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CHEMOSELECTIVE PROTECTION OF HETEROAROMATIC ALDEHYDES AS IMIDAZOLIDINE DERIVATIVES. PREPARATION OF 5-SUBSTITUTED FURAN- AND THIOPHENE-2-CARBOXALDEHYDES VIA METALLO-IMIDAZOLIDINE INTERMEDIATES

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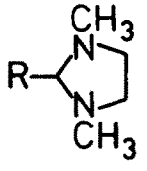
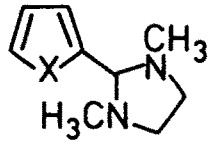
Abstract - Furan-, thiophene- and N-methylpyrrole-2-carboxaldehydes may be transformed into the corresponding N,N'-dimethylimidazolidines in a reaction not requiring acid catalysis. The resulting furan and thiophene (but not N-methylpyrrole) derivatives may be metallated in high yields [predominantly at the 5 (α-) positions of the heteroaromatic rings] and the carboxaldehyde functionality regenerated under very mild conditions. Treatment of the aldehydoketone 2-acetyl-5-formylthiophene with N,N'-dimethylethylenediamine gives only the product of reaction at the aldehyde function thus establishing this methodology as a potentially valuable method for the protection of an aldehyde in the presence of a ketone.

I. INTRODUCTION

From time to time, N,N'-disubstituted imidazolidines (1) have been prepared as derivatives of aldehydes. For example, Billman et al.,[1] synthesised crystalline imidazolidines from a wide range of aldehydes using 1,2-bis(p-methoxybenzylamino)ethane, whereas of eight aliphatic and aromatic ketones examined, only acetone reacted with the diamine under the same conditions as those used for the aldehydes. More recently, Harris and Roth have shown[2] that the N,N'-dimethylimidazolidino substituent serves in the 2-phenyl derivative [(1), R = C_6H_5)] to direct metallation [Bu^nLi, ether, N,N,N',N'-tetramethylethylenediamine (TMEDA), 25°C, 7h] into an adjacent ortho position of the benzene ring furnishing a synthetical method for ortho-substituted benzaldehyde derivatives.



(1)



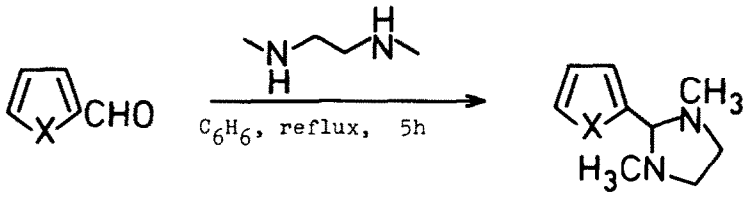
(2)

X = O, S, or NCH_3

As part of our continuing interest in the metallation of heteroaromatic compounds,[3] it seemed to us of value to explore the preparation of the corresponding furan, thiophene and N-methylpyrrole derivatives (2) (hitherto unknown) and to study their metallation. It further appeared opportune for us to examine whether the chemoselectivity implied by Billman's results could be used to advantage for the selective protection of the aldehyde function in an aldehydoketone. The results of these investigations are presented here.

II. RESULTS AND DISCUSSION

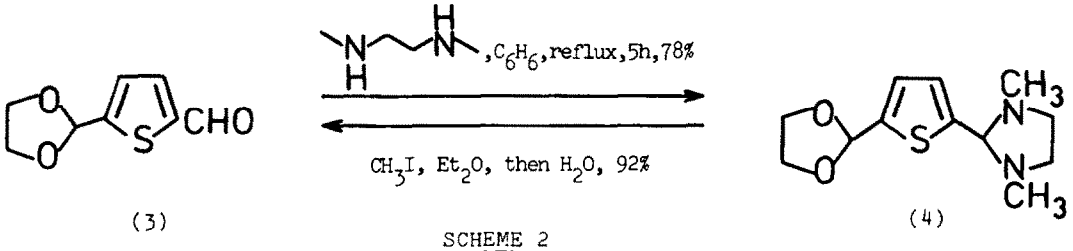
The required imidazolidine derivatives [(2), X = O, S, NCH_3] were prepared easily and in good (non-optimised) yields (Scheme 1). Importantly (especially for the acid-sensitive furan and pyrrole ring systems) the reaction proceeds well



X =	S	O	NCH_3
yield (%) =	81	74	70

SCHEME 1

without acid catalysis, azeotropic removal of water sufficing. (This is in agreement with the mechanistic study of Chapuis et al.,[4] who report that secondary 1,2-diamines in which the nitrogen substituents are aliphatic react with aliphatic and aromatic aldehydes without acid catalysis.) Regeneration of the aldehydes may be achieved either by dilute aqueous acidic hydrolysis (giving the thiophene- and furan-2-carboxaldehydes in 95 and 93% yields respectively) or by treatment of the imidazolidide with a slight excess of iodomethane and then water (giving the thiophene- and N-methylpyrrole-2-carboxaldehydes in 93 and 92% yields respectively) : to our knowledge, this is the first time that such mild deprotection methodology has been utilised for this system. The mild protection-deprotection techniques permit masking and unmasking of aldehyde functionality in the presence of an acetal moiety (Scheme 2).



