents. For example, 3-methylthiophene gives upon acylation a mixture consisting of 80% 3,2 isomer and 20% 3,5 isomer.[9]

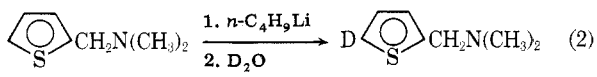
Ideally, directed metalation of a 2-substituted thiophene to give a 3-lithio intermediate would be most desirable, since 2-substituted thiophenes are much more readily available as starting materials. In no instance during this study was this lithiation pattern for 2-substituted thiophenes realized; rather 5 metalation was observed. This suggests that the thiophene sulfur is a stronger director than the carboxamide and dimethylaminomethyl groups, which are among the strongest directors known.[10] Likewise the 2-alkylsulfonamides were found to be weaker directors than the thiophene sulfur, although other reactions at times ensued upon metalation of

N,N-dialkyl-2-thiophenesulfonamides.[11] Blocking the 5 position with an alkyl group or a trimethylsilyl group served to eliminate competition by the 5 position and 3 lithiation was then observed for several 2,5-disubstituted thiophenes. Interestingly, a recent communication[12] has described 3 lithiation of thiophene in 2-(2′-thienyl)pyridine, a surprising observation in view of the results described herein.

For several substituents in the 3 position of thiophene, directed lithiation to the 2 position in high yield was observed.

Results and Discussion

The compound *N,N*-dimethyl-2-thenylamine (2-DTA, **1**) was initially chosen for this study since the dimethylaminomethyl substituent was a well-known director and was easily attached to the thiophene nucleus. However, metalation of this amine followed by condensation of its lithio intermediate with D_2O afforded an 88% recovery of what was found to be 5-deuterio-2-DTA (**1a**) (eq 2). Presumably, interaction



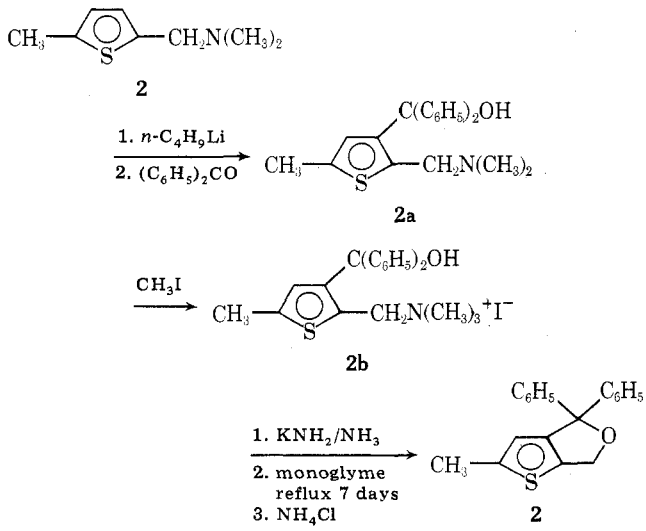
(2)

1 1a

between the coordinating nitrogen and the lithium atom must be less important than factors tending to favor substitution adjacent to the sulfur atom. The reactivity of the 5 position in 2-substituted thiophenes has been demonstrated by the fact that 2-alkyl-,[13,14] 2-methoxy-,[14,15] 2-alkylthio-,[16] and 2-alkylsulfonamide[11] derivatives of thiophene are known to undergo metalation in the 5 position. 5-Methyl- (**2**), 5-trimethylsilyl- (**1b**), and 5-formyl-2-DTA (**1c**) were also prepared by 5 lithiation (cf. Experimental Section).

Introduction of a blocking methyl group into the 5 position of 2-DTA to give 5-methyl-2-DTA (**2**) allowed directed lithiation in the 3 position to be easily effected. Metalation of 5-methyl-2-DTA with *n*-butyllithium followed by condensation with benzophenone gave a 65% yield of 5-methyl-3-diphenylhydroxymethyl-2-DTA (**2a**). The orientation of substituents in compound **2a** was verified by cyclization to the phthalan derivative **2c** via treatment of the methiodide **2b** with KNH_2 in liquid ammonia (Scheme I). Ir, NMR, and elemental analytical data supported the structure assigned phthalan **2c**.

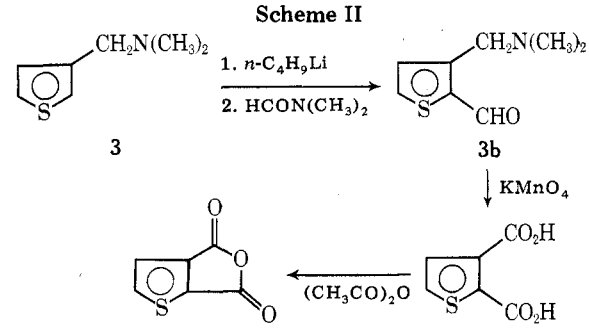
Scheme I



This result suggested a modified route to 2,3-disubstituted thiophenes via directed metalation of appropriate 2,5-disubstituted thiophenes where one substituent was a metalation director and the other was not and in addition could be reversibly removed. Such a removable substituent might be the trimethylsilyl group which is easily cleaved in aromatic systems upon treatment with strong acids.[17] 5-Trimethylsilyl-2-DTA (**1b**) was prepared, treated with *n*-butyllithium, and condensed with benzophenone; however, no condensation product was obtained. Failure of such a stratagem to provide a general route to 2,3-disubstituted thiophenes has also been reported for 5-trimethylsilyl-2-*N,N*-dialkyl thiophenesulfonamides.[11]

