mL of deuterated methanol (or 1:2 CD_3CN/D_2O or CD_3CN + 0.3 M benzenethiol), and the solution was degassed with argon and irradiated in a quartz cell with an Ealing 3130-Å interference filter in combination with a 200-W Hg-Xe lamp for 1 h. Product analysis (quantum yield) was determined by ^1H NMR. The rearranged product **2a** was produced in each case without significant quenching as compared to the value determined in dry acetonitrile.

Acknowledgment. We acknowledge the contribution of L. W. Kelts for the CIDNP investigations of the photorearrangement product and process.

Registry No. **1a**, 98088-07-4; **1b**, 90555-48-9; **1c**, 90584-13-7; **2a**, 98088-08-5; **2b**, 98088-09-6; **2c**, 98088-10-9; **3**, 10075-72-6; **4a**, 98088-13-2; **5a**, 98088-11-0; **5b**, 98088-12-1; **5c**, 1846-33-9; HBF_4, 16872-11-0; F_3CSO_3H, 1493-13-6.

Supplementary Material Available: Crystal data and structural parameters (Tables II-V), absorption curves of **1(a-c)** (Figure 1), and the X-ray crystal structure of **2a** (Figure 2) (7 pages). Ordering information is given on any current masthead page.

The Scope and Limitations of Carboxamide-Induced β-Directed Metalation of 2-Substituted Furan, Thiophene, and 1-Methylpyrrole Derivatives. Application of the Method to Syntheses of 2,3-Disubstituted Thiophenes and Furans

Andrew J. Carpenter and Derek J. Chadwick*

The Robert Robinson Laboratories, Department of Organic Chemistry, University of Liverpool, Liverpool L69 3BX, U.K.

Received April 5, 1985

The effects of change of solvent, metalating agent, reaction time, and reaction temperature on the lithiation of *N,N*-diethylthiophene-2-carboxamide and of the *N*-*tert*-butyl 2-carboxamide derivatives of furan, thiophene, and 1-methylpyrrole are explored, and optimum conditions are established for ring β-directed metalation. The tertiary carboxamido group is less effective in this context than the secondary amide function and appears to be of limited value in these heteroaromatic systems. The high metalation levels achievable with the furan and thiophene secondary amides allow high-yielding syntheses (through reaction of the lithiated intermediates with a wide range of electrophiles) of otherwise inaccessible 2,3-disubstituted derivatives. The synthetical value of this methodology appears to be limited only by the forcing conditions required for amide hydrolysis.

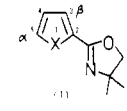
In recent papers,[1,2] we have established optimum conditions for β-directed metalation of furan, 1-methylpyrrole, and thiophene bearing the 4,4-dimethyloxazolin-2-yl substituent (**1**, X = O, NCH_3, S). Although the methodology furnishes a synthetically useful route to the otherwise inaccessible 2,3-disubstituted derivatives, there are drawbacks. In particular, the β-metallo intermediates may be contaminated with small amounts of the α (**5**) analogues or of starting material (or of both) and appear to be of only moderate nucleophilicity. Furthermore, in the 1-methylpyrrole case,[2] high β-selectivity is only achievable at the expense of a considerably lowered yield.

We have therefore continued the search for other 2-substituents as β-directing groups in metalation with a view to securing high-yielding, regioselective syntheses of 2,3-disubstituted furans, 1-protected pyrroles, and thiophenes. (A computer search of the Fine Chemicals Directory (version of October 1984 containing 47 177 compounds) for commercially available 2,3-disubstituted furans, thiophenes, and 1-H- or 1-substituted pyrroles not fused to another ring reveals only seven thiophenes, three furans, and no pyrroles, nor are there any commercially-available 3-substituted pyrroles. This may be taken as a crude measure of the inaccessibility of these deceptively simple compounds.) The results of our studies on the utility of carboxamido functionality in this connection are presented here.

Results and Discussion

(A) Tertiary Carboxamido Functionality. There is ample precedent for the use of tertiary amides as directing groups in the metalation of benzene derivatives.[3,4] Generally, lithiation adjacent to the *N,N*-diethylcarboxamido function has been achieved with *sec*-BuLi, but *n*-BuLi may be used with the more sterically congested diisopropyl analogues.

The results of an exploratory series of experiments on *N,N*-diethylthiophene-2-carboxamide (**2**) (Table I) are disappointing. Use of *sec*-BuLi in dimethoxyethane (DME) or diethyl ether gives no product from β-lithiation and only moderate selectivity for β-metalation when tetrahydrofuran (THF) is the solvent. For comparison purposes, the 2,5-disubstituted acid-amide **3** was synthesized



(1)

(3)

by the use of lithium diisopropylamide (LDA) as the metalating agent. Previous experience with the oxazolinyl

(1) Carpenter, A. J.; Chadwick, D. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 173.
(2) Chadwick, D. J.; McKnight, M. V.; Ngochindo, R. I. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1343.
(3) Snieckus, V. *Heterocycles* **1980**, *14*, 1650.
(4) Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34.

0022-3263/85/1950-4362$01.50/0

Table I. Lithiations of *N,N*-Diethylthiophene-2-carboxamide (2)[a]

expt	base	solv	electrophile	product composition, % 2,3-disubstd	product composition, % 2,5-disubstd	yield, %
1	LDA	THF	CO_2	0	100	85
2	*sec*-BuLi	DME	D_2O	0	100	*b*
3	*sec*-BuLi	DME	CO_2	0	100	82
4	*sec*-BuLi	ether	CO_2	0	50[c]	82
5	*sec*-BuLi	THF	CO_2	50	41[d]	99

[a] The reaction mixtures were stirred at −78 °C for 0.5 h; the ratio of base to **2** was 1.1:1. [b] For this experiment, an aliquot was removed from the reaction mixture of experiment 3; the yield is incorporated into the yield for the latter. [c] Estimated by ^1H NMR integration; starting substrate constitutes the material balance. [d] Analyzed as the methyl esters.

Table II. Lithiations of *N*-*tert*-Butylthiophene-2-carboxamide (4)

expt	base[a]	solv[b]	temp °C	time, h	product composition,[c] % 2,3-disubstd	product composition,[c] % 2,5-disubstd	yield, %
6	1	D	−78	0.5	24	0	100
7	1	D	−78	2	52	0	96
8	1	D	0	0.5	73	6	100
9	1	D	0	2	88	8	91
10	1	B	−78	0.5	74	6	99
11	1	B	−78	2	100	0	85
12	1	B	−10	0.5	95	0	99
13	1	B	−10	2	93	0	95
14	1	C	−78	0.5	100	0	100
15	1	C	−78	2	82	0	97
16	1	C	0	0.5	100	0	99
17	1	C	0	2	74	0	99
18	1	A	−78	0.5	0	0	98
19	1	A	−78	2	0	0	99
20	1	A	0	0.5	20	0	98
21	1	A	0	2	20	0	99
22	2	C	0	0.5	5	48	99
23	2	C	0	2	9	65	99
24	2	C	−78	0.5	13	35	99
25	2	C	−78	2	23	42	99

[a] The ratio of base to **4** was 2.2:1, 1 = *n*-BuLi, 2 = LDA. [b] A = hexane, B = DME, C = THF, D = diethyl ether. [c] Estimated after workup with a 3 M excess of CH_3OD and ^1H NMR integration of ring proton resonances after addition of a small quantity of $Eu(fod)_3$ to separate resonances due to 3-H and 5-H.