(3) (4)

SCHEME 2

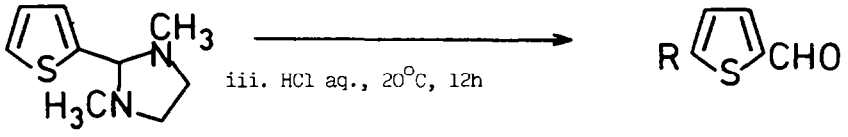
In a range of experiments (1 - 28, Table 1), the effects of change of solvent, metallating agent, reaction temperature and time, and of the presence or absence of TMEDA on the course of metallation of 1,3-dimethyl-2-(2-thienyl)-imidazolidine [(2), X = S] have been explored. In contrast to the situation found for the phenyl analogue [(1), R = C_6H_5][2] and for the related 4,4-dimethyl-2-(2-thienyl)oxazoline,[3] only low levels of directed- (β-) metallation into the thiophene ring are achievable. Dimethoxyethane (DME) as solvent and/or TMEDA as additive seem generally to have a deleterious effect on β-metallation, perhaps through their competing for lithium complexation with the probably rather weakly-complexing imidazolidine nitrogen. Not surprisingly, change of metallating agent from Bu^nLi to the co-ordinatively saturated lithium di-isopropylamide (LDA) reduces the propensity for β-metallation. The conditions established in experiment 15 for high-yielding (91%) generation of the 5-lithio-intermediate [tetrahydrofuran (THF) as solvent, -78°C, 2h, TMEDA present] were used in reactions with a range of electrophiles to yield the 5-substituted aldehydes (after hydrolytic unmasking of the aldehyde function) (Scheme 3).

The results of a similar range of experiments (29 - 52, Table 2) on the metallation of 1,3-dimethyl-2-(2-furyl)imidazolidine [(2), X = O] again show only low levels of β- (directed) metallation. The optimal conditions (experiment 50) for preparation of the 5-lithio-intermediate (THF as solvent, -78°C, 2h) were used in a similar manner to the analogous thiophene system to produce a series of 5-substituted furan aldehydes (Scheme 4).

TABLE 1 : Lithiations of 1,3-dimethyl-2-(2-thienyl)imidazolidine [(2), X = S]

Expt.	Bu^nLi: Substrate Ratio	Solvent[a]	Temp. (°C)	Time (h)	Additive[b]	% Lithiation[c] 2,3-Product	2,5-Product	Recovered[d] Yield (%)
1	3	A	20	7	3 TMEDA	13	34	*
2	1.1	A	20	2	TMEDA	0	51	*
3	1.1	A	20	2	-	5	21	*
4	1.1	A	70	2	TMEDA	13	16	*
5	1.1	A	70	2	-	0	43	*
6	1.1	A	20	7	TMEDA	8	32	*
7	1.1	A	70	48	-	0	0	*
8	1.1	B	-78	2	-	0	50	91
9	1.1	B	-78	2	TMEDA	0	41	100
10	1.1	B	-19	2	-	0	27	100
11	1.1	B	-19	2	TMEDA	0	0	*
12	1.1	C	-78	0.5	-	6	88	87
13	1.1	C	-78	2	-	12	82	100
14	1.1	C	-78	0.5	TMEDA	8	86	96
15	1.1	C	-78	2	TMEDA	0	91	96
16	1.1	C	0	0.5	-	18	88	82
17	1.1	C	0	0.5	TMEDA	9	83	99
18	1.1	D	-78	0.5	-	14	12	97
19	1.1	D	-78	2	-	3	5	90
20	1.1	D	-78	0.5	TMEDA	16	16	96
21	1.1	D	-78	2	TMEDA	16	28	100
22	1.1	D	0	0.5	-	20	49	88
23	1.1	D	0	0.5	TMEDA	0	83	98
24	1.1	C	-78	0.5	DIA	5	75	95
25	1.1	C	-78	2	DIA	7	80	88
26	1.1	C	0	0.5	DIA	7	57	75
27	1.1	C	0	2	DIA	11	54	88
28	1.1	C	-78	0.5	DIA/TMEDA	1	66	91

[a] A = hexane, B = dimethoxyethane, C = tetrahydrofuran, D = diethyl ether. [b] DIA = di-isopropylamine. [c] Estimated by quenching of the reaction mixtures with an excess of $CH_3O[^2H]$ and integration of the aromatic ring ^1H n.m.r. signals. [d] * Denotes corrupted material present.



E =	CO_2	$(CH_3)_2S_2$	CH_3I	C_6H_5CHO	$C_6H_5CH_2Br$
R =	CO_2H	CH_3S	CH_3	C_6H_5CO	$C_6H_5CH_2$
Yield (%) =	95	88	82	51[a]	98
Compound=	(5)	(6)	(7)	(8)	(9)

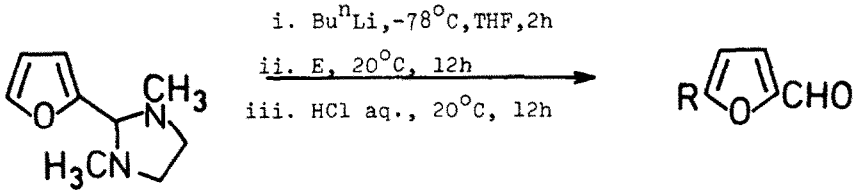
[a] via aerial oxidation during work-up.

