Tetrahedron Vol. 47, No. 47, pp. 9901-9914, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00
Pergamon Press plc

Directed Metallation Studies on 2-(2-Heteroaryl)imidazolines: Synthesis of some 2,3-Disubstituted Thiophenes and Furans

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(*Received in UK* 4 *October* 1991)

Key Words: imidazoline; directed metallation; thiophenes; furans

Abstract: *A general method for the synthesis of 2-(2-heteroaryl)imidazolines (**1a-c**) has been developed and subsequent metallation studies have shown the imidazoline group to be a strong director of ortho-metallation. The synthetic utility of lithio intermediates (5) and (7) has been shown by reaction with a series of electrophiles.*

In recent years, our group has become interested in devising regiochemically-controlled methods for the preparation of lithium derivatives of five-membered heteroaromatic compounds, especially those of furan, pyrrole, thiophene and imidazole[3]. Of late, we have been exploring the utility of directed metallation techniques (from a 2-substituent to an adjacent 3-position) in the first three of these systems. This approach affords a new route to the 2,3-disubstituted heterocycles.

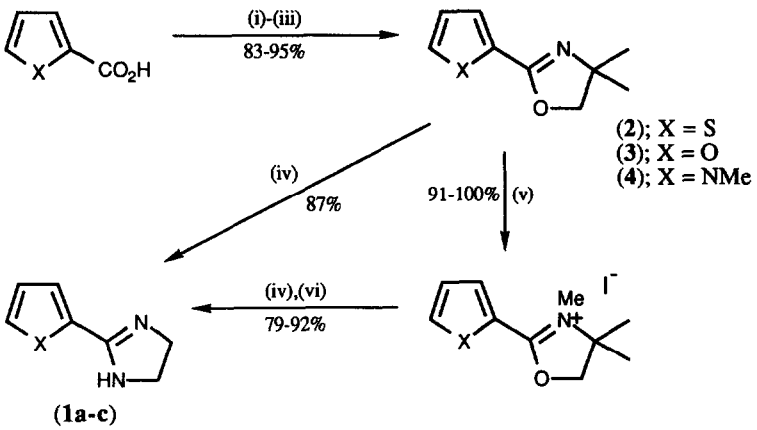
The group has investigated in considerable detail the utility of oxazolino[3-5], imidazolidino[6], secondary amido[3,7] and tertiary amido[7] functionality in directing metallation. The secondary amido function seems to be the best in terms of selectivity for 3-metallation: unfortunately, the utility of the group is to some extent vitiated by transformation difficulties. Hydrolysis by aqueous base is exceedingly slow, and removal under acidic conditions requires boiling with mineral acid for an extended period: such robust conditions are incompatible with several functional groups and in general, with the furan and pyrrole ring systems.

As part of our continuing programme, we have synthesised and carried out metallation studies on the heteroaromatic imidazoline derivatives 2-thienyl-, 2-furyl- and 1-methyl-2-pyrrylimidazoline (**1a-c**) (the latter two compounds being hitherto unknown) with a view to establishing optimum conditions for the controlled introduction of lithium at the 3-position of the heteroaromatic nuclei. We have further explored the reactions of the lithio intermediates with a range of electrophiles.

Although a number of synthetical methods are available for arylimidazolines[8], none of these seemed particularly appropriate to the heteroaromatic systems of interest to us, since they require starting materials which are not readily available or expensive, or forcing conditions of elevated temperature or strongly acidic media. Given our previous, successful experience with heteroaromatic oxazolines[3-5], the report by Magosch[9] that

ethylenediamine will, at elevated temperatures in excess of 250°C, displace 2-aminoethanol from oxazolines to yield the corresponding imidazolines seemed promising.

The 2-heteroaryloxazolines required are readily obtained from the corresponding carboxylic acids by Meyers' general method[10]. 2-(2-Thienyl)imidazoline (**1a**; X=S) was prepared in 87% yield by boiling an equimolar mixture of 2-thienyloxazoline (**2**) and ethylenediamine under reflux for twelve hours. Application of the method to the 2-furyl and 1-methyl-2-pyrryl analogues (**3**) and (**4**) yielded only intractable tars, the conditions being too robust to permit the survival of the furan and pyrrole ring systems. However, by the simple expedient of quaternisation of the oxazoline nitrogen prior to addition of the diamine, it has proved possible to prepare the 2-heteroarylimidazolines (**1a-c**) in boiling acetonitrile (at a much lower temperature than the initial method) in good yields (79-92%) (Scheme 1).



Reagents:(i) $SOCl_2$, reflux, 2 h; (ii) $H_2NC(Me)_2CH_2OH$, CH_2Cl_2, 20°C, 16 h; (iii) $SOCl_2$, PhMe, 20°C, 16 h; (iv) $H_2NCH_2CH_2NH_2$, reflux, 10 h; (v) MeI, 20°C, 24 h; (vi) MeCN.