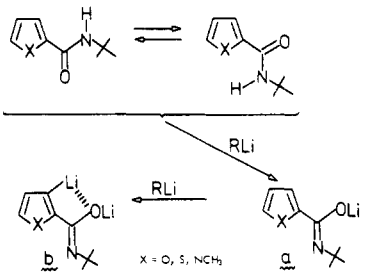
directing group indicates that directed metalation becomes increasingly difficult in the order thiophene < furan < 1-methylpyrrole. Further studies on the tertiary carboxamido function were therefore abandoned.

(B) Secondary Carboxamido Functionality. *N*-Methyl and -*tert*-butyl secondary amides have been used extensively in the synthesis of ortho-substituted benzene derivatives[4,5,6] with a facility apparently similar to tertiary amides.

In the present work the N-substituent was chosen to be *tert*-butyl in order to minimize the possibility of incursion of nucleophilic addition to the carbonyl group and to increase the solubility of the derived anions in ethereal solvents since heterogeneous mixtures obtained on metalation of 4,4-dimethyl-2-(2-thienyl)oxazoline (1, X = S) in hexane have proved to be of low nucleophilicity and in the expectation that the *tert*-butyl group would serve to predispose the dilithio amide to a conformation allowing maximum stabilization of the lithiated intermediate. Such a conformation may also, perhaps, permit efficient delivery of the lithiating agent by the lithio amide group to the proximate β-position (Scheme I).

The results of a wide range of experiments designed to identify the important variables in the metalation of *N*-*tert*-butylthiophene-2-carboxamide (**4**) (Table II) clearly demonstrate the superiority of secondary over tertiary carboxamido functionality for directed metalation of thiophene. Essentially quantitative β-metalation is achieved within 0.5 h with DME as solvent at −10 °C

Scheme I



(experiment 12)* or THF at −78 or 0 °C (experiments 14 and 16) and *n*-BuLi as the base. (*Fitt and Gschwend[7] have reported half-lives of solutions of *n*-, *sec*-, and *t*-BuLi in DME and conclude that "the scarcity of reports on DME as solvent in metalations is not surprising, and its use for these purposes is discouraged". The present work clearly shows that this is an overstatement. If adequate cognizance is given to the well-known instability of such solutions and rigid temperature control is maintained throughout a reaction, then great success can be achieved with this valuable solvent.) Extension of the reaction time to 2 h has a generally deleterious effect on lithiation levels (but not on recovered yields) probably as a consequence of proton abstraction from the solvent. Change of base to LDA alters the bias of regioselectivity in favor of 5-metalation (as expected) but to a lesser degree than was found in the analogous 2-(2-thienyl)oxazoline system.[1] This is consistent with the secondary carboxamido group

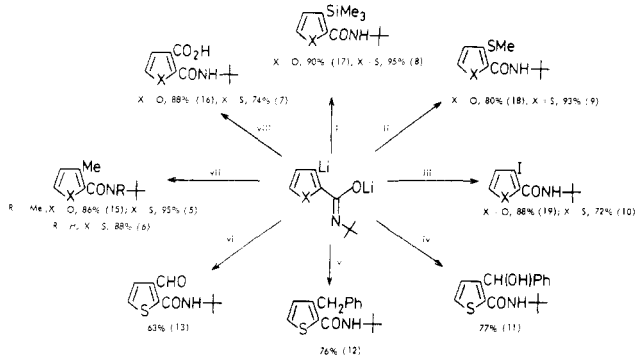
(5) Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653.
(6) Bhide, B. H. *Chem. Ind. (London)* **1974**, *19*, 75.
(7) Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* **1984**, *49*, 209.

Table III. Lithiations of *N-tert*-Butylfuran-2-carboxamide (14)

expt	base[a]	solv[b]	temp, °C	time	product composition,[c] % 2,3-disubstd	2,5-disubstd	yield, %
26	1	C	−78	0.5 h	46	52	89
27	1	C	−78	2 h	50	50	90
28	1	C	0	0.5 h	24	72	81
29	1	C	0	2 h	11	82	83
30	1	B	−78	0.5 h	79	19	93
31	1	B	−78	2 h	79	21	94
32	1	B	−10	0.5 h	0	75	88
33	1	B	−10	2 h	0	62	82
34	1	B	−78	5 min	72	18	95
35	1	B	−78	10 min	68	16	93
36	1	B	−78	0.25 h	78	20	96
37[d]	1	D	−78	0.5 h	9	8	93
38[d]	1	D	−78	2 h	12	0	94
39	1	D	0	0.5 h	3	47	89
40	1	D	0	2 h	5	54	90
41	2	B	−78	0.25 h	79	0	97
42	2	B	−78	1 h	87	0	91

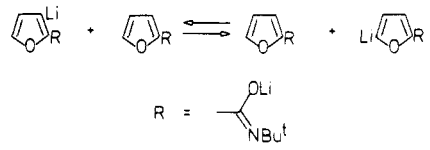
[a] The ratio of base to 14 was 2.2:1; 1 = *n*-BuLi, 2 = *sec*-BuLi. [b] Conventions are those of Table II. [c] Estimated after workup with a 3 M excess of CH_3OD and ^1H NMR integration of ring proton resonances. [d] The reaction mixture was heterogeneous in these experiments.

Scheme II[a]



[a] Reagents: (i) Me_3SiCl; (ii) Me_2S_2; (iii) I_2; (iv) PhCHO; (v) $PhCH_2Br$; (vi) $HCONMe_2$; (vii) MeI; (viii) CO_2.

Scheme III



interacting more strongly than the oxazolinyl group with an incoming organolithium reagent and thus still being able to exercise some directing effect with the "coordinatively saturated" LDA reagent. This view is supported by the insensitivity of regioselectivity of metalation of **4** to the identity of the ethereal solvent compared with the oxazoline analogue (**1**, X = S); i.e., the carboxamido group competes with ethereal solvent for organolithium reagent more successfully than does the oxazolinyl group. The low levels of lithiation achieved when hexane is the solvent (experiments 18–21) probably stem from the low solubility of the monolithio intermediate a (X = S; Scheme I) in this solvent.

The synthetical utility of the dilithio intermediate b (X = S; Scheme I) (which is soluble in THF and DME even at −78 °C) is demonstrated by its reaction with a wide variety of electrophilic reagents (Scheme II; X = S). Alkylation with methyl iodide in THF requires a large excess of the reagent for good conversion and consequently gives the tertiary amide **5** (Scheme II). Change of solvent to DME, however, enhances the nucleophilicity of the dilithio intermediate, permits use of equimolar methyl iodide, and allows preparation of the secondary amide **6** (Scheme II) in excellent yield.

