A General Route to 4-Substituted Imidazoles[1]

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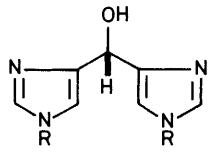
Literature routes to di(imidazol-4-yl)methanol (**1a**) dinitrate and tri(imidazol-4-yl)methanol (**2a**) trihydrochloride were improved to give 32 and 16% overall yields, respectively; but we failed to synthesize bis- (**1b**) and tris-(1-methylimidazol-4-yl)methanol (**2b**) by the methylation of the corresponding *N*-methoxymethyl compounds (**3**; $x = 2$ and $x = 3$). Attempted 4-lithiation of the 1,2,5-protected imidazole (**4a**) with BuLi–TMEDA failed, giving after hydrolysis 1-methyl-5-trimethylsilyl-imidazole (**4b**); similar failures were observed for 2,5-dicarboxy-1-methylimidazole, which after metallation with BuLi–TMEDA and hydrolysis afforded 1-methylimidazole-5-carboxylic acid (**5**). Our attempts to obtain 4-bromo-1-methylimidazole (**10a**) and 4-bromo-1-ethylimidazole suitable for a halogen–lithium exchange or for Grignard reaction also failed. Attempted selective lithiation of 2-phenylthio-1-tritylimidazole (**16**) at the 4-position, then treatment with ethyl formate, led only to a mixture of 4- and 5-substituted products in very low yield, and 1-diethoxymethyl-2-phenylthioimidazole (**18**) was unstable and difficult to purify.

4-Bromoimidazole with two mol equiv. of t-butyl-lithium gives 1,4-dilithioimidazole, which is now shown to provide a general route to 4-substituted imidazoles.

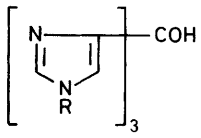
In metalloenzymes, imidazole rings of histidine residues frequently form part of the metal-binding site. For example, in carbonic anhydrase,[2,3] the zinc is bound to three imidazole ligands. In other metalloproteins, covering a large spectrum of enzymatic activity, one or more imidazole nuclei are bound to Cu^{II},[4] Co^{II},[2,5] and Fe^{II},[6] and Fe^{III} ions. The construction of ligands containing two or three imidazoles is thus important in the study of structural models of the active sites of metalloproteins.

The attachment of imidazole rings at the 2-position to molecular frameworks *via* 2-lithioimidazoles is relatively simple, and we have recently described new methods for the protection of the imidazole 1-position in such work.[7,8] However, *in vivo*, the imidazole ring is attached *via* the 4-position to the histidine side chain when the imidazole is co-ordinated to metal ions. Therefore, the linkage of two or three imidazole rings at their 4-positions *via* a single carbon atom would be advantageous, and it is towards this much less accessible goal that the work currently reported was directed. We describe in turn (a) attempted applications of a literature route, (b) attempts to lithiate protected 1-methylimidazoles at the 4-position, and (c) lithium–halogen exchange of 4(5)-bromoimidazole. This last path finally led to a convenient novel route to 4-substituted imidazoles.

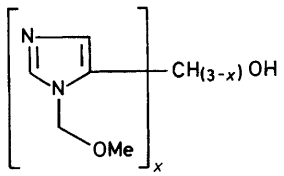
The Literature Method.—Breslow *et al.* have described[9–12] the synthesis of di- (**1a**) and tri-(imidazol-4-yl)methanol (**2a**), which were isolated as the more stable nitrate salts or hydrochloride, in 7—12 and 3—16% overall yields,[10] respectively, in five-step sequences from imidazole. We have repeated the literature routes (see Table 1) to (**1a**) and (**2a**) and have obtained these compounds in 32 and 16% overall yield, respectively. Several of the steps were modified slightly (see Experimental section) and the yields usually increased, although we found the Raney-nickel desulphurization difficult to control. However, this method is unsuited to the preparation of large quantities of these compounds. Attempts to synthesize bis- (**1b**) and tris-(1-methylimidazol-4-yl)methanol (**2b**) using the so-called 'switching method' (described[9,11] for similar



(**1**) **a**; R = H
b; R = Me



(**2**) **a**; R = H
b; R = Me



(**3**)

imidazoles) by the methylation of the *N*-methoxymethyl compounds (**3**; $x = 2$ and 3), previously used[6] as precursors for (**1a**) and (**2a**), failed. We successfully prepared compounds (**3**; $x = 2$) and (**3**; $x = 3$), but in both cases attempted reaction with trimethyloxonium tetrafluoborate did not succeed. Similar failures had been reported[11,12] for tris-(1-ethoxymethyl-2-phenylimidazol-5-yl)methanol, although the switching method was successfully used for bis-(1-ethoxymethyl-2-phenylimidazol-5-yl) ketone.[11]

Attempted 4-Lithiation of Protected 1-Substituted Imidazoles.—We therefore turned our attention to ways to lithiate the 4-position of a suitably protected 1-methylimidazole.

