2,5-Dilithiation of *N*-Protected Imidazoles. Syntheses of 2,5-Disubstituted Derivatives of 1-Methoxymethyl-, 1-Triphenylmethyl-, and 1-(*N*,*N*-Dimethylsulphonamido)-imidazole

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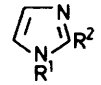
The conditions previously established for the dilithiation of 1-methylimidazole are shown to be applicable to 1-methoxymethyl- and 1-triphenylmethyl-imidazole allowing good-yielding syntheses of 1,2,5-trisubstituted imidazole derivatives. The suitability of the 1-substituents (and of other groups) for the *N*-protection of imidazoles in dilithiation experiments is discussed and the use of the *N*,*N*-dimethylsulphamoyl protecting group is proposed. 1-Sulphamoylimidazole undergoes mono- and 2,5-di-lithiation quantitatively at low temperatures and in short reaction times. The results of work-up of the 2,5-dilithio intermediate with 1 mol equiv. of iodomethane or dimethyl sulphate indicate selectivity in favour of reaction at the 5-position.

The reaction between organolithium reagents and *N*-protected imidazoles provides a valuable route to 1,2-disubstituted derivatives: some of the extensive work in this area has been reviewed recently.[1] The only report of dilithiation prior to our own work describes the synthesis of a 2,5-disilylated derivative of 1-methylimidazole in poor (32%) yield.[2] Our preliminary work on the dilithiation of 1-methylimidazole, however,[3] has established that by a judicious choice of reaction conditions dilithiation to the extent of 99% may be achieved. This success stimulated a wider investigation into the dilithiation of a range of *N*-protected imidazoles, with syntheses of 2,4(5)-disubstituted (NH-free) imidazoles as the ultimate goal: the results of these investigations are presented here.



(1) $R^1 = CH_2Ph$, $R^2 = H$
(2) $R^1 = CH_2OR$, $R^2 = H$
(3) $R^1 = CPh_3$, $R^2 = H$
(4) $R^1 = SO_2Ar$, $R^2 = H$
(5) $R^1 = CH(OR)_2$, $R^2 = H$
(6) $R^1 = SiMe_3$, $R^2 = H$
(7) $R^1 = CH_2Ph$, $R^2 = Me$
(8) $R^1 = CHMePh$, $R^2 = Me$

Results and Discussion

(*A*) *Existing Imidazole* N-*Protecting Groups*.—The *N*-protected imidazoles, of which significant use has been made in monolithiation studies, are shown in formulae (1)—(6). We find that benzylic *N*-protection [4a] is inadequate for dilithiation studies since benzylic deprotonation is favoured over imidazole 5-lithiation. The results of a series of experiments under a range of reaction conditions in which the lithio intermediates were quenched with iodomethane are shown in Table 1. The best yield of the 2-methyl derivative (7) is obtained with 1.1 mol equiv. of n-butyl-lithium to (1). Extension of the reaction time (experiment 2) leads to only a small increase in the yield of product (7) indicating that the non-quantitative yield is not due to the short duration of the experiment; neither is it due to the low temperature of the reaction mixture since the mixture was stirred at room temperature for an additional hour. Increase in the excess of n-butyl-lithium over starting compound (1) results in benzylic lithiation. Ogura and Takahashi report [5] the intermediacy of the unusual 1-benzyl-5-lithioimidazole. The methyl derivative that we have obtained (64% yield) under their lithiation conditions (experiment 4, Table 1) is identified as the product from benzylic and ring 2-lithiation, (8). Their claim, that they observed 5-lithiation, probably stems from a misinterpretation of the result of the nucleophilic attack of the dilithio intermediate on their unusual, carbohydrate-derived electrophile. Significantly, the present work establishes that quantitative monolithiation of 1-benzylimidazole is probably unachievable: attempts to improve the level of 2-lithiation lead to benzylic lithiation.

Table 1. Lithiation of 1-benzylimidazole (1) in diethyl ether

Expt.	Bu^nLi : (1)	Temp. (°C)	Time (h)	Product composition (%) [a] (1)	(7)	(8)
1	1.1 : 1	−78	0.5	34	66	0
2	1.1 : 1	−78 [b]	2.5			
		20 [b]	1.0	31	69	0
3	1.6 : 1	−78	0.5	29	46	25
4	2.0 : 1	20	2.0	0	0	100 [c]

[a] Determined by n.m.r. analysis. [b] The reaction mixture was stirred at −78 °C for 2.5 h and at 20 °C for 1 h. [c] Isolated yield was 64%.