Scheme 1

Little is known of the metallation characteristics of arylimidazolines and the heteroaromatic analogues are largely unexplored. To our knowledge, the only metallation study is due to Houlihan and Parrino[11] who report ortho- (and N-) lithiation in 2-phenylimidazoline and lithiation into the methyl group (and of nitrogen) in 2-(o-methylphenyl)imidazoline (Figures 1 and 2).

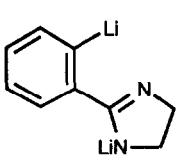


Figure 1

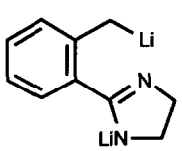


Figure 2

So, having prepared the heteroaromatic imidazolines (**1a-c**), we undertook metallation studies in order to investigate the applicability of the imidazoline moiety in the control of regioselectivity in heteroaromatic metallation.

In Table 1 are listed the results of experiments on the lithiation of 2-(2-thienyl)imidazoline (**1a**). The solubility characteristics of the imidazoline are such that THF is to be prefered over ether and hexane as the metallation solvent. Use of BuLi (2.5 equivalents) in THF at -78°C for two hours (Experiment 5) gives a high level of metallation and regiospecific reaction at the 3-position as judged (as in our previous work) by D_2O work-up and NMR analysis.

Table 1. Lithiation of 2-(2-thienyl)imidazoline (**1a**).

Expt.	RLi[b]	Temp (°C)	Time (h)	Additives[c]	Product composition (%)[d] derived from 3-Lithiation	5-Lithiation
1	2.2 A	-78	0.5		80	0
2	2.2 A	-78	2.0		88	0
3	2.2 A	-78	2.0	TMEDA	87	0
4	2.5 A	-78	0.5		91	0
5	2.5 A	-78	2.0		98	0
6	2.5 A	-78	2.0	TMEDA	95	0
7	2.2 B	-78	2.0		0	78

a 0.5 g of substrate was treated with RLi in THF at -78°C for the time specified.

b A = BuLi, B = LDA.

c If TMEDA was required it was added immediately after and in equimolar ratio to BuLi.

d Starting imidazoline constitutes the balance to 100%.

Prior experience would lead us to expect a change in regioselectivity of reaction with the change from the coordinately-unsaturated carbon base to the coordinately saturated amide base lithium diisopropylamide (LDA) and this is borne out spectacularly in practice with a complete change of metallation pattern (Experiment 7 in Table 1). Particularly instructive is the absence of any effect of addition of the lithium complexing agent N,N,N',N'-tetramethylethylenediamine (TMEDA) on the regioselectivity of metallation (Experiments 3 and 6 in Table 1). Directed metallation by heteroatom-containing groups such as oxazolines, amides and by analogy, imidazolines is thought to occur *via* initial complex formation between the directing group and the incoming metallation agent with subsequent delivery of the metal to an adjacent ortho-position[12] (Figure 3). Not surprisingly, then, addition of TMEDA is often detrimental to directed metallation since the reagent can compete with the directing group for complex formation with the organolithium reagent. That TMEDA has no effect in the imidazoline-mediated metallations is a measure of the potency of the imidazoline moiety as a chelating-directing group.

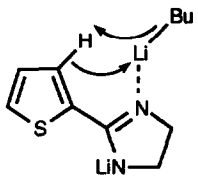
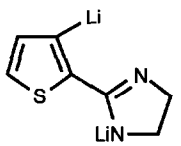
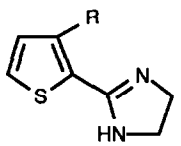


Figure 3

The synthetic utility of the lithio intermediate (**5**) has been investigated through its reactions with a range of electrophiles leading to 2,3-disubstituted thiophenes (**6a-e**) (Table 2). Quenching of the lithio intermediate (**5**) in THF with TMSCl yields some 3,5-disilylated product along with the expected 3-trimethylsilyl compound (**6e**), probably a consequence of 5-metallation of the 3-silylated product by the excess BuLi present during the early stages of the quench (the reaction between organolithium reagents and TMSCl is not "instantaneous" at low temperatures).



(**5**)



(**6**) **a**; R = D
b; R = SMe
c; R = C(OH)Ph_2
d; R = CH(OH)Ph
e; R = TMS

Table 2

Electrophile	Products and Yield (%)[a]
D_2O	(**6a**) (98)
Me_2S_2	(**6b**) (84)
Ph_2CO	(**6c**) (94)
PhCHO	(**6d**) (92)
TMSCl	(**6e**) (76)

a. Yields are for isolated products

Simple change of solvent from THF to dimethoxyethane (DME) is sufficient to prevent the disilylation, presumbly by increasing the nucleophilicity of the lithio compounds (be they the lithio-heterocycle or excess BuLi) through lithium complexation and hence the rate of their reaction with TMSCl.

Tosyl azide, used successfully as an electrophile with other directing groups, failed to react in this case[3,5].

In Table 3 are summarised the results of a range of experiments in which the extent and position of metallation of 2-(2-furyl)imidazoline (**1b**) with BuLi have been studied.