With these unsuccessful attempts to prepare 2,3-disubstituted thiophenes a switch in emphasis to the study of the directed metalation of a number of 3-substituted thiophenes was undertaken. Lithiation of *N,N*-dimethyl-3-thenylamine (3-DTA, **3**) with *n*-butyllithium followed by condensation of the lithio intermediate with dimethylformamide gave a 75% yield of 2-formyl-3-DTA (**3b**) (Scheme II). The orientation

Scheme II



of substituents in compound **3b** was confirmed by their oxidation with $KMnO_4$ to give the known 2,3-thiophenedicarboxylic acid[18] in 21% yield. Cyclization of this diacid with acetic anhydride gave the 2,3-anhydride, also a known compound[18] (Scheme II). An NMR spectrum of compound **3b** gave a well-resolved AB pattern for the two ring protons. The coupling constant for these protons was 5.0 Hz which falls in the region observed for a large number of 2,3-disubstituted thiophenes.[19] Spin–spin coupling of 1.0 Hz was also observed between the side-chain hydrogen of the aldehyde group and the 5-position ring proton. Studies by Gronowitz have shown that various 2-thiophenecarboxaldehydes possess a $J_{CHO\text{-}H_5}$ = 1.05–1.40 Hz.[19]

The exclusive 2 lithiation observed for 3-DTA indicated that nitrogen coordination with the metalating agent reenforces ring sulfur coordination. At present, one can only speculate at what stage of the metalation reaction nitrogen coordination becomes important or what is the structure of the coordinated species. A complex of the organolithium tetramer and 3-DTA containing a pseudo-six-membered chelated ring could conceivably be formed by transfer of the hydrogen at the 2 position of 3-DTA to a coordinated *n*-butyl group (Scheme III). Some inferential evidence for coordination of 3-DTA with butyllithium has recently been provided by Wiswanathan and Wilkie.[20]

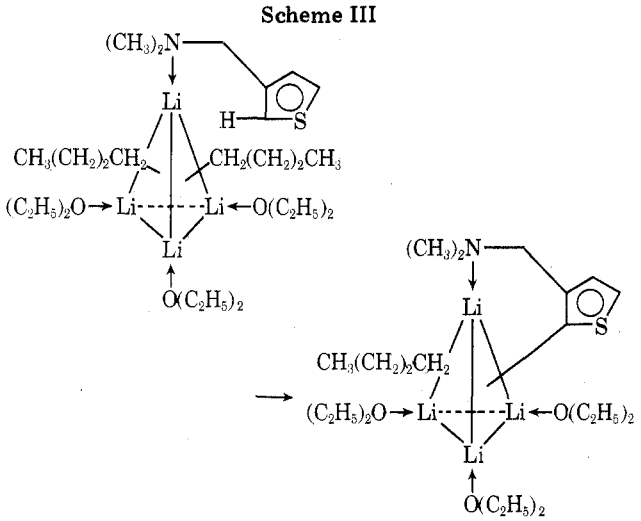
2-Lithio-3-DTA was also treated with D_2O, benzophenone, benzonitrile, *p*-toluenesulfonyl chloride, and *p*-toluenesulfonyl bromide to form 2-deuterio- (**3c**), 2-diphenylhydroxymethyl- (**3a**), 2-benzoyl- (**3d**), 2-chloro- (**3e**), and 2-bromo- (**3f**) 3-DTA, respectively. Physical and spectral data for these compounds are summarized in Tables I and II, respectively (see paragraph at end of paper regarding supplementary material). NMR spectra of these products with the exception of that for the 2-benzoyl derivative exhibited well-resolved AB patterns for the two thiophene ring protons. The coupling constant of these protons in each case was 5 Hz, exactly that observed for a large number of 2,3-disubstituted thiophenes.[19] For 2-benzoyl-3-DTA (**3d**) a resolved AB pattern for the thiophene ring protons was not observed owing to overlap with

Table I. Physical Data of Substituted Thiophenes[c]

Registry no.	Compd	% yield	Mp or bp, °C (mm)	Purification[a]
59906-28-4	**1b**	71	bp 65–67 (0.9)	
59906-29-5	**1c**	40	bp 95–104 (2.5)	
19260-96-9	**2**	86	108–110	B
59906-30-8	**2a**	65	117–118	A (100% ethanol)
59906-31-9	**2b**	98	194	A (100% ethanol)
32281-35-9	**2c**	45	117–119	A (1005 ethanol)
22601-13-4	**3**	42	bp 28–32 (0.12)	
32281-32-6	**3a**	67	88–88.5	A (50:50 petroleum ether/ether,
32281-31-5	**3b**	75	bp 62–63 (0.03)	100% ethanol)
32281-33-7	**3d**	54	bp 122–124 (0.5)	
59906-32-0	**3e**	25	bp 31–32 (0.6)	
59906-33-1	**3f**	32	bp 59–60 (1.3)	
53229-44-0	**4**	38	bp 26 (0.2)	
59906-34-2	**4a**	46	102–104	A (100% ethanol)
59906-35-3	**4b**	54	bp 122–124 (0.5)	
59906-36-4	**4c**	61	bp 65–68 (0.03)	
59906-37-5	**5**	6.7[b]	bp 89–90 (0.5)	
32281-36-0	**5a**	41	258–260	C (150 °C)
59906-38-6	**6**	13	115–117	A (100% ethanol)
59906-39-7	**6a**	55	107–110	
59906-40-0	**6b**	23	172.5–173 dec	A (50:50 methanol/THF)