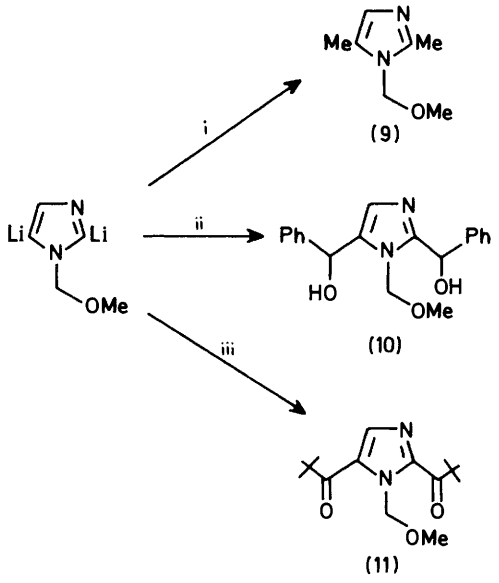
Alkoxymethyl-protected imidazoles (2) [4b] may be dilithiated in high yields. Dideuteriation of 1-methoxymethylimidazole (2; R = Me) *via* dilithiation and work-up with deuterium oxide (Table 2) give results similar to those obtained previously with 1-methylimidazole [3] (the yields increase with increasing reaction time and increasing ratio of lithiating agent to the substrate). Use of electrophiles other than deuterium oxide allows high-yielding syntheses of 2,5-disubstituted derivatives [Scheme 1, (9)—(11)]. An important disadvantage of the methoxymethyl protecting group, however, is that the severe deprotection conditions lead to at best moderate and at worst negligible isolated yields of deprotected products.[4b,6]

1-Triphenylmethylimidazole (3) has, unfortunately, only a slight (*ca.* 2.5 mg ml^{-1} at 20 °C) solubility in diethyl ether and yet this is the ethereal solvent of choice for the dilithiation of *N*-substituted imidazoles.[3] The solubility increases 10-fold in dimethoxyethane (DME) and rises to *ca.* 60 mg ml^{-1} in tetrahydrofuran (THF). Appreciable (but not quantitative) di-

Table 2. Dideuteriation of 1-methoxymethylimidazole (2; R = Me) *via* dilithiation with the Bu^{n}Li–TMEDA complex in diethyl ether at 20 °C

Expt.	Complex : substrate	Time (h)	Dideuteriation level [a] (%)
1	2.1 : 1	0.25	65
2	2.1 : 1	1.0	66
3	2.1 : 1	6.0	71
4	5.0 : 1	0.25	86
5	5.0 : 1	1.0	88
6	5.0 : 1	6.0	92

[a] Determined by n.m.r. analysis with respect to the imidazole 4-H integral.

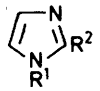


Scheme 1. *Reagents:* i, MeI; ii, PhCHO; iii, ClCOCMe$_3$

lithiation was achieved with a mixed solvent system [THF–diethyl ether (1 : 5)] and a large (*ca.* 9 molar) excess of the lithiating agent over the substrate. Work-up of the lithio intermediates with iodomethane gave a mixture of the 2-mono- and 2,5-di-methyl derivatives in the ratio 1 : 1.8. The lack of quantitative dilithiation and profligacy in lithiating agent requirements makes the triphenylmethyl group unattractive as an *N*-protecting group for imidazole dilithiation.

Introduction of an arylsulphonyl group[4d–f] on to an imidazole nitrogen (4) appears to reduce the ease of metallation at the ring carbons. Thus, whereas 1-methylimidazole is monometallated readily at −78 °C by n-butyl-lithium, monolithiation of 1-phenylsulphonylimidazole (4; Ar = Ph) requires a temperature of −20 °C, no lithiation being observed at −78 °C during 0.5 h: at 0 °C, there is evidence of decomposition.[4d] These observations suggest that forcing conditions would be required for an appreciable dilithiation level to be attained, but that concomitant decomposition is likely. The arylsulphonyl group may therefore be dismissed as a potential *N*-protecting group for imidazole in the present circumstances.

The diethoxymethyl group in (5; R = Et) is unstable under the conditions required for dilithiation (excess of the organolithium reagent over the substrate and reaction at room temperature). Attempts at 2,5-dilithiation at lower temperatures aided by the addition of the Li^+-chelating agent *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) were unsuccessful. The ready decomposition of compound (5; R = Et) (to imidazole) is consistent with the known ease of removal of the protecting group, possible even in the presence of the very labile 2-carboxy group.[4g]



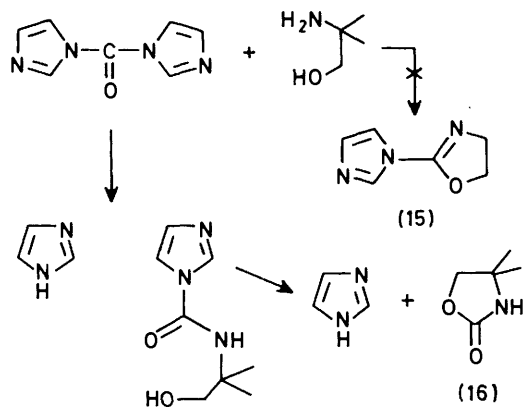
(12) R^1 = COR (R = OEt, CMe$_3$, OCMe$_3$, or NMe$_2$), R^2 = H
(13) R^1 = CMe$_3$, R^2 = H
(14) R^1 = CMe$_3$, R^2 = C(OH)Ph$_2$