As with thiophene, use of BuLi in THF at -78°C for two hours (Experiments 1 and 2) gives high levels of regiospecific metallation at the 3-position, although low yields of metallation make this a less efficient reaction.

Reactivity of (**1b**) towards BuLi is improved by the introduction of TMEDA to the reaction mixture (Experiments 3-5 in Table 2). No loss of regioselectivity results from the addition of TMEDA, again demonstrating the strong lithium-complexing ability of the imidazoline group, in contrast to the other groups.

Experiment 5 provides the optimum conditions in terms of reactivity and regioselectivity for the 3-lithiation of 2-furylimidazoline (**1b**). The change of solvent from THF to DME appears to be responsible, presumably a consequence of the greater ability of DME to promote Li^+ complexation.

As can be envisaged, increasing the molar equivalents of BuLi (Experiments 10 and 11) leads to an emergence of 5-lithiated product. Similarly, elevation of the temperature at which lithiation is conducted (Experiments 6-9) fails to improve the yield of metallation: complete reversal of regioselectivity occurs, presumably *via* a transmetallation process to give, exclusively, the 5-lithiated furylimidazoline.

Table 3. Lithiation of 2-(2-furyl)imidazoline (**1b**).

Expt.	RLi[b]	Solvent[c]	Temp (°C)	Time (h)	Additives[d]	Product composition (%)[e] derived from 3-Lithiation	5-Lithiation
1	2.2 A	X	-78	2.0		46	0
2	2.5 A	X	-78	2.0		50	0
3	2.5 A	X	-78	2.0	TMEDA	60	0
4	2.5 A	X	-78	3.0	TMEDA	63	0
5	2.5 A	Y	-78	2.0	TMEDA	67	0
6	2.5 A	X	-20	0.5		0	58
7	2.5 A	X	-20	2.0		0	90
8	2.5 A	X	0	0.5		0	31
9	2.5 A	X	0	2.0		0	36
10	3.0 A	X	-78	2.0		64	11
11	5.0 A	Y	-78	2.0		64	30
12	2.5 B	Y	-78	2.0		46	15

a 0.5 g of substrate was treated with RLi at the temperature and for the time specified.

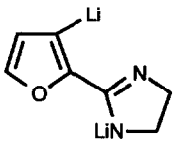
b A = BuLi, B = ^{s}BuLi.

c X = THF, Y = DME.

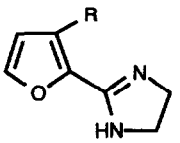
d If TMEDA was required it was added immediately after and in equimolar ratio to BuLi.

e Starting imidazoline constitutes the balance to 100%.

The synthetic utility of the 3-lithio-2-furylimidazoline (**7**) (formed using the conditions in experiment 5) has been explored through its reactions with several electrophiles (Table 4). In each case, the 3-substituted products (**8a-d**) could be separated from unreacted starting material by recrystallisation from appropriate solvents.



(7)



(**8**) **a**; R = D
b; R = SMe
c; R = C(OH)Ph_2
d; R = CH(OH)Ph

Table 4

Electrophile	Products and Yield (%)[a]
D_2O	(**8a**) (67)
Me_2S_2	(**8b**) (58)
Ph_2CO	(**8c**) (59)
PhCHO	(**8d**) (49)

a. Yields are for isolated products.

Previous studies on the metallation of 1-substituted pyrroles[4,13] show that they are less easily deprotonated than furans or thiophenes. By the use of 2-substituents as β-directing groups high levels of β-selectivity can be achieved but only at the expense of considerably lowered yields of metallation. The carboxamide group[7], to our knowledge is the most successful in accomplishing respectable yields of 3-metallation, an optimum 62% being possible.

Prior to the metallation study on 2-(1-methyl-2-pyrryl)imidazoline (**1c**), it was necessary to establish which signal in the ^1H NMR is due to the C-3 proton and which one is responsible for the C-5 proton. The coupling constants allow us to tentatively assign the signal furthest downfield as the C-5 proton (as in the thienyl- and furylimidazolines). This assignment was verified by two NMR experiments.

(i) Addition of the lanthanide shift reagent, Eu(fod)$_3$ (30 mg) to a $CDCl_3$ solution of imidazoline (**1c**) results in a downfield shift (0.8 ppm) of the suspected C-3 signal. Assuming the lanthanide shift reagent coordinates with the unsaturated nitrogen of the imidazoline group it is expected that the greater downfield shift will be observed for the C-3 proton as this is closer to the imidazoline ring.

(ii) Irradiation of the pyrrole-N-methyl signal leads to enhancement of the signal furthest downfield. This signal therefore corresponds to the C-5 proton, the latter being closer in space to the N-substituted methyl group.

Having confidently assigned the C-3 and C-5 proton signals, a metallation study was carried out in order to investigate the ability of the imidazoline group to direct 3-metallation into the pyrrole ring. The results are listed in Table 5.

Table 5. Lithiation of 2-(1-methyl-2-pyrryl)imidazoline (**1c**).