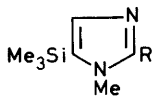
(i) Metallation of 1-methylimidazole with excess of BuLi–tetramethylethylenediamine (TMEDA) followed by addition of trimethylsilyl chloride gave 1-methyl-2,5-bis(trimethylsilyl)-imidazole (**4a**) as reported by Jutzi.[13] Attempted lithiation of compound (**4a**) with BuLi–TMEDA failed: after water

Table 1. Comparison of ^{1}H n.m.r. chemical shifts and assignments of imidazoles with literature values[10]

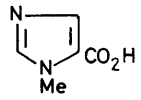
Compound	Origin[a]	2-H (1 H, s)	4-H (1 H, br s)	5-H (1 H, br s)	OMe (s)	NCH_2O	OH (1 H, br s)	HOCHIm (1 H)	ArH (br s)
1-$MeOCH_2$Im	P	7.61	7.06	7.10	3.37 (3 H)	5.24 (2 H, s)			
	L	7.03	7.02—7.08 (m)		3.17 (3 H)	5.18 (2 H, s)			
1-$MeOCH_2$-2-PhSIm	P		7.26	7.26	3.16 (3 H)	5.32 (2 H, s)			7.26 (5 H)
	L		7.17	7.17	3.13 (3 H)	5.28 (2 H, s)			7.17 (5 H)
Bis-(1-*MeOCH*$_2$-2-*PhSIm*-5-yl)-methanol	P			7.04	3.08 (6 H)	5.35 (4 H, q)[c]	5.15	6.12 (br s)	7.22 (10 H)
	L			7.08	3.08 (6 H)	5.38 (4 H, q)[c]	5.77	6.20 (br s)	7.27 (10 H)
Tris-(1-$MeOCH_2$-2-PhSIm-5-yl)-methanol	P			6.54	3.12 (9 H)	5.45 (6 H, s)			7.26 (15 H)
	L			6.55	3.11 (9 H)	5.43 (6 H, s)			7.26 (15 H)
(**3**; x = 2)	P	7.50		6.79	3.22 (6 H)	5.25 (4 H, q)[c]			
	L	7.50		6.80	3.23 (6 H)	5.23 (4 H, q)[c]			
(**3**; x = 3)	P	7.67		6.49	3.23 (9 H)	5.27 (6 H, s)	6.34		
	L	7.81		6.58	3.28 (9 H)	5.35 (6 H, s)	6.42		
(**1a**)[b]	P	8.97		7.66				6.37 (s)	
	L	8.70		7.44				6.25 (s)	
(**2a**)[b]	P	9.06		7.81					
	L	8.76		7.49					

[a] P = Present work; L = ref. 10. [b] [$^2H_6$]Acetone–D_2O. [c] J_{AB} 11 Hz, diastereotopic.

quenching, 1-methyl-5-trimethylsilylimidazole (**4b**) resulted by hydrolysis of the labile trimethylsilyl group at C-2: Jutzi also reported the easy scission of the 2-trimethylsilyl group in compound (**4a**).



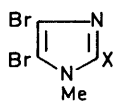
(**4**) **a**; R = $SiMe_3$
b; R = H



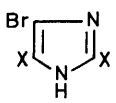
(**5**)

(ii) The C-2 and C-5 positions of 1-methylimidazole are easy to metallate in one step with BuLi–TMEDA complex;[13,14] we thus formed dilithium 1-methylimidazole-2,5-dicarboxylate by the reaction of 2,5-dilithio-1-methylimidazole with CO_2. However, a further equivalent of lithiating agent (BuLi–TMEDA) failed to metallate the unprotected C-4 position of the imidazole nucleus in the 2,5-dicarboxylate. After hydrolysis of the reaction mixture, we obtained 1-methylimidazole-5-carboxylic acid (**5**), the result of decarboxylation at C-2.

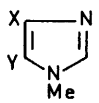
(iii) We next attempted to obtain 4-halogenoimidazoles suitable for a halogen–lithium exchange or for a Grignard reaction. The reaction of 4-bromo-1-methylimidazole (**10a**) with one mol equiv. of ethylmagnesium bromide was previously used by Borai *et al.*[15] to obtain (1-methylimidazol-4-yl)-magnesium bromide. 2,4,5-Tribromo-1-methylimidazole (**6**) was prepared[16] by the bromination of 1-methylimidazole. As attempted debromination of compound (**6**) with Na_2SO_3 was reported[16] to fail, we tried to obtain 4-bromo-1-methylimidazole (**10a**) by reaction of two mol equiv. of ethylmagnesium bromide with 2,4,5-tribromo-1-methylimidazole (**6**) in benzene under reflux followed by water hydrolysis. However, this gave 4,5-dibromo-1-methylimidazole (**7**) instead of the expected and desired 4-monobromo compound.



(**6**) X = Br
(**7**) X = H



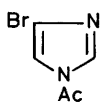
(**8**) X = Br
(**9**) X = H



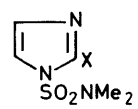
(**10**) **a**; X = Br, Y = H
b; X = H, Y = Br

Following Stensiö,[17] 2,4,5-tribromoimidazole (**8**) was obtained by bromination of imidazole, and reduced by sodium sulphite to 4-bromoimidazole (**9**). Reaction of the lithium salt of (**9**) with dimethyl sulphate[18] gave a mixture of 4- and 5-bromo-1-methylimidazole (**10a** and **b**) which failed to undergo lithium–bromine exchange with BuLi or BuLi–TMEDA. (Similar failures were previously reported by Breslow and co-workers,[9] in attempts to make organometallic reagents from 1-protected 4-bromoimidazoles; either reduction products or C-2-metallated derivatives were obtained.) Attempts to form a Grignard reagent from ethylmagnesium bromide and compounds (**10**), and then to react further with ethyl formate, failed.

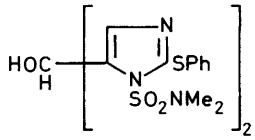
N-Acylation of the bromide (**9**) in acetic anhydride proceeded as expected by thermodynamic control and gave exclusively 1-acetyl-4-bromoimidazole (**11**) as shown by comparison of the ^{13}C n.m.r. spectrum of compound (**11**) with that of 1-acetylimidazole:[19] the C-4 peak is shifted from δ 118.33 ($CDCl_3$) to δ 130.50 due to the presence of the bromine atom. Attempts to reduce the acetyl group of compound (**11**) to an *N*-ethyl group with diborane–tetrahydrofuran (THF) failed.