1,2-Bis(trimethylsilyl)imidazole has been prepared *via* monolithiation of the 1-trimethylsilyl derivative (6) and subsequent work-up with trimethylchlorosilane.[4h] Since the 1-trimethylsilyl group in compound (6) is readily removed by hydrolysis it must be considered as a potential vehicle for imidazole *N*-protection. However, the poor literature yield of 14.2% reported for the 1,2-disilyl compound, combined with our own experiences[7] of lithiations of 1-trialkylsilylpyrroles (in which yields were only mediocre and the reactions were complicated by, *inter alia*, the lability of the N–Si bond and the occurrence of N to C silyl group rearrangement), discouraged further investigation of the trialkylsilyl group as a method of imidazole *N*-protection in dilithiation work.

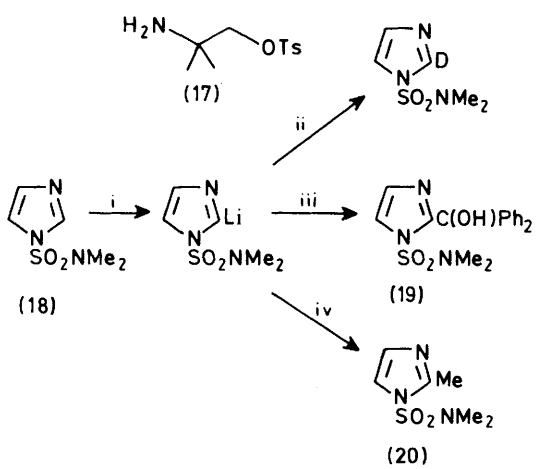
(*B*) *Potential Imidazole* N-*Protecting Groups.*—*N*-Acylimidazoles are well-known as acyl transfer reagents. Not surprisingly, therefore, the acyl groups in the derivatives (12; R = OEt, CMe$_3$, OCMe$_3$, and NMe$_2$) were cleaved in minutes by n-butyl-lithium or lithium di-isopropylamide (LDA): these groups are therefore unsuitable as *N*-protecting groups for lithiation experiments.

The investigation of the t-butyl group for imidazole *N*-protection required the preparation of 1-t-butylimidazole (13). The literature procedure,[8] which involves the heating of the potassium salt of imidazole with 2-chloro-2-methylpropane at 140 °C under pressure, gives poor yields (5%): in the present work, it has proved possible to improve upon this yield, but only to 12%. Generally, thermal decarboxylation of 1-alkoxycarbonylimidazoles furnishes a reliable route to the 1-alkyl derivatives: thermal decarboxylation of (12; R = OCMe$_3$), however, gave imidazole as the only aromatic product. Although 1-t-butylimidazole is readily monolithiated at the 2-position, an attempt at dilithiation was unsuccessful, work-up with benzophenone affording only the monosubstituted product (14) in 98% yield. In any event, the t-butyl group proved resistant to removal by treatment with any of sulphuric acid, boiling, methanolic hydrochloric acid, potassium amide in liquid ammonia, and a boiling mixture of potassium iodide and iodine in THF, and is thus unsuitable as an *N*-protecting group.

(*C*) *A New* N-*Protected Imidazole.*—Hitherto, the syntheses of 2,5-disubstituted derivatives of *N*-protected imidazoles *via* lithiation have required the use of a large excess of the organolithium reagent over the substrate. It was felt that this undesirable aspect might be avoidable if the features of *N*-protection and *ortho*- (directed) lithiation were combined in the one ' protecting-directing' *N*-substituent. None of the immediately obvious groups is satisfactory. Thus, the tertiary amido functionality [section (*B*), (12; R = NMe$_2$)] is too fragile to be useful here, and the arylsulphonyl group poses potential difficulties as discussed in section (*A*). Furthermore, attempted syntheses of the 2-imidazol-1-yldihydro-oxazole derivative (15) along the lines shown in Scheme 2 were unsuccessful, the isolated products being imidazole and the oxazolidin-2-one



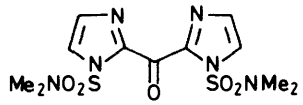
Scheme 2.



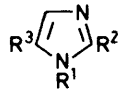
Scheme 3. *Reagents:* i, Bu"Li; ii, D_2O; iii, Ph_2CO; iv, MeI

(16). An approach which would avoid closure to (16), involving the intermediacy of the aminotoluene-p-sulphonate (17), was thwarted by cyclisation of the latter to an aziridine. Attention was therefore directed towards *N,N*-dimethylimidazole-1-sulphonamide [1-(*N,N*-dimethylsulphamoyl)-imidazole] (18).