Expt.	RLi[b]	Temp (°C)	Time (h)	Additives[c]	Product composition (%)[d] derived from 3-Lithiation	5-Lithiation
1	2.5 A	-78	2.0		11	0
2	2.5 A	-78	2.0	TMEDA	13	0
3	2.5 A	65	0.25		63	0
4	2.5 A	65	1.0		69	0
5	2.5 B	-78	2.0		0	0
6	2.5 B	65	0.5		0	0

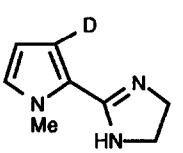
a 0.5 g of substrate was treated with RLi in THF at the temperature and for the time specified.

b A = BuLi, B = LDA.

c If TMEDA was required it was added immediately after and in equimolar ratio to BuLi.

d Starting imidazoline constitutes the balance to 100%.

At low temperatures, the reactivity of (**1c**) towards BuLi is negligible (Experiments 1 and 2); the majority of recovered material is unreacted imidazoline. Work with other pyrrole derivatives has shown improved reactivity at higher temperatures[7]. In contrast to the observations with furylimidazoline (**1b**) (see Table 3), the elevation of reaction temperature is not detrimental to the regioselectivity. Lithiation of (**1c**) in refluxing THF (Experiments 3 and 4) leads to much more respectable yields of exclusively 3-lithiated product, as evinced by D_2O work-up and isolation of 2-(3-deuterio-1-methyl-2-pyrryl)imidazoline (**9**). Thus, the 2-imidazolino moiety improves upon the 2-amido function as a director of 3-metallation in the pyrrole ring.



(**9**)

Experimental

General. ^{1}H NMR spectra were recorded on a Perkin-Elmer R34 spectrometer operating at 220 MHz; signals are singlets where no multiplicity is shown. IR spectra were recorded on a Mattson Alpha Centauri spectrometer. Microanalyses were performed in the University of Liverpool Microanalysis Laboratory. DME and THF were distilled from sodium-benzophenone before use. Commercial argon was used to provide an inert atmosphere in all reactions. M.p.'s were recorded on a Reichert hot stage apparatus and are uncorrected.

4,4-Dimethyl-2-(2-thienyl)oxazoline (2)[5]

The oxazoline was prepared from thiophene-2-carboxylic acid by the method of Meyers et al[10], and was isolated (4.88 g, 85%) as a colourless solid, m.p. 29-30°C (lit.[5], 29-30°C); δ ($CDCl_3$) 7.58 (1H, dd, J 2.88 and 1.3Hz, 5-H of thiophene), 7.40 (1H, dd, J 5.41 and 1.3 Hz, 3-H of thiophene), 7.05 (1H, dd, J 5.41 and 2.88 Hz, 4-H of thiophene), 4.07 (2H), 1.36 (6H); $\upsilon_{max.}$ (film), 3160, 2960, 1640, 1425 and 1025 cm^{-1}; m/z 181 (M^+, 21%), 166 (100) and 138 (24).

4,4-Dimethyl-2-(2-furyl)oxazoline (3)[4]

The oxazoline was prepared from 2-furoic acid (20 g, 0.18 mol) by the method of Chadwick[4] and coworkers and was isolated (25.5 g, 86%) as a colourless waxy solid, m.p. 36-37°C (lit.[4], 36-37°C); δ ($CDCl_3$) 7.52 (1H, dd, J 0.7 and 1.0 Hz, 5-H of furan), 6.91 (1H, dd, J 0.7 and 2.8 Hz, 3-H of furan), 6.47 (1H, dd, J 1.0 and 2.8 Hz, 4-H of furan), 4.07 (2H), 1.36 (6H); $\upsilon_{max.}$ (film), 3100, 2950, 1655 and 1305 cm^{-1}; m/z 165.0787 (M^+, 20%. $C_9H_{11}NO_2$ requires 165.0789) and 150 (100).

4,4-Dimethyl-2-(1-methyl-2-pyrryl)oxazoline (4)[4]

The oxazoline was prepared according to the method of Chadwick[4] from 1-methyl-2-pyrrole-carboxylic acid (3.83 g, 30.6 mmol). It was isolated (1.3 g, 95%) as a colourless liquid, b.p. 59°C, 0.5 mmHg (lit.[4], 55°C at 0.3 mmHg); δ ($CDCl_3$) 6.73 (2H, m, 3-H and 5-H of pyrrole), 6.12 (1H, dd, J 1.2 and 2.7 Hz, 4-H of pyrrole), 3.95 (2H), 3.93 (3H), 1.32 (6H); $\upsilon_{max.}$ (film), 2970, 2890, 1660 and 1265 cm^{-1}; m/z 178 (M^+, 27%) and 135 (100).

General Method for the Synthesis of 2-(2-Heteroaryl)imidazolines (1a-c)

4,4-Dimethyl-2-(2-heteroaryl)oxazoline (5.0 g, x mol) was stirred in excess methyl iodide (z mol) at the required temperature and for the requisite time. The ensuing solid was filtered, washed with light petroleum and dried *in vacuo* to give the 2-(2-heteroaryl)-3,4,4-trimethyloxazolinium iodide which was used without further purification.

