Regioselective α- and β-Metallations of Thiophene Derivatives Bearing the 4,4-Dimethyloxazolin-2-yl Group. Application of the Method to Syntheses of 2,3- and 2,5-Disubstituted Thiophene Derivatives†

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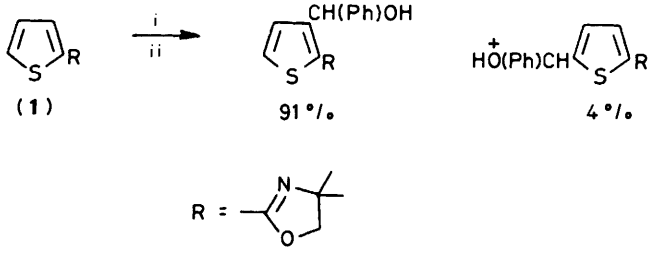
The effects of change of solvent, metallating agent, reaction time and temperature, and of the presence or absence of agents capable of complex formation with either the lithium cation or the oxazoline moiety, on the lithiation of 4,4-dimethyl-2-(2-thienyl)oxazoline are explored. Conditions are thereby established for high-yielding syntheses of the 3- and 5-lithio-intermediates and for control of regioselectivity of metallation. The nucleophilicity of the 3-lithio-intermediate is profoundly solvent dependent, and appropriate conditions for reaction of both 3- and 5-lithiated species with a wide variety of electrophiles are presented. Syntheses of a range of 2,3- and 2,5-disubstituted thiophene derivatives have thereby been achieved, utilising, in addition, a new method for the transformation of oxazolino into carboxy functionality.

The balance between basicity and nucleophilicity of the 3-lithio-intermediate in its reaction with [$^1H_6$]- and [$^2H_6$]-acetone is shown to be sensitive to isotope effects.

Furan, thiophene, and *N*-alkylpyrroles undergo electrophilic substitution and metallation predominantly at α-positions. New methodology for the preparation of β-substituted derivatives is therefore valuable.

In 1977, Vecchia and Vlattas[1] reported briefly on the ability of the oxazolino substituent at an α-position in thiophene to direct metallation into the adjacent β-position. Work-up of the metallated intermediates with benzaldehyde gave predominantly a 2,3-disubstituted product in high yield (Scheme 1):



Scheme 1. *Reagents:* i, Bu^{n}Li, Et_2O, −70 to 25 °C; ii, PhCHO

reactions with other electrophiles were not explored. More recently,[2] Ribéreau and Quéguiner have investigated the effect of change in composition of a variety of solvent mixtures (based, principally, on hexane, diethyl ether, and tetrahydrofuran), temperature, and starting material concentration on the progress of the reaction between n-butyl-lithium and 2-(2-thienyl)oxazoline (**1**) and have shown, through work-up of the lithio intermediates with chlorotrimethylsilane (TMSCl), CH_3OH, and CH_3OD that β-lithiation is kinetically controlled. Although broadly self-consistent, their results display some anomalies depending on the nature of the electrophile.

In view of our continuing interest in the metallation of heteroaromatic systems[3] and of the synthetical versatility of the oxazolino moiety[4] we have sought to establish conditions not only for high-yielding and regioselective syntheses of the 3- and 5-lithio intermediates derived from (**1**), but also for their subsequent reaction with a wide range of electrophiles. The successful outcome of these investigations, which considerably extend and complement the previous work discussed above, and which include studies of the role of solvent, time, temperature, and metallating agent and the effects of the presence or absence of agents capable of complex formation with either the lithium cation or the oxazoline nitrogen (or oxygen) atom, is reported here.

Results and Discussion

Regioselectivity of Metallation of (**1**).—In Table 1 are presented the results of a range of experiments designed to elucidate the factors affecting regioselectivity of metallation. The extent of lithiation was generally estimated, as in our previous work,[3] by quenching of the reaction mixtures with an excess of either CH_3OD or D_2O and integration of the aromatic ring ^1H n.m.r. signals. The two electrophiles gave identical results to within experimental error (*cf.* entries 14 and 15). Work-up with TMSCl gave broadly similar indications (*vide* entries 7 and 19) and a very close correspondence between analytical results derived from integration of ^1H n.m.r. ring signals and from g.l.c. analysis for the case of a mixture of the 3- and 5-methylthienyloxazolines (**2**) and (**25**) has been found (*vide infra*). We are confident, therefore, that the deuteriation experiments provide a simple but sufficiently reliable monitoring technique for present purposes.

Greatest selectivity for β-lithiation of (**1**) is found when hexane is the solvent and n-butyl-lithium the metallating agent in a heterogeneous reaction mixture at −78 °C. Presumably a 'co-ordination only' mechanism (following the terminology espoused by Gschwend and Rodriguez[5]) is in operation (Figure 1). Inclusion of the Li^+-complexing diamine *N,N,N',N'*-tetra-

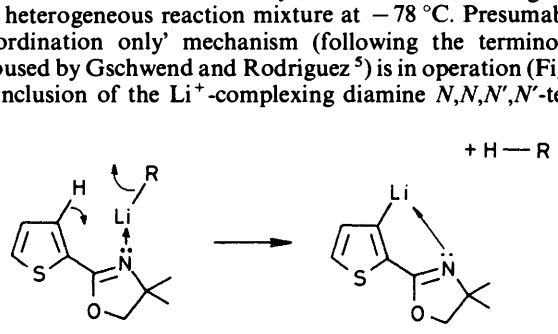


Figure 1.

† Some of the results described herein were presented in preliminary form at the R.S.C. Heterocyclic Group Symposium, Queen Elizabeth College, London, January 1984.

Table 1. Lithiation of 4,4-dimethyl-2-(2-thienyl)oxazoline (**1**)

Expt.	Solvent[a]	Temp. (°C)	RLi[b]	Time (min)	Additives	Electrophile	Product composition (%)[c] derived from 3-Lithiation	5-Lithiation	Recovered Yield[d]
1	A	−78	X	30		D_2O	71	0	98
2	A	−78	X	120		D_2O	38	0	88
3	A	0	X	30		MeOD	64	0	85
4	A	0	X	15		MeOD	70	0	90
5	A	20	X	30		MeOD	71	0	80
6	A	20	X	15		MeOD	68	0	89
7	A	−78	X	30		TMSCl	85	0	86
8	A	−78	X	30	TMEDA	D_2O	24	49	100
9	A	0	X	30	TMEDA	D_2O	70	21	100
10	A	−78	Y	30		D_2O	54	0	100
11	A	−78	Y	30	TMEDA	D_2O	17	41	94
12[e]	TMEDA	−78	X	30		D_2O	12	18	100
13	TMEDA	0	X	30		D_2O	0	11	96
14	B	−78	X	30		MeOD	60	32	100
15	B	−78	X	30		D_2O	58	35	76
16	B	−19	X	30		MeOD	54	35	91
17	B	−78	Y	30		D_2O	5	74	83
18	B	−78	Y	30	TMEDA	MeOD	18	82	100
19	B	−78	X	30		TMSCl	59	41	88
20	B	−78	X	30		CO_2	39	36	100
21	C	−78	Y	30		MeOD	0	82	71
22	C	0	Y	30		MeOD	0	74	96
23	C	0	Y	120		MeOD	0	73	92
24	C	0	Y	120		MeOD	0	74	100
25	C	67	Y	30		MeOD	5	57	98
26	D	−78	X	30		MeOD	25	18	97
27	D	−78—0	X	15 then 30		PhCHO	100	0[f]	100
28	B	−78	X	30	CuF_2	MeOD	11	35	87
29	A	−78	Y	30	CuF_2	MeOD	41	0	100
30	A	−78	X	30	BF_3·Et_2O	MeOD	70	0	99
31	A	−78—0	X	30		CO_2	80	0	98
32	B	−78	X	30		MeI	29[g]	46[g]	98

[a] A = hexane, B = DME, C = THF, D = Et_2O. [b] X = Bu^nLi, Y = LDA. [c] Estimated by n.m.r. analysis (see text) and expressed as a percentage of the recovered yield. Starting oxazoline (**1**) constitutes the balance to 100%. [d] Constitution (in mol) estimated by n.m.r. analysis and expressed as a percentage with respect to the molarity of starting material. [e] TMEDA crystallised out during this experiment. [f] Product from 5-lithiation could not be detected by n.m.r. analysis owing to overlap of signals: the presence of a 4.1% yield of this material is reported in ref. 1. [g] The corresponding figures from g.l.c. analysis are 30 and 47%.

methylethylenediamine (TMEDA) in the reaction mixture at −78 °C (entry 8) gives no increase in the overall lithiation level but leads to a decrease in regioselectivity and the emergence of the 5-lithio intermediate. Use of lithium di-isopropylamide (LDA) instead of Bu^nLi in hexane at −78 °C (entry 10) gives lower overall lithiation, which may be a reflection of the reagent's reduced basicity. Addition of TMEDA substantially raises the lithiation level (entry 11), but 5-lithiation then predominates.