The sulphonamide (18) (Scheme 3) was prepared, as a low-melting, white solid, in near quantitative yield and at room temperature, from imidazole and *N,N*-dimethylchlorosulphonamide in the presence of triethylamine. 2-Substituted derivatives of compound (18) were synthesised *via* monolithiation at −78 °C, during 15 min, with 1.1 mol equiv. of n-butyl-lithium with respect to the substrate. Work-up of the lithio intermediate with D_2O gave the 2-deuterio analogue quantitatively, as judged by n.m.r. product analysis, although the material was isolated in only 25% yield by extraction from water into organic solvents (continuous extraction would presumably aid recovery of this appreciably water-soluble material). Work-up with benzophenone gave the alcohol (19) (100% yield by n.m.r. analysis; 60% isolated) and with iodomethane the methyl derivative (20) (95% yield by n.m.r. analysis; 82% isolated), slightly reduced yields resulting from the replacement of iodomethane by dimethyl sulphate as the electrophile. Interestingly, extended reaction times, after addition of the electrophile, are necessary for high yields: when iodomethane was added to the 2-lithio intermediate at −78 °C and the mixture stirred for just 20 min (with the cooling bath removed) before subsequent work-up, only a 29% yield of



(21)



(22) $R^1 = SO_2NMe_2$, $R^2 = R^3 = Me$
(23) $R^1 = SO_2NMe_2$, $R^2 = Me$, $R^3 = H$
(24) $R^1 = SO_2NMe_2$, $R^2 = H$, $R^3 = Me$

compound (20) was detected in the n.m.r. product analysis. This contrasts sharply with the situation found for the 2-lithio derivative of 1-methylimidazole, which reacts quantitatively with iodomethane under similar conditions,[3] thus demonstrating the stabilising effect of the sulphonamido substituent on the 2-anion. Treatment of the lithio intermediate with oxirane afforded the 2-hydroxyethyl derivative in poor (25%) yield, and reaction of the lithio compound with methyl chloroformate gave a mixture of the 2-methoxycarbonyl derivative and the bis(imidazol-2-yl) ketone (21) in the ratio *ca.* 4 : 1, separable by column chromatography.

2,5-Dilithiation of the sulphonamide (18) may be achieved by its reaction with an 0.2 molar excess of n-butyl-lithium in DME during 15 min at a temperature below −15 °C. Work-up with D_2O and n.m.r. product analysis indicated quantitative dilithiation. This result should be contrasted with the situation found for *N*-methylimidazole,[3] quantitative dilithiation of which requires forcing conditions (4 molar excess of lithiating agent, admixture of TMEDA, several hours' reaction time, and temperatures of ambient or above). These have the following disadvantages: (i) the use of typical metallation solvents (THF or DME) is precluded by their reaction with the metallating agent at the elevated temperatures; (ii) the product of electrophilic work-up is necessarily contaminated by a large excess of the product of reaction between the electrophile and the unconsumed metallating agent; and (iii) the product imidazole derivative must be separated from TMEDA.

Work-up of the dilithio compound with iodomethane as electrophile during 12 h at room temperature gave the 2,5-dimethyl derivative (22) in 53% isolated yield, there being no spectroscopic evidence for the presence of unchanged starting material or the 2-monomethyl derivative. Reduction of the reaction time to 30 min and the temperature to −78 °C, however, gave a mixture of products; n.m.r. analysis of this indicated the presence of the 2,5-dimethyl derivative (22) and the 2- and 5-monomethyl compounds (23) and (24) in the ratio 1 : 1 : 5. Replacement of iodomethane by oxirane as electrophile gave (after reaction at room temperature during 12 h) a mixture of the expected 2,5-disubstituted product and the *5-monosubstituted* product in a ratio of *ca.* 1.6 : 1. These results suggest that the dilithio intermediate reacts more rapidly with electrophiles at the 5-position than at the 2-position and is consonant with the view that the 2-anion, being adjacent to two heteroatoms, is more stabilised than the 5-anion.

This observation reveals a further advantage of the sulphamoyl protecting group in that, permitting as it does the dilithiation of the *N*-protected imidazole without recourse to the use of a large excess of the lithiating agent, it allows the possibility of an experiment whose aim is the exploration of the selectivity for reaction at the 2- or 5-position in the di-

lithio intermediate by sequential addition of two different electrophiles, each equimolar with the lithio compound. (The interpretation of the results of such an experiment, but in which a large excess of the lithiating agent was present, as is necessary for the dilithiation of, *e.g.*, *N*-methylimidazole, would be confused by the inevitable competition between the dilithio-imidazole and the unconsumed lithiating agent for insufficient electrophile.) Reaction of the dilithio derivative with an equimolar amount of iodomethane for 30 min at −78 °C and subsequent aqueous work-up gave a mixture, n.m.r. analysis of which (after distillation) indicated the presence of the 5-methyl and 2,5-dimethyl derivatives, (24) and (22), in the ratio 5.6 : 1, as the only ring-methylated products. A similar experiment, with dimethyl sulphate as the electrophile, yielded the products (24) and (22) in the ratio 1.1 : 1.