The oxazolinium salt (5.0 g, x' mol) and ethylenediamine (y' g, equimolar ratio to oxazolinium salt) were boiled under reflux in acetonitrile (100 ml) for 10 h. Acetonitrile was removed under pressure, the residue basified (4M NaOH solution) and the product extracted into methylene chloride. The extracts were dried ($MgSO_4$) and the solvent removed to leave the crude product. Recrystallisation from the appropriate solvent(s) afforded the pure imidazoline.

	x mmol	z mol
2-Thienyloxazoline (**2**)	28	1.4
2-Furyloxazoline (**3**)	30	1.5
1-Methyl-2-pyrryloxazoline (**4**)	28	1.4

	x' mmol	y' g
2-Thienyloxazolinium iodide	15	0.90
2-Furyloxazolinium iodide	16	0.96
1-Methyl-2-pyrryloxazolinium iodide	15	0.90

2-(2-Thienyl)imidazoline (**1a**)

Method 1

4,4-Dimethyl-2-(2-thienyl)oxazoline (**2**) (28 mmol) and methyl iodide (1.4 mol) were stirred at 20°C for 24 h. Isolation of the product (general method) afforded 2-(2-thienyl)-3,4,4-trimethyloxazolinium iodide (8.68 g, 96%) as a pale yellow solid, m.p. 215°C; δ (CD_3OD) 8.38 (1H, dd, J 1.0 and 5.4 Hz, 5-H of thiophene), 8.34 (1H, dd, J 1.0 and 4.3 Hz, 3-H of thiophene), 7.49 (1H, dd, J 4.3 and 5.4 Hz, 4-H of thiophene), 4.88 (2H), 3.61 (3H), 1.62 (6H); $\upsilon_{max.}$ (KBr), 3085, 3025, 2955, 1635, 1425 and 1080 cm-1; m/z 196 (M^+, 100%).

Oxazolinium salt (15 mmol) and ethylenediamine (15 mmol) were boiled under reflux in acetonitrile. Work-up (general method) gave an off-white solid. Recrystallisation from acetone afforded thiophene (**1a**) (1.99 g, 87%) as a colourless solid, m.p. 179-180°C; (Found: C, 55.11; H, 5.30; N, 18.64. $C_7H_8N_2S$ requires C, 55.26; H, 5.26; N, 18.42%); δ (d_6-DMSO) 7.61 (1H, dd, J 1.2 and 4.36 Hz, 5-H of thiophene), 7.48 (1H, dd, J 1.12 and 2.57 Hz, 3-H of thiophene), 7.09 (1H, dd, J 1.12 and 3.47 Hz, 4-H of thiophene), 3.55 (4H); $\upsilon_{max.}$ (nujol), 3130, 2920, and 1594 cm^{-1}; m/z 152 (M^+, 70%), 123 (100), 110 (13) and 96 (27).

Method 2

4,4-Dimethyl-2-(2-thienyl)imidazoline (**2**) (5.0 g, 28 mmol) and ethylenediamine (1.66 g, 28 mmol - an excess is detrimental to the reaction) were boiled under reflux for 10 h. Cooling to 20°C afforded a tan solid. Recrystallisation in acetone gave thiophene (**1a**) (3.81 g, 87%) as a colourless solid.

2-(2-Furyl)imidazoline (**1b**)

4,4-Dimethyl-2-(2-furyl)imidazoline (**3**) (30 mmol) and methyl iodide (1.5 mol) were stirred at 20°C for 24 h. 2-(2-Furyl)-3,4,4-trimethyloxazolinium iodide (9.21 g, quantitative) was isolated as a pale yellow solid, m.p. 200-205°C; δ (d_6-DMSO) 8.46 (1H, d, J 1.3 Hz, 5-H of furan), 8.01 (1H, d, J 3.55 Hz, 3-H of furan), 7.06 (1H, dd, J 1.3 and 3.55 Hz, 4-H of furan), 4.83 (2H), 3.50 (3H), 1.53 (6H); $\upsilon_{max.}$ (nujol), 3040, 2910 and 1650 cm^{-1}; m/z 180 (M^+, 100%).

Oxazolinium salt (16 mmol) and ethylenediamine (16 mmol) were heated under reflux in acetonitrile. Work-up in the usual way gave the product which was recrystallised from acetone affording imidazoline (**1b**) (2.0 g, 92%) as a colourless solid, m.p. 175-176°C; (Found: C, 61.79; H, 5.95; N, 20.71. $C_7H_8N_2O$ requires C, 61.76; H, 5.88; N, 20.59%); δ (d_6-DMSO) 7.75 (1H, d, J 1.1 Hz, 5-H of furan), 6.90 (1H, d, J 3.3 Hz, 3-H of furan), 6.56 (1H, dd, J 2.0 and 2.0 Hz, 4-H of furan), 3.51 (4H); $\upsilon_{max.}$ (nujol), 3120, 2980, 2830 and 1650 cm^{-1}; m/z 136.0639 (M^+, 80%. $C_7H_8N_2O$ requires 136.0637), 107 (100) and 79 (46).