Change of solvent to 1,2-dimethoxyethane (DME) confers homogeneity on the reaction mixtures (entries 14—20), permits generally greater total lithiation, and shifts the bias for selectivity from 3- towards 5-metallation compared with the situation when hexane is the solvent. This last observation contrasts significantly with the results of our previous study on the furan- and *N*-methylpyrrole-oxazolines[3b] where DME is the solvent of choice for the achievement of high selectivity for 3-metallation. We argued that partial or complete 'de-oligomerisation' of the Bu^nLi hexamer by the DME would assist subsequent complex formation between the oxazoline moiety and Bu^nLi and hence encourage 3-metallation. This is clearly an over-simplification. Disruption of the Bu^nLi hexamer, whilst assisting oxazoline–Bu^nLi complex formation, may also enhance the kinetic basicity of the organolithium reagent and hence accelerate 5-metallation by the acid–base mechanism. Furthermore, we have shown previously[6] that furan and thiophene display differential sensitivities towards the effect of change of solvent on the rate of 2-metallation by Bu^nLi: when the solvent is hexane, thiophene is lithiated more slowly than furan, but when TMEDA is added or ether is used instead of hexane, then thiophene is lithiated more rapidly than furan. It seems that thiophene reacts less rapidly than furan under conditions where ionisation of the C–Li bond is not encouraged. We have suggested that this may be a consequence of the superior ability of oxygen to interact synergically with lithium (which is a σ donor and a π-acceptor) (Figure 2a) as compared with sulphur: the more ionic the C–Li bond becomes, the less is this synergesis realisable and the more do carbanion stabilisation effects become dominant (Figure 2b). The 3-lithio intermediates are probably intrinsically less ionic than their 2-substituted counterparts (Figure 2c) and the rate of their formation would therefore be expected to be less sensitive to the operation of the above effects. Replacement of Bu^nLi by

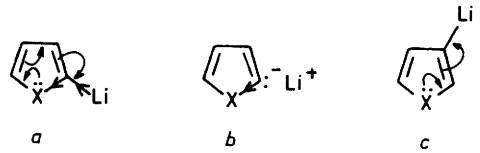


Figure 2.

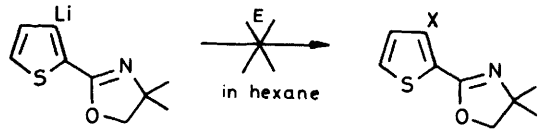
LDA as the metallating agent (entries 17 and 18, Table 1) leads to predominant 5-lithiation. LDA has been described as a 'co-ordinatively saturated' reagent:[5] as such, it would be expected to eschew oxazoline co-ordination preferring acid–base controlled α-lithiation, as is observed.

Hitherto, selectivity for 5-lithiation may best be achieved (entry 18) with the LDA–DME–TMEDA mixture (β-: α-lithiation 1:4.6; yield 100%) but this can be improved upon by change of solvent to tetrahydrofuran (THF) (entry 21), no product from 3-lithiation being detected. Increase in the temperature of the reaction mixture from −78 to 0 °C (entries 22—24) leads to somewhat lower deuteriation levels, perhaps as a result of proton abstraction from the solvent, and boiling of the mixture under reflux (entry 25) leads to further reduction in the deuteriation level and the emergence of a small amount of β-deuteriated material.

The use of diethyl ether as the metallation solvent has been reported briefly by Vecchia and Vlattas[1] as affording high selectivity for 3-metallation: this is confirmed in the present work (Table 1, entry 27) and in the studies of Ribéreau and Quéguiner.[2]

Finally, the possibility that addition of Lewis acids might serve to 'switch off' the directing effect of the oxazoline group has been explored for CuF_2 and BF_3·Et_2O (entries 28—30). The figures for the former show a decrease in the level of β-lithiation (*cf.* entries 28 and 29 with 14 and 10 respectively) indicative of competitive complexation by the CuF_2 at the oxazoline nitrogen, but the effect is not large. The latter seems to have no effect (*cf.* entries 30 and 1) perhaps indicating preferential complexation by boron at the oxazoline or diethyl ether oxygen atoms.

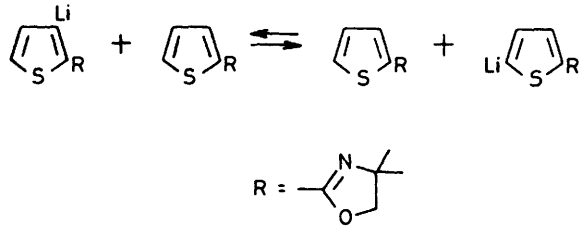
Synthetical Applications.—With conditions established for high-yielding and regioselective lithiations at the 3- and 5-positions of (**1**), attention has subsequently been directed towards an exploration of the scope and limitations of the reactions of the lithio-intermediates with a wide range of electrophiles. In particular, reliable and general routes to 2,3-disubstituted thiophenes have been sought, since such compounds are not easily obtained by traditional methods. However, the 3-lithio-derivative of (**1**), when prepared under conditions affording maximum selectivity for 3-metallation (Bu^nLi/hexane/−78 °C/0.5 h), fails to react with a wide range of electrophiles (Scheme 2), recovery of starting material being



Scheme 2. E = DMF or MeI (at 20 or 68 °C), or any one of $MeOSO_2CF_3$, $PhOCH(OEt)_2$, allyl bromide, MeCN, methyl vinyl ketone, tosyl azide, I_2, MeCHO, or Me_2CO (all at 20 °C).

very high in all cases. (It is probable that acetonitrile, methyl vinyl ketone, acetaldehyde, and acetone suffer deprotonation by the lithiothienyloxazoline: this has been proved to be the case when acetone and acetonitrile are the electrophiles, *vide infra.*) This lack of nucleophilicity of the lithio-intermediate, at first sight surprising, presumably stems from the heterogeneity of the reaction mixture and the aggregated nature of the intermediate.

The question naturally arises as to whether there are appreciable, intrinsic, differences in reactivity between the 3- and 5-lithio-derivatives of (**1**) generated under circumstances in which aggregation effects are minimised. The conditions of experiment 14 (Table 1) were therefore used to generate a mixture of the 3- and 5-metallated intermediates in DME. Work-up with MeOD, D_2O, and TMSCl respectively gives essentially the same result in each case (entries 14, 15, and 19, Table 1), as noted previously. However, when iodomethane is the electrophile (entry 32, Table 1), n.m.r. and g.l.c. analyses of the product mixture indicate a substantial decrease in the concentration of product derived from the 3-lithio-intermediate (29% by n.m.r., 30% by g.l.c.), and a small increase in that derived from the 5-lithio-isomer (46% by n.m.r., 47% by g.l.c.). These results imply that iodomethane is a more selective electrophile than MeOD, D_2O, and TMSCl and that the 3-lithio-intermediate is inherently less reactive than the 5-intermediate as a result of the proximate oxazoline group. The small increase in the concentration of the 5-substituted product over that expected on the basis of the results with the more reactive (and unselective) electrophiles may arise from a transmetallation process (Scheme 3). The occurrence of transmetallation



Scheme 3.

equilibria has been proposed previously by us for the case of lithio-*N*-methylpyrroles[6] and, very recently, by Ribéreau and Quéguiner[2] for the lithio-thienyloxazoline system, when the starting thienyloxazoline is present in large excess over the Bu^nLi.