(**11**)



(**12**) X = H
(**13**) X = SPh



(**14**)

(iv) Reaction of dimethylsulphamoyl chloride with imidazole in triethylamine gave the sulphonamide (**12**) as previously described.[20] Lithiation with BuLi in THF and treatment with diphenyl disulphide gave 1-dimethylsulphamoyl-2-phenylthioimidazole (**13**), reaction of which with lithium di-isopropylamide (LDA) in THF followed by addition of 0.5 mol equiv. of ethyl formate produced the expected di(imidazol-5-yl)methanol (**14**). Unfortunately, attempts to promote reaction of compound (**14**) with trimethyloxonium tetrafluoroborate failed to give methylation at the 3-position.

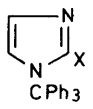
(v) Reaction of trityl chloride with imidazole in triethylamine gave[21] compound (**15**). Lithiation of the product with LDA in THF and treatment with diphenyl disulphide resulted in the formation of 2-phenylthio-1-tritylimidazole (**16**). Unfortunately,

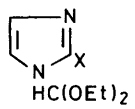
Table 2. Lithiation of 4(5)-bromoimidazole (**9**) in THF

Expt.	Base[a]	Time (h)	Molar quotient benzophenone/(**9**)	Yield of (**20a**) (%)
1	BuLi	5.5	1.2	28
2	BuLi	1.5	1.2	33
3	BuLi	1.5	2.0	47
4	Bu^{t}Li	1.5	1.2	64

[a] 2.3 Mol equiv.

attempted lithiation of compound (**16**) with LDA in THF failed: evidently the 5-position is sterically hindered (as reported in a patent[22] for 2-fluoro-1-tritylimidazole) and the 4-position is insufficiently reactive. It has been reported in the patent literature[22] that metallation at the 4-position in the case of analogous 2-fluoro-1-tritylimidazole was satisfactorily performed with Bu^{t}Li. In our hands selective metallation of compound (**16**) with Bu^{t}Li in THF led to a mixture of 4- and 5-substituted products in very low yield.





(**15**) X = H (**16**) X = SPh

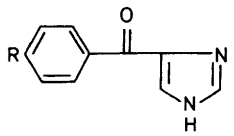
(**17**) X = H (**18**) X = SPh

(vi) Reaction of imidazole with triethyl orthoformate and a catalytic amount of toluene-*p*-sulphonic acid[23] gave the acetal (**17**). Compound (**17**) was lithiated at the C-2 position with BuLi in THF and the product treated with diphenyl disulphide to yield 1-diethoxymethyl-2-phenylthioimidazole (**18**), which unfortunately was difficult to purify from side products. A similar result was obtained when Bu^{t}Li was used instead of LDA. Attempted column chromatography of the mixture on silica gel removed the protecting group. N.m.r. spectra of the fractions obtained from the column showed a large excess of aromatic protons and a significantly decreased integral for the aliphatic protons from the protecting diethoxymethyl group. It seems that, under mildly acidic conditions with silica gel, cleavage of C–S bond also occurs because thiophenol was isolated as an early fraction.

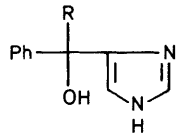
Attempted 4-Lithiation of Unprotected NH-*Free Imidazole.*—The next part of our research concerned selective substitution on the 4-position of the imidazole ring *via* metal–halogen exchange reactions. Tertov *et al.* have described[24] the synthesis of [imidazol-4(5)-yl]diphenylmethanol (**20a**) which was achieved by treatment of 4(5)-bromoimidazole with two mol equiv. of lithium naphthalenide followed by quenching with benzophenone. Iddon[25] confirmed this result but failed to synthesize other 4(5)-substituted imidazoles by this route. The lithiation of 4(5)-bromoimidazole (**9**) followed by reaction with benzophenone was studied under a variety of conditions (Table 2) which showed that the yield of compound (**20a**) depends on the base used, the time for carbanion generation, and the amount of benzophenone used. Replacement of BuLi with Bu^{t}Li or increasing the amount of electrophile to 2.0 mol equiv. considerably improved the yield. Metallation of compound (**9**) with BuLi or Bu^{t}Li in THF followed by treatment with benzaldehyde, *p*-methylbenzaldehyde, *p*-methoxybenzaldehyde, or *p*-chlorobenzaldehyde gave the corresponding intermediate substituted methanols, which underwent spontaneous air oxidation to give ketones (**19a**—**d**), respectively, in moderate to good yields. Reaction of compound (**9**) with Bu^{t}Li in THF followed by addition of 0.5 mol equiv. of ethyl benzoate produced the expected di(imidazolyl)methanol (**20b**). Direct lithiation of the bromide (**9**) with Bu^{t}Li in THF and subsequent treatment with cyclopentanone or cyclohexanone led to 1-[imidazol-4(5)-yl]cyclopentanol (**21a**) or 1-[imidazol-4(5)-yl]cyclohexanol (**21b**), respectively, in moderate yield.

Reaction of the bromide (**9**) with Bu^{t}Li in THF followed by addition 2.0 mol equiv. of diphenyl disulphide or phenyl isocyanate produced the expected 4(5)-phenylthioimidazole (**22a**) or 4(5)-phenylcarbamylimidazole (**22b**), respectively. Preparative and analytical results for compounds (**19**)—(**22**) are given in Table 3.