The results of experiments on the parent sulphonamide (18) show that the sulphamoyl protecting group may be removed completely by boiling of a solution in 2M-aqueous hydrochloric acid under reflux for 4 h. The group is stable to cold, 2M-aqueous hydrochloric acid during 12 h, and to ethanolic ammonia. This constitutes a further advantage over triphenylmethyl-*N*-protected imidazoles which may undergo deprotection during acidic work-up procedures.

(*D*) *Conclusions.*—For a variety of reasons discussed above, existing imidazole *N*-protecting groups are unsatisfactory for ring 2,5-dilithiation. In this connection, the sulphamoyl protecting–directing group appears to offer several advantages over the existing methodology, *viz.* (i) neither the presence of TMEDA nor the use of a large excess of n-butyl-lithium are necessary for successful dilithiation; (ii) protection and deprotection steps are simple, comparatively mild, and controllable; (iii) high lithiation levels may be achieved at low temperatures; and (iv) selectivity for reaction at the 5-position of 2,5-dilithio-*N*-sulphamoylimidazole with 1 mol equiv. of electrophile offers a potential new route to 5-substituted imidazoles which does not involve prior blocking of the 2-position.

Experimental

General procedures for the lithiation of imidazole derivatives and their reaction with electrophiles, and for spectroscopic characterisation and solvent preparation, have been described in earlier papers.[3,9]

In general method A, Bu^{n}Li (*a* mmol) in Et_2O (*b* ml) was added to a stirred solution of the substrate and, where appropriate, TMEDA in Et_2O (*c* ml). In general method B, the inverse approach, whereby the substrate solution was added to the Bu^{n}Li solution, was adopted. In both cases, metallation was allowed to continue for *d* hours at *e* °C after which the lithio intermediates were usually quenched by addition of an electrophile to the solution cooled to −78 °C. Generally, imidazolic products were isolated from aqueous solutions *via* repeated extraction with $CHCl_3$ (*f* × *g* ml), drying of the combined extracts ($MgSO_4$) and evaporation of the solvent under reduced pressure.

1-*Benzyl*-2-*methylimidazole* (7).—1-Benzylimidazole (0.38 g, 2.4 mmol) was metallated (*a* = 2.7, *b* = 2, *c* = 20, *d* = 0.5, *e* = −78) according to method A. An aliquot (5.2 ml) was removed and iodomethane (1 ml) was added to this sample. Work-up of the resulting mixture (*vide infra*) gave a sample (a) of (7). The remainder of the mixture was stirred for a further 2 h at −78 °C and 1 h at room temperature, cooled to −78 °C, and iodomethane (1 ml) was added. Work-up of the reaction product gave a sample (b) of (7).

Work-up procedure for sample (a). After addition of iodomethane, the mixture was stirred at room temperature for 15 min and H_2O (2 ml) was added. Extraction (*f* = 6, *g* = 2.5) and drying gave a mixture which was shown by n.m.r. analysis to comprise the methyl derivative (7) (66%) and 1-benzylimidazole (34%).

A similar procedure and analysis gave sample (b) as a mixture of the methyl derivative (7) (69%) and 1-benzylimidazole (31%); δ ($CDCl_3$) 2.30 (s, 3 H, Me), 5.04 (s, 2 H, NCH_2), and 6.85– 7.55 (m, 7 H, Ph and imidazole 4- and 5-H).

2-*Methyl*-1-(1-*phenylethyl*)*imidazole* (8).—1-Benzylimidazole (0.41 g, 2.6 mmol) was metallated (*a* = 5.2, *b* = 3, *c* = 15, *d* = 2, *e* = 18) according to method B. The resulting solution was cooled to −78 °C and iodomethane (0.4 ml, 6.4 mmol) was added. Stirring was continued at 18 °C for 0.5 h and volatile substances were evaporated under reduced pressure. H_2O (5 ml) was added and the mixture was acidified with 2M-aqueous HCl. The acidic solution was washed with Et_2O (5 × 12 ml) and then basified with 45% aqueous NaOH solution. The usual work-up (*f* = 5, *g* = 4) gave 2-*methyl*-1-(1-*phenylethyl*)*imidazole* (8) (0.31 g, 64%), m.p. 83—86 °C (from EtOAc) (Found: C, 77.2; H, 7.6; N, 14.9. $C_{12}H_{14}N_2$ requires C, 77.38; H, 7.58; N, 15.04%); δ ($CDCl_3$) 1.78 (d, 3 H, *J* 7.3 Hz, phenylethyl Me), 2.25 (s, 3 H, imidazole Me), 5.29 (q, 1 H, *J* 7.3 Hz, NCH), 6.98—7.09 and 7.26—7.37 (m, 7 H, Ph and imidazole 4- and 5-H); *m/z* 186 (M^+, 100%), 105 (100), and 77 (100).