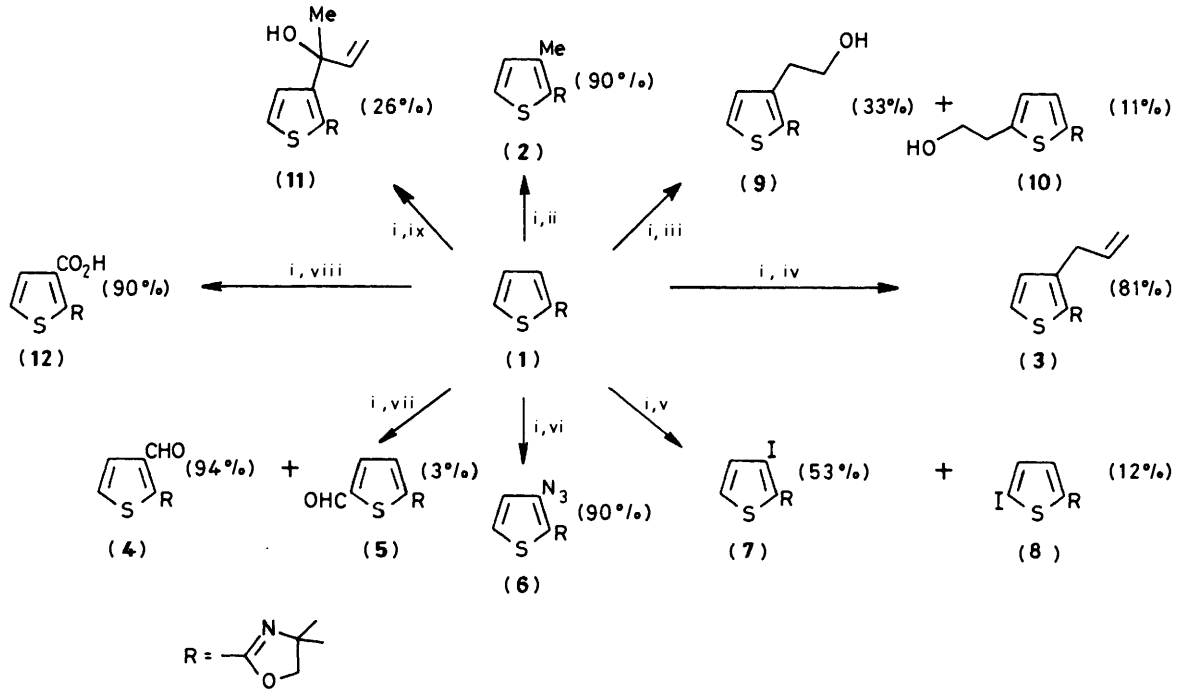
In Table 2 are summarised the results of experiments designed to explore the possibility of enhancement of the nucleophilicity of the 3-lithio-intermediate, generated in hexane, through the addition of Li^+-complexing agents or Lewis acids, or *via* change of cation.[7] Only TMEDA proved to have any appreciable effectiveness in this connection. The yields of 2,3-disubstituted products are still not synthetically useful, however, and transmetallation becomes significant when the lithio-intermediate is left for longer than a few minutes in contact with TMEDA (*cf.* entries 33 and 35). (Experiment 41, with TMSCl as electrophile, provides a check that the TMEDA is not significantly deprotonated by the lithio-intermediate throughout the duration of the experiments listed in Table 2.)

Successful reactions between the 3-lithio-thienyloxazoline and a wide range of electrophiles may be achieved by change of solvent from hexane to ether. Use of the latter leads to a homogeneous reaction mixture, and a presumably less aggregated[8] lithio-intermediate, whilst sacrificing little in regioselectivity (*vide supra*). Under the conditions shown in Scheme 4, the 3-lithio-thienyloxazoline behaves as a moderately reactive nucleophile (several of the electrophiles being used in large excess). Particularly high yields are achievable with the non-protic electrophiles CO_2, DMF, allyl bromide, MeI, and tosyl azide displaying the versatility and utility of the method. The 5-lithio-intermediate (generated in DME or THF) is equally versatile, the reactions shown in Scheme 5 being typical. When acetone (with hexane as solvent) or acetonitrile is used as the electrophile in the work-up of the 3-lithio-intermediate, proton abstraction seems to be preferred over nucleophilic attack at carbon (Table 3): the incursion of this process probably also accounts for the poor yield of the product of

Table 2. Effect of additives introduced after 3-lithiation of thienyloxazoline (**1**) in hexane.

Expt.	Species[a]	Time (min) until addition of E	Electrophile[b] E	Product composition disubstituted product (2,3)	(2,5)	(%)[c] (1)
33	TMEDA	2	MeI	50	0	50
34	TMEDA	2	7DMF	14	0	86
35	TMEDA	30	MeI	47	18	35
36	5TMEDA	5	MeI	44	14	42
37	TMEDA	5	5MeI	45	16	39
38	TMEDA	5	MeI	44	8	48
39	5TMEDA	5	15MeI	58	11	31
40	TMEDA	5	$MeOSO_2CF_3$	44	11	45
41	TMEDA	5	TMSCl	83	10	7
42	TMEDA	5	$PhOCH(OEt)_2$	0	0	100
43	BF_3-Et_2O	5	MeI	0	0	100
44	$MgBr_2$-Et_2O	5	MeI	0	0	100
45	HMPA	2	MeI	0	0	100
46	HMPA	2	7DMF	0	0	100
47	KOBu^t	—	2MeI	17	20	63
48	2KOBu^t	10	$3MeOSO_2CF_3$	multicomponent mixture		
49	2KOBu^t	10	$3PhOCH(OEt)_2$	0	0	100

[a] Introduced into the reaction mixture cooled to −78 °C. [b] After addition of E, the solution was left at 20 °C for 12 h, except for expt. 38 in which the solution was boiled under reflux for 12 h. [c] Determined as in Table 1: recovered yields were high (>90%) except for expt. 48 where the yield could not be estimated.

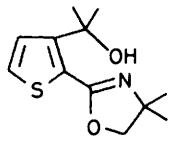


Scheme 4. *Reagents:* i, Bu^{n}Li, Et_2O, −78 °C, 0.25 h then 0 °C, 0.5 h; ii, MeI; iii, oxirane; iv, allyl bromide; v, I_2; vi, tosyl azide; vii, DMF; viii, CO_2, Et_2O, then aq. HCl; ix, methyl vinyl ketone.

nucleophilic addition to methyl vinyl ketone recorded in Scheme 4. With [$^1H_6$]acetone as electrophile and hexane as solvent, only deprotonation occurs (as shown by addition of TMSCl 3 h subsequent to the acetone addition, and the absence of silylated thiophene-containing products, entry 52, Table 3); in contrast, [$^2H_6$]acetone is only slowly dedeuteriated (entry 51, Table 3). Interestingly, the recovered yield of (**1**) in this last experiment (64%) is significantly lower than the yields recovered from the experiments with [$^1H_6$]acetone [entry 50 (97%) and entry 52 (96%)]. This supports the view that whereas deprotonation occurs rapidly, dedeuteriation is much slower: when [$^2H_6$]acetone is the electrophile, therefore, the 3-lithiated intermediate is effectively standing at 20 °C for an extended period of time with some concomitant self-corruption as already noted in Table 1, experiment 2. This decomposition seems to provide a ready supply of protons since addition of [$^2H_6$]acetone followed, 3 h later, by TMSCl gives recovered oxazoline (**1**) (in diminished yield, as expected) but no silylated oxazoline product (entry 53, Table 3). Addition of TMEDA (entries 54 and 55) encourages nucleophilic addition, although