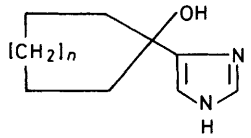
Synthetic Conclusions.—This paper describes (a) attempted applications of a literature route, (b) attempts to lithiate



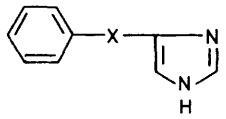
(**19**) **a**; R = H
b; R = Me
c; R = MeO
d; R = Cl



(**20**) **a**; R = Ph
b; R = imidazol-4(5)-yl



(**21**) **a**; *n* = 0
b; *n* = 1



(**22**) **a**; X = S
b; X = NHCO

Table 3. 4(5)-Substituted imidazoles (**19a**—**d**), (**20a** and **b**), (**21a** and **b**), and (**22a** and **b**)

Compd.	R	Method[a]	% Yield	M.p. (°C)	Molecular formula	Required			Found		
(19a)*	Bz	A	54[b]	145.5—147.5	$C_{10}H_8N_2O$	69.75	4.68	16.26	69.8	4.7	16.2
(19b)*	4-MeC_6H_4C=O	B	36[b]	159—162.5	$C_{11}H_{10}N_2O$	70.95	5.41	15.04	70.9	5.4	15.0
(19c)*	4-$MeOC_6H_4C$=O	A	61[c]	188—190	$C_{11}H_{10}N_2O_2$	65.33	4.98	13.85	65.4	5.0	13.8
(19d)*	4-ClC_6H_4C=O	B	37[b]	180—182	$C_{10}H_7ClN_2O$	58.13	3.41	13.56	58.25	3.4	13.5
(20a)†	$(Ph)_2CH(OH)$	A	64[c]	170—172	$C_{16}H_{14}N_2O$	76.77	5.62	11.09	76.3	5.6	11.1
(20b)	PhC(4-imid)(OH)	C	22[b]	258—260[d]	$C_{13}H_{12}N_4O{\cdot}H_2O$	60.45	5.46	21.69	60.5	5.1	21.9
(21a)	$[CH_2]_4C(OH)$	A	29[e]	151—153[d]	$C_8H_{12}N_2O$	63.13	7.95	18.40	62.95	7.95	18.4
(21b)	$[CH_2]_5C(OH)$	A	48[f]	163.5—165.5[d]	$C_9H_{14}N_2O$	65.03	8.49	16.85	64.75	8.5	16.8
(22a)	PhS	A	62.5[g]	125—127	$C_9H_8N_2S$	61.33	4.85	15.89	61.0	4.5	15.9
(22b)	PhNHCO	A	33[h]	224—225.5	$C_{10}H_9N_3O$	64.16	4.85	22.45	63.9	4.9	22.4

[a] A, Bu^{t}Li (2.3 mol equiv.) electrophile (2.0 mol equiv.); B, Bu^{t}Li (2.3 mol equiv.) electrophile (1.2 mol equiv.); C, Bu^{t}Li (2.0 mol equiv.) ethyl formate (0.5 mol equiv.). [b] Purified by flash chromatography. [c] Purified by recrystallization from C_6H_{12}/AcOEt, 1:1. [d] Decomposed. [e] Recrystallization from THF. [f] Purified by recrystallization from AcOEt–MeOH, 5.5:1. [g] Purified by recrystallization from $CHCl_3$. [h] Purified by recrystallization from MeOH. * Known compound see ref. 34, but not previously characterized. † Ref. 24, gives, m.p. 168—169 °C.

Table 4. ^{13}C N.m.r. chemical shifts and assignments of 4(5)-substituted imidazoles (**19a**—**d**), (**20a** and **b**), (**21a** and **b**), and (**22a** and **b**)[a]

Compd.	C-2	C-4	C-5	C=O	C-α	C-1′	C-2′	C-3′	C-4′	R
(19a)	132.32	138.44	129.45	185.91[e]		138.02	128.42	*c*	*c*	
(19b)	138.04	135.19	116.71[e]	185.29[e]		130.40[d]	128.66	129.02	142.36	21.13
(19c)	137.77[d]	137.80[d]	*b*	184.09[e]		130.40	131.83	113.57	162.60	55.41
(19d)	131.43	138.00[d]	123.30[e]	184.99[e]		136.59	128.55	*c*	137.40	
(20a)	135.31	147.64	126.43		76.50	135.00	127.13	*c*	127.32	
(20b)	134.82	146.84	118.20[d]		75.56	142.50	126.57	127.17	126.34	
(21a)	134.47	143.25	116.25			78.08	40.46	32.35		
(21b)	134.18	144.23	116.50			68.08	37.72	21.82	25.42	
(22a)	137.20	135.00	125.80[d]			137.95	126.55	128.64	125.32	
(22b)	135.99[d]	135.99[d]	120.40[d]	160.75[e]		139.01	119.86	128.63	123.19	

[a] (**22a**) in $CDCl_3$; all others in $(CD_3)_2SO$. [b] Resonance not observed. [c] Equivalent to C-2′. [d] Broad peak. [e] Weak peak.

protected 1-methylimidazole at the 4-position, and (c) lithium–halogen exchange of 4(5)-bromoimidazole.