[a] Purification methods: A, recrystallization (solvent); B, steam distillation; C, sublimation (temperature). [b] Overall yield in five synthetic steps. [c] Satisfactory analytical data (±0.3% for C, H, and in some cases for N, S, and O) were obtained for compounds **1b, 1c, 2a, 2b, 2c, 3, 3a, 5a, 6,** and **6b** with the following exceptions: **1c,** S, 19.04 (19.39); **2b,** C, 55.04 (54.66), H, 5.95 (5.42); **2c,** C, 77.67 (78.05), O, 5.86 (5.47); **3a,** N, 4.53 (4.15). Elemental analyses were not obtained for the remaining compounds.

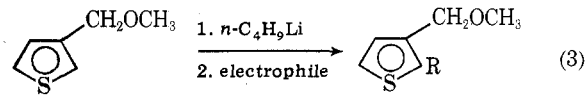
Scheme III



the phenyl proton signals. However, indirect evidence for the site of the benzoyl substituent in **3b** was obtained from the observed downfield shift of the methylene resonance from τ 7.03 in 3-DTA to τ 6.40 in **3b.** This large downfield shift would only be explicable if the benzoyl group were adjacent to the dimethylaminomethyl (DMAM) group. From the metalation patterns observed thus far for thiophenes, the benzoyl group must be positioned at the far more reactive 2 position.

Of interest was the fact that the NMR spectrum of the benzophenone condensation product **3a** exhibited a two-proton methylene resonance at τ 7.03 (upfield τ 0.45 from the methylene singlet in 3-DTA) and a six-proton methyl singlet of the two amine methyls at τ 7.92 (upfield τ 0.09 from the same group in 3-DTA). These upfield shifts can be attributed to the anisotropic effect arising from the geminal phenyl groups situated adjacent to the DMAM group and are diagnostic of the assigned substitution pattern.[10,21]

With the excellent directing ability of the DMAM group in the 3 position of thiophene successfully demonstrated, it was anticipated that the oxygen analogue would similarly coordinate with *n*-butyllithium to afford significant concentrations of an oxygen-directed 2-lithiothiophene. This was realized in the case of 3-thenylmethyl ether (3-TME, **4**). Metalation of 3-TME followed by condensation with benzophenone, dimethylformamide, and dimethyl disulfide afforded good yields of compounds **4a, 4b,** and **4c,** respectively (eq 3).



(3)

4

4a, R = $C(C_6H_5)_2OH$
b, R = CHO
c, R = SCH_3

Physical and spectral data for these compounds are summarized in Tables I and II (see paragraph at end of paper regarding supplementary material). NMR spectra of **4b** and **4c** exhibited well-resolved AB patterns for the two thiophene ring protons.[19] The values of J_{AB}, in each case ca. 5.0 Hz, i.e., that expected for 2,3 disposition of the ring protons, substantiated the indicated substitution pattern of the substituents. For 2-diphenylhydroxymethyl-3-TME the thiophene ring proton resonances were obscured by the phenyl resonances but these same phenyls produced the expected anisotropic effect[21] upon the adjacent methoxymethyl substituent. The methylene protons in **4a** exhibited a resonance at τ 6.00 (upfield τ 0.45 from the methylene resonance in 3-TME). Interestingly, this chemical shift difference is exactly that found between 2-diphenylhydroxymethyl-3-DTA (**3a**) and 3-DTA (**3**) itself. The terminal methyl resonance was shifted from τ 6.63 in the 3-TME to τ 6.92 in 2-diphenylhydroxymethyl-3-TME (Δ = 0.29 τ).

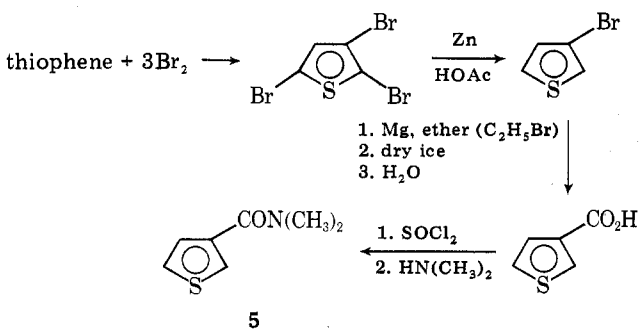
In an attempt to extend these results, *N,N*-dimethyl-3-thiophenecarboxamide (3-DTC, **5**) was prepared and metalated. Before considering the results of its metalation, its multistep synthesis deserves some attention. One of the most suitable methods for preparing 3-substituted thiophenes is that based on the use of 3-bromothiophene. The synthetic route utilized is illustrated in Scheme IV.