SCHEME 3

TABLE 2 : Lithiations of 1,3-dimethyl-2-(2-furyl)imidazolidine [(2), X = O][a]

Expt.	Solvent.	Temp. (°C)	Time (h)	Additive	% Lithiation 2,3-product	2,5-product	Recovered Yield (%)
29	A	0	0.5	-	14	81	64
30	A	0	0.5	TMEDA	28	59	79
31	A	-78	0.5	-	31	59	82
32	A	-78	2	-	28	67	80
33	A	-78	0.5	TMEDA	21	46	86
34	A	-78	2	TMEDA	22	52	82
35	D	0	0.5	-	12	88	62
36	D	0	0.5	TMEDA	15	73	78
37	D	-78	0.5	-	16	30	73
38	D	-78	2	-	21	38	70
39	D	-78	0.5	TMEDA	15	30	89
40	D	-78	2	TMEDA	15	46	86
41	B	-10	0.5	-	12	45	67
42	B	-10	0.5	TMEDA	10	58	63
43	B	-78	0.5	-	28	36	98
44	B	-78	2	-	31	52	95
45	B	-78	0.5	TMEDA	16	43	99
46	B	-78	2	TMEDA	20	46	98
47	C	0	0.5	-	0	63	73
48	C	0	0.5	TMEDA	7	76	79
49	C	-78	0.5	-	0	59	99
50	C	-78	2	-	10	83	97
51	C	-78	0.5	TMEDA	8	63	93
52	C	-78	2	TMEDA	3	79	96

[a] The footnotes to Table 1 apply. The ratio of Bu^nLi to substrate was 1.1:1 throughout.



E	=	CO_2	$(CH_3)_2S_2$	$HCON(CH_3)_2$	$(CH_3)_3SiCl$	CH_3I	C_6H_5CHO
R	=	CO_2H	CH_3S	CHO	$Si(CH_3)_3$	CH_3	C_6H_5CO[a]
Yield (%)	=	83	83	71	76	80	64
Compound	=	(10)	(11)	(12)	(13)	(14)	(15)

[a] via aerial oxidation during work-up.

SCHEME 4

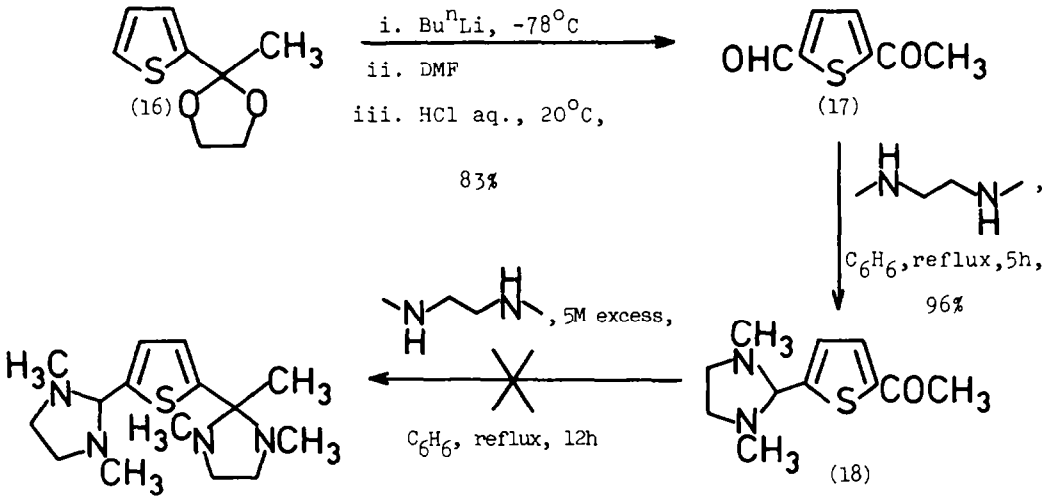
We have previously shown[5] that N-methylpyrrole derivatives are in general less easily metallated than the corresponding furans or thiophenes. It is not surprising, therefore, that only moderate lithiation levels could be achieved for 1,3-dimethyl-2-(1-methylpyrrol-2-yl)imidazolidine [(2), X = NCH_3] (Table 3).

Finally, the chemoselectivity for imidazolidide formation from an aldehyde or ketone and N,N'-dimethylethylenediamine has been investigated through the synthesis of the aldehydoketone (17) (Scheme 5) and the study of its reaction with the diamine. Even when the latter was present in 5M excess over the former, no trace of any product from reaction at the ketonic centre was observed. Attempts to force a reaction through boiling of this mixture for 12h with added p-toluenesulphonic acid as catalyst led to a ca. 1:1 mixture of mono- and di- imidazolidides contaminated with corrupted material. This methodology thus displays the highest level of chemoselectivity for reaction of an aldehyde function in the presence of a ketone.