2-(1-Methyl-2-pyrryl)imidazoline (**1c**)

4,4-Dimethyl-2-(1-methyl-2-pyrryl)imidazoline (**4**) (28 mmol) and methyl iodide (1.4 mol) were stirred at 20°C for 24 h. Isolation of the quaternary salt was carried out in the usual way, giving 2-(1-methyl-2-pyrryl)-3,4,4-trimethyloxazolinium iodide (8.20 g, 91%) as a yellow solid, m.p. 228-229°C; δ (d_6-DMSO) 7.59 (1H, d, J 0.45 Hz, 5-H of pyrrole), 7.47 (1H, dd, J 2.24 and 2.46 Hz, 3-H of pyrrole), 6.47 (1H, dd, J 2.24 and 2.46 Hz, 4-H of pyrrole), 4.79 (2H), 3.90 (3H), 3.39 (3H), 1.50 (6H); $\upsilon_{max.}$ (nujol), 2960, 2860, 1634 and 1079 cm^{-1}; m/z 193 (M^+, 100%).

Quaternary oxazolinium salt (15 mmol) and ethylenediamine (15 mmol) were boiled under reflux in acetonitrile for 10 h. Work-up (general method) gave the crude product. Recrystallisation from light petroleum afforded imidazoline (**1c**) (1.77 g, 79%) as a colourless solid, m.p. 46-47°C; (Found: C, 63.91; H, 7.38; N, 28.13. $C_8H_{11}N_3$ requires C, 64.43; H, 7.38; N, 28.19%); δ (d_6-DMSO) 6.86 (1H, dd, J 1.2 and 2.1 Hz, 5-H of pyrrole), 6.55 (1H, dd, J 2.1 and 2.2 Hz, 3-H of pyrrole), 6.01 (1H, dd, J 1.2 and 2.67 Hz, 4-H of pyrrole), 3.87 (3H), 3.50 (4H); $\upsilon_{max.}$ (nujol), 3190, 2980, 2870 and 1630 cm^{-1}; m/z 149.0951 (M^+, 100%. $C_8H_{11}N_3$ requires 149.0953), 120 (21) and 107 (42).

General Method for the Lithiation of 2-(2-Thienyl)imidazoline (**1a**)

Method A: BuLi, DME or THF as solvent

To the 2-(2-thienyl)imidazoline (**1a**) (0.5 g, 3.29 mmol) in DME or THF was added commercial BuLi (8.23 mmol) in hexane at the required temperature. The mixture was stirred under an inert atmosphere (argon) for the requisite time. The electrophile was added, the mixture allowed to warm to 20°C, and the mixture left at this temperature for 16 h, unless stated otherwise. The solvent was removed *in vacuo*, the residue extracted with methylene chloride, washed (brine), dried ($MgSO_4$) and the solvent removed affording the crude product. If TMEDA was required, it was added immediately, and in equimolar ratio to, the BuLi.

Method B: Lithiations with LDA

To diisopropylamine (1.01 ml, 7.24 mmol) in the required solvent was added commercial BuLi (7.24 mmol) in hexane. 2-(2-Thienyl)imidazoline (**1a**) (0.5 g, 3.29 mmol) in the required solvent was then added and the experiment continued as in Method A.

2-(3-Deuterio-2-thienyl)imidazoline (**6a**)

To the 3-lithio intermediate (**5**) (3.29 mmol) prepared in THF at -78°C (general method) was added excess D_2O (1 ml, 50 mmol). The mixture was then worked-up in the usual way. Recrystallisation in acetone gave the deuterated thiophene derivative (**6a**) (0.49 g, 98%), m.p. 180-181°C; δ (d_6-DMSO) 7.61 (1H, d, J 5.6 Hz, 5-H of thiophene), 7.10 (1H, d, J 5.6 Hz, 4-H of thiophene), 3.55 (4H); $\upsilon_{max.}$ (nujol), 3130, 2960, 2840 and 1590 cm^{-1}; m/z 153 (M^+, 87%) and 124 (100).

2-(3-Methylthio-2-thienyl)imidazoline (**6b**)

To the lithiothienylimidazoline mixture (3.29 mmol) prepared in THF at -78°C (general method) was added methyl disulphide (1.17 ml, 13 mmol). Usual work-up afforded the crude product as a tan solid. Recrystallisation from ethyl acetate/petroleum ether (b.p. 60-80°C) gave the imidazoline (**6b**) (0.55 g, 84%) as a colourless solid, m.p. 57-58°C; (Found: C, 48.82; H, 5.08; N, 14.32. $C_8H_{10}N_2S_2$ requires C, 48.48; H, 5.05; N, 14.14%); δ (d_6-DMSO) 7.61 (1H, d, J 5.6 Hz, 5-H of thiophene), 7.09 (1H, d, J 5.6 Hz, 4-H of thiophene), 3.55 (4H), 2.45 (3H); $\upsilon_{max.}$ (nujol), 3125, 2960, 2860 and 1590 cm^{-1}; m/z 198.0287 (M^+, 100%. $C_8H_{10}N_2S_2$ requires 198.0285), 183 (40), 141 (34), 123 (39) and 97 (17).

