

3,5-DILITHIATED TERTIARY THIOPHENE 2-CARBOXAMIDE.

REGIOSELECTIVE ENTRIES INTO DIVERSELY SUBSTITUTED THIOPHENES

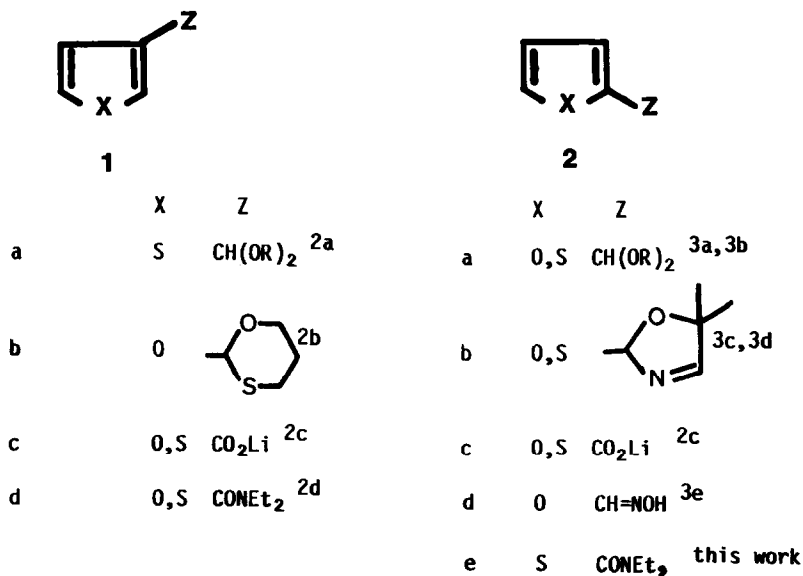
E.G. Doadt and V. Snieckus*

The Guelph-Waterloo Centre for Graduate Work in Chemistry

University of Waterloo, Waterloo, Canada N2L 3G1

Abstract: 3,5-Dilithiated N,N-diethyl thiophene 2-carboxamide (**3**) undergoes reaction with a single electrophile in excess, or two different electrophiles in tandem, to give 2,3- and 2,3,5-substituted thiophene derivatives (**4**).

2,3-Disubstituted thiophenes and furans are available via metalation¹ of 3-substituted (**1**)² but generally not the much more accessible 2-substituted (**2**)³ systems which, with two notable exceptions (**2b**),^{3c,3d,4} suffer exclusive C-5 deprotonation thereby leading to 2,5-disubstituted products. As an extension of work on dimetalated aromatics,⁵ we report on the direct generation of the 3,5-dilithiated thiophene-2-carboxamide (**3**)⁶ from **2e** and demonstrate the utility of this synthon for the regioselective construction of diversely functionalized 2,3- and 2,3,5-substituted thiophene derivatives **4**.



Metalation of **2e** under standard conditions (1.1 equiv \underline{s} -BuLi/TMEDA/THF/-78°C)⁵ leads to C-5 deprotonation as confirmed by reaction with TMSCl to give **4a** in high yield. However, when the in situ generated 5-lithio species is exposed to 1.1 equiv of \underline{s} -BuLi/TMEDA/THF/-78°C, followed by EtOD quench, the dideuterated compound **4b** is obtained in high yield and > 95% d₂ content (MS) (Table). This result strongly suggests the intermediacy of the 3,5-dilithiated species **3** and is supported by the successful introduction of a variety of other electrophiles to give products **4c - 4f**.

The order of deprotonation, based on the formation of **4a** with 1 equiv of base, predicted that in **3**, the C-3 anion would be the more reactive towards electrophiles. As a test of this prediction, **3** was quenched at -78°C with 1 equiv of TMSCl followed by excess of MeOH and gave 3-silylated product **4g** together with some 3,5-disilylated material (Table). Similarly, treatment with other electrophiles gave modest yields of products **4h - 4j** with varying amounts of 2,5-disubstituted amides or starting material, which appeared to be a function of the reactivity of the electrophile.⁷

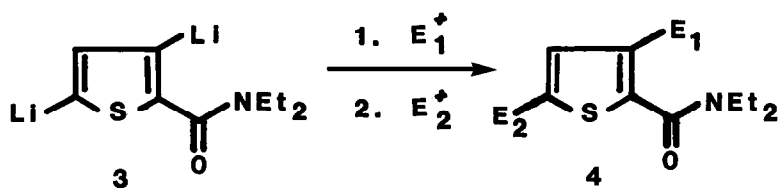
The sequential, one-pot introduction to two different electrophiles into **3** was moderately successful using the more reactive TMSCl and (MeS)₂ as the first electrophiles. In this manner, compounds **4k - 4m** were obtained accompanied by substantial amounts of 3,5-disilylated or -dithiomethylated products.