TABLE 3 : Lithiations of 1,3-dimethyl-2-(1-methylpyrrol-2-yl)imidazolidine [(2), X = NCH_3][a].

Expt.	Bu^nLi: Substrate Ratio	Solvent	Temp (°C)	Time (h)	Additive	% Lithiation 2,3-product	% Lithiation 2,5-product	Recovered Yield (%)
53	2	A	20	0.5	TMEDA	8	43	100
54	1.1	D	40	3	-	24	43	94
55	1.1	C	-78	0.25	-	7	12	94

[a] The footnotes to Table 1 apply.



SCHEME 5

In conclusion, the imidazolidine system appears to be of considerable value for the protection of aldehyde functionality since it may be both introduced and removed under very mild conditions and yet is able to survive in the strongly basic and nucleophilic environment necessary for heteroaromatic metallations. Furthermore, the high degree of chemoselection that has been achieved for aldehyde derivatisation in the presence of ketone functionality, if general, suggests that the method should be of considerable value for selective functional group protection.

III. EXPERIMENTAL

Procedures for analysis, purification and characterisation have been described in an earlier paper.[3] 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 di-isopropylamine were distilled from CaH_2 *in vacuo*, and *N*,*N*'-dimethylethylenediamine was distilled from KOH; the reagents 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.[6]

1,3-Dimethyl-2-(2-thienyl)imidazolidine [(2), X = S]. - A solution of thiophene-2-carboxaldehyde (4g, 35.7 mmol) and N,N'-dimethylethylenediamine (3.15g, 35.8 mmol) in benzene (50 ml) was boiled under reflux for 12h with azeotropic removal of water. The benzene was removed by evaporation and the residue distilled (81°C at 0.5 mmHg) to give the 2-thienylimidazolidine [(2), X = S] (5.69g, 87%) as a colourless oil (Found: C, 59.1; H, 7.8; N, 15.2; S, 17.4. $C_9H_{14}N_2S$ requires C, 59.32; H, 7.74; N, 15.37; S, 17.56%); δ ($CDCl_3$), 7.23 (1H, d, J 5.02 Hz, thiophene 5-H), 6.99 (1H, d, J 3.35 Hz, thiophene 3-H), 6.86 (1H, m, J 5.02, 3.35 Hz, thiophene 4-H), 2.24 (1H, s, CH), 3.34 (2H, m, CH_2), 2.51 (2H, m, CH_2), 2.21 (6H, s, NCH_3); m/z 182 (M^+, 85%) and 99 (100).

1,3-Dimethyl-2-(2-furyl)imidazolidine [(2), X = O]. - The above procedure was applied to a mixture of furan-2-carboxaldehyde (72g , 0.75 mol), benzene (400 ml) and N,N'-dimethylethylenediamine (75g, 0.85 mol) to give the pure 2-furylimidazolidine [(2), X = O] (116.3g , 94%), b.p. 100°C at 12 mmHg, as a colourless oil (Found: C, 64.3; H, 8.7; N, 16.9. $C_9H_{14}N_2O$ requires C, 65.03; H, 8.49; N, 16.85%); δ ($CDCl_3$), 7.38 (1H, d, J 1.18 Hz, furan 5-H), 6.36 (1H, d, J 2.73 Hz, furan 3-H), 6.29 (1H, dd, J 1.18, 2.73 Hz, furan 4-H), 3.61 (1H, s, C-H), 3.27 (2H, m, CH_2), 2.56 (2H, m, CH_2), 2.23 (6H, s, NCH_3); m/z 166 (M^+, 85%) and 123 (100).

1,3-Dimethyl-2-(1-methylpyrrol-2-yl)imidazolidine [(2), X = NCH_3]. - The procedure used for the thiophene analogue was applied to a mixture of 1-methylpyrrole-2-carboxaldehyde (25g, 0.23 mol) and N,N'-dimethylethylenediamine (22.9g, 0.26 mol) in benzene (100 ml) to give the 1-methylpyrrol-2-ylimidazolidine [(2), X = NCH_3] (28.7g, 70%), b.p. 110°C at 12 mmHg, as a clear oil (Found: C, 66.9; H, 9.6; N, 23.6 $C_{10}H_{17}N_3$ requires C, 66.99; H, 9.57; N, 23.44%); δ ($CDCl_3$), 6.53 (1H, m, pyrrole 5-H), 6.04 (1H, m, pyrrole 3-H), 5.96 (1H, m, pyrrole 4-H), 3.71 (3H, s, pyrrole NCH_3), 3.38 (1H, s, CH), 3.23 (2H, m, CH_2), 2.41 (2H, m, CH_2), 2.13 (6H, s, NCH_3); m/z 179 (M^+, 93%) and 135 (100).

General Methods for Lithiation Studies. Method A : Bu^nLi as Base. - To a solution of the imidazolidine (3.0 mmol) in the required solvent (30 ml) at the required temperature were added TMEDA (0.47 ml, 3.1 mmol) (if required) and Bu^nLi (3.1 mmol) in hexane and the reaction mixture was stirred for the required time. The electrophile was then added, the mixture allowed to warm to 20°C and then left for either 1h ($CH_3O[^2H]$ as electrophile) or 12h (all other electrophiles) at this temperature. If the solvents were THF or DME then these were removed under reduced pressure and the residue was suspended in a 1:1 mixture of ethyl ethanoate and diethyl ether (200 ml). The organic solution or suspension was washed with water (3 x 10 ml) and brine (1 x 10 ml) and dried ($MgSO_4$). The solvent was then evaporated under reduced pressure.