αα-Diphenyl-2-[(4,5-dihydroimidazol-2-yl)thiophene]-3-methanol (**6c**)

BuLi (8.23 mmol) in hexane was added to the imidazoline (**1a**) (0.5 g, 3.29 mmol) in THF at -78°C. Benzophenone (2.40 g, 13 mmol) was added and stirring was continued at 20°C for 24 h. The solvent was removed by evaporation, the residual solid was suspended in water and the aqueous layer acidified to pH 1. Excess benzophenone was removed by extraction with ether. The acidic aqueous layer was then basified (4M NaOH solution), the product extracted with methylene chloride and dried ($MgSO_4$). Removal of the solvent afforded crude imidazoline. Recrystallisation from ethyl acetate/ petroleum ether (b.p. 60-80°C) (1:1) gave the pure imidazoline (**6c**) (1.03 g, 94%) as a colourless solid, m.p. 184-186°C; (Found: C, 72.09; H, 5.16; N, 8.33. $C_{20}H_{18}N_2OS$ requires C, 71.86; H, 5.39; N, 8.38%); δ (d_6-DMSO) 7.61 (1H, d, J 5.6 Hz, 5-H of thiophene), 7.32 (11H, m, 4-H of thiophene and 2 Ph's) 3.55 (4H); $\upsilon_{max.}$ (nujol), 3169, 3021, 2973, 2860 and 1598 cm^{-1}; m/z 334.1137 (M^+, 11%. $C_{20}H_{18}N_2OS$ requires 334.1139), 316 (32), 239 (100), 105 (8) and 77 (13).

α-Phenyl-2-[(4,5-dihydroimidazol-2-yl)thiophene]-3-methanol (**6d**)

To the lithio imidazoline (**5**) (3.29 mmol) prepared in THF at -78°C was added benzaldehyde (1.34 ml, 13mmol). Work-up as for (**6c**) gave the product as a yellow oil. Kugelrohr distillation afforded imidazoline (**6d**) (0.78 g, 92%) as a colourless oil, b.p. 53°C (bath) at 2 mmHg; δ (d_6-DMSO) 7.61 (1H, d, J 5.6 Hz, 5-H of thiophene), 7.41 (5H, m, Ph), 7.09 (1H, d, J 5.6 Hz, 4-H of thiophene), 3.55 (4H), 3.19 (1H); $\upsilon_{max.}$ (film),

3480, 3160, 3100, 2940, 2860 and 1600 cm^{-1}; m/z 258.0829 (M^+, 100%. $C_{14}H_{14}N_2OS$ requires 258.0827), 240 (18), 181 (19), 153 (21), 123 (32), 108 (19) and 77 (45).

2-(3-Trimethylsilyl-2-thienyl)imidazoline (6e)

To the lithio imidazoline (5) (3.29 mmol) prepared in DME at -78°C (general method) was added TMSCl (1.25 ml, 9.87 mmol). Work-up in the usual way gave a product which was recrystallised from light petroleum affording the 3-silylated imidazoline (6e) (0.56 g, 76%) as a colourless solid, m.p. 184-186°C; (Found: C, 53.72; H, 7.19; N, 12.42. $C_{10}H_{16}N_2SSi$ requires C, 53.57; H, 7.14; N, 12.50%); δ (d_6-DMSO) 7.61 (1H, d, J 4.82 Hz, 5-H of thiophene), 7.10 (1H, d, J 4.82 Hz, 4-H of thiophene), 3.55 (4H), 0.25 (9H); $\upsilon_{max.}$ (nujol), 3020, 2970, 2860 and 1600 cm^{-1}; m/z 224.0799 (M^+, 9%. $C_{10}H_{16}N_2SSi$ requires 224.0802), 209 (49), 191 (18), 166 (32) and 133 (19).

General Method for the Lithiation of 2-Furylimidazoline (1b)

BuLi, DME or THF as solvent

To 2-(2-furyl)imidazoline (**1b**) (0.5 g, 3.68 mmol) in DME or THF (30 ml) was added commercial BuLi (9.2 mmol) in hexane followed by TMEDA (9.2 mmol) at the required temperature. The mixture was stirred under an inert atmosphere for the requisite time, after which time the electrophile was added. The mixture was allowed to warm to 20°C and then left at this temperature for 16 h, unless otherwise stated. The solvent was removed under reduced pressure, the residue extracted with methylene chloride, washed (brine), dried ($MgSO_4$) and the solvent removed to give the crude product.