Translation of the metalation procedures established for the thiophene amide to the analogous furan derivative **14** (Table III) reveals a very different pattern of regioselectivity: in particular, α-lithiation is much in evidence and, indeed, predominates in some instances (e.g., experiments 28, 29, 32, and 33; Table III). This is consonant with the results of our earlier work on furan and thienyloxazolines.[1,2] Elevation of reaction temperature from −78 °C encourages a substantial shift from β- to α-lithiation (cf. experiments 26, 27, 30, and 31 with 28, 29, 32, and 33, respectively; Table III) probably stemming from a transmetalation equilibrium (Scheme III). (The occurrence of transmetalation equilibria has been suggested previously by us for the case of lithio-1-methylpyrroles[8,9] and, more recently, by Ribéreau and Quéguiner[10] for the (lithiothienyl)oxazoline system.) Use of *sec*-BuLi (which is presumably a kinetically stronger base than *n*-BuLi) is especially advantageous for directed metalation, leading to ca. 90% β-metalation (experiment 42) and no detectable α-lithiation. The resulting dilithio intermediate reacts with a wide range of electrophiles (Scheme II; X = O) and the absence of products from α-metalation permits easy purification.

Previous experience in the metalation of 1-substituted pyrroles[2,9] shows that they are less easily deprotonated than furans or thiophenes. The data presented in Table IV on the lithiation of *N-tert*-butyl-1-methylpyrrole-2-carboxamide (**21**) are no exception to this, a lithiation level of only 62% (experiment 50) having been achieved. Comparisons between the results of experiments listed in Table IV and those of experiments on the analogous 2-pyrrolyloxazoline (**1**, X = NMe) (Table II in ref 2) indicate generally lower levels of metalation in the former than in the latter. This is presumably a reflection of the greater electron-withdrawing character of the oxazolinyl group compared with the lithiated secondary carboxamido function (which bears a formal negative charge).

(C) Hydrolysis of the Carboxamido Functionality. A full realization of the synthetical potential of carboxamide-assisted directed metalation in these heteroaromatic systems is only achievable if appropriate methodology can be found for the transformation of the carboxamido group

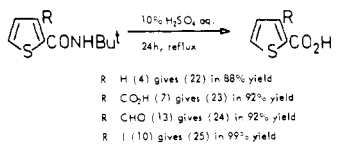
(8) Chadwick, D. J.; Willbe, C. *J. Chem. Soc., Perkin Trans. 1* **1977**, 887.
(9) Chadwick, D. J.; Cliffe, I. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2845.
(10) Ribéreau, P.; Quéguiner, G. *Tetrahedron*, **1983**, *39*, 3593.

Table IV. Lithiations of *N-tert*-Butyl-1-methylpyrrole-2-carboxamide (21)[a]

expt	base	solv	temp, °C	time, h	product composition,[b] % 2,3-disubstd	2,5-disubstd	yield, %
43	2.2 × 1	C	0	0.5	0	0	99
44	2.2 × 1	C	0	2	0	0	94
45	2.2 × 1	C	−78	2	0	0	99
46	3 × 1	C	65	0.5	51	6	97
47	3 × 1	C	25	0.5	41	9	96
48	3 × 1	B	−10	0.5	22	0	97
49	3 × 1[c]	B	−10	0.5	24	0	99
50	3 × 2	C	65	0.5	53	9	91

[a] The conventions of Table II are used. [b] Estimated as in Table III. [c] 3 mol equiv of TMEDA was also added.

Scheme IV



into another functionality. The results of exploratory experiments on *N-tert*-butylthiophene-2-carboxamide (**4**) show that the traditional method[11] for amide hydrolysis (boiling under reflux with 70% aqueous H_2SO_4) leads to degradation of the starting material in less than 2 h. Acceptable conversion under less forcing conditions (boiling with 10% aqueous H_2SO_4) requires at least 24 h: these conditions were applied successfully to the 3-carboxy-, -formyl-, and -iodothiophene-2-carboxamides (Scheme IV), giving the corresponding acids in excellent yields. The 3-trimethylsilyl derivative **8**, however, undergoes concomitant desilylation and amide hydrolysis (probably via a reversed Friedel–Crafts-type reaction), and a similar process may be responsible for the failure of the 3-methyl, -benzyl, and -methylthio analogues to hydrolyze cleanly.

Several base-mediated hydrolysis procedures were also investigated. Boiling of **4** under reflux for 48 h with 10% NaOH in aqueous dioxane (1:1) or for 24 h with 20% aqueous KOH is ineffective. The tertiary amide *N-tert*-butyl-*N*-methyl-3-methylthiophene-2-carboxamide (**5**) is resistant to Gassman's procedure[12] (KOH, KO-*t*-Bu, THF, reflux) during 24 h, and further heating leads to its degradation. The amide is likewise resistant to hydrolysis by boiling under reflux for 12 h with 40% KOH in aqueous methanol (1:1), though this approach is effective for the hydrolysis of *N-tert*-butyl-*N*-methylthiophene-2-carboxamide. Under these conditions, the 3-(trimethylsilyl)-thiophene secondary amide **8** undergoes hydrolysis and desilylation.

Conclusions. The work described in this paper demonstrates the utility of the secondary carboxamido group for directing lithiation into the β-positions of furan, thiophene, and 1-methylpyrrole derivatives. For the first two systems, the high metalation levels that are achievable permit access, through reaction of the lithiated intermediates with a wide range of electrophiles, to otherwise inaccessible 2,3-disubstituted derivatives. The tertiary carboxamido group is less effective in directing metalation and appears to be of little value in these heteroaromatic systems.

Comparison between the results presented here and those described previously[1,2] for the corresponding 4,4-dimethyloxazolin-2-yl derivatives indicates the superior directing ability of the lithiated secondary carboxamido group. The oxazoline system seems, however, to have a greater electron-withdrawing effect on the heteroaromatic rings permitting much higher metalation levels for the 1-methylpyrrole–oxazoline derivative than are possible with the analogous amide.

The synthetical value of amide-directed metalation in the heteroaromatic field appears to be limited by the forcing conditions required for amide hydrolysis (a problem not unique to this area[12,13]).

Experimental Section

Procedures for thin-layer chromatography, melting point measurement, microanalysis, spectroscopic characterization, and solvent purification have been described in a previous paper.[1]

The concentrations of solutions of commercial *n*- and *sec*-BuLi were determined by means of the double-titration method of Jones and Gilman.[14]

***N-tert*-Butylthiophene-2-carboxamide (4).** A mixture of thiophene-2-carboxylic acid (38.4 g, 0.3 mol) and thionyl chloride (71.4 g, 0.6 mol) was boiled under reflux for 3 h. Excess of thionyl chloride was removed by distillation under reduced pressure, the residue was taken up in CH_2Cl_2 (100 mL), and a solution of *tert*-butylamine (43.9 g, 0.6 mol) in CH_2Cl_2 (100 mL) was added with stirring, the temperature of the mixture being kept below 10 °C. The resulting solution was stirred at 25 °C for 12 h, washed with water (3 × 30 mL), and dried ($MgSO_4$). The combined washings were basified to pH 11 (concentrated aqueous KOH) and extracted with CH_2Cl_2 (3 × 30 mL) and the extracts dried ($MgSO_4$). The combined organic solutions were evaporated under reduced pressure to give the crude product (51.1 g). Recrystallization ($C_6H_{12}/CHCl_3$) gave the pure amide **4** (50.0 g, 91%) as a white solid: mp 144–145 °C (lit.[15] mp 146–147 °C); ^{1}H NMR ($CDCl_3$) δ 7.42 (2 H, m, thiophene 3-H and 5-H), 7.04 (1 H, m, thiophene 4-H), 5.84 (1 H, br s, NH), 1.46 (9 H, s, CH_3); mass spectrum, *m/z* (relative intensity) 183 (M^+, 17), 115 (100).