A preliminary metalation of 3-DTC followed by hydrolysis

Table III. Experimental Conditions for the Metalation of Various Substituted Thiophenes

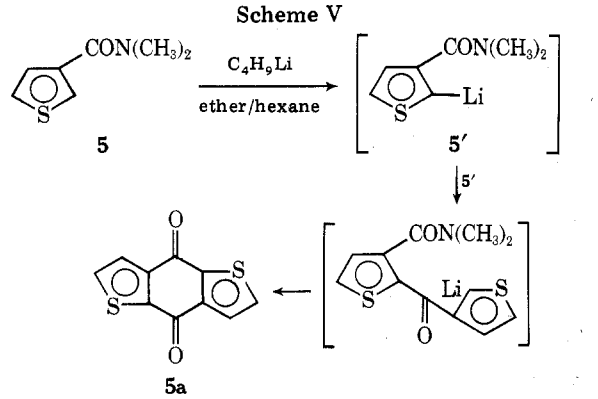
Compd	Substrate:*n*-BuLi: condensing agent	Substituent	Condensing agent (E)	Metalation period, h	Condensation period, h	Temp, °C
1a	1:1:8	2-CH_2NMe_2	D_2O	7	0.5	25–35 (ambient)
1b	1:1.2:1.7	2-CH_2NMe_2	Me_3SiCl	1	12	25–35 (ambient)
1c	1:1.2:1.8	2-CH_2NMe_2	$CHONMe_2$	12	12	25–35 (ambient)
2a	1:10:10	2-CH_2NMe_2; 5-Me	Ph_2CO	4	0.5	25–35 (ambient)
3a	1:1.2:1	3-CH_2NMe_2	Ph_2CO	1	4	25–35 (ambient)
3b	1:1.2:1	3-CH_2NMe_2	$CHONMe_2$	1	5	25–35 (ambient)
3c	1:1.2:6	3-CH_2NMe_2	D_2O	4	1	25–35 (ambient)
3d	1:1.1:1.1	3-CH_2NMe_2	PhCN	1	12	25–35 (ambient)
3e	1:1:1	3-CH_2NMe_2	*p*-$C_7H_7SO_2Cl$	1	3	−70
3f	1:1.2:1.4	3-CH_2NMe_2	*p*-$C_7H_7SO_2Br$	1	3	−70 warm to 25
4a	1:1.2:1.2	3-CH_2OMe	Ph_2CO	1	12	25–35 (ambient)
4b	1:1.1:2	3-CH_2OMe	$CHONMe_2$	1	12	25–35 (ambient)
4c	1:1.1:2	3-CH_2OMe	Me_2S_2	1.5	5	25–35 (ambient)
6a	1:2.4:10	3-COHNMe	D_2O	1	0.25	25–35 (ambient)
6b	1:2.1:1.2	3-CONHMe	Ph_2CO	3	7	25–35 (ambient)

Scheme IV



5

Scheme V



5a

failed to return the original carboxamide. Instead, the lithio intermediate formed, presumably **5′**, condensed with itself to form 4,8-dehydrobenzo[1,2-*b*:4,5-*b*′]dithiophene-4,8-dione (**5a**) (Scheme V). The product was deduced to have the structure shown based on the following data: (1) molecular weight and elemental analysis were in accord with theory; (2) its NMR spectrum exhibited two equivalent doublets for the ring protons at τ 2.79 and 3.39 with a coupling constant of 5.0 Hz.[19] In addition a paper published after this work was completed has reported an independent synthesis of this quinone.[22]

With the failure of the 3-*N*,N-dimethylcarboxamide group to effect utilizable metalation in the 2 position of thiophene, our attention was turned to the possible use of the *N*-methylcarboxamide group, for which there was ample precedent in other systems.[6,7] It was anticipated that this substituent would initially undergo N-metalation with *n*-butyllithium thus deactivating the carbonyl group toward nucleophilic attack. 2-Lithiation by a second equivalent of *n*-butyllithium might then be realized. Metalation of *N*-methyl-3-thiophenecarboxamide (3-MTC, **6**) with 2.2 equiv of base followed by hydrolysis with deuterium oxide gave a 55% recovery of 2-deuterio-3-MTC (**6a**). An NMR spectrum of the product showed an AB pattern for the two ring protons with J_{AB} = 5.0 Hz. In the spectrum of 3-MTC itself the downfield proton resonance centered at τ 2.13 can be reasonably assigned to the proton adjacent to both the sulfur atom and the carbonyl. This resonance was not detectable in the product **6a** indicating incorporation of one atom of deuterium at the 2 position of 3-MTC.

Condensation of 2-lithio-3-MTC with benzophenone afforded a 23% yield of 2-diphenylhydroxymethyl-3-MTC (**6b**). The compound's structure was supported by both ir and NMR evidence. The location of the diphenylhydroxymethyl substituent in the 2 position in this molecule can, in addition to being inferred by the previously described deuteration experiment, be substantiated by the upfield shift (τ 0.29) of the methyl group in this compound vs. that of the unsubstituted amide, 3-MTC.[21]

Experimental Section

General. All lithiation reactions were run under dry nitrogen or argon. *n*-Butyllithium (1.6 M in hexane) was purchased from Foote Mineral Co. *N,N,N′N′*-Tetramethylethylenediamine (TMEDA) was obtained from Aldrich Chemical Co. and stored over KOH pellets. Ethers used as reaction solvents were Matheson Coleman and Bell "absolute" grade which was stored over Linde 3A molecular sieves or sodium metal and tetrahydrofuran (THF) which was distilled from lithium aluminum hydride immediately before use. Aldrich Chemical Co. was the supplier of thiophene and 3-methylthiophene. *N*-Bromosuccinimide and benzoyl peroxide were purchased from Matheson Coleman and Bell. The former reagent was recrystallized from H_2O immediately before use. Condensing reagents (benzonitrile, benzophenone, *p*-toluenesulfonyl chloride, and methyl disulfide) were supplied by Matheson Coleman and Bell. Dimethylformamide was purchased from Mallinckrodt Chemical Works and stored over Linde 3A molecular sieves.