Dilithiated species **3** should have utility for attaining varied thiophene substitution patterns in general and 2,3-disubstitution in particular. It may also stimulate interest to generate dianions of other heteroaromatic systems.^{8,9,10}

References and Footnotes:

1. Review: Gronowitz, S. Advan. Heterocyclic Chem. **1963**, 1, 1; Gronowitz, S. In Stirling, C.J.M., Ed. "Organic Sulfur Chemistry," Butterworths, London, **1975**, p. 203.
2. (a) MacDowell, D.W.H.; Patrick, T.B. J. Org. Chem. **1966**, 31, 3592; (b) Reich, H.J.; Shah, S.K.; Gold, P.M.; Olsen, R.E. J. Am. Chem. Soc. **1981**, 103, 3112; (c) Knight, D.W.; Nott, A.P. J. Chem. Soc. Perkin Trans. I, **1981**, 1125; Knight, D.W.; Nott, A.P. ibid. **1983**, 791; (d) Watanabe, M.; Snieckus, V. J. Am. Chem. Soc. **1980**, 102, 1457.
3. (a) Thames, S.F.; Odom, Jr., H.C. J. Heterocyclic Chem. **1966**, 3, 490 and refs. therein; Pastour, P.; Mantard, C. Compt. Rend. **1966**, 262C, 1539; (b) 3-Lithiated **2a**, X = 0 may be

TABLE Synthesis of 2,3- and 2,3,5-Substituted Thiophene 2-Carboxamides



Electrophile		Product ^a	E ₁	E ₂	Yield, % ^b	Mp(bp) ^c °C
E ₁ ⁺	E ₂ ⁺					
TMSCl		4a	H	TMS	85	65-66 ^d
Et ₂ O		4b	D	D	83	46-48 ^d
TMSCl		4c	TMS	TMS	82	105-110/0.15 mm
(MeS) ₂		4d ^e	SMe	SMe	65	100-105/0.15 mm
CICONEt ₂		4e	CONEt ₂	CONEt ₂	82	210-220/0.02 mm
PhCHO		4f ^e	PhCH(OH)	PhCH(OH)	48	f
TMSCl	MeOH	4g ^g	TMS	H	40	71-75/0.2 mm
(MeS) ₂	MeOH	4h ^g	SMe	H	34	80-85/0.05 mm
MeI	MeOH	4i ^h	Me	H	57	68-72/0.08 mm
CICONEt ₂	MeOH	4j ^h	CONEt ₂	H	38	130-135/0.01 mm
TMSCl	(MeS) ₂	4k ⁱ	TMS	SMe	35	90-95/0.05 mm
(MeS) ₂	TMSCl	4l ^j	SMe	TMS	30	100-102/0.2 mm
(MeS) ₂	CICONEt ₂	4m ^j	SMe	CONEt ₂	26	135-140/0.08 mm

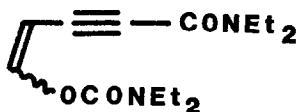
^a All new compounds show analytical and spectral (IR, NMR, MS) data consistent with the assigned structures. ^b Yields are based on isolated (chromatographed and/or distilled) material. ^c Temperature of the Kugelrohr oven. ^d Recrystallized from Et₂O-hexane.

^e Accompanied by 10% of 3-substituted product. ^f Oil, homogeneous by TLC, partially converted into the corresponding phthalide upon distillation. ^g Accompanied by 25% of 3,5-disubstituted product. ^h Accompanied by 10-20% of **2e**. ⁱ Accompanied by 20% of **4c**.

^j Accompanied by 20-30% of **4d**.

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6. Dilithiated thiophenes have been available only by metal-halogen exchange processes: Wakefield, B.J. "The Chemistry of Organolithium Compounds," Pergamon Press, Oxford, **1974**, pp. 60, 210; Chadwick, D.J.; Willbe, C. J. Chem. Soc. Perkin Trans. I, **1977**, 887.
7. An alternative, albeit 3-step procedure to prepare compounds **4h-4j** has also been developed using the tactic of silicon protection of preferred metalation sites (Mills, R.J.; Snieckus, V. J. Org. Chem. **1983**, 48, 1565). Standard metalation of **4a** followed by reaction with the appropriate electrophiles and desilylation (TBAF/THF/RT/30 min) smoothly gave **4h-4j** in 60-70% overall yields. Details of these results will be provided in the full paper.
8. N,N-Diethyl furan 2-carboxamide undergoes 3-metalation but suffers rapid ring opening at -78°C to give ene-yne products, e.g. **1** using ClCONEt_2 as electrophile (Doadt, E.G.; Snieckus, V. unpublished results). For related metalation-induced ring scissions, Karlsson, J.O.; Svensson, A.; Gronowitz, S. J. Org. Chem. **1984**, 49, 2018; Gribble, G.W.; Saulnier, M.G. ibid. **1983**, 48, 607 and references cited therein.



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9. For 2,5-dilithiated imidazoles, see Chadwick, D.J.; Ngochindo, R.I. J. Chem. Soc. Perkin Trans. I, **1984**, 481.
10. We thank NSERC Canada for financial support and M. Kerr for technical assistance.

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