***N-tert*-Butylfuran-2-carboxamide (14).** This was prepared in a similar manner to the thiophene analogue (**4**) from furan-2-carboxylic acid (100 g, 0.9 mol) except that the intermediate acid chloride was purified by distillation under reduced pressure [78 °C (12 mmHg)].

The crude product (143 g) was recrystallized ($C_6H_{12}/CHCl_3$), giving the pure amide **14** (140 g, 93%) as white needles: mp 100.0–100.5 °C (lit.[16] mp 100 °C); ^{1}H NMR ($CDCl_3$) δ 7.39 (1 H, d, J = 1.3 Hz, furan 5-H), 7.03 (1 H, d, J = 3.8 Hz, furan 3-H), 6.46 (1 H, dd, J = 1.3, 3.8 Hz, furan 4-H), 6.44 (1 H, br s, NH), 1.45 (9 H, s, CH_3); mass spectrum, *m/z* (relative intensity) 167 (M^+, 52), 95 (100).

***N-tert*-Butyl-1-methylpyrrole-2-carboxamide (21).** A mixture of 1-methylpyrrole-2-carboxylic acid (8.0 g, 63.9 mmol) and sodium hydride (3.8 g, 128 mmol) in benzene (50 mL) was stirred for 10 min at 25 °C. Oxalyl chloride (21 mL, 245 mmol) was then added and the mixture boiled under reflux for 15 min. Benzene and excess oxalyl chloride were removed by evaporation

(11) "Vogel's Textbook of Practical Organic Chemistry", 4th ed.; Longman: London, 1978; p 1081.
(12) Gassman, P. G.; Hodgson, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275.
(13) Beak, P.; Zajdel, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 1010.
(14) Jones, R. G.; Gilman, H. *Org. React. (N.Y.)* **1951**, *6*, 353.
(15) Cymerman-Craig, J.; Noik, A. R. *J. Am. Chem. Soc.* **1962**, *84*, 3410.
(16) Kawabe, K.; Suzui, T.; Iguchi, M. *Yakugaku Zasshi* **1960**, *80*, 50; *Chem. Abstr.* **1960**, *54*, 12090.

under reduced pressure, the residue was taken up in ether (100 mL), *tert*-butylamine (9.4 g, 128 mmol) was added dropwise during 15 min, and the resulting solution was boiled under reflux for 2 h. The cooled solution was washed with water (3 × 10 mL), and the washings were extracted with $CHCl_3$ (5 × 20 mL). All organic solutions were combined and dried ($MgSO_4$) and the solvents removed by evaporation under reduced pressure to give the crude product (10.6 g). Recrystallization (C_6H_{12}/ethyl acetate) gave the pure amide **21** (10.5 g, 91%): mp 84–85 °C. Anal. Found: C, 66.4; H, 9.0; N, 15.4. Calcd for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.54. ^1H NMR ($CDCl_3$) δ 6.66 (1 H, dd, J = 2.5, 1.9 Hz, pyrrole 5-H), 6.43 (1 H, dd, J = 4.1, 1.9 Hz, pyrrole 3-H), 6.04 (1 H, dd, J = 4.1, 2.5 Hz, pyrrole 4-H), 5.71 (1 H, br s, NH), 3.92 (3 H, s, NCH_3), 1.43 (9 H, s, CCH_3); mass spectrum, m/z (relative intensity) 180 (M^+, 23), 108 (100).

General Methods for Lithiations. Method A: *n*- or *sec*-BuLi as Base, Hexane or Ether as Solvent. To the amide (5 mmol) in hexane or ether (50 mL) was added a solution of the organolithium reagent (*n*-BuLi in hexane, *sec*-BuLi in cyclohexane) at the required temperature. The mixture was stirred under an atmosphere of argon for the requisite time. The electrophile was then added, and the mixture was left for a further 15 min (unless stated otherwise; vide infra) and then allowed to attain 20 °C. The mixture was washed with water (3 × 10 mL), the organic solutions were dried ($MgSO_4$), and the solvents were evaporated under reduced pressure.

Method B: *n*- or *sec*-BuLi as Base, DME or THF as Solvent. The procedure was the same as above except that the solvents were removed by evaporation under reduced pressure prior to the washing with water. Solids were then suspended in ethyl acetate (200 mL), and the extraction process was continued as in Method A.

Method C: LDA as Base. To diisopropylamine (1.01 g, 10 mmol) in the required solvent at the required temperature was added *n*-BuLi (10.2 mmol) in hexane. The mixture was left for 5 min and the amide (5 mmol) was then added as a solution in the minimum amount of the required solvent. The experiment then continued as in Method A or B.

General Method for Amide Hydrolysis. Method D. The amide was boiled under reflux with aqueous H_2SO_4 (10% w/w, x mL) for 24 h under an atmosphere of argon. The resulting solution was saturated with NaCl and extracted with CH_2Cl_2 (7 × 20 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated under reduced pressure.

***N*-*tert*-Butyl-3-(trimethylsilyl)thiophene-2-carboxamide (8).** To the dilithio intermediate generated from **4** (1.0 g, 5.46 mmol) according to method B (from *n*-BuLi in THF at 0 °C for 0.5 h) was added Me_3SiCl (2.54 mL, 20 mmol) and the mixture stirred at 25 °C for 2 h. Water (3 mL) was added, and the solvent was removed by distillation under reduced pressure. The usual workup gave the crude product (1.83 g), which was purified by dry flash chromatography (hexane/ethyl acetate, 5% gradient) to give the amide **8** as a clear oil (1.34 g, 95%). Anal. Found: C, 56.7; H, 8.4; N, 5.3. Calcd for $C_{12}H_{21}NOSSi$: C, 56.42; H, 8.29; N, 5.48. ^1H NMR ($CDCl_3$) δ 7.29 (1 H, d, J = 4.83 Hz, thiophene 5-H), 7.12 (1 H, d, J = 4.83 Hz, thiophene 4-H), 5.71 (1 H, br s, NH), 1.45 (9 H, s, CCH_3), 0.34 (9 H, s, $SiCH_3$); IR (film) ν 1670 cm^{-1}; mass spectrum (CI, NH_3), m/z (relative intensity) 256 (M + 1, 99), 240 (100).

***N*-*tert*-Butyl-3-(methylthio)thiophene-2-carboxamide (9).** To the dilithio intermediate generated from **4** (1.0 g, 5.46 mmol) according to method B (from *n*-BuLi in THF at 0 °C for 0.5 h) was added Me_2S_2 (1.54 g, 16.4 mmol) and the mixture stirred at 25 °C for 12 h. The usual workup gave the crude product as a yellow oil (1.352 g), which was purified by dry flash chromatography (hexane/ethyl acetate, 5% gradient) to yield the pure thioether **9** (1.182 g, 93%) as a light tan oil. Anal. Found: C, 52.7; H, 6.8; N, 5.9. Calcd for $C_{10}H_{15}NOS_2$: C, 52.39; H, 6.60; N, 6.11. ^1H NMR ($CDCl_3$) δ 7.77 (1 H, br s, NH), 7.40 (1 H, d, J = 4.9 Hz, thiophene 5-H), 7.06 (1 H, d, J = 4.9 Hz, thiophene 4-H), 2.49 (3 H, s, SCH_3), 1.47 (9 H, s, CCH_3); IR (film) ν 1650 cm^{-1}; mass spectrum m/z (relative intensity) 229 (M^+, 33), 81 (100).