2-(3-Deuterio-2-furyl)imidazoline (8a)

To the 3-lithiofurylimidazoline (7) (3.68 mmol) prepared in DME at -78°C (general method) was added excess D_2O (1 ml, 50 mmol). The mixture was then worked-up in the usual way. Recrystallisation from acetone afforded 2-(3-deuterio-2-furyl)imidazoline (**8a**) (0.34 g, 67%) as a colourless solid, m.p. 175-176°C; δ (d_6-DMSO) 7.75 (1H, d, J 1.57 Hz, 5-H of furan), 6.56 (1H, d, J 1.57 Hz, 4-H of furan), 3.51 (4H); m/z 137.0698 (M^+, 100%. $C_7H_7DN_2O$ requires 137.0699).

2-(3-Methylthio-2-furyl)imidazoline (8b)

To the 3-lithioimidazoline (7) (3.68 mmol) prepared in DME at -78°C (general method) was added methyl disulphide (1.32 ml, 15 mmol). Work-up in the usual way gave a yellow solid which on recrystallisation (several times) from light petroleum afforded imidazoline (**8b**) (0.33 g, 49%) as a colourless solid, m.p. 179-180°C; (Found: C, 52.69; H, 5.41; N, 15.44. $C_8H_{10}N_2OS$ requires C, 52.75; H, 5.49; N, 15.38%); δ (d_6-DMSO) 7.79 (1H, d, J 1.45 Hz, 5-H of furan), 6.71 (1H, d, J 1.45 Hz, 4-H of furan), 3.51 (4H), 2.37 (3H); m/z 182.0283 (M^+, 100%. $C_8H_{10}N_2OS$ requires 182.0281), 167 (45), 125 (39) and 107 (42).

αα-Diphenyl-2-[(4,5-dihydroimidazol-2-yl)furan]-3-methanol (**8c**)

BuLi (9.2 mmol) in hexane was added to imidazoline (**1b**) (0.5 g, 3.68 mmol) in DME at -78°C. The subsequent lithio species was quenched with benzophenone (2.68 g, 15 mmol), the mixture warmed to 20°C and left at this temperature for 16 h. Work-up as for imidazoline (**6c**) gave the crude product. Recrystallisation from ethyl acetate/light petroleum (1:1) afforded imidazoline (**8c**) (0.68 g, 58%) as a colourless solid, m.p. 222-223°C; (Found: C, 75.59; H, 5.59; N, 8.72. $C_{20}H_{18}N_2O_2$ requires C, 75.47; H, 5.66; N, 8.81%); δ (d_6-DMSO) 7.73 (1H, d, J 1.9 Hz, 5-H of furan), 7.24 (10H, m, 2 Ph's), 5.85 (1H, d, J 1.9 Hz, 4-H of furan), 3.54 (4H); $\upsilon_{max.}$ (nujol), 3460, 3120, 2960, 2840 and 1605 cm^{-1}; m/z 318.1364 (M^+, 100%. $C_{20}H_{18}N_2O_2$ requires 318.1368), 241 (95), 213 (14), 136 (12) and 77 (28).

α-Phenyl-2-[(4,5-dihydroimidazol-2-yl)furan]-3-methanol (**8d**)

To the 3-lithiofurylimidazoline (**7**) (3.68 mmol) prepared in DME at -78°C was added benzaldehyde (1.49 ml, 15 mmol). Work-up as for (**8c**) gave a yellow/orange solid. Recrystallisation from light petroleum afforded the imidazoline (**8d**) (0.44 g, 49%) as a colourless solid, m.p. 201-204°C; δ (d_6-DMSO) 7.67 (1H, d, J 2.01 Hz, 5-H of furan), 7.29 (5H, m, Ph), 6.43 (1H, d, J 2.01 Hz, 4-H of furan), 6.00 (1H), 3.38 (4H); $\upsilon_{max.}$ (nujol), 3465, 3100, 2960, 2860 and 1600 cm^{-1}; m/z 242.1058 (M^+, 100%. $C_{14}H_{14}N_2O_2$ requires 242.1055), 165 (74) and 77 (43).

2-(3-Deuterio-1-methyl-2-pyrryl)imidazoline (**9**)

To 2-(1-methyl-2-pyrryl)imidazoline (**1c**) (0.5 g, 3.36 mmol) in THF (30 ml) was added commercial BuLi (8.4 mmol) in hexane at 65°C and the mixture stirred at this temperature for 1 h. The 3-lithiopyrrylimidazoline thus formed was then quenched with D_2O (1 ml, 50 mmol). Work-up in the usual way gave the crude product. Recrystallisation from light petroleum afforded pyrrole (**9**) (0.35 g, 69%) as an off-white solid, m.p. 229-231°C; δ ($CDCl_3$) 6.68 (1H, d, J 2.8 Hz, 5-H of pyrrole), 6.08 (1H, d, J 2.8 Hz, 4-H of pyrrole), 4.85 (1H,b.s., NH), 3.92 (3H), 3.64 (4H); m/z 150.1017 (M^+, 100%. $C_8H_{10}DN_3$ requires 150.1016).

Acknowledgements

Support for this work was provided by the S.E.R.C.(studentship to D.S.E). We thank T.L.Gilchrist for helpful discussions.

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