Table 3. Isotope effects on proton abstraction from electrophiles by lithiated thienyloxazoline (1)[a]

Expt.	Solvent	TMEDA?[b]	Electrophile(s)[c]	Result	Recovered yield (%)
50	A	—	Me_2CO	Substrate (1) recovered	97
51	A	—	$[^2H_6]Me_2CO$	(1) recovered, <10% D-incorporation	64
52	A	—	Me_2CO then TMSCl[d]	(1) recovered	96
53	A	—	$[^2H_6]Me_2CO$ then TMSCl[d]	(1) recovered	67
54	A	√	Me_2CO	(1) (73%), (23) (27%)	88
55	A	√	$[^2H_6]Me_2CO$	(1) (69%), (23) (31%)	66
56	D	—	Me_2CO	(1) (35%), (23) (65%)	78
57	D	—	$[^2H_6]Me_2CO$	(24) (30%), (23) (70%)	75
58	D	—	MeCN	(1) recovered	100
59	D	—	$[^2H_3]$MeCN	(1) recovered, >93% D-incorporation	100



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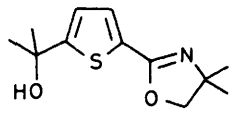

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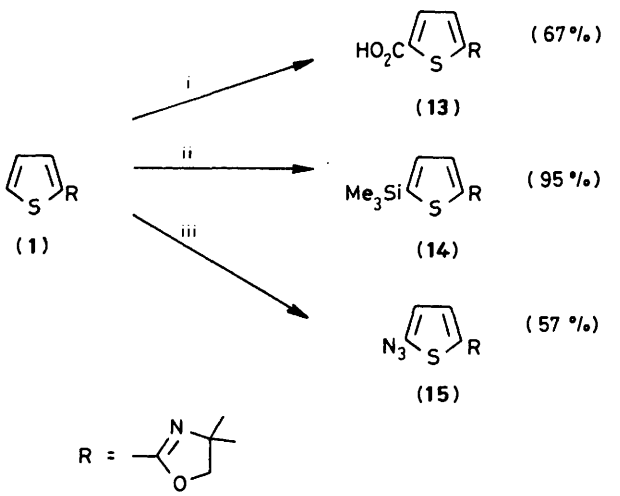
[a] The conventions of Table 1 are used. [b] A tick implies that TMEDA equimolar with Bu^nLi was added to the reaction mixture cooled to −78 °C: the electrophile was added 2 min subsequently. [c] Electrophiles were added in > 3M excess over Bu^nLi. Except where stated otherwise, the reaction mixture was stirred for 12 h at 20 °C after addition of the electrophile. [d] In these experiments, lithiated (1) was stirred with $[^1H_6]$- or $[^2H_6]$-Me_2CO for 3 h at 20 °C, TMSCl was then added and the mixture stirred for a further 3 h.



Scheme 5. *Reagents:* i, LDA, DME, −78 °C, 0.75 h then CO_2, Et_2O then aq. HCl; ii, LDA, DME, −78 °C, 0.75 h then TMSCl; iii, LDA, THF, −78 °C, 0.5 h then TsN_3, Et_2O.

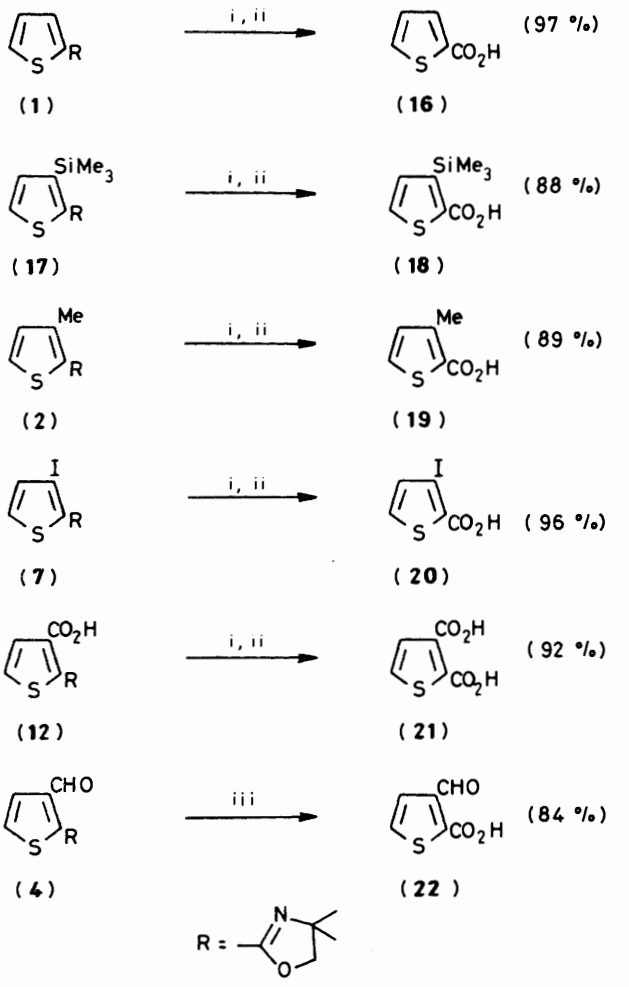
deprotonation from $[^1H_6]$acetone or from corrupted substrate (when $[^2H_6]$acetone is the electrophile) is still dominant. However, when ether is the solvent, nucleophilic addition becomes the preferred pathway: with $[^1H_6]$acetone as electrophile, the ratio of the product from the former to that from deprotonation is *ca.* 2:1 (entry 56). When $[^2H_6]$acetone is the electrophile, the deuterium isotope effect is sufficient to suppress dedeuteriation essentially completely in favour of nucleophilic addition (entry 57) the significant amount of the 2,5-disubstituted product (**24**) presumably arising from the incursion of the transmetallation process alluded to earlier (Table 2, entries 33 and 35). When $[^2H_3]$acetonitrile is employed as the electrophile, complete dedeuteriation is observed: the protio-analogue must also, therefore, suffer complete deprotonation under the same reaction conditions.

The full realisation of the synthetical potential of lithiated heteroaromatic oxazoline derivatives can only be attained if appropriate methodology is available for the transformation of the oxazoline moiety into more useful functionality. Although conventional hydrolytic[9] and alkylative/reductive methods may be used for its conversion into the carboxy or aldehyde function, such methods may not always be compatible with the heteroaromatic nucleus or with other functionality. The recently published mild technique of Levin and Weinreb[10] for the conversion of 2-phenyloxazoline into benzoic acid is, therefore, particularly welcome and is applied here to a range of 2,3-disubstituted thiophene derivatives (Scheme 6) with excellent results. (The last entry in the Scheme illustrates the use of the simple hydrolytic method in a situation where the oxidising ability of the sodium hypochlorite might have proved problematic.)

Conclusions.—The work described in this paper demonstrates not only that the oxazoline moiety may be used to overcome the natural preference of thiophene to metallate at the α-positions, but that the directing effect of the group is only realisable if the metallating agent and solvent are carefully chosen. It is, therefore, possible, by variation of these parameters, to prepare 2,3- and 2,5-disubstituted thiophene derivatives with a high level of regioselection. The synthetical potential of this approach to the synthesis of disubstituted thiophenes has been enhanced by the application of a new method[10] for transformation of an oxazolino into a carboxy functionality.