***N*-*tert*-Butyl-3-iodothiophene-2-carboxamide (10).** To the dilithio intermediate generated from **4** (1.0 g, 5.46 mmol) according to method B (from *n*-BuLi in THF at −78 °C for 0.5 h) was added iodine (4.16 g, 16.4 mmol) in THF (10 mL). The solution was left for 2 h at −78 °C and then for 12 h at 25 °C. The reaction mixture was then worked up as usual except that the solution in ethyl acetate was washed with aqueous sodium thiosulfate solution (10 mL) prior to the washing with water. The crude product was purified by preparative thin-layer chromatography (PTLC) (9:1 light petroleum–ethyl acetate as eluant) to give the 3-iodo compound **10** (1.21 g, 72%), as a white solid: mp 69–70 °C. (Anal. Found: C, 35.2; H, 4.1; N, 4.2. Calcd for $C_9H_{12}NOSI$: C, 34.96; H, 3.91; N, 4.53. ^1H NMR ($CDCl_3$) δ 7.34 (1 H, d, J = 4.9 Hz, thiophene 5-H), 7.07 (1 H, d, J = 4.9 Hz, thiophene 4-H), 6.72 (1 H, br s, NH), 1.46 (9 H, s, CCH_3); IR ($CHCl_3$) ν 1645 cm^{-1}; mass spectrum, m/z (relative intensity) 309 (M^+, 31), 237 (100).

Phenyl-[3-(2-(*N*-*tert*-butylcarbamoyl)thienyl)]methanol (11). To the dilithio intermediate generated from **4** (1.0 g, 5.46 mmol) as in method B (from *n*-BuLi in THF at −78 °C for 0.5 h) was added benzaldehyde (0.57 mL, 5.56 mmol). The solution was left for 2 h at −78 °C and then for 12 h at 25 °C. The usual workup gave the crude product, which was recrystallized (C_6H_{12}) to give the alcohol **11** (1.215 g, 77%) as white needles: mp 100–101 °C. Anal. Found: C, 66.6; H, 6.7; N, 4.7. Calcd for $C_{16}H_{19}NO_2S$: C, 66.42; H, 6.62; N, 4.84. ^1H NMR ($CDCl_3$) δ 7.42–7.23 (5 H, m, C_6H_5), 7.19 (1 H, d, J = 4.8 Hz, thiophene 5-H), 6.73 (1 H, d, J = 4.8 Hz, thiophene 4-H), 6.51 (1 H, br s, NH), 6.0 (1 H, s, OH), 1.30 (9 H, s, CCH_3); IR ($CHCl_3$) ν 1640 cm^{-1}; mass spectrum, m/z (relative intensity) 289 (M^+, 7), 215 (100).

***N*-*tert*-Butyl-*N*-methyl-3-methylthiophene-2-carboxamide (5).** To the dilithio intermediate generated from **4** (1.0 g, 5.46 mmol) as in general method B (from *n*-BuLi in THF at −78 °C for 0.5 h) was added methyl iodide (3.5 mL, 56 mmol). The mixture was stirred at −78 °C for 2 h and 25 °C for 12 h. The usual workup gave the crude product, which was purified by dry flash chromatography (hexane/ethyl acetate, 5% gradient) to give the pure amide **5** (1.094 g, 95%) as a white solid: mp 68–69 °C. Anal. Found: C, 62.8; H, 8.3; N, 6.4. Calcd for $C_{11}H_{17}NOS$: C, 62.54; H, 8.11; N, 6.63. ^1H NMR ($CDCl_3$) δ 7.20 (1 H, d, J = 5.5 Hz, thiophene 5-H), 6.76 (1 H, d, J = 5.5 Hz, thiophene 4-H), 2.91 (3 H, s, NCH_3), 2.25 (3 H, s, $ArCH_3$), 1.46 (9 H, s, CMe_3); IR (CCl_4) ν 1635 cm^{-1}; mass spectrum, m/z (relative intensity) 211 (M^+, 10), 125 (100).

2-(*N*-*tert*-Butylcarbamoyl)thiophene-3-carboxylic Acid (7). The dilithio intermediate generated from **4** (1.0 g, 5.46 mmol) as in general method B (from *n*-BuLi in THF at −78 °C for 0.5 h) was poured with stirring onto a slurry of solid CO_2 and Et_2O, and the mixture was left until the ethers had evaporated. The white solids were taken up in 0.01 M aqueous KOH (50 mL), and the solution was washed with EtOAc (2 × 10 mL). The aqueous layer was acidified to pH 1 (concentrated HCl), saturated with NaCl, and extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to yield the crude acid. Recrystallization (C_6H_{12}/CH_2Cl_2) gave the pure carboxylic acid **7** (0.919 g, 74%) as white needles: mp 185–186 °C. Anal. Found: C, 53.0; H, 5.8; N, 6.3. Calcd for $C_{10}H_{13}NO_3S$: C, 52.86; H, 5.77; N, 6.17. ^1H NMR (CD_2Cl_2) δ 7.71 (1 H, d, J = 5.54 Hz, thiophene 5-H), 7.39 (1 H, d, J = 5.54 Hz, thiophene 4-H), 7.30 (1 H, br s, NH), 1.44 (9 H, s, CCH_3); IR (KBr) ν 1687, 1610 cm^{-1}; mass spectrum, m/z (relative intensity) 227 (M^+, 14), 155 (100).

***N*-*tert*-Butyl-3-formylthiophene-2-carboxamide (13).** To the dilithio intermediate generated from **4** (1.0 g, 5.46 mmol) as in general method B (from *n*-BuLi in THF at −78 °C for 0.5 h) was added dimethylformamide (4.3 mL, 55.6 mmol), and the mixture was stirred at −78 °C for 2 h and at 25 °C for 12 h. The usual workup gave the crude product, which was purified by PTLC (19:1 hexane–ethyl acetate as eluant, five elutions) to give the pure aldehyde **13** (0.73 g, 63%) as a clear oil. Anal. Found: C, 57.1; H, 6.4; N, 6.5. Calcd for $C_{10}H_{13}NO_2S$: C, 56.86; H, 6.20; N, 6.63. ^1H NMR ($CDCl_3$) δ 9.92 (1 H, s, CHO), 9.60 (1 H, br s, NH), 7.53 (1 H, d, J = 5.52 Hz, thiophene 5-H), 7.47 (1 H, d, J = 5.52 Hz, thiophene 4-H), 1.49 (9 H, s, CCH_3); IR ($CHCl_3$) ν 1685, 1650 cm^{-1}; mass spectrum, m/z (relative intensity) 211 (M^+, 32), 139 (100).