A convenient novel route to 4-substituted imidazoles, which does not involve prior blocking of the 1-, 2-, and 5-position, was achieved in our investigations. Selective substitution of the 4-position of the imidazole ring *via* metal–halogen exchange reaction was performed by treatment of 4(5)-bromoimidazole with Bu^{t}Li (or BuLi) in THF followed by reaction with a number of substituted benzaldehydes to give (**19a**—**d**), aromatic and cycloaliphatic ketones to give (**20a**) and (**21a** and **b**), as well as ethyl benzoate [(**20b**)], diphenyl disulphide [(**22a**)], and phenyl isocyanate [(**22b**)]; these reactions all produced the expected 4(5)-substituted NH-free imidazoles in moderate to good yields. Significantly, alcohols (**20b**) and (**21a** and **b**) have been successfully prepared; the presence of the OH group may be beneficial in stabilizing complexes of oxophilic metals such as Fe^{III} as previously demonstrated.[26,27]

Chemical Shift Assignments.—The ^{13}C chemical shifts of the heterocyclic ring carbons (Table 4) were assigned by comparison with literature values for the parent imidazole,[28] and the type of C-atom (CH, CH_2, CH_3) was assigned using the APT (attached-proton test[29]). The aryl carbonyl groups substituted at C-4 of the imidazole ring caused a downfield shift of *ca.* 16—13 p.p.m. for C-4. A much stronger downfield shift effect (25—21 p.p.m. for C-4) was observed in the cases of 1-hydroxycycloalkyl or 1,1-diaryl-1-hydroxymethyl groups substituted at C-4 of imidazole. For compounds (**19c**) and (**22b**) (Table 4), the signal for C-4 is presumed to coincide with that for C-2 at δ 136—138. The aryl ring carbons (Table 4) were also assigned by APT and by comparison of their chemical shifts to those calculated by means of substituent parameters.[30]

Experimental

M.p.s were determined on a Kofler hot-stage microscope and are uncorrected. ^1H (200 MHz) N.m.r. spectra were recorded on a Varian XL-200 (FT mode) spectrometer with Me_4SI as internal standard; ^{13}C (50 MHz) n.m.r. on the above instrument, referring to the centre signal of $CDCl_3$ (δ_C 77.0). Mass spectra were obtained at 70 eV on an AEI MS 30 spectrometer operating with a DS-55 data system. Elemental analyses were performed under the supervision of Dr. R. W. King of this department.

THF and diethyl ether were dried by distillation from sodium–benzophenone ketyl. All reactions were carried out in oven-dried (120 °C overnight) apparatus under a slight positive pressure of dry argon. Transferring operations were performed using syringe techniques. Flash chromatography was carried out with MCB silica gel (230—400 mesh).

The following products were synthesized according the literature procedures quoted (with the modifications noted): 1-methoxymethylimidazole (reaction 4 h), b.p./mmHg 87—89 °C/8, 84% (lit.,[31] 111—112 °C/23, 81%); 1-methoxymethyl-

2-phenylthioimidazole, (formation of the lithio derivative at −23 °C during 4 h, distillation under low pressure to avoid decomposition), b.p./mmHg 100—105 °C/0.25, 76% (lit.,[10] 123 °C/0.37, 50—75%); bis-(1-methoxymethyl-2-phenylthioimidazol-5-yl)methanol (formation of the lithio derivative at −35 °C during 4 h, purification by recrystallization from hexane–ethyl acetate), m.p. 100—102 °C, 97% (lit.,[10] 96—102 °C, 41%); tris-(1-methoxymethyl-2-phenylthioimidazol-5-yl)methanol (formation of the lithio derivative at −23 °C for 2 h), m.p. 45—47 °C, 90% (lit.,[10] 139.5—142 °C, 30—70%); bis-(1-methoxymethylimidazol-5-yl)methanol (**3**; $x = 2$) (desulphurization with Raney-nickel in EtOH), 60%, oil (lit.,[10] 85—93%, oil); tris-(1-methoxymethylimidazol-5-yl)methanol (**3**; $x = 3$) (desulphurization with Raney-nickel in EtOH), 31%, white oil (lit.,[10] 61—92%, white foam); di(imidazol-4-yl)methanol (**1a**) dinitrate (reflux 48 h in HNO_3 5M-aqueous), m.p. (decomp.) 150—151 °C, 87% (lit.,[10] 148—150 °C, 50%); tri(imidazol-4-yl)methanol (**2a**) trihydrochloride (reflux 18 h in 8M-aqueous HCl, no recrystallization), m.p. (decomp.) > 170 °C, 88% (lit.,[10] > 165 °C, 42%); 1-methyl-2,4-bis-(trimethylsilyl)imidazole (**4a**), m.p. 121—122 °C (lit.,[13] 119—121 °C); 2,4,5-tribromo-1-methylimidazole (**6**), m.p. 92—93 °C (lit.,[16] 92 °C); 2,4,5-tribromoimidazole (**8**), m.p. 221—222 °C (lit.,[17] 222 °C); 4-bromoimidazole (**9**), m.p. 129—130 °C (lit.,[17] 130 °C); 4- and 5-bromo-1-methylimidazole (**10**), b.p./mmHg 100 °C/1 × 10^{-4} (lit.,[18] 95 °C/6 × 10^{-4}); 1-dimethylsulphamoylimidazole (**12**), m.p. 43—45 °C (lit.,[20] 42—44 °C); 1-tritylimidazole (**15**), m.p. 222—223 °C (lit.,[21] 221—223 °C); 1-diethoxymethylimidazole (**17**), b.p./mmHg 78—80 °C/0.1 (lit.,[23] 52 °C/0.02).