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Alfred Bernhardt Laboratories, Mulheim, West Germany. Melting points were determined on a Hoover melting point apparatus and have been corrected. Ir spectra were obtained as Nujol mulls unless otherwise indicated on a Perkin-Elmer Model 137 Infracord spectrometer using the 5.14- and 11.03-μ bands of polystyrene as references. NMR spectra were obtained on a Varian A-56/60 spectrometer using tetramethylsilane as an internal standard. Gas chromatographic analyses were performed on a Varian Aerograph Model 90-P gas chromatograph, using a 10-ft column packed with 6% Apiezon L on Chromosorb W.

General Metalation Procedure. The substrate was dissolved in dry ether (1 ml ether/mmol substrate) at room temperature under nitrogen and 1.6 M *n*-butyllithium in hexane was slowly added. After an appropriate period a condensing agent was added at such a rate as to produce only a slight exotherm. The reaction solution was stirred for a designated period and then with the exception of compound **3d** hydrolyzed with water (dilute acid was used in the case of **3d**). Exact conditions for each metalation are provided in Table III.

Table IV. Study of the Extent of Metalation of *N,N*-Dimethyl-3-thenylamine (3) with Time

Metalation time, h	Yield, g	%	Mp, °C
1	0.52	58	86–88
3	0.58	64	84–87
4	0.60	66	87–88
6	0.61	67	86–88
12	0.56	62	87–88

The workup procedure used for the hydrolyzed mixtures (with the exceptions described below) called for separating the ether layer, then combining it with ether extracts of the aqueous layer. The combined ether extracts were dried over $MgSO_4$ and stripped under vacuum. The condensation product was then purified by the appropriate procedure designated in Table I.

For compounds **2a, 3a, 3e,** and **3f** the ether layer and ether extracts of the aqueous layer were combined and extracted with 10% HCl. The acid layer was separated and neutralized with 10% NaOH. Ether extracts of the neutralized portion were dried over $MgSO_4$. After the ether was removed under vacuum the condensation product was purified as indicated in Table I.

Physical data for various substrates and metalation products are given in Table I. Ir and NMR data are provided in Table II (see paragraph at end of paper regarding supplementary material).

***N,N*-Dimethyl-2-thenylamine (2-DTA, 1).** Thiophene was chloromethylated[23] to give 2-chloromethylthiophene, bp 40–43 °C (6 mm). 2-Chloromethylthiophene (30.2 g, 2.28 mol) was added dropwise to a fourfold excess of dimethylamine. Excess dimethylamine was evaporated and 100 ml of water and 100 ml of ether were added. The ether layer and two ether extracts of the aqueous layer were combined, dried over anhydrous $MgSO_4$, and stripped. A brown oil was obtained which was vacuum distilled to give 18.5 g (57%) of 2-DTA, bp 58–60 °C (8 mm) [lit.[24] 60–61 °C (10 mm)].

5-Methyl-*N,N*-dimethyl-2-thenylamine (2). Aldehyde **1c** (8.0 g, 0.047 mol) was reduced via the Wolff–Kishner reduction method. The product was steam distilled and the fraction boiling at 108–110 °C collected. The yield was 6.6 g (86%) of 5-methyl-*N,N*-dimethyl-2-thenylamine (**2**) [lit.[25] bp 83–84 °C (13 mm)).

Preparation of the Methiodide (2b) of 5-Methyl-3-diphenylhydroxymethyl-2-DTA (2a). Carbinolamine **2a** (1.30 g, 0.0027 mol) was dissolved in 50 ml of acetonitrile and a large excess of methyl iodide (10.0 g, 0.070 mol) was added. After the reaction mixture was refluxed for 6 h, the solvent was stripped under reduced pressure to give 1.80 g (98%) of 5-methyl-3-diphenylhydroxymethyl-*N,N,N*-trimethyl-2-thenylammonium iodide (**2b**). An analytical sample, mp 194 °C dec, was obtained after recrystallization from absolute ethanol.

Cyclization of Methiodide 2b to Produce Ether 2c. A solution of 0.004 mol of KNH_2 in 175 ml of liquid NH_3 was prepared from potassium metal (0.15 g, 0.004 mol) in the manner described by Hauser and Harris.[27] Methiodide **2b** (1.15 g, 0.0024 mol) was added to the stirred solution. After 0.5 h, 50 ml of dry dimethoxyethane was added and the condenser was fitted with a $CaCl_2$ drying tube. After the reaction mixture was refluxed for 7 days evolution of trimethylamine was no longer detected with litmus paper. Excess NH_4Cl was added followed by 100 ml of water. The organic layer was separated, dried over anhydrous $MgSO_4$, and stripped to give a light orange powder. Recrystallization from absolute ethanol gave 0.48 g (45%) of a white powder, mp 117–119 °C. The product was assigned structure **2c** on the basis of its spectral and analytical data.