***N*-*tert*-Butyl-3-benzylthiophene-2-carboxamide (12).** To the dilithio intermediate generated from **4** (1.0 g, 5.46 mmol) as in general method B (from *n*-BuLi in DME at −78 °C for 2 h) was added benzyl bromide (0.66 mL, 5.56 mmol), and the mixture was stirred at −10 °C for 2 h and for 12 h at 25 °C. The usual workup and purification by PTLC (17:3 hexane–ethyl acetate as

eluant, two elutions) gave the pure amide **12** as a white solid (1.133 g, 76%): mp 85–86 °C. Anal. Found: C, 70.6; H, 7.1; N, 4.8. Calcd for $C_{16}H_{19}NOS$: C, 70.31; H, 7.01; N, 5.13. ^1H NMR ($CDCl_3$) δ 7.23 (6 H, m, Ar), 6.82 (1 H, d, J = 5.6 Hz, thiophene 4-H), 5.59 (1 H, br s, NH), 4.26 (2 H, s, CH_2), 1.30 (9 H, s, CCH_3); IR ($CHCl_3$) ν 1650 cm^{-1}; mass spectrum, m/z (relative intensity) 273 (M^+, 27), 200 (100).

***N*-*tert*-Butyl-3-methylthiophene-2-carboxamide (6).** To the dilithio intermediate generated from **4** (1.0 g, 5.46 mmol) as in general method B (from *n*-BuLi in DME at −78 °C for 2 h) was added methyl iodide (0.35 mL, 5.56 mmol), and the mixture was stirred at −10 °C for 2 h and at 25 °C for 12 h. The usual workup and purification by PTLC (19:1 hexane–ethyl acetate as eluant, two elutions) gave the pure amide **6** (0.947 g, 88%) as a waxy solid: mp 32–34 °C. Anal. Found: C, 61.2; H, 7.9; N, 6.8. Calcd for $C_{10}H_{15}NOS$: C, 60.88; H, 7.66; N, 7.10. ^1H NMR ($CDCl_3$) δ 7.18 (1 H, d, J = 4.9 Hz, thiophene 5-H), 6.83 (1 H, d, J = 4.98 Hz, thiophene 4-H), 5.63 (1 H, br s, NH), 2.47 (3 H, s, aryl CH_3), 1.45 (9 H, s, CCH_3); IR (film) ν 1640 cm^{-1}; mass spectrum, m/z (relative intensity) 197 (M^+, 42), 125 (100).

***N*-*tert*-Butyl-*N*-methylthiophene-2-carboxamide (20).** To sodium hydride (1.57 g, 65.6 mmol) in THF at 25 °C was added *N*-*tert*-butylthiophene-2-carboxamide (**4**) (6.0 g, 32.8 mmol). The mixture was stirred for 0.5 h, and methyl iodide (4.1 mL, 65.6 mmol) was added. The mixture was left for 2 h at 25 °C and filtered and the THF removed by evaporation under reduced pressure. The resulting solid material was suspended in ethyl acetate (100 mL), and the mixture was washed with water (3 × 10 mL) and dried ($MgSO_4$). Evaporation of the solvent and recrystallization ($C_6H_{12}/CHCl_3$) gave the pure amide **20** (6.33 g, 98%) as white rods: mp 97–98 °C. Anal. Found: C, 61.0; H, 7.8; N, 6.9. Calcd for $C_{10}H_{15}NOS$: C, 60.89; H, 7.67; N, 7.10. ^1H NMR ([$^2H_6$]acetone) δ 7.53 (1 H, d, J = 4.98 Hz, thiophene 5-H), 7.34 (1 H, d, J = 2.2 Hz, thiophene 3-H), 7.03 (1 H, dd, J = 4.98, 2.2 Hz, thiophene 4-H), 3.10 (3 H, s, NCH_3), 1.44 (9 H, s, CCH_3); IR (KBr disk) ν 1605 cm^{-1}; mass spectrum, m/z (relative intensity) 197 (M^+, 13), 111 (100).

***N*-*tert*-Butyl-3-(trimethylsilyl)furan-2-carboxamide (17).** To the dilithio intermediate generated from **14** (0.8 g, 4.79 mmol) as in general method B (from *sec*-BuLi in DME at −78 °C for 1 h) was added Me_3SiCl (0.53 g, 4.89 mmol), and the mixture was stirred at −78 °C for 1 h and for 12 h at 25 °C. The usual workup and purification by PTLC (9:1 hexane–ethyl acetate as eluant) gave the pure amide **17** (1.030 g, 90%) as a clear oil. Anal. Found: C, 60.3; H, 9.0; N, 5.8. Calcd for $C_{12}H_{21}NO_2Si$: C, 60.21; H, 8.84; N, 5.85. ^1H NMR ($CDCl_3$) δ 7.37 (1 H, d, J = 1.9 Hz, furan 5-H), 6.44 (1 H, d, J = 1.9 Hz, furan 4-H), 6.24 (1 H, br s, NH), 1.44 (9 H, s, CCH_3), 0.31 (9 H, s, $SiCH_3$); IR (film) ν 1680 cm^{-1}; mass spectrum, m/z (relative intensity) 239 (M^+, 11), 168 (100).

2-(*N*-*tert*-Butylcarbamoyl)furan-3-carboxylic Acid (16). The dilithio intermediate generated from **14** (0.8 g, 4.79 mmol) as in general method B (from *sec*-BuLi in DME at −78 °C for 1 h) was poured with stirring onto a slurry of solid CO_2 and Et_2O, and the mixture was left for 4 h. Solvents were removed by evaporation under reduced pressure, the resulting solid material was taken up in water (100 mL), and the solution was washed with CH_2Cl_2 (2 × 10 mL). The aqueous layer was acidified to pH 1 (concentrated aqueous HCl), saturated with NaCl, and extracted with ethyl acetate (6 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give the crude product. Recrystallization ($C_6H_{12}/CHCl_3$) yielded the pure acid **16** (0.889 g, 88%) as white needles: mp 125–126 °C. Anal. Found: C, 57.0; H, 6.1; N, 6.6. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. ^1H NMR ([$^2H_6$]acetone) δ 8.03 (1 H, br s, NH), 7.74 (1 H, d, J = 2.23 Hz, furan 5-H), 6.95 (1 H, d, J = 2.23 Hz, furan 4-H), 1.52 (9 H, s, CCH_3); IR (KBr disk) ν 1720, 1600 cm^{-1}; mass spectrum, m/z (relative intensity) 211 (M^+, 26), 139 (100).

***N*-*tert*-Butyl-3-(methylthio)furan-2-carboxamide (18).** To the dilithio intermediate generated from **14** (0.8 g, 4.79 mmol) as in general method B (from *sec*-BuLi in DME at −78 °C for 1 h) was added dimethyl disulfide (0.461 g, 4.89 mmol), and the mixture was stirred at −78 °C for 1 h and then for 12 h at 25 °C. The usual workup and purification by PTLC (9:1 hexane–ethyl acetate as eluant, seven elutions) gave the amide **18** (0.817 g, 80%) as white crystals: mp 71–72 °C. Anal. Found: C, 56.5; H, 7.0; N, 6.5. Calcd for $C_{10}H_{15}NO_2S$: C, 56.32; H, 7.09; N, 6.57. ^1H NMR ($CDCl_3$) δ 7.35 (1 H, d, J = 2.2 Hz, furan 5-H), 6.46 (1 H, d, J = 2.2 Hz, furan 4-H), 6.22 (1 H, br s, NH), 2.43 (3 H, s, SCH_3), 1.44 (9 H, s, CCH_3); IR ($CHCl_3$) ν 1650 cm^{-1}; mass spectrum, m/z (relative intensity) 213 (M^+, 24), 141 (100).