When trimethylsilylchloride was used as the electrophile, dilute aqueous sodium bicarbonate solution replaced the water in the work-up procedure.

When carbon dioxide was used as the electrophile, the lithio-intermediate was poured onto a slurry of solid carbon dioxide and diethyl ether and the mixture left for 12h at 20°C. Solvents were removed under reduced pressure and the residue was stirred with 10% w/w H_2SO_4 aq. for 12h at 20°C. The resulting acid-aldehyde was extracted into dichloromethane (5 x 20 ml), the organic solution dried ($MgSO_4$) and the solvent evaporated under reduced pressure.

Method B : LDA as Base. - To di-isopropylamine (0.31g, 3.1 mmol) in the required solvent at the required temperature was added Bu^nLi (3.1 mmol) in hexane. The mixture was stirred for 5m and the imidazolidine (3.0 mmol) in the required solvent (10 ml) was then added. The experiment was then continued as in method A.

2-(2-Thienyl)-1,3-dioxolan. - To thiophene-2-carboxaldehyde (10.8g, 0.096 mol) in benzene (400 ml) was added ethylene glycol (10g) and p-toluenesulphonic acid (0.2g). The mixture was heated under reflux for 16h, cooled, washed with

10% (w/w) aqueous sodium bicarbonate solution (3 x 10 ml) and then dried ($MgSO_4$). Evaporation of the solvent and distillation under reduced pressure gave the acetal (14.02g, 94%), b.p. 116°C at 12 mmHg (lit.[7] 110 - 111°C at 15 mmHg), δ ($CDCl_3$), 7.25 (1H, d, J 4.99 Hz, thiophene 5-H), 7.11 (1H, d, J 3.32 Hz, thiophene 3-H), 6.92 (1H, dd, J 4.99, 3.32 Hz, thiophene 4-H), 6.05 (1H, s, CH), 3.96 (4H, m, CH_2CH_2); m/z 156 (M^+, 96%) and 111 (100).

2-(5-Formyl-2-thienyl)-1,3-dioxolan (3). - To a solution of 2-thienyl-1,3-dioxolan from above (2.0g, 12.8 mmol) in THF (60 ml) cooled to -78°C was added TMEDA (1.95 ml, 12.9 mmol) and Bu^nLi (12.9 mmol) in hexane. The mixture was stirred for 2h at -78°C, DMF (4 ml) was added and the mixture was allowed to warm to 20°C; stirring was then continued for 12h. The solvents were removed by evaporation and the residues taken up in ethyl ethanoate (100 ml). The organic mixture was washed with water (3 x 10 ml) and brine (1 x 10 ml) and dried ($MgSO_4$). Purification by p.t.l.c. (ethyl ethanoate - light petroleum 1:19 as eluant, 5 elutions) gave the crude product which was distilled under reduced pressure, b.p. 180°C at 1 mmHg, to give the pure 2-(5-formyl-2-thienyl)-dioxolan (3) as an oil (1.00g, 43%); δ ($CDCl_3$), 9.88 (1H, s, CHO), 7.67 (1H, d, J 3.83 Hz, thiophene 4-H), 7.23 (1H, d, J 3.83 Hz, thiophene 3-H), 6.12 (1H, s, CH), 4.14 - 4.01 (4H, m, CH_2CH_2); $\nu_{max.}$ (film), 1670 cm^{-1}; m/z 184.0177 (M^+, 55%, $C_8H_8O_3S$ requires 184.0194) and 155 (100).

2-[5-(1,3-Dimethyl-2-imidazolidinyl)-2-thienyl]-1,3-dioxolan (4). - A solution of the formyl-thienyl-dioxolan (3) (0.588g, 3.19 mmol) and N,N'-dimethyl-ethylenediamine (0.42 ml, 3.99 mmol) in benzene (25 ml) was boiled under reflux for 24h using a Dean-Stark apparatus containing activated molecular sieves type 4A. Benzene was removed by evaporation and the residue was taken up in ethyl ethanoate (100 ml). The organic solution was washed with water (3 x 10 ml) and brine (1 x 10 ml) and dried ($MgSO_4$). The solvent was removed by evaporation to give the imidazolidinyl-thienyl-dioxolan (4) (0.631g, 78%); δ ($CDCl_3$), 6.99 (1H, d, J 3.33 Hz, thiophene 3-H), 6.93 (1H, d, J 3.33 Hz, thiophene 4-H), 6.03 (1H, s, -OCHO-), 4.08 - 3.95 (4H, m, $-OCH_2CH_2O-$), 3.61 (1H, s, -NCHN-), 3.32 (2H, m, $-NCH_2CH_2N-$), and 2.53 (2H, m, $-NCH_2CH_2N-$), 2.22 (6H, s, NCH_3); m/z 254.1089 (M^+, 34%, $C_{12}H_{18}N_2O_2S$ requires 254.1089) and 99 (100).