Preparation of *N,N*-Dimethyl-3-thenylamine (3). A solution of 3-methylthiophene (44 g, 0.45 mol) and benzoyl peroxide (0.8 g) in 150 ml of dry CCl_4 (stored over molecular sieves) was brought to rapid reflux and a mixture of *N*-bromosuccinimide (72 g, 0.4 mol) and benzoyl peroxide (0.8 g) was added portionwise as rapidly as the vigorous foaming would permit. As soon as the foaming from the last addition of *N*-bromosuccinimide had subsided, the flask was cooled and the succinimide filtered off and washed with CCl_4. The filtrate was stripped under reduced pressure and the residue vacuum distilled at 0.12 mm to give 53.0 g (67%) of 3-(α-bromomethyl)thiophene, bp 75–77 °C (1.0 mm) [lit.[28] 75–78 °C (1.0 mm)]. Ir and NMR were in accord with the assigned structure. The 3-(α-bromomethyl)thiophene (10.0 g, 0.056 mol) was added dropwise to 150 ml (2.26 mol) of dimethylamine, then 100 ml of distilled water was added and the reaction mixture was refluxed for 1 h. After standing overnight, the crude product was extracted with ether. The ether extracts were combined, dried over anhydrous $MgSO_4$, and stripped of solvent. Resulting was a light brown oil which was vacuum distilled at 0.12 mm and the fraction boiling between 28 and 32 °C collected. A yield of 7.9 g (42%) of 3-DTA was obtained.

Metalation of *N,N*-Dimethyl-3-thenylamine (3). Time Study. 3-DTA was metalated over a period of 1, 3, 6, and 12 h. Each run was carried out as follows.

To a solution of 3-DTA (0.41 g, 0.0028 mol) in 30 ml of dry ether was added 2.1 ml (0.0034 mol) of 1.6 M *n*-butyllithium. After stirring for between 1 and 12 h, benzophenone (1.24 g, 0.0028 mol) was added and the reaction mixture was stirred for 4 h. The mixture was hydrolyzed with H_2O, the aqueous layer was separated and extracted with ether, and the combined ether extracts in turn were extracted with 10% HCl. The acidic extracts were carefully neutralized with NaOH and extracted once again with ether. These ether extracts were dried over anhydrous $MgSO_4$ and stripped. After the resulting clear, viscous oil had stood overnight under a vacuum, a white solid crystallized. The crude solid was washed several times with petroleum ether.

Table IV gives the melting point and yield of product obtained for each run. The data indicate that metalation is essentially complete after 1 h.

2-Formyl-*N,N*-dimethyl-3-thenylamine (3b). 3-DTA (3, 0.67 g, 0.0048 mol) was dissolved in 50 ml of dry ether at room temperature and 3.3 ml (0.0052 mol) of 1.6 M *n*-butyllithium in hexane was slowly added. After stirring for 1 h, dimethylformamide (0.70 g, 0.0096 mol) dissolved in 10 ml of dry ether was slowly added and the solution stirred for 5 h. To the resultant cloudy mixture 50 ml of water was added and the ether layer was separated, dried over anhydrous $MgSO_4$, and stripped. The resulting light brown oil was vacuum distilled at 0.03 mm and the fraction boiling between 62 and 63 °C collected. A yield of 0.60 g (75%) of 2-formyl-3-DTA (**3b**) was obtained.

Oxidation of 2-Formyl-3-DTA (3b) to 2,3-Thiophenedicarboxylic Acid. Carboxaldehyde **3b** (1.1 g, 0.0065 mol) was added to 20 ml of 0.5 N NaOH, the mixture was cooled to 20 °C, and $KMnO_4$ (3.6 g, 0.023 mol) was slowly added with stirring. After stirring for an additional 1 h at room temperature, Na_2SO_3 (0.5 g, 0.004 mol) was added, whereupon MnO_2 precipitated and was filtered off; the remaining reaction mixture was extracted twice with ether. The ether layer was separated, dried over anhydrous $MgSO_4$, and stripped of solvent. No unreacted starting material was recovered. After the aqueous layer had been acidified with 10% HCl, it was extracted with ether. These ether extracts were dried over anhydrous $MgSO_4$ and stripped to give 0.3 g (21%) of 2,3-thiophenedicarboxylic acid, mp 268–270 °C (lit.[18] 270 °C dec).

Formation of 2,3-Thiophenedicarboxylic Acid Anhydride (TCA). 2,3-Thiophenecarboxylic acid (0.23 g, 0.0013 mol) was treated with 4.8 ml (0.051 mol) of acetic anhydride and the solution refluxed for 30 min. Excess acetic anhydride was boiled off under reduced pressure. The resulting crude solid was sublimed at 85 °C (0.4 mm) to give 0.10 g (50%) of the anhydride, mp 137–138 °C (lit.[18] mp 140 °C).