1-*Methyl*-5-*trimethylsilylimidazole* (**4b**).—1-Methyl-2,5-bis-(trimethylsilyl)imidazole (**4a**) (5.12 g, 23 mmol) in THF (60 ml) at 78 °C under Ar was treated with BuLi–TMEDA (1:1, 24 mmol) in THF (30 ml). The reaction mixture was then warmed to −40 °C for 2 h. After the mixture had been cooled to −78 °C, a solution of ethyl formate (1.19 ml, 14 mmol) in THF (2 ml) was added *via* a syringe and the reaction mixture was allowed to warm to 20 °C overnight, then quenched with saturated aqueous NH_4Cl, and extracted with ether (4 × 50 ml), and the extract was dried over $MgSO_4$ and filtered. The filtrate yielded, after distillation under reduced pressure, the imidazole (**4b**) (1.88 g, 53%), b.p./mmHg 70 °C/0.3 (lit.,[13] 58 °C/0.2); δ_H[$(CD_3)_2SO$] 0.29 (9 H, s, $SiMe_3$), 3.70 (3 H, s, NMe), 7.00 (1 H, s, 4-H), and 7.74 (1 H, s, 2-H); δ_C −1.6, 1.2, and 1.7 ($SiMe_3$), 33.7 (NMe), 130.0 (C-5), 138.3 (C-2), and 141.2 (C-4); M^+, 154.

1-*Methylimidazole*-5-*carboxylic Acid* (**5**).—A solution of 1-methylimidazole (4.85 ml, 60.9 mmol) in THF (100 ml) was treated with BuLi–TMEDA (1:1; 125 mmol) in ether (100 ml) at −80 °C and then kept for 1 h at 20 °C. Dry CO_2 was bubbled into the mixture, first at 0 °C during 30 min, then at 20 °C (10 min). Evaporation to dryness at 20 °C yielded a white powder. Addition of ether (100 ml) and BuLi–TMEDA (1:1; 62.5 mmol) in ether, at −80 °C, was followed successively by stirring of the mixture for 2 h at 20 °C, addition of a solution of ethyl formate (2.4 ml, 31 mmol) in ether (5 ml) (at −80 °C), and stirring of the mixture for 12 h at 20 °C. After quenching with aqueous NH_4Cl (10%) and extraction (15M-aqueous HCl; 5 ml), the white precipitate of the acid (**5**) was filtered off and dried (4.8 g, 63%), m.p. 253—254 °C (lit.,[32] 256—257 °C); δ_H 3.84 (3 H, s, NMe), 7.60 (1 H, s, 2-H), 7.88 (1 H, s, 4-H), and 8.80 (1 H, br, OH); δ_C 33.6 (NMe), 123.5 (C-3), 136.3 (C-2), 143.0 (C-5), and 161.2 (CO_2H); M^+, 154.

4,5-*Dibromo*-1-*methylimidazole* (**7**).—A solution of 2,4,5-tribromo-1-methylimidazole (**6**) (10 g, 31.3 mmol) in benzene (20 ml) under Ar was added to ethylmagnesium bromide (31.5 mmol) [prepared from Mg (0.79 g) and ethyl bromide (3.43 g) in THF (20 ml)]. The mixture was heated under reflux overnight, quenched successively with water (5 ml) followed by HCl (10%; 25 ml), and then extracted with ether. After the extract had been dried ($MgSO_4$), filtered and evaporated, a yellow solid containing starting material (14% recovery) and 4,5-dibromo-1-methylimidazole (**7**) (28%) was isolated (ratio based on ^1H n.m.r. analysis). The acid mother liquor of the former extraction was then basified (2M-NaOH; 10 ml), extracted, and treated as before to give the pure product (**7**) as white plates (3.61 g, 48%), m.p. 81 °C (lit.,[33] 80 °C); δ_H 3.62 (3 H, s, NMe) and 7.48 (1 H, s, 2-H); δ_C 33.8 (NMe), 104.9 (C-5), 116.2 (C-4), and 137.3 (C-2).

1-*Acetyl*-4-*bromoimidazole* (**11**).—A solution of bromoimidazole (**9**) (5.0 g, 34 mmol) in acetic anhydride (15 ml) was stirred for 30 min. The excess of acetic anhydride was evaporated off to yield white needles (7.69 g, 99%), m.p. 93—94 °C. The product obtained was stored under Ar to prevent its decomposition (Found: C, 31.0; H, 2.3; N, 14.6. $C_5H_5BrN_2O$ requires C, 31.8; H, 2.7; N, 14.8%); δ_H($CDCl_3$) 2.64 (3 H, s, COMe), 7.49 (1 H, d, J 1 Hz, 5-H), and 8.07 (1 H, d, J 1 Hz, 2-H); δ_C($CDCl_3$) 22.3 (Me), 115.6 (C-5), 118.3 (C-4), 135.8 (C-2), and 165.2 (CO); m/z (%) 40 (14), 43 (100), 67 (7), 119 (7), 121 (6), 146 ($M^+ - 43$, 60), 148 (47), 188 (10), and 190 (10).