1-*Methoxymethyl*-2,5-*dimethylimidazole* (9).—1-Methoxymethylimidazole [4b] (0.93 g, 8.3 mmol) in the presence of TMEDA (6.25 ml, 41.4 mmol) was metallated (*a* = 41.4, *b* = 26, *c* = 30, *d* = 1, *e* = 14) according to method A. The mixture was cooled to −78 °C and iodomethane (9 ml, 140.0 mmol) was added. Stirring was continued at 14 °C for 1 h. The excess of iodomethane and the solvent were evaporated and H_2O (20 ml) was added. The usual work-up (*f* = 4, *g* = 20) with EtOAc and column chromatography (SiO_2 with 10% MeOH in EtOAc) afforded the *dimethyl derivative* (9), which was purified by distillation (0.99 g, 86%), b.p. 36.5 °C at 0.4 mmHg, δ ($CDCl_3$) 2.19 (s, 3 H, Me), 2.39 (s, 3 H, Me), 3.24 (s, 3 H, OMe), 5.09 (s, 2 H, NCH_2), and 6.62 (s, 1 H, imidazole 4-H); *m/z* 140.0956 (M^+, 97%, $C_7H_{12}N_2O$ requires 140.0946) and 96 (100).

2,5-*Bis*[*hydroxy*(*phenyl*)*methyl*]-1-*methoxymethylimidazole* (10).—1-Methoxymethylimidazole (0.92 g, 8.2 mmol) in the presence of TMEDA (6.25 ml, 41.4 mmol) was metallated (*a* = 41.4, *b* = 30, *c* = 20, *d* = 1, *e* = 18) according to method A and quenched with benzaldehyde (12 ml, 117.6 mmol). Stirring was continued at 18 °C for 1.3 h and the mixture was acidified to pH 2 with 2M-aqueous HCl. The organic layer was separated and washed with 2M-aqueous HCl (10 ml). The combined acidic solutions were washed with Et_2O (3 × 40 ml), basified with 45% aqueous NaOH solution, and worked up in the usual way (*f* = 3, *g* = 30) with EtOAc to give the *dialcohol* (10) (2.24 g, 84%), m.p. 162—165 °C (from Et_2O–C_6H_{14}) (Found: C, 69.5; H, 6.2; N, 8.7. $C_{19}H_{20}N_2O_3$ requires C, 70.35; H, 6.22; N, 8.64%); δ (C_2D_6SO–$CDCl_3$) 3.10 (s, 3 H, OMe), 3.30 (br s, 1 H, OH), 5.34 (m, 2 H, CH), 5.80 (s, 2 H, NCH_2), 6.14 (br s, 1 H, OH), 6.30 (s, 1 H, imidazole 4-H), and 7.17—7.43 (m, 10 H Ph); *m/z* 324.1496 (M^+, 13%, $C_{19}H_{20}N_2O_3$ requires 324.1474) and 77 (100).

1-*Methoxymethyl*-2,5-*bis*(2,2-*dimethylpropanoyl*)*imidazole* (11).—1-Methoxymethylimidazole (0.43 ml, 4.1 mmol) was metallated (*a* = 20.7, *b* = 15, *c* = 0, *d* = 1, *e* = 18) according to method B with admixture of TMEDA (3.13 ml, 20.7 mmol) to the Bu^{n}Li solution. An aliquot (2 ml) was removed

for D_2O work-up and n.m.r. analysis, indicating 87% dilithiation. The remainder was quenched with 2,2-dimethylpropanoyl chloride (2.6 ml, 21.1 mmol) in the usual way. Stirring was continued at room temperature for 0.5 h and the mixture was poured into H_2O (20 ml). The organic layer was separated, Et_2O (20 ml) was added, the mixture was washed with H_2O (4 × 10 ml), dried and the solvent was evaporated to give a yellow oil (2.90 g). This was distilled (33 °C at 0.5 mmHg) to give the 2,5-*diketone* (11) (81%), δ ($CDCl_3$) 1.36 (s, 9 H, Me), 1.45 (s, 9 H, Me), 3.24 (s, 3 H, OMe), 5.98 (s, 2 H, NCH_2), and 7.77 (s, 1 H, imidazole 4-H); *m/z* 280.1780 (M^+, 42%, $C_{15}H_{24}N_2O_3$ requires 280.1787) and 56 (100).

2,5-*Dimethyl*-1-*triphenylmethylimidazole*.—1-Triphenylmethylimidazole [4c] (0.21 g, 0.7 mmol) in THF (3.5 ml) was metallated (*a* = 6.9, *b* = 17.5, *c* = 0, *d* = 6, *e* = 18) according to method B with admixture of TMEDA (1.05 ml, 6.9 mmol) to the Bu^nLi solution and quenched at 0 °C with iodomethane (0.44 ml, 7.0 mmol). Stirring was continued at 0 °C for 0.5 h and H_2O (20 ml) was added. The aqueous layer was worked up in the usual way (*f* = 3, *g* = 20) with EtOAc to give a mixture of products (0.30 g), n.m.r. analysis of which indicated the presence of the monomethyl derivative (36%) and the dimethyl derivative (64%); δ ($CDCl_3$) 1.26 (s, 3 H, 5-Me), 1.66 (s, 3 H, 2-Me), and 6.70—7.36 (m, arom H); *m/z* 338 (M^+, 5%) and 165 (100).