Experimental

Product purity was checked by thin layer chromatography (t.l.c.) on Merck 10 × 2-cm aluminium-backed plates with a 0.2 mm layer of Kieselgel 60 F_{254}. Preparative thin-layer chromatography (p.t.l.c.) was carried out on 100 × 20-cm plates coated with a 1-mm layer of Merck Kieselgel GF_{254}. Gas liquid chromatography (g.l.c.) was carried out on a 25m OV351 capillary column with flame ionisation detection. M.p.s were determined on a Köfler block and are corrected. Microanalyses



Scheme 6. *Reagents:* i, NaOCl, H_2O, EtOAc, $Bu^t_4N^+HSO_4^-$, 12 h, 20 °C; ii, KOH aq., 5 h, 20 °C; iii, aq. HCl, reflux under N_2 for 14 h.

were performed in the University of Liverpool Micro-Analysis Laboratory. ^{1}H n.m.r. spectra were recorded either on a Perkin-Elmer R34 (220 MHz) or a Brüker WM250 (250 MHz) spectrometer. For signals other than singlets (s), doublets (d), triplets (t), quartets (q) and multiplets (m) the number of lines is indicated. I.r. spectra were recorded on a Perkin-Elmer 298 spectrophotometer. Mass spectra were recorded either on an A.E.I. MS902 or a V.G. Analytical 7070E spectrometer. Solvents were dried and distilled prior to use: diethyl ether, DME and THF from sodium-benzophenone, light petroleum (b.p. 60—80 °C) from CaH_2, and dichloromethane from P_4O_{10}. DMF, TMEDA, and HMPA were distilled from CaH_2 under reduced pressure and were stored under an inert atmosphere over molecular sieves type 4A.

The concentrations of solutions of commercial Bu^nLi were determined by means of the double-titration method of Jones and Gilman.[11]

4,4-*Dimethyl*-2-(2-*thienyl*)*oxazoline* (**1**).[1]—Meyers' general approach to oxazoline synthesis was followed.[12] Commercial thiophene-2-carboxylic acid (5.0 g, 0.039 mol) and freshly distilled thionyl chloride were boiled under reflux for 2 h. The excess of thionyl chloride was removed by distillation and the residue distilled under reduced pressure (100 °C, 15 mmHg) to give the acid chloride (4.64 g, 82%) as a colourless liquid.

A solution of commercial 2-amino-2-methylpropan-1-ol (5.70 g, 0.064 mol) in dichloromethane (50 ml) was added dropwise to a solution of the acid chloride (4.64 g, 0.032 mol) in dichloromethane (50 ml), with the reaction temperature held below 20 °C. The mixture was stirred for 12 h, washed (water), dried ($MgSO_4$), and evaporated, giving the crude amide, *N*-(2-hydroxy-1,1-dimethylethyl)thiophene-2-carboxamide as a tan solid which was used without further purification.

The amide was suspended in toluene (50 ml) and thionyl chloride (12.7 g, 107.3 mol) was added dropwise with stirring, with the reaction temperature held below 30 °C. Stirring was continued for 12 h at 25 °C, after which the toluene was removed by distillation and the residue taken up into water (30 ml). The solution was basified (4.0M-NaOH solution; *ca.* 20 ml) and the product extracted with ether. The combined extracts were washed (water), dried ($MgSO_4$), and the solvent removed to leave the crude product as an oil; this was distilled under reduced pressure (120 °C, 15 mmHg) to give the product (**1**) (4.82 g, 83%) as a white solid, m.p. 29—30 °C, δ($CDCl_3$), 7.58 (1 H, dd, *J* 3.9, 1.3 Hz, thiophene 3-H), 7.38 (1 H, dd, *J* 5.4, 1.3 Hz, thiophene 5-H), 7.01 (1 H, dd, *J* 5.4, 3.9 Hz, thiophene 4-H), 4.04 (2 H, s, OCH_2), and 1.34 (6 H, s, CH_3).

4,4-*Dimethyl*-2-(5-*deuterio*-2-*thienyl*)*oxazoline*.—To Bu^nLi (71.4 mmol) in hexane was added TMEDA (3.30 g, 71.4 mmol) at 20 °C. Thiophene (3.02 g, 36.0 mmol) was added and the mixture was boiled under reflux for 0.5 h. D_2O (10 ml) was added to the cooled solution and the whole was then left for 12 h. The mixture was dried ($MgSO_4$), filtered, and the filtrate cooled to 0 °C. Bu^nLi (35.7 mmol) in hexane was added and the mixture then stirred at 20 °C for 0.5 h; subsequently it was poured onto a slurry of solid CO_2 in ether. Water (20 ml) was added and the ethereal solution separated off. The aqueous layer was acidified to pH 1 with concentrated hydrochloric acid, saturated with NaCl, and extracted with Et_2O (3 × 20 ml). Removal of solvent under reduced pressure gave the deuterio-acid (4.39 g) which was converted into the deuteriated oxazoline following the method described above for (**1**), δ($CDCl_3$), 7.56 (1 H, d, *J* 3.8 Hz, thiophene 3-H), 7.02 (1 H, d, *J* 3.8 Hz, thiophene 4-H), 4.04 (2 H, s, OCH_2), and 1.34 (6 H, s, CH_3).

General Methods for Lithiations with Bu^nLi.—*Method A: hexane or ether as solvent.* To the oxazoline (**1**) (1.0 g, 5.52 mmol) in hexane or ether (60 ml) was added commercial Bu^nLi (5.62 mmol) in hexane at the required temperature. The mixture was stirred under an atmosphere of argon for the requisite time. The electrophile was added, the mixture allowed to warm to 20 °C, and the mixture then left at this temperature for 12 h. Water (5 ml) and then ether (60 ml) were added. If TMSCl was the electrophile then the mixture was basified to pH 11 with 40% aqueous KOH. The organic solution was separated, washed with water (3 × 10 ml) and brine (10 ml), and dried ($MgSO_4$). The solvent was then evaporated under reduced pressure.

If TMEDA was required, it was added immediately after the Bu^nLi in equimolar ratio to oxazoline (**1**).

Method B: DME and THF as solvent. The procedure was the same as above except that the solvent was removed under reduced pressure prior to the addition of water. Solids were then suspended in ether (60 ml). The electrophiles MeOD, D_2O, and TMSCl were added in excess (1 ml, 1 ml, and 2 ml respectively).

Method C: lithiations with LDA. To di-isopropylamine (0.79 ml, 5.62 mmol) in the required solvent was added commercial

* The assignments given here for the resonances due to 3-H and 5-H are the reverse of those given in ref. 1 but are the same as those given in ref. 2. They are confirmed through the preparation of the 5-deuteriated derivative.

Bu^nLi (5.62 mmol) in hexane. Oxazoline (**1**) (1.0 g, 5.52 mmol) in the required solvent (10 ml) was then added and the experiment continued as in method A.

Hypochlorite Cleavage of the Oxazoline Ring: Method D.[10]—To the oxazoline derivative (0.33 mmol) in ethyl acetate (10 ml) was added a catalytic amount of $Bu^t_4N^+HSO_4^-$ (20 mg) and water (10 ml). 3M-Aqueous sodium hypochlorite (7 ml) was added and the mixture stirred for 12 h at 20 °C. The organic solution was separated, the aqueous solution acidified to pH 1 with concentrated hydrochloric acid and extracted with ethyl acetate (5 × 20 ml). Most of the solvent was removed under reduced pressure from the combined organic extracts and the residue was taken up into water (20 ml) and MeOH (30 ml). Aqueous KOH (5% w/w; 10 ml) was added and the mixture left for 12 h at 20 °C. The solution was acidified (concentrated hydrochloric acid), saturated with NaCl, and extracted with CH_2Cl_2 (5 × 20 ml). The extracts were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the crude carboxylic acid.