***N*-*tert*-Butyl-3-iodofuran-2-carboxamide (19).** To the dilithio intermediate generated from **14** (0.8 g, 4.79 mmol) as in general method B (from *sec*-BuLi in DME at −78 °C for 1 h) was added iodine (1.24 g, 4.89 mmol) in DME (10 mL). The mixture was stirred at −78 °C for 1 h and for 12 h at 25 °C. The reaction mixture was worked up as usual except that the solution in ethyl acetate was washed with saturated aqueous sodium thiosulfate solution (1 × 10 mL) prior to the washing with water. The crude product was purified by PTLC (9:1 hexane–ethyl acetate as eluant, four elutions) to give the pure amide **19** (1.235 g, 88%) as white crystals: mp 95–96 °C. Anal. Found: C, 36.6; H, 4.0; N, 4.6. Calcd for $C_9H_{12}NO_2I$: C, 36.86; H, 4.13; N, 4.78. ^1H NMR ($CDCl_3$) δ 7.36 (1 H, d, J = 2.2 Hz, furan 5-H), 6.61 (1 H, d, J = 2.2 Hz, furan 4-H), 6.25 (1 H, br s, NH), 1.44 (9 H, s, CCH_3); IR ($CHCl_3$) ν 1670 cm^{-1}; mass spectrum, m/z (relative intensity) 293 (M^+, 24), 221 (100).

***N*-*tert*-Butyl-*N*-methyl-3-methylfuran-2-carboxamide (15).** To the dilithio intermediate generated from **14** (0.8 g, 4.79 mmol) as in general method B (from *sec*-BuLi in DME at −78 °C for 1 h) was added methyl iodide (3.0 mL, 48 mmol). The mixture was stirred for 1 h at −78 °C and for 12 h at 25 °C. The usual workup and purification by PTLC (9:1 hexane–ethyl acetate as eluant) gave the pure amide **15** (0.803 g, 86%) as white rods: mp 53–55 °C. Anal. Found: C, 67.6; H, 8.9; N, 7.4. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. ^1H NMR ($CDCl_3$) δ 7.31 (1 H, d, J = 2.0 Hz, furan 5-H), 6.62 (1 H, d, J = 2.0 Hz, furan 4-H), 2.92 (3 H, s, aryl CH_3), 2.23 (3 H, s, NCH_3), 1.45 (9 H, s, CCH_3); IR ($CHCl_3$) ν 1625 cm^{-1}; mass spectrum, m/z (relative intensity) 195 (M^+, 11), 109 (100).

Thiophene-2,3-dicarboxylic Acid (23). The amide **7** (0.1 g, 0.441 mmol) was hydrolyzed following general method D (x = 50). Recrystallization (C_6H_{12}/ethyl acetate) of the resulting white solid gave the pure diacid **23** (0.058 g, 92%) as white needles: mp 270–271 °C (lit.[17] mp 270–272 °C); ^1H NMR ($CDCl_3$) δ 9.3 (2 H, br s, OH), 7.88 (1 H, d, J = 4.84 Hz, thiophene 5-H), 7.67 (1 H, d, J = 4.84 Hz, thiophene 4-H); mass spectrum, m/z (relative intensity) 172 (M^+, 21), 111 (100).

3-Formylthiophene-2-carboxylic Acid (24). The 3-formyl amide **13** (0.1 g, 0.47 mmol) was hydrolyzed following general method D (x = 50). Recrystallization (C_6H_{12}/ethyl acetate) of the resulting solid gave the pure acid **24** (0.068 g, 92%): mp 129–130 °C (lit.[18] mp 130–131 °C); ^1H NMR ($CDCl_3$) δ 10.39 (1 H, s, CHO), 9.66 (1 H, br s, OH), 7.63 (2 H, m, thiophene 4-H and 5-H); mass spectrum m/z (relative intensity) 156 (M^+, 23), 111 (100).

3-Iodothiophene-2-carboxylic Acid (25). The 3-iodo amide **10** (0.1 g, 0.324 mmol) was hydrolyzed following general method D (x = 50). Recrystallization ($C_6H_{12}/CHCl_3$) of the resulting solid gave the pure 3-iodo 2-carboxylic acid **25** (0.082 g, 99%) as white needles: mp 194–196 °C (lit.[19] mp 193–195 °C); ^1H NMR ([$^2H_6$]acetone) δ 7.91 (1 H, d, J = 5.18 Hz, thiophene 5-H), 7.31 (1 H, d, J = 5.18 Hz, thiophene 4-H).

Thiophene-2-carboxylic Acid (22). (a) From *N*-*tert*-Butylthiophene-2-carboxamide (4). The amide **4** (1.0 g, 5.46 mmol) was hydrolyzed following general method D (x = 75). Recrystallization ($C_6H_{12}/CHCl_3$) of the resulting solid gave the pure acid **22** (0.664 g, 95%) as white needles: mp 126–127 °C (lit.[20] mp 123–124 °C).

(b) From *N*-*tert*-Butyl-3-(trimethylsilyl)thiophene-2-carboxamide (8). The amide **8** (0.1 g, 0.375 mmol) was hydrolyzed following general method D (x = 7.5) and purified as in a to give the desilylated product **22** (0.042 g, 88%): mp 128–129 °C.

Methyl Thiophene-2-carboxylate from *N*-*tert*-Butyl-3-(trimethylsilyl)thiophene-2-carboxamide (8). To the amide **8** (0.15 g, 0.59 mmol) in THF (10 mL) was added sodium hydride

(17) Reinecke, M. G.; Newsom, J. G.; Almqvist, K. A. *Synthesis* **1980**, 327.
(18) Michael, U.; Gronowitz, S. *Acta Chem. Scand.* **1968**, *22*, 1353.
(19) Gronowitz, S.; Holm, B. *Acta Chem. Scand., Ser. B* **1976**, *30*, 505.
(20) Steinkopf, W.; Ohse, W. *Justus Liebigs Ann. Chem.* **1924**, *437*, 14.

(0.029 g, 1.2 mmol), and the mixture was stirred for 0.5 h at 25 °C. Methyl iodide (0.075 mL, 1.2 mmol) was added and the mixture left at 25 °C for a further 0.5 h. The precipitate was filtered off and the solvent evaporated. To the residue was added aqueous KOH solution (40% w/w, 10 mL) and MeOH (10 mL), and the mixture was boiled under reflux for 12 h. The solution was acidified to pH 4 (concentrated HCl) and extracted with CH_2Cl_2 (7 × 20 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated. The crystalline residue was dissolved in Et_2O (50 mL) and the solution treated with ethereal diazomethane. Removal of excess of diazomethane and the solvent gave the methyl ester (0.078 g, 93%): ^1H NMR ($CDCl_3$) δ 7.78 (1 H, d, J = 3.4 Hz, thiophene 3-H), 7.54 (1 H, d, J = 4.5 Hz, thiophene 5-H), 7.09 (1 H, dd, J = 4.5, 3.4 Hz, thiophene 4-H), 3.83 (3 H, s, OCH_3); mass spectrum, m/z (relative intensity) 142 (M^+, 24), 111 (100).