1-*t*-*Butylimidazole* (13).—Imidazole (6.81 g, 0.10 mol) was added to potassium (3.9 g, 0.1 g atom) dispersed in hot benzene (150 ml). The mixture was boiled under reflux for 10 min, transferred to a glass pressure flask, cooled, and 2-chloro-2-methylpropane (14 ml, 0.13 mol) was added. The flask was closed and the mixture was heated at 140 °C for 18 h. The flask was cooled, opened, and the benzene solution was decanted from the precipitate which was washed with more benzene. The solvent was evaporated from the combined solutions and the resulting material was distilled to give the t-butylimidazole (13) (1.53 g, 12%) as a colourless oil, b.p. 70 °C at 0.8 mmHg; δ ($CDCl_3$) 1.56 (s, 9 H, Me), 7.06 and 7.07 (m, 2 H, imidazole 4- and 5-H), and 7.62 (m, 1 H, imidazole 2-H); *m/z* 124 (M^+, 39%) and 69 (100).

1-t-*Butylimidazol*-2-*yldiphenylmethanol* (14).—1-t-Butylimidazole (0.12 g, 1.0 mmol) was metallated (*a* = 5.1, *b* = 4, *c* = 2, *d* = 6.5, *e* = 18) according to method A with admixture of TMEDA (0.77 ml, 5.1 mmol) to the Bu^nLi solution and quenched at 0 °C with benzophenone (0.93 g, 5.1 mmol) in Et_2O (1 ml). Stirring was continued at room temperature for 16 h and H_2O (3 ml) was added. The mixture was acidified to pH 2 with 2M-aqueous HCl (15 ml), the organic layer was separated and then washed with 0.1M-aqueous HCl (2 × 5 ml). The combined acidic layer and washings were basified with conc. aqueous NaOH solution to pH 11. The resulting solid was filtered off, washed with H_2O and dried *in vacuo* to give a solid (0.22 g). The remaining solution was worked up in the usual way (*f* = 4, *g* = 10) with EtOAc to give a further sample (0.09 g) of the solid. Recrystallisation from $CHCl_3$–C_6H_{14} afforded the *alcohol* (14) (0.30 g, 98%), m.p. 218—219 °C (Found: C, 78.2; H, 7.1; N, 9.0. $C_{20}H_{22}N_2O$ requires C, 78.40; H, 7.24; N, 9.14%); δ ($CDCl_3$) 1.46 (s, 9 H, Me), 6.10 (d, 1 H, *J* 0.7 Hz, imidazole 5-H), 7.10—7.33 (m, 10 H, Ph), and 7.70 (d, 1 H, *J* 0.7 Hz, imidazole 4-H); *m/z* 306 (M^+, 15%) and 77 (100).

4,4-*Dimethyloxazolidin*-2-*one* (16).—2-Amino-2-methylpropan-1-ol (0.12 ml, 1.3 mmol) was added to *N,N'*-carbonyldi-imidazole (0.20 g, 1.2 mmol) in dry Et_2O (5 ml). The solution was stirred at room temperature for 10 min, Et_2O was evaporated, and the resulting material was dried at 31—33 °C at 0.3 mmHg to give imidazole and compound (16) (0.29 g, 94%) which was purified by distillation, b.p. 39.5—40.5 °C at 0.2 mmHg; δ ($CDCl_3$) 1.34 (s, 6 H, Me), 4.06 (s, 2 H, CH_2), and 6.10 (br s, 1 H, NH); *m/z* 115 (M^+, 21%), 100 (100), and 68 (100); δ_C ($CDCl_3$) 27.35 (q, Me), 55.25 (s, C), 76.93 (t, CH_2), and 159.39 p.p.m. (s, CO).

N,N-*Dimethylimidazole*-1-*sulphonamide* (18).—Dimethylchlorosulphonamide (13.0 ml, 0.12 mol) was stirred with imidazole (9.54 g, 0.14 mol) and triethylamine (18.0 ml, 0.13 mol) in benzene (160 ml) at room temperature for 16 h. The mixture was filtered and the precipitate washed with benzene (100 ml *in toto*). The filtrate and washings were combined and the solvent was evaporated. The resulting material (22.45 g) was distilled to yield the *sulphonamide* (18) (19.94 g, 95%), b.p. 110 °C at 0.4 mmHg, which formed a white solid on standing, m.p. 42—44 °C (Found: C, 34.4; H, 5.4; N, 23.9. $C_5H_9O_4N_3$ requires C, 34.28; H, 5.18; N, 23.99%); δ ($CDCl_3$) 2.83 (s, 6 H, NMe), 7.15 (m, 1 H, imidazole 5-H), 7.26 (m, 1 H, imidazole 4-H), and 7.91 (m, 1 H, imidazole 2-H); *m/z* 175 (M^+, 12%), 108 (64), and 40 (100); δ_C ($CDCl_3$) 38.14 (q, NMe), 117.65 (d, imidazole C-5), 130.34 (d, imidazole C-4) and 136.60 p.p.m. (d, imidazole C-2).