4,4-*Dimethyl*-2-(3-*trimethylsilyl*-2-*thienyl*)*oxazoline* (**17**).—To the 3-lithio-oxazoline (5.52 mmol) prepared in hexane at −78 °C (method A) was added TMSCl (0.73 ml, 5.8 mmol). After being stirred at 20 °C for 24 h, the mixture was worked up in the usual way. Distillation under reduced pressure gave the *silylated thiophene derivative* (**17**) (1.08 g, 78%), b.p. 148 °C at 0.5 mmHg (Found: C, 57.1; H, 7.4; N, 5.5. $C_{12}H_{19}NOSSi$ requires C, 56.87; H, 7.55; N, 5.53%); δ($CDCl_3$), 7.36 (1 H, d, *J* 4.9 Hz, thiophene 5-H), 7.12 (1 H, d, *J* 4.9 Hz, thiophene 4-H), 4.05 (2 H, s, OCH_2), 1.35 (6 H, s, CCH_3), and 0.32 (9 H, s, $SiCH_3$); *m/z* (FAB) 253 (M^+, 13%) and 238 (100).

4,4-*Dimethyl*-2-(3-*methyl*-2-*thienyl*)*oxazoline* (**2**).—Bu^nLi (5.62 mmol) in hexane was added to the oxazoline (**1**) (1.0 g, 5.52 mmol) in ether (30 ml) and the solution was left for 15 min at −78 °C and for a further 30 min at 0 °C. Iodomethane (3.44 ml, 55.2 mmol) was added and work-up (general method A) gave the crude product as a yellow oil. Purification by p.t.l.c. (ethyl acetate–light petroleum 2:3 as eluant) afforded the *methylated oxazoline* (**2**) (0.97 g, 90%) as a tan oil (Found: C, 61.4; H, 6.8; N, 7.2. $C_{10}H_{13}NOS$ requires C, 61.52; H, 6.71; N, 7.18%); δ($CDCl_3$), 7.24 (1 H, d, *J* 5.3 Hz, thiophene 5-H), 6.84 (1 H, d, *J* 5.3 Hz, thiophene 4-H), 4.01 (2 H, s, OCH_2), 2.49 (3 H, s, thiophene CH_3), and 1.36 (6 H, s, oxazoline CH_3); *m/z* 195 (M^+, 82%) and 180 (100).

4,4-*Dimethyl*-2-(3-*prop*-2-*enyl*-2-*thienyl*)*oxazoline* (**3**).—The lithiothienyloxazoline mixture (5.52 mmol) was generated in ether and allyl bromide (4.76 ml, 55 mmol) was added. Work-up (method A) and p.t.l.c. purification (ethyl acetate–light petroleum 1:2 as eluant) gave the 3-*propenyl*-2-*thienyloxazoline derivative* (**3**) (0.99 g, 81%) as a colourless oil (Found: C, 65.6; H, 7.0; N, 6.0. $C_{12}H_{15}NOS$ requires C, 65.14; H, 6.83; N, 6.33%); δ($CDCl_3$), 7.31 (1 H, d, *J* 5.1 Hz, thiophene 5-H), 6.92 (1 H, d, *J* 5.1 Hz, thiophene 4-H), 5.98 (1 H, m, *J* 19.2, 11.6, 6.7 Hz, CH_2CH=), 5.08 (1 H, dd, *J* 19.2, 1.7 Hz, =CH_2), 5.04 (1 H, dd, *J* 11.6, 1.7 Hz, =CH_2), 4.05 (2 H, s, OCH_2), 3.76 (2 H, d, *J* 6.7 Hz, propenyl CH_2), and 1.36 (6 H, s, CH_3); *m/z* 221.087 20 (M^+, 21%. $C_{12}H_{15}NOS$ requires 221.087 426) and 206 (100).

2-(3-*Formyl*-2-*thienyl*)-4,4-*dimethyloxazoline* (**4**) *and* 2-(5-*formyl*-2-*thienyl*)-4,4-*dimethyloxazoline* (**5**).—To the lithiothienyloxazoline mixture (5.52 mmol) in ether was added excess of DMF (*ca.* 30 mmol). After stirring of the solution for 18 h at 20 °C and work-up (method A), purification by p.t.l.c. (ethyl acetate–light petroleum 1:3 as eluant, two elutions) gave the 3-*formyl derivative* (**4**) (1.08 g, 93%), m.p. 64—65 °C (Found: C, 57.3; H, 5.3; N, 6.7. $C_{10}H_{11}NO_2S$ requires C, 57.41; H, 5.30; N, 6.70%); δ($CDCl_3$), 10.61 (1 H, s, CHO), 7.56 (1 H, d, *J* 4.8 Hz, thiophene 5-H), 7.40 (1 H, d, *J* 4.8 Hz, thiophene 4-H), 4.15 (2 H, s, OCH_2), and 1.39 (6 H, s, CH_3); *m/z* 209 (M^+, 9%) and 181 (100); and the 5-*formyl derivative* (**5**) (0.035 g, 3%), m.p. 84—87 °C (Found: C, 57.2; H, 5.4. $C_{10}H_{11}NO_2S$ requires C, 57.41; H, 5.30%); δ($CDCl_3$), 9.91 (1 H, s, CHO), 7.75 (1 H, d, *J* 4.4 Hz, thiophene 4-H), 7.69 (1 H, d, *J* 4.4 Hz, thiophene 3-H), 4.12 (2 H, s, OCH_2), and 1.38 (6 H, s, CH_3); *m/z* 209.052 29 (M^+, 19%. $C_{10}H_{11}NO_2S$ requires 209.051 046) and 194 (100).

2-(3-*Azido*-2-*thienyl*)-4,4-*dimethyloxazoline* (**6**).—To the lithiothienyloxazoline mixture (5.52 mmol) generated in ether following method A was added tosyl azide[13] (1.11 g, 5.62 mmol) in ether (10 ml) and the solution was left at 20 °C for 12 h. Aqueous sodium pyrophosphate (2.6 g in 15 ml) was added and the whole was stirred for 12 h at 0 °C with light excluded. Ether (60 ml) was then added and the mixture worked up as usual to give the crude product which was purified by p.t.l.c. (ethyl acetate–light petroleum 2:3 as eluant, at 0 °C, with exclusion of light) giving the *azide* (**6**) (1.10 g, 90%) as a red oil (Found: C, 49.3; H, 4.6; N, 24.5. $C_9H_{10}N_4OS$ requires C, 48.65; H, 4.54; N, 25.22%); δ($CDCl_3$), 7.39 (1 H, d, *J* 5.5 Hz, thiophene 5-H), 6.92 (1 H, d, *J* 5.5 Hz, thiophene 4-H), 4.06 (2 H, s, OCH_2), and 1.38 (6 H, s, CH_3); *m/z* 222.0569 (M^+, 13%, $C_9H_{10}N_4OS$ requires 222.057 529) and 84 (100).

2-(3-*Iodo*-2-*thienyl*)-4,4-*dimethyloxazoline* (**7**) *and* 2-(5-*Iodo*-2-*thienyl*)-4,4-*dimethyloxazoline* (**8**).—To the lithiothienyloxazoline mixture (2.76 mmol) prepared in ether (method A) was added iodine (0.71 g, 2.80 mmol) in ether (10 ml) and the solution was stirred at 0 °C for 12 h. Work-up and p.t.l.c. (ethyl acetate–light petroleum 3:25 as eluant, 7 elutions) gave the 3-*iodo-oxazoline derivative* (**7**) (0.45 g, 53%) as an oil (Found: C, 35.3; H, 3.2; N, 4.7. $C_9H_{10}INOS$ requires C, 35.19; H, 3.28; N, 4.8%); δ($CDCl_3$), 7.29 (1 H, d, *J* 5.4 Hz, thiophene 5-H), 7.14 (1 H, d, *J* 5.4 Hz, thiophene 4-H), 4.11 (2 H, s, OCH_2), and 1.36 (6 H, s, CH_3); *m/z* 307 (M^+, 31%) and 294 (100), and the 5-*iodo-oxazoline derivative* (**8**) (0.11 g, 12%) as a white solid, m.p. 95—97 °C (Found: C, 35.7; H, 3.2; N, 4.5. $C_9H_{10}INOS$ requires C, 35.19; H, 3.28; N, 4.8%); δ($CDCl_3$), 7.20 (2 H, m, thiophene H's), 4.06 (2 H, s, OCH_2), and 1.37 (6 H, s, CH_3); *m/z* 307 (M^+, 56%) and 293 (100).