Preparation of 2-Chloro-*N,N*-dimethyl-3-thenylamine (3e). 3-DTA (**3**, 1.1 g, 0.0078 mol) was dissolved in 50 ml of dry ether and 4.9 ml (0.0078 mol) of 1.6 M *n*-butyllithium was added. After stirring for 1 h, the reaction flask was placed in a dry ice–acetone bath and *p*-toluenesulfonyl chloride (1.48 g, 0.0078 mol) was slowly added. After stirring for 3 h at −70 °C, 100 ml of H_2O was added. The aqueous layer was separated and extracted with ether and the combined ether extracts extracted with 10% HCl. The combined acid extracts were carefully neutralized with NaOH and this neutralized solution was extracted with ether. The combined ether extracts were dried over anhydrous $MgSO_4$ and filtered and the solvent stripped under vacuum. The resulting dark brown oil was vacuum distilled at 0.6 mm to give one fraction, bp 31–32 °C. A yield of 0.34 g (25%) of 2-chloro-3-DTA (**3e**) was obtained. A similar synthesis of the 3-bromo analogue utilizing *p*-toluenesulfonyl bromide prepared by the method of Kovar et al.[29] yielded 2-bromo-3-DTA.

Preparation of 3-Thenyl Methyl Ether (4). Sodium methoxide was prepared by reacting sodium metal (2.3 g, 0.10 mol) with 100 ml of absolute methanol at room temperature. To this solution, 3-(α-bromomethyl)thiophene (10.5 g, 0.059 mol) was added and the resulting mixture was refluxed for 7 h. The mixture was concentrated to 20 ml and extracted with ether. The combined ether extracts were washed once with water, dried over anhydrous $MgSO_4$, and filtered and the solvent removed under vacuum. Distillation of the resultant oil gave 2.9 g (38%) of 3-TME (**4**), bp 26 °C (0.2 mm) [lit.[30] bp 65–67 °C (17 mm)].

Preparation of *N,N*-Dimethyl-3-thiophenecarboxamide (3-DTC, 5). Thiophene (282 g, 3.35 mol) was treated with bromine (1620 g, 10.05 mol) in chloroform to give 876 g (82%) of 2,3,5-tribro-

mothiophene, bp 150–152 °C (16 mm) [lit.[31] bp 120–122 °C (11 mm)]. The latter compound (642 g, 2.0 mol) was debrominated by treatment with zinc (392 g, 6.0 mol) and 350 ml of acetic acid to give 233 g (72%) of 3-bromothiophene, which was isolated by steam distillation (lit.[32] bp 159–160 °C). The Grignard reagent was prepared via the entrainment method by reacting 3-bromothiophene (40 g, 0.25 mol) with magnesium metal (36.5 g, 1.5 mol) and ethyl bromide (138 g, 1.25 mol) in dry ether. After refluxing several hours the reaction mixture was poured over a dry ice/ether slurry. Workup gave 13 g (41%) of 3-thiophenecarboxylic acid, mp 136–137.5 °C (lit.[33] mp 137.5–138.5 °C). The carboxylic acid (13 g, 0.102 mol) was treated with 37.7 g (0.329 mol) of thionyl chloride to afford 9.1 g (62%) of 3-thenoyl chloride, mp 50–52 °C (lit.[34] mp 51–52 °C). A solution of 2.5 g (0.017 mol) of 3-thenoyl chloride in 20 ml of benzene was slowly added to a large excess of dimethylamine. After stirring overnight the crude product was taken up in ether and washed once with water. The ether layer was dried over anhydrous $MgSO_4$ and stripped of solvent. The resultant oil was vacuum distilled at 0.5 mm to give a single fraction boiling at 89–90 °C. A yield of 1.2 g (45%) of 3-DTC (**5**) was obtained.

Metalation of *N,N*-Dimethyl-3-thiophenecarboxamide (5) and Hydrolysis with H_2O. 3-DTC (**5**, 0.90 g, 0.0058 mol) in 50 ml of dry ether was treated with 4.0 ml (0.0066 mol) of 1.6 M *n*-butyllithium with stirring. After 10 min a light yellow precipitate formed. The reaction mixture was stirred for another 10 min and then hydrolyzed with water. A white, crystalline material precipitated from the resulting mixture which was isolated by filtration. Ether extracts of the aqueous layer did not give any further product. The filtered solid was sublimed at 150 °C (0.2 mm) to give 0.26 g (41%) of 4,8-dehydrobenzo[1,2-*b*:4,5-*b'*]dithiophene-4,8-dione, mp 258–260 °C (lit. mp 258–260 °C).[22]

***N*-Methyl-3-thiophenecarboximide (3-MTC, 6).** A solution of 3-thenoyl chloride (9.1 g, 0.062 mol) in 50 ml of benzene was added slowly to 31 g (0.40 mol) of 40% methylamine. After the reaction mixture was refluxed for 45 min, the benzene layer was separated, washed once with water, and dried over anhydrous $MgSO_4$ and the solvent stripped under vacuum. A white powder was obtained which was recrystallized from ethanol to give 1.1 g (13%) of 3-MTC (**6**), mp 115–117 °C.

Acknowledgments. We are grateful for partial support of this research by the Office of Research and Projects, Southern Illinois University, and to Dr. C. A. Jennings for help in the preparation of this manuscript.