1-*Dimethylsulphamoyl*-2-*phenylthioimidazole* (**13**).—1-Dimethylsulphamoylimidazole (10 g, 57 mmol) in THF (50 ml) was lithiated under Ar with BuLi (63 mmol; 2.5M in hexane) first at −78 °C then for 4 h at −35 °C. After the mixture had been cooled again to −78 °C, a solution of diphenyl disulphide (12.46 g, 57 mmol) in THF (20 ml) was added. The mixture was allowed to warm to 20 °C overnight. Quenching with aqueous NH_4Cl (10%), extraction (ether), and drying of the organic layers ($MgSO_4$) gave, after filtration and evaporation of the solvents, a yellow oil, which was purified by column chromatography (CH_2Cl_2) to yield the *title compound* as yellow plates (9.15 g, 56%), m.p. 79—82 °C (Found: C, 46.8; H, 4.6; N, 14.4. $C_{11}H_{13}N_3O_2S_2$ requires C, 46.6; H, 4.6; N, 14.8%); δ_H($CDCl_3$) 2.99 (6 H, s, NMe_2), 7.03 (4 H, s, 4-H), and 7.30—7.55 (6 H, m, Ph and 5-H); δ_C($CDCl_3$) 38.4 (NMe), 122.1 (C-5), 128.4 (C-4), and 129.2, 129.3, and 132.2; m/z (%) 40 (21), 44 (22), 51 (31), 72 (34), 77 (43), 108 (117), 116 (59), 117 (34), 148 (11), 175 ($M^+ - 108$, 100), 176 (31), 282 (20), and 283 (M^+, 37).

Bis-(1-*dimethylsulphamoyl*-2-*phenylthioimidazol*-5-*yl*)*methanol* (**14**).—1-Dimethylsulphamoyl-2-phenylthioimidazole (4.0 g, 14.11 mmol) in THF (30 ml) was treated under Ar at −78 °C with a solution of LDA (15 mmol) in THF (5 ml). The mixture was stirred at −23 °C for 4 h. To the reaction mixture cooled to 78 °C was added a solution of ethyl formate (0.57 ml, 7.05 mmol) in THF (2 ml). The mixture was allowed to warm to 20 °C during 12 h. Quenching with aqueous NH_4Cl (10%), extraction with ether (4 × 50 ml), and drying ($MgSO_4$), filtration, and evaporation of the extracts gave a yellow oil, which was purified by column chromatography ($CHCl_3$–MeOH, 3% v/v) to yield the *alcohol* (**14**) as yellow plates (3.5 g, 84%), m.p. 55—56 °C (Found: C, 46.5; H, 4.1; N, 13.8. $C_{23}H_{26}N_6O_5S_4$ requires C, 46.4; H, 4.4; N, 14.1%); δ_H($CDCl_3$) 2.98 (12 H, s, NMe_2), 6.50 (1 H, s, C*H*OH), 6.84 (1 H, s, 4-H), and 7.33—7.45 (12 H, m, =CH and OH); δ_C($CDCl_3$) 38.4 (NMe), 61.1 (COH), 128.7 (C-5), 129.4 (C-4), 130.2, 132.4, 136.3, and 144.5; m/z (%) 44 (64), 48 (49), 65 (48), 66 (47), 77 (36), 109 (79), 110 ($M^+ - 326$, 100), 121 (13), 154 (11), 175 (80), 176 (43), and 218 (41).

2-*Phenylthio*-1-*tritylimidazole* (**16**).—*N*-Tritylimidazole (**15**) (3.0 g, 9.63 mmol) in THF (50 ml) was treated under Ar with a

solution of LDA (10 mmol) in THF (10 ml), first at −78 °C, then for 3 h at −35 °C. After the mixture had been cooled again to −78 °C, a solution of diphenyl disulphide (2.1 g, 9.63 mmol) in THF (10 ml) was added. The mixture was then allowed to reach 20 °C during 12 h. Quenching with aqueous NH_4Cl (10%), extraction (ether; 4 × 50 ml), and drying ($MgSO_4$), filtration, and evaporation of the extracts gave a crude material (5 g), which was washed twice with ether (3 ml) to obtain the *title compound* as white needles (4.0 g, 99%), m.p. 170—172 °C (Found: C, 79.7; H, 5.1; N, 6.3. $C_{27}H_{22}N_2S$ requires C, 80.3; H, 5.3; N, 6.7%); $\delta_H(CDCl_3)$ 6.90—7.40 (m, ArH); $\delta_C(CDCl_3)$ 123.6 (C-4), 126.8 (C-5), 127.6, 127.8, 128.0, 128.2, 128.4, 129.7, 129.9, and 130.1, and 142.2 (C-2); *m/z* (%) 165 (49), 228 (16), 243 (M^+ − 175, 100), and 418 (M^+, 1).

1-*Diethoxymethyl*-2-*phenylthioimidazole* (**18**).—1-Diethoxymethylimidazole (**17**) (4.0 g, 23.5 mmol) in THF (20 ml) under Ar was lithiated at −78 °C with BuLi (10 ml; 2.5M in hexane), then the mixture was warmed to −35 °C for 3 h. After the mixture had been cooled again to −78 °C, a solution of diphenyl disulphide (5.13 g, 23.5 mmol) in THF (10 ml) was added, and the mixture was allowed to warm to 20 °C overnight. After quenching with aqueous NH_4Cl (10%), extraction (ether; 4 × 50 ml), and drying ($MgSO_4$), filtration, and evaporation of the extracts, the yellow oil obtained was chromatographed twice ($CHCl_3$) to yield a yellow solid (0.5 g, 8%). N.m.r. analysis showed the correct structure, but the product still contained many impurities. $\delta_H(CDCl_3)$ 1.21 (6 H, t, Me), 3.74 (4 H, q, CH_2), 5.89 (1 H, s, CH), and 7.10—7.55 (7 H, m, =CH); $\delta_C(CDCl_3)$ 14.6 (Me), 109.6 (C–O), 127.1 (CH), 128.5, 128.8, 128.9, and 132.4.