Deprotection of 1,3-dimethyl-2-(2-thienyl)imidazolidine [(2), X = S].

Method C : Under acidic conditions. - To the imidazolidine (0.2g, 1.1 mmol) was added 10% aqueous H_2SO_4 (w/w, 25 ml). The mixture was stirred for 2h at 20°C and then saturated with NaCl. Extraction with CH_2Cl_2 (5 x 20 ml), drying of the organic extracts ($MgSO_4$) and removal of solvent therefrom yielded thiophene-2-carboxaldehyde (0.12g, 95%).

Method D : Under neutral conditions. - A mixture consisting of the imidazolidine (1.0g, 5.52 mmol), iodomethane (10 ml) and ether (10 ml) was stirred for 1h at 20°C. The solvents were removed giving an orange precipitate which was suspended in water (30 ml) and stirred for 1h at 20°C. Extraction with CH_2Cl_2 (3 x 10 ml), drying of the combined organic extracts ($MgSO_4$) and removal of solvent gave thiophene-2-carboxaldehyde (0.575g, 93%).

Deprotection of an imidazolidine in the presence of dioxolan functionality. - In a manner similar to method D described above, imidazolidinyl-thienyl-dioxolan (4) (0.07g, 0.275 mmol) was stirred with iodomethane (0.5 ml) and ether (5 ml) for 1h at 20°C. Hydrolysis and work-up as before gave the formyl-thienyl-dioxolan (3) (0.047g, 92%).

General Procedure for Isolation of the Disubstituted Heteroaromatic Products. Method E. - The products from lithiations following general method A were immediately hydrolysed for 12h at 20°C with 10% aqueous H_2SO_4 (w/w, 50 ml). Extraction with CH_2Cl_2 (5 x 30 ml), drying of the combined extracts ($MgSO_4$), and evaporation of solvent gave the substituted aldehyde products.

5-Formylthiophene-2-carboxylic acid (5). - Lithiation of the 2-thienylimidazolidine [(2), X = S] following general method A (5.52 mmol scale), work-up with a solid CO_2/ether slurry, acid hydrolysis (method E with 10 x 50 ml extractions), and recrystallisation of the crude product from C_6H_{12}/ethyl ethanoate gave the pure formylcarboxylic acid (5) (0.816g, 95%), m.p. 165 - 167°C (lit.[8] 165 - 166°C); δ ($CDCl_3$), 11.18 (1H, br s, OH), 10.0 (1H, s, CHO), 7.97 (1H, d, J 3.82 Hz, thiophene 3-H), 7.87 (1H, d, J 3.82 Hz, thiophene 4-H); m/z 156 (M^+, 90%) and 155 (100).

5-Methylthiothiophene-2-carboxaldehyde (6). - Lithiation of the 2-thienylimidazolidine [(2), X = S] following general method A (5.52 mmol scale), work-up with $(CH_3)_2S_2$,(1.04g, 11.04 mmol), acid hydrolysis (method E) and distillation under reduced pressure, b.p. 95°C at 0.4 mmHg (lit.[9] 86°C at 0.3 mmHg) gave the pure aldehyde (6) (0.764g, 88%); δ ($CDCl_3$), 9.72 (1H, s, CHO), 7.59 (1H, d, J 3.56 Hz, thiophene 4-H), 6.96 (1H, d, J 3.56 Hz, thiophene 3-H), 2.58 (3H, s, CH_3); m/z 158 (M^+, 100%).

5-Methylthiophene-2-carboxaldehyde (7). - Lithiation of the 2-thienylimidazolidine [(2), X = S] following general method A (5.52 mmol scale), work-up with iodomethane (0.8g, 5.62 mmol), acid hydrolysis (method E) and distillation under reduced pressure, b.p. 98°C at 12 mmHg (lit.[10] 52.5°C at 0.7 mmHg) gave the pure aldehyde (7) (0.570g, 82%) as an oil; δ ($CDCl_3$), 9.78 (1H, s, CHO), 7.59 (1H, d, J 3.34, thiophene 3-H), 6.90 (1H, d, J 3.34, thiophene 4-H), 2.56 (3H, s, CH_3); m/z 126 (M^+, 88%) and 125 (100).

5-Formyl-2-thienyl phenyl ketone (8). - Lithiation of the 2-thienylimidazolidine [(2), X = S] following general method A (5.52 mmol scale), work-up with benzaldehyde (5 ml, 49.2 mmol), and acid hydrolysis (method E) gave a mixture of starting material and product. Recrystallisation ($C_6H_{12}/CHCl_3$) and preparative thin layer chromatography (p.t.l.c.) (ethyl ethanoate-light petroleum, 1:3, as eluant, four elutions) gave the pure keto-aldehyde (8)[11] (0.605g, 51%), as a white solid, m.p. 106 - 107°C; δ ($CDCl_3$), 10.0 (1H, s, CHO), 7.9 (2H, d, J 8.46 Hz, phenyl ortho-H), 7.82 (1H, d, J 3.98 Hz, thiophene 4-H), 7.73 (1H, d, J 3.98 Hz, thiophene 3-H), 7.67 (1H, t, J 7.59 Hz, phenyl para-H), 7.55 (2H, m, J 7.59, 8.46 Hz, phenyl meta-H); $\nu_{max.}$ ($CHCl_3$), 1690, 1650 cm^{-1}; m/z 216.0261 (M^+, 95%, $C_{12}H_8O_2S$ requires 216.0245) and 105 (100).