2-[3-(2-*Hydroxyethyl*)-2-*thienyl*]-4,4-*dimethyloxazoline* (**9**) *and* 2-[5-(2-*Hydroxyethyl*)-2-*thienyl*]-4,4-*dimethyloxazoline* (**10**).—Oxirane (0.14 ml, 2.76 mmol) was added to the lithiothienyloxazoline mixture (2.76 mmol) in ether in the usual way (method A). Work-up and p.t.l.c. (ethyl acetate–light petroleum 1:3 as eluant, 5 elutions) gave the 3-(2-*hydroxyethyl*)-2-*thienyloxazoline derivative* (**9**) (0.20 g, 33%) as an oil (Found: C, 58.2; H, 6.9; N, 6.2. $C_{11}H_{15}NO_2S$ requires C, 58.65; H, 6.71; N, 6.22%); δ($CDCl_3$), 7.35 (1 H, d, *J* 5.2 Hz, thiophene 5-H), 6.94 (1 H, d, *J* 5.2 Hz, thiophene 4-H), 5.00 (1 H, br s, OH), 4.06 (2 H, s, OCH_2), 3.90 (2 H, t, *J* 4.9 Hz, $HOCH_2$), 3.24 (2 H, t, *J* 4.9 Hz, CH_2CH_2OH), and 1.36 (6 H, s, CH_3); *m/z* 225 (M^+, 22%) and 205 (100); and the 5-*substituted isomer* (**10**) (0.07 g, 11%) as colourless rods, m.p. 64—65 °C (Found: C, 58.5; H, 6.8; N, 6.2. $C_{11}H_{15}NO_2S$ requires C, 58.65; H, 6.71; N, 6.22%); δ($CDCl_3$), 7.43 (1 H, d, 3.5 Hz, thiophene 3-H), 6.82 (1 H, d, *J* 3.5 Hz, thiophene 4-H), 4.07 (2 H, s, OCH_2), 3.90 (2 H, t, *J* 6.8 Hz, $HOCH_2$), 3.07 (2 H, t, *J* 6.8 Hz, CH_2CH_2OH), 2.69 (1 H, br s, OH), and 1.34 (6 H, s, CH_3); *m/z* 225 (M^+, 14%) and 207 (100).

2-[3-(1-*Hydroxy*-1-*methylpropenyl*)-2-*thienyl*]-4,4-*dimethyloxazoline* (**11**).—Methyl vinyl ketone (0.39 g, 5.62 mmol) was added to the lithiothienyloxazoline mixture (5.52 mol) in ether in the usual way (method A). Work-up and p.t.l.c. (ethyl

acetate–light petroleum 2:3 as eluant) gave the *oxazoline derivative* (**11**) (0.37 g, 26%) as a colourless oil (Found: C, 62.2; H, 6.8; N, 5.3. $C_{13}H_{17}NO_2S$ requires C, 62.14; H, 6.82; N, 5.57%); δ($CDCl_3$), 8.73 (1 H, s, OH), 7.34 (1 H, d, *J* 5.4 Hz, thiophene 5-H), 7.06 (1 H, d, *J* 5.4 Hz, thiophene 4-H), 6.11 (1 H, dd, *J* 10.6, 17.3 Hz, =CH), 5.15 (1 H, dd, *J* 17.3, 1.7 Hz, $=CH_2$), 4.99 (1 H, dd, *J* 10.6, 1.7 Hz, $=CH_2$), 4.11 (2 H, s, OCH_2), 1.67 (3 H, s, CH_3), 1.36 (3 H, s, oxazoline CH_3), and 1.34 (3 H, s, oxazoline CH_3); *m/z* 253 (M^+, 27%) and 169 (100).

2-(3-*Carboxy*-2-*thienyl*)-4,4-*dimethyloxazoline* (**12**).—The lithiothienyloxazoline mixture (5.52 mmol) in ether was poured onto a stirred slurry of crushed, solid CO_2 in ether. After the ether had evaporated, the solids were taken up into water (60 ml) and the solution was washed with ether (10 ml). The aqueous solution was acidified to pH 1 (concentrated hydrochloric acid), saturated with NaCl, and extracted repeatedly with CH_2Cl_2 (200 ml *in toto*). Drying of the organic solution ($MgSO_4$), removal of solvent under reduced pressure, and recrystallisation of the resulting solid from cyclohexane–ethyl acetate gave the *acid* (**12**) (1.11 g, 90%) as colourless needles, m.p. 154—156 °C (Found: C, 53.5; H, 5.0; N, 6.1. $C_{10}H_{11}NO_3S$ requires C, 53.33; H, 4.92; N, 6.22%); δ($CDCl_3$), 7.87 (1 H, d, *J* 5.4 Hz, thiophene 5-H), 7.46 (1 H, d, *J* 5.4 Hz, thiophene 4-H), 4.30 (2 H, s, OCH_2), and 1.48 (6 H, s, CH_3); *m/z* 225 (M^+, 14%) and 169 (100).

2-(5-*Carboxy*-2-*thienyl*)-4,4-*dimethyloxazoline* (**13**).—The oxazoline (**1**) (1.0 g, 5.52 mmol) in DME (60 ml) was metallated with LDA in DME following general method C. The mixture was stirred at −78 °C for 0.5 h and then poured onto a slurry of crushed, solid CO_2 in ether. Work-up as for the 3-carboxy-derivative (**12**) but with continuous extraction of the acidified, aqueous solution with $CHCl_3$ (60 ml), and recrystallisation of the resulting solid from light petroleum—ethyl acetate gave the 5-carboxylated derivative (**13**) (0.82 g, 67%) as a white solid, m.p. 130—132 °C; δ($CDCl_3$), 11.58 (1 H, s, OH), 7.77 (1 H, d, *J* 3.5 Hz, thiophene 4-H), 7.71 (1 H, d, *J* 3.5 Hz, thiophene 3-H), 4.15 (2 H, s, OCH_2), and 1.44 (6 H, s, CH_3); *m/z* 225 (M^+, 17%) and 210 (100). Methylation of the acid with ethereal diazomethane and p.t.l.c. (ethyl acetate–light petroleum 2:3 as eluant) gave the *methyl ester* (0.87 g, 98%) as a white solid, m.p. 82—85 °C (Found: C, 55.4; H, 5.7; N, 6.1. $C_{11}H_{13}NO_3S$ requires, C, 55.23; H, 5.48; N, 5.86%); δ($CDCl_3$), 7.70 (1 H, d, *J* 3.6 Hz, thiophene 4-H), 7.54 (1 H, d, *J* 3.6 Hz, thiophene 3-H), 4.10 (2 H, s, OCH_2), 3.88 (3 H, s, OCH_3), and 1.36 (6 H, s, CCH_3); *m/z* 239 (M^+, 23%) and 224 (100).

4,4-*Dimethyl*-2-(5-*trimethylsilyl*-2-*thienyl*)*oxazoline* (**14**).—TMSCl (2.54 ml, 20 mmol) was added to the 5-lithiothienyloxazoline (5.62 mmol) generated in DME as in general method C and the mixture was left for 12 h at 20 °C. Work-up as in general methods A and B and p.t.l.c. afforded the 5-*silylated derivative* (**14**) (1.33 g, 95%) as a white solid, m.p. 53—55 °C (Found: C, 57.2; H, 7.5; N, 5.3. $C_{12}H_{19}NOSSi$ requires C, 56.9; H, 7.55; N, 5.52%); δ($CDCl_3$), 7.63 (1 H, d, *J* 3.7 Hz, thiophene 3-H), 7.18 (1 H, d, *J* 3.7 Hz, thiophene 4-H), 4.10 (2 H, s, OCH_2), 1.38 (6 H, s, CH_3), and 0.32 (9 H, s, $SiCH_3$); *m/z* 253 (M^+, 21%) and 238 (100).