4(5)-*Substituted Imidazoles* (**19a**—**d**), (**20a** *and* **b**), *and* (**22a** *and* **b**).—*General synthetic procedure.* 4(5)-Bromoimidazole (**10**) (1.0 g, 6.8 mmol) in THF [14 ml; 20 ml for (**19c**), (**22a** and **b**)] was lithiated under Ar at −78 °C with Bu^{t}Li (9.6 ml, 1.7M in pentane; Method A, C, see Table 3) or BuLi (6.5 ml; 2.5M in hexane; Method B, see Table 3), then the mixture was warmed to 10—15 °C for 1.5 h. After the mixture had been cooled again to −78 °C, a solution of an electrophile (13.4 mmol, Method A; 8.16 mmol, Method B; 3.4 mmol, Method C, see Table 3) in THF (10 ml) was added, and the mixture was allowed to warm to 20 °C overnight. After quenching with saturated NH_4Cl (15 ml), extraction (THF; 3 × 20 ml), and drying ($MgSO_4$), filtration, and evaporation of the extracts, the crude materials obtained were purified by (a) flash chromatography [(**19a**, **b**, and **d**) AcOEt; (**20b**) AcOEt then AcOEt–MeOH, 5:1], (b) recrystallization (see Table 3). The following compounds were thus prepared.

4(5)-Benzoylimidazole (**19a**).[34] $\delta_H[(CD_3)_2SO]$ 7.66—7.53 (3, H, m, arom 3-, 4-, and 5-H), 7.95 (1 H, s, 2-H), 8.0 (1 H, s, 5-H), and 8.14—8.17 (2 H, d, arom 2- and 6-H); *m/z* (%) 40 (43), 51 (46), 67 (22), 77 (67), 105 (70), 145 (68), 172 (M^+, 100).

4(5)-(*p*-Toluoyl)imidazole (**19b**).[34] $\delta_H(CDCl_3)$ 2.42 (3 H, s, Me), 7.27—7.31 (2 H, d, arom 3- and 5-H), 7.70 (1 H, s, 5-H), 7.82 (1 H, s, 2-H), 7.94 (2 H, m, arom 2- and 6-H), *m/z* (%) 40 (26), 65 (31), 77 (5), 91 (61), 95 (45), 119 (91), 159 (37), 171 (43), and 186 (M^+, 100).

4(5)-(*p*-Anisoyl)imidazole (**19c**).[34] $\delta_H(Me_2SO)$ 3.80 (3 H, s, OMe), 7.01—7.05 (2 H, d, arom 3- and 5-H), 7.85 (1 H, s, 5-H), 7.92 (1 H, s, 2-H), and 8.17—8.21 (2 H, d, arom 2- and 6-H); *m/z* (%) 40 (23), 77 (32), 95 (23), 135 (98), 175 (25), and 202 (M^+, 100).

4(5)-(*p*-Chlorobenzoyl)imidazole (**19d**).[34] $\delta_H(Me_2SO)$ 7.52—7.56 (2 H, d, arom 3- and 5-H), 7.93 (2 H, s, Im 2- and 5-H), and 8.15 (2 H, m, arom 2- and 6-H), *m/z* (%) 40 (45), 95 (92), 111 (42), 139 (67), 171 (52), 179 (47), and 206 (M^+, 100).

[4(5)-Imidazolyl]diphenylmethanol (**20a**). M.p. 170—172 °C (lit.,[24] 168—169 °C; lit.,[35] 171—172 °C); $\delta_H(Me_2CO)$ 6.53 (1 H, s, 5-H), 7.18—7.43 (10 H, m), and 7.56 (1 H, s, 2-H); $\delta_H[(CD_3)_2SO]$ 6.16 (1 H, s, br, OH), 6.60 (1 H, s, 5-H), 7.18—7.38 (10 H, m), and 7.61 (1 H, s, 2-H); *m/z* (%) 77 (68), 95 (100), 105 (32), 173 (85), and 250 (M^+, 41).

Di[imidazol-4(5)-yl]phenylmethanol hydrate (**20b**)·H_2O. $\delta_H(Me_2SO)$ 5.66 (3 H, br, s, 2 × NH and OH) 6.67 (2 H, s), and 7.25—7.55 (7 H, m); *m/z* (%) 222 (M^+ − H_2O, 100).

1-[Imidazol-4(5)-yl]cyclopentanol (**21a**). $\delta_H(Me_2SO)$ 1.61—1.86 (8 H, m, CH_2), 6.82 (1 H, s, 5-H), and 7.50 (1 H, s, 2-H); *m/z* (%) 39 (29), 68 (81), 95 (100), 123 (94), and 152 (M^+, 5).

1-[Imidazol-4(5)-yl]cyclohexanol (**21b**). $\delta_H(Me_2SO)$ 1.40—1.70 (10 H, m, CH_2), 6.78 (1 H, s, 5-H), and 7.48 (1 H, s, 2-H); *m/z* (%) 41 (29), 68 (29), 95 (60), 110 (36), 123 (100), and 166 (M^+, 44).

4(5)-Phenylthioimidazole (**22a**). $\delta_H(CDCl_3)$ 7.11—7.26 (6 H, m), 7.67 (1 H, s, 2-H), and 11.50 (1 H, br, s, NH); *m/z* (%) 40 (39), 51 (62), 77 (53), 121 (52), 149 (42), and 176 (M^+, 100).

4(5)-Phenylcarbamoylimidazole (**22b**). $\delta_H(Me_2SO)$ 3.45 (1 H, br, NHCO), 7.04 (1 H), 7.27—7.34 (2 H, m), 7.81—7.83 (4 H, m), and 9.83 (1 H, s, NH); *m/z* (%) 40 (20), 68 (17), 93 (100), 95 (58), and 187 (M^+, 56).

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