5-Benzylthiophene-2-carboxaldehyde (9). - Lithiation of the 2-thienylimidazolidine [(2), X = S] following general method A (5.52 mmol scale), work-up with benzyl bromide (0.96g, 5.62 mmol) and acid hydrolysis (method E) for 3h gave the crude product. Purification by p.t.l.c. (ethyl ethanoate - light petroleum, 2:3, as eluant) yielded the pure aldehyde (9) (1.093g, 98%) as an oil (b.p. 175°C at 12 mmHg, lit.[12] 195°C at 13 mmHg); δ ($CDCl_3$), 9.78 (1H, s, CHO), 7.57 (1H, d, J 3.52 Hz, thiophene 3-H), 7.24 (5H, m, phenyl H), 6.88 (1H, d, J 3.52 Hz, thiophene 4-H), 4.18 (2H, s, CH_2); $\nu_{max.}$ (film), 1670 cm^{-1}; m/z 202 (M^+, 90%) and 173 (100).

5-Formylfuran-2-carboxylic acid (10). - Lithiation of the 2-furylimidazolidine [(2), X = O] following general method A (6.06 mmol scale), work-up with a solid CO_2/ether slurry and acid hydrolysis (method E) gave the crude product. Recrystallisation (C_6H_{12}/ethyl ethanoate) yielded the pure acid (10) (0.704g, 83%) as a white solid, m.p. 205 - 206°C (lit.[13] 207 - 208°C), δ [$(CD_3)_2CO$], 9.79

(1H, s, CHO), 7.48 (1H, d, J 3.6 Hz, furan 3-H), 7.36 (1H, d, J 3.6 Hz, furan 4-H).

5-Methylthiofuran-2-carboxaldehyde (11). - Lithiation of the 2-furylimidazolidine [(2), X = O] following general method A (6.06 mmol scale), work-up with $(CH_3)_2S_2$ (1.71g, 18.2 mmol) and acid hydrolysis (method E) gave the thioether (11) as a clear oil (0.714g, 83%), b.p. 98°C at 12 mmHg (lit.[14] 128 - 130°C at 19 mmHg), δ ($CDCl_3$), 9.50 (1H, s, CHO), 7.24 (1H, d, J 3.2 Hz, furan 4-H), 6.40 (1H, d, J 3.2 Hz, furan 3-H), 2.56 (3H, s, SCH_3); m/z 142 (M^+, 100%).

Furan-2,5-dicarboxaldehyde (12). - Lithiation of the 2-furylimidazolidine [(2), X = O] following general method A (6.06 mmol scale), work-up with $HCON(CH_3)_2$ (10 ml) and acid hydrolysis (method E) gave the crude dialdehyde. Recrystallisation ($C_6H_{12}/CHCl_3$) gave pure product (12) (0.532g, 71%), m.p. 108 - 109°C (lit.[15] 109 - 110°C), δ ($CDCl_3$), 8.49 (2H, s, CHO), 7.3 (2H, s, furan H); m/z 124 (M^+, 62%) and 77 (100).

5-Trimethylsilylfuran-2-carboxaldehyde (13). - Lithiation of the 2-furylimidazolidine [(2), X = O] following general method A (6.06 mmol scale), work-up with trimethylchlorosilane (0.69g, 6.38 mmol) and acid hydrolysis (method E) gave the crude aldehyde. Distillation under reduced pressure gave purified product (13) (0.773g, 76%), b.p. 110°C at 0.1 mmHg (lit.[16] 117°C at 0.23 mmHg) as a clear oil, δ ($CDCl_3$), 9.7 (1H, s, CHO), 7.23 (1H, d, J 3.25 Hz, furan 4-H), 6.76 (1H, d, J 3.25 Hz, furan 3-H), 0.34 (9H, s, $SiCH_3$); m/z 168 (M^+, 31%) and 153 (100).

5-Methylfuran-2-carboxaldehyde (14). - Lithiation of the 2-furylimidazolidine [(2), X= O] following general method A (6.06 mmol scale), work-up with iodomethane (8.65g, 61 mmol) and acid hydrolysis (method E) gave the crude aldehyde. Distillation gave purified product (14) (0.533g, 80%), b.p. 180°C at 760 mmHg (lit.[17] 187°C) as an oil, δ ($CDCl_3$), 9.51 (1H, s, CHO), 7.17 (1H, d, J 3.59 Hz, furan 3-H), 6.24 (1H, d, J 3.59 Hz, furan 4-H), 2.42 (3H, s, CH_3); m/z 110 (M^+, 100%).

5-Formyl-2-furyl phenyl ketone (15). - Lithiation of the 2-furylimidazolidine [(2), X = O] following general method A (6.06 mmol scale), work-up with benzaldehyde (0.653g, 6.16 mmol) and acid hydrolysis (method E) gave the crude ketone.