Acknowledgment. A.J.C. is indebted to the SERC UK for a research studentship.

Registry No. **2**, 14313-93-0; **4**, 90642-98-1; **4** (dilithio intermediate), 98331-18-1; **5**, 98331-02-3; **6**, 76656-00-3; **7**, 98331-03-4; **8**, 98331-04-5; **9**, 98331-05-6; **10**, 98331-06-7; **11**, 98331-07-8; **12**, 98331-08-9; **13**, 98331-09-0; **14**, 98331-10-3; **14** (dilithio intermediate), 98331-19-2; **15**, 98331-11-4; **16**, 98331-12-5; **17**, 98331-13-6; **18**, 98331-14-7; **19**, 98331-15-8; **20**, 98331-16-9; **21**, 98331-17-0; **23**, 1451-95-2; **24**, 19991-68-5; **25**, 60166-84-9; LDA, 4111-54-0; *sec*-BuLi, 598-30-1; *n*-BuLi, 109-72-8; thiophene-2-carboxylic acid, 527-72-0; furan-2-carboxylic acid, 88-14-2; methyl thiophene-2-carboxylate, 5380-42-7; 5-(*N*,*N*-diethylcarboxamide)-2-thiophenecarboxylic acid, 98331-20-5; 5-deuterio-*N*,*N*-diethyl-2-thiophenecarboxamide, 98331-21-6; 2-(*N*,*N*-diethylcarboxamide)-3-thiophenecarboxylic acid, 98331-22-7; 5-(*N*-*tert*-butylcarbamoyl)thiophene-2-carboxylic acid, 98331-23-8; 5-(*N*-*tert*-butylcarbamoyl)furan-2-carboxylic acid, 98331-24-9; 2-(*N*-*tert*-butylcarbamoyl)-1-methylpyrrole-3-carboxylic acid, 98331-25-0; 5-(*N*-*tert*-butylcarbamoyl)-1-methylpyrrole-2-carboxylic acid, 98331-26-1; 1-methylpyrrole-2-carboxylic acid, 6973-60-0.

Efficient and Convenient Method for Synthesis of Solenopsin A and Its Analogues Using 1-Benzyl-2,6-dicyanopiperidine

Kazumasa Takahashi,* Hideki Kurita, Katsuyuki Ogura, and Hirotada Iida

Department of Synthetic Chemistry, Faculty of Engineering, Chiba University, Yayoi-cho, Chiba 260, Japan

Received April 30, 1985

An efficient synthetic sequence proposed here provides a new method for preparation of not only solenopsin A, i.e., *trans*-2-methyl-6-undecylpiperidine, but also coniine, i.e., 2-propylpiperidine, and other 2,6-dialkylpiperidine alkaloids: A reaction of 1-benzyl-2,6-dicyanopiperidine (**1**) with alkyl halides selectively gives 2-alkyl- and 2,6-dialkyl-1-benzyl-2,6-dicyanopiperidines (**2** and **3**), decyanation of which affords respectively 2-alkyl- and 2,6-dialkyl-1-benzylpiperidines (**4** and **5**) in high yields.

In our previous paper, the stereoselective synthesis and the utility as synthetic reagents of 1-substituted 2,6-dicyanopiperidines have been reported.[1] We report here a new synthetic method for preparation of 2-alkyl- and 2,6-dialkylpiperidine alkaloids **6** and **7** using 1-benzyl-2,6-dicyanopiperidine (**1**). Reaction of **1** with various alkyl halides gave 2-alkyl- and 2,6-dialkyl-1-benzyl-2,6-dicyanopiperidines **2** and **3** in high yields. When the alkylated products **2** and **3** were heated at 70 °C with sodium borohydride in isopropyl alcohol, decyanation took place to give 2-alkyl- and 2,6-dialkyl-1-benzylpiperidines **4** and **5**.[3b] The subsequent debenzylation of **4** and **5** by catalytic hydrogenolysis[2] proceeded smoothly to give 2-monoalkyl- and 2,6-dialkylpiperidine alkaloids **6** and **7**, respectively (Scheme I). Solenopsin A, *trans*-2-methyl-6-*n*-undecylpiperidine (**7a**), which is a component in the venom of the fire ant (*Solenopsis saevissima*), is conveniently prepared by the present method. Several synthetic routes to solenopsin A have been reported: 2,6-Dimethylpyridine,[3a] 2-picoline,[3b] unsymmetrical alkane-2,5-diones,[3c] *N*-(methoxycarbonyl)-2-alkylpyridinium salts,[3d] α-alkylcyclopentanones,[3e] and 6-methyl-2-piperidone[3f] have been used as starting materials. Many of these methods, however, lack effective procedures or require starting materials which are difficult to synthesize. However, the present method is useful for preparation of not only solenopsin A but also other 2-alkylated and 2,6-dialkylated piperidines (**6** and **7**).

The alkylation of 1-phenyl-2,6-dicyanopiperidine gave predominantly symmetrical dialkylated products as reported in our previous paper.[2] Alkylation of the benzyl compound **1**, however, selectively gave monoalkylated products **2**. The selective formation of **2** is important for the subsequent preparation of unsymmetrical dialkylated products **3**. For example, the reaction of **1** with methyl iodide in tetrahydrofuran containing lithium isopropylamide gave 1-benzyl-2,6-dicyano-2-methylpiperidine (**2a**) in 82% yield. Likewise, the reaction of **1** with undecyl, tridecyl, *n*-propyl, and benzyl bromides gave the 2-alkyl-1-benzyl-2,6-dicyanopiperidines **2b**, **2c**, **2d**, and **2e** in 83–90% yields. The monoalkylated products **2** were isolated by means of column chromatography using Florisil. When silica gel was used, the products **2** decomposed on the column. The monoalkylated products such as **2b** and **2c** are easily isolated from a reaction mixture containing unreacted **1**, but isolation of **2a** and **2d** having shorter polymethylene chains is very difficult. Accordingly, the yields of **2a** and **2d** were estimated from the ^1H NMR spectra of the purified reaction mixture containing **1**.

(1) Takahashi, K.; Mikajiri, T.; Kurita, H.; Ogura, K.; Iida, H. *J. Org. Chem.*, accompanying paper in this issue.
(2) Hartung, W. H.; Simonoff, R. *Org. React.* (*N.Y.*) **1953**, *7*, 263.
(3) (a) MacConnell, J. G.; Blum, M. S.; Fales, H. M. *Tetrahedron 27*, 1971, 1129. (b) Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1982**, *23*, 3369. (c) Abe, K.; Okumura, H.; Tsugoshi, T.; Nakamura, N. *Synthesis* **1984**, 597. (d) Nakazono, Y.; Yamaguchi, R.; Kawanishi, M.; *Chem. Lett.* **1984**, 1129. (e) Matsumura, Y.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1982**, *23*, 1929. (f) Hill, R. K.; Yuri, T. *Tetrahedron* **1977**, *33*, 1569.

0022-3263/85/1950-4368$01.50/0