2-(5-*Azido*-2-*thienyl*)-4,4-*dimethyloxazoline* (**15**).—The oxazoline (**1**) (1.0 g, 5.52 mmol) in THF (60 ml) was metallated with LDA in THF following general method C. After 0.5 h, tosyl azide (1.97 g, 10 mmol) in THF (10 ml) was added and the mixture left for 12 h at 20 °C. The solids were filtered off, washed with THF (10 ml), and suspended in ether (30 ml). Aqueous sodium pyrophosphate (2.6 g in 10 ml) was added and the mixture stirred at 0 °C for 12 h with light excluded. The organic layer was separated off and the aqueous layer saturated with NaCl and extracted with ether (4 × 30 ml). The combined organic solutions were dried ($MgSO_4$) and the solvent was evaporated to give the *azide* (**15**) (0.69 g, 57%), a small sample of which was purified by p.t.l.c. (ethyl acetate–light petroleum as eluant) (Found: C, 48.3; H, 4.5; N, 25.0. $C_9H_{10}N_4OS$ requires C, 48.65; H, 4.54; N, 25.22%); δ($CDCl_3$), 7.32 (1 H, d, *J* 4.0 Hz, thiophene 3-H), 6.55 (1 H, d, *J* 4.0 Hz, thiophene 4-H), 4.06 (2 H, s, OCH_2), and 1.34 (6 H, s, CH_3); *m/z* 222.0573 (M^+, 81%, $C_9H_{10}N_4OS$ requires 222.057 529) and 96 (100).

2-[3-(1-*Hydroxy*-1-*trideuteriomethyl*-2-*trideuterioethyl*)-2-*thienyl*]-4,4-*dimethyloxazoline and* 2-[5-(1-*Hydroxy*-1-*trideuteriomethyl*-2-*trideuterioethyl*)-2-*thienyl*]-4,4-*dimethyloxazoline*.—Hexadeuterioacetone (5 ml) was added to the lithiothienyloxazoline mixture (5.52 mmol) prepared in ether following general method A. Work-up gave an inseparable mixture of the isomeric alcohols, δ($CDCl_3$), 7.43 (1 H, d, *J* 4.8 Hz and 1 H, d, *J* 3.9 Hz), 7.32 (1 H, d, *J* 4.8 Hz and 1 H, d, *J* 3.9 Hz), 4.12 (2 H, s), 4.07 (2 H, s), 1.35 (6 H, s), and 1.33 (6 H, s).

Transformation of an Oxazolino to Carboxy Functionality

4,4-*Dimethyl*-2-(2-*thienyl*)*oxazoline* (**1**) *to Thiophene*-2-*carboxylic Acid* (**16**).—Following general method D, the oxazoline (**1**) (1.0 g, 5.52 mmol) gave the crude product which was recrystallised (ethyl acetate–light petroleum) affording the carboxylic acid (**16**) (0.68 g, 97%) as a white solid, m.p. 124—126 °C (lit.,[14] 123—124 °C); δ($CDCl_3$) 7.90 (1 H, 4, *J* 4.4, 1.2 Hz, thiophene 5-H), 7.64 (1 H, 4, *J* 4.9, 1.2 Hz, thiophene 3-H), and 7.14 (1 H, 4, *J* 4.4, 4.9 Hz, thiophene 4-H).

4,4-*Dimethyl*-2-(3-*trimethylsilyl*-2-*thienyl*)*oxazoline* (**17**) *to* 3-*Trimethylsilylthiophene*-2-*carboxylic Acid* (**18**).—Application of general method D to the silylthienyloxazoline (**17**) (0.53 g, 2.08 mmol) and recrystallisation of the crude product (ethyl acetate–light petroleum) gave the carboxylic acid (**18**) (0.37 g, 88%) as a white solid, m.p. 214—216 °C, δ($CDCl_3$), 8.8 (1 H, br s, OH), 7.52 (1 H, d, *J* 4.8 Hz, thiophene 5-H), 7.17 (1 H, d, *J* 4.8 Hz, thiophene 4-H), and 0.29 (9 H, s, CH_3); *m/z* 200 (M^+, 10%), 185 (34), and 72 (100). Methylation with ethereal diazomethane gave the *methyl ester* (0.28 g, 71%) as a colourless oil (Found: C, 50.3; H, 6.7. $C_9H_{14}O_2SSi$ requires C, 50.43; H, 6.58%); δ($CDCl_3$) 7.52 (1 H, d, *J* 4.9 Hz, thiophene 5-H), 7.20 (1 H, d, *J* 4.9 Hz, thiophene 4-H), 3.88 (3 H, s, OCH_3), and 0.32 (9 H, s, $SiCH_3$); *m/z* 214 (M^+, 2%) and 199 (100).

2-(3-*Iodo*-2-*thienyl*)-4,4-*dimethyloxazoline* (**7**) *to* 3-*Iodothiophene*-2-*carboxylic Acid* (**20**).—Application of general method D to the iodothienyloxazoline (**7**) (0.1 g, 0.33 mmol) and recrystallisation of the product from ethyl acetate–cyclohexane gave the carboxylic acid (**20**) (0.08 g, 96%) as a white solid, m.p. 195—196 °C (lit.,[15] 199—201 °C), δ[$(CD_3)_2CO$], 8.57 (1 H, br s, OH), 7.77 (1 H, d, *J* 5.1 Hz, thiophene 5-H), and 7.31 (1 H, d, *J* 5.1 Hz, thiophene 4-H); *m/z* 254 (M^+, 100%) and 237 (80).

2-(3-*Formyl*-2-*thienyl*)-4,4-*dimethyloxazoline* (**4**) *to* 3-*Formylthiophene*-2-*carboxylic Acid* (**22**).—The formylthienyloxazoline (**4**) (0.10 g, 0.48 mmol) was boiled under reflux with hydrochloric acid. (4M; 10 ml) for 14 h in an atmosphere of N_2. The cooled solution was saturated with NaCl and extracted repeatedly with ethyl acetate (100 ml *in toto*). The separated organic solution was dried ($MgSO_4$), the solvent evaporated under reduced pressure, and the product recrystallised from ethyl acetate–hexane to afford the pure acid (**22**) (0.06 g, 84%) as a white solid, m.p. 129—130 °C (lit.,[16] 130—131 °C); δ($CDCl_3$), 10.35 (1 H, s, CHO), 8.51 (1 H, br s, OH), and 7.65 (2 H, m, thiophene H's); *m/z* 156 (M^+, 61%) and 111 (100).

4,4-Dimethyl-2-(3-methyl-2-thienyl)oxazoline (**2**) *to* 3-*Methylthiophene-2-carboxylic Acid* (**19**).—Application of general method D to the methylthienyloxazoline (**2**) (0.150 g, 0.77 mmol) and recrystallisation of the product from ethyl acetate–light petroleum gave the carboxylic acid (**19**) (0.10 g, 89%) as a white solid, m.p. 146—149 °C (lit.,[17] 147—148 °C), δ($CDCl_3$), 10.34 (1 H, br s, OH), 7.45 (1 H, d, *J* 5.2 Hz, thiophene 5-H), 6.92 (1 H, d, *J* 5.2 Hz, thiophene 4-H), and 2.58 (3 H, s, CH_3); *m/z* 142 (M^+, 100%).

2-(3-Carboxy-2-thienyl)-4,4-dimethyloxazoline (**12**) *to Thiophene-2,3-dicarboxylic Acid* (**21**).—Application of general method D to the carboxythienyloxazoline (**12**) (0.173 g, 0.77 mmol) and recrystallisation of the product from ethyl acetate–light petroleum gave the dicarboxylic acid (**21**) (0.122 g, 92%) as a white solid, m.p. 269—270 °C (lit.,[18] 270—272 °C), δ[$(CD_3)_2CO$], 8.16 (2 H, br s, OH), and 7.59 (2 H, m, thiophene H's); *m/z* 172 (M^+, 14%) and 170 (100).

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