Registry No.—**1**, 26019-17-0; D_2O, 7789-20-0; benzophenone, 119-61-9; benzonitrile, 100-47-0; *p*-toluenesulfonyl chloride, 98-59-9; *p*-toluenesulfonyl bromide, 1950-69-2; *N,N*-dimethylformamide, 68-12-2; dimethyl disulfide, 624-92-0; 2-chloromethylthiophene, 765-50-4; dimethylamine, 124-40-3; 3-methylthiophene, 616-44-4; 3-(α-bromomethyl)thiophene, 34846-44-1; 2,3-thiophenedicarboxylic acid, 1451-95-2; TCA, 6007-83-6; thiophene, 110-02-1; 2,3,5-tribromothiophene, 3141-24-0; 3-bromothiophene, 872-31-1; 3-thiophenecarboxylic acid, 88-13-1; 3-thenoyl chloride, 41507-35-1.

Supplementary Material Available. Table II, ir and NMR spectral data of substituted thiophenes (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) For part 7 of this series, cf. D. W. Slocum and B. P. Koonsvitsky, *J. Org. Chem.*, preceding paper in this issue.
(2) To whom correspondence should be addressed.
(3) F. N. Jones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, **28**, 663 (1963); F. N. Jones, R. L. Vaulx, and C. R. Hauser, *ibid.*, **28**, 4361 (1963).
(4) D. W. Slocum, B. W. Rockett, and C. R. Hauser, *Chem. Ind. (London)*, 1831 (1964); D. W. Slocum, B. W. Rockett, and C. R. Hauser, *J. Am. Chem. Soc.*, **87**, 1241 (1965).
(5) For recent reviews, cf. (a) D. W. Slocum, T. R. Engelmann, C. R. Ernst, C. A. Jennings, W. E. Jones, B. Koonsvitsky, J. Lewis, and P. Shenkin, *J. Chem. Educ.*, **46**, 144 (1969); (b) D. W. Slocum and E. Kaiser in "organic Reactive Intermediates", S. McManus, Ed., Academic Press, New York, N.Y., 1973, pp 337–422; (c) D. W. Slocum and D. I. Sugarman, *Adv. Chem. Ser.*, **No. 130**, 222 (1974).
(6) W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **29**, 853 (1964).
(7) D. W. Slocum and F. E. Stonemark, *J. Org. Chem.*, **38**, 1677 (1973).
(8) A. R. Katritzky, *Adv. Heterocycl. Chem.*, **1**, 46–56 (1963).
(9) H. D. Hartough and A. J. Kosak, *J. Am. Chem. Soc.*, **69**, 3093 (1947).
(10) D. W. Slocum and C. A. Jennings, *J. Org. Chem.*, accompanying paper in this issue.
(11) D. W. Slocum and P. L. Gierer, *J. Org. Chem.*, **38**, 4189 (1973).
(12) T. Kauffman and A. Mitschker, *Tetrahedron Lett.*, 4039 (1973).
(13) S. Gronowitz and B. Gestblom, *Ark. Kemi*, **18**, 513 (1962).
(14) S. Gronowitz, P. Moses, A. B. Hornfeldt, and R. Hakansson, *Ark. Kemi*, **17**, 165 (1961).
(15) J. Sice, *J. Am. Chem. Soc.*, **75**, 3697 (1953).
(16) Ya. L. Goldfarb, M. A. Kalik, and M. L. Kirmalova, *J. Gen. Chem. USSR (Engl. Transl.)*, **29**, 3592 (1959).
(17) F. B. Deans and C. Eaborn, *J. Chem. Soc.*, 2303 (1959).
(18) R. P. Linstead, E. G. Noble, and J. M. Wright, *J. Chem. Soc.*, 911 (1937).
(19) R. A. Hoffman and S. Gronowitz, *Ark. Kemi*, **16**, 563 (1960).
(20) C. T. Wiswanathan and C. A. Wilkie, *J. Organomet. Chem.*, **54**, 1 (1973).
(21) D. W. Slocum and C. A. Jennings, *J. Chem. Soc., Chem. Commun.*, **54** (1972).
(22) D. W. H. MacDowell and J. C. Wisowaty, *J. Org. Chem.*, **37**, 1712 (1972).
(23) K. B. Wiberg and H. F. McShane, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 197.
(24) H. D. Hartough, S. L. Meisel, E. Koft, and J. W. Schich, *J. Am. Chem. Soc.*, **70**, 4013 (1949).
(25) Ya. L. Goldfarb and A. P. Yakubov, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 2509 (1967).
(26) K. Schultz, A. Kreutzberger, and G. Bohn, *Chem. Ber.*, **97**, 3263 (1964).
(27) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6460 (1958).
(28) E. Campaigne and B. F. Tuldar, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 921.
(29) R. F. Kovar, M. D. Rausch, and H. Rosenberg, *Organomet. Chem. Synth.*, **1**, 173 (1970/1971).
(30) K. Takahashi, T. Sone, Y. Mutsuki, and G. Hazato, *Bull. Chem. Soc. Jpn.*, **36**, 108 (1963).
(31) S.-O. Lawesson, *Ark. Kemi*, **11**, 373 (1957).
(32) S. Gronowitz and T. Raznikiewicz, *Org. Synth.*, **44**, 9 (1964).
(33) S. Gronowitz, *Ark. Kemi*, **7**, 2 7 (1954).
(34) E. Campaigne and W. M. LeSuer, *J. Am. Chem. Soc.*, **70**, 1555 (1948).
(35) K. Nakanishi, "Infrared Absorption Spectroscopy", Holden-Day, San Francisco, Calif., 1962.