Recrystallisation (C_6H_{14}) gave purified product (15) (0.781g, 64%), m.p. 94 - 95°C (lit.[16] 95°C) as a white solid, δ ($CDCl_3$), 9.88 (1H, s, CHO), 8.09 (1H, d, J 1.62 Hz, furan 4-H), 8.06 (1H, d, J 1.62 Hz, furan 3-H), 7.69 - 7.34 (5H, m, phenyl); m/z 200 (M^+, 46%) and 105 (100).

2-Acetyl-5-formylthiophene (17). A mixture of 2-acetylthiophene (10g, 79.4 mmol), ethane-1,2-diol (24.88g, 0.4 mol) and p-toluenesulphonic acid (0.05g) in benzene (100 ml) was boiled under reflux for 16h with azeotropic removal of water. Ethyl ethanoate (100 ml) was added to the cooled solution and the resulting mixture was washed with water (3 x 20 ml) and dried ($MgSO_4$). Evaporation of solvents and recrystallisation (light petroleum) gave 2-methyl-2-(2-thienyl)-1,3-dioxolan (16) (6.96g, 79%) as a colourless solid, m.p. 32 - 33°C, (Found: C, 56.7; H, 6.1. $C_8H_{10}O_2S$ requires C, 56.46; H, 5.92%); δ ($CDCl_3$), 7.21 (1H, dd, J 0.99, 4.94 Hz, thiophene 5-H), 7.03 (1H, dd, J 0.99, 3.29 Hz, thiophene 3-H), 6.93 (1H, dd, J 4.94, 3.29 Hz, thiophene 4-H), 4.00 (4H, m, CH_2), 1.76 (3H, s, CH_3); $\nu_{max.}$ (CCl_4), 2980, 1370 cm^{-1}; m/z 170 (M^+, 2.5%) and 57(100).

To a solution of dioxolan (16) (2.0g, 11.76 mmol) in THF (60 ml) cooled to -78°C was added TMEDA (1.8 ml, 12 mmol) and Bu^nLi (12 mmol) in hexane. The mixture was stirred at -78°C for 2h, DMF (2.8 ml, 36 mmol) was added and the mixture left for 12h at 25°C. Solvents were removed by evaporation, the resulting residue was taken up in ethyl ethanoate (100 ml) and the solution was washed with water (3 x 20 ml) and brine (1 x 10 ml) and dried ($MgSO_4$). Removal of solvent gave 2-(5-formyl-2-thienyl)-2-methyl-1,3-dioxolan as an oil (2.1g, 90%)

pure by TLC analysis; δ ($CDCl_3$), 9.82 (1H, s, CHO), 7.67 (1H, d, J 3.2 Hz, thiophene 4-H), 7.16 (1H, d, J 3.2 Hz, thiophene 3-H), 4.01 (4H, m, CH_2CH_2), 1.76 (3H, s, CH_3); $\nu_{max.}$ ($CHCl_3$), 1670 cm^{-1}; m/z 198 (M^+, 22%) and 87 (100).

A sample of the formylthienyldioxolan (1.6g, 8.08 mmol) was stirred with 2M HCl aq. at 25°C for 2h. The resulting precipitate was extracted into $CHCl_3$ (5 x 20 ml) and the organic extracts were dried ($MgSO_4$). Removal of solvent by evaporation and recrystallisation of the residue (C_6H_{12}/ethyl ethanoate) gave the pure keto-aldehyde (17) (1.15g, 92%) as white crystals m.p. 103 - 104°C (lit.[18] m.p.104 - 105°C); δ ($CDCl_3$), 9.96 (1H, s, CHO), 7.81 (1H, d, J 3.86 Hz, thiophene 4-H), 7.77 (1H, d, J 3.86 Hz, thiophene 3-H), 2.58 (3H, s, CH_3); $\nu_{max.}$ ($CHCl_3$), 1680, 1670 cm^{-1}; m/z 154 (M^+, 63%) and 139 (100).

1,3-Dimethyl-2-(5-acetyl-2-thienyl)imidazolidine (18). - A solution of keto-aldehyde (17) (0.25g, 1.62 mmol) and N,N'-dimethylethylenediamine (0.17 ml, 1.62 mmol) in benzene (20 ml) was boiled under reflux for 2h with azeotropic removal of water. Removal of benzene by evaporation gave the imidazolidine (18) (0.35g, 96%) as an oil, (Found: C, 55.0 ; H, 6.7 . $C_{11}H_{16}N_2OS$ requires C, 58.91; H, 7.19%); δ ($CDCl_3$), 7.59 (1H, d, J 3.68 Hz, thiophene 3-H), 7.10 (1H, d, J 3.68, thiophene 4-H), 3.73 (1H, s, -NCHN-), 3.37 (2H, m, $-CH_2CH_2-$), 2.62 (2H,m, $-CH_2CH_2-$), 2.52 (3H, s, $COCH_3$), 2.26 (6H, s, NCH_3); $\nu_{max.}$ ($CHCl_3$), 1670 cm^{-1}; m/z 224.0970 (M^+, 80%, $C_{11}H_{16}N_2OS$ requires 224.0983) and 99 (100).

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