2-*Hydroxy*(*diphenyl*)*methyl*-N,N-*dimethylimidazole*-1-*sulphonamide* (19).—The sulphonamide (18) (0.50 g, 2.9 mmol) in THF (10 ml) was metallated (*a* = 3.2, *b* = 0, *c* = 0, *d* = 0.25, *e* = −78) by Bu^nLi in hexane (2.3 ml) and quenched with benzophenone (0.8 g, 4.4 mmol) in Et_2O (5 ml). Stirring was continued at room temperature for 19.5 h. The mixture was extracted with 2M-aqueous HCl and the acidic extract washed with Et_2O and basified with aqueous NaOH solution. The usual work-up gave the *hydroxy derivative* (19) (0.62 g, 60%), m.p. 136—138 °C (Found: C, 60.3; H, 5.2; N, 11.7. $C_{18}H_{19}N_3SO_3$ requires C, 60.49; H, 5.36; N, 11.76%); δ ($CDCl_3$) 2.70 (s, 6 H, NMe), 5.24 (s, 1 H, OH), 7.00 (d, 1 H, *J* 1.6 Hz, imidazole 5-H), 7.20—7.35 (m, 11 H, Ph and imidazole 4-H); *m/z* 357.1144 (M^+, 3%, $C_{18}H_{19}N_3SO_3$ requires 357.1147), 183 (100), 105 (100), and 51 (100).

N,N-*Dimethyl*-2-*methylimidazole*-1-*sulphonamide* (20).—(*a*) *Using iodomethane as electrophile*. The sulphonamide (18) (0.56 g, 3.2 mmol) in THF (10 ml) was metallated (*a* = 3.5, *b* = 0, *c* = 0, *d* = 0.25, *e* = −78) by Bu^nLi in hexane (2.55 ml) according to method A and quenched with iodomethane (0.3 ml, 4.8 mmol). The stirring was continued at room temperature for 12 h and the mixture was extracted five times with 2M-aqueous HCl (12 ml *in toto*). The combined acidic solutions were washed with Et_2O (10 ml) and basified with aqueous NaOH solution. After saturation with NaCl, the solution was worked up in the usual way (*f* = 4, *g* = 7) to yield the sulphonamide (18) (0.01 g) and the 2-methyl derivative (20) (0.49 g, 82%); δ ($CDCl_3$) 2.56 (s, 3 H, Me), 2.86 (s, 6 H, NMe), 6.89 (d, 1 H, *J* 1.7 Hz, imidazole 5-H), and 7.20 (d, 1 H, *J* 1.7 Hz, imidazole 4-H); *m/z* 189.0567 (M^+, 11%, $C_6H_{11}N_3SO_2$ requires 189.0572), 108 (66), and 44 (100).

(*b*) *Using dimethyl sulphate as electrophile*. The sulphonamide (18) (0.60 g, 3.4 mmol) in THF (10 ml) was metallated (*a* = 3.7, *b* = 0, *c* = 0, *d* = 0.25, *e* = −78) by Bu^nLi in hexane (2.7 ml) according to method A and quenched with freshly distilled dimethyl sulphate (0.36 ml, 3.8 mmol). The mixture was stirred at −78 °C for 23 min and at room temperature for 15.8 h. NH_3 was bubbled through the solution which was then poured into H_2O (2 ml) and extracted six times with 2M-aqueous HCl (9 ml *in toto*). The combined acidic solutions were washed with Et_2O (2 × 40 ml) and basified with aqueous NaOH solution. After saturation with

NaCl, the resulting solution was worked up in the usual way ($f = g = 5$) affording the sulphonamide (18) (0.09 g) and the 2-methyl derivative (20) (0.40 g, 63%).

2-(2-*Hydroxyethyl*)-N,N-*dimethylimidazole*-1-*sulphonamide*.—The sulphonamide (18) (2.71 g, 15.5 mmol) in THF (50 ml) was metallated ($a = 17.0$, $b = c = 0$, $d = 0.25$, $e = -78$) by Bu^{n}Li in hexane (12.34 ml) according to method A and quenched with oxirane (*ca.* 2.4 ml, 43.6 mmol). Stirring was continued at room temperature for 12 h after which the mixture was extracted with 2M-aqueous HCl (10 × 6.5 ml). The combined extracts were washed with Et_2O (2 × 50 ml), basified with aqueous NaOH solution, and saturated with NaCl. The usual work-up ($f = 6$, $g = 30$) gave a mixture of the sulphonamide (18) and the 2-hydroxyethyl derivative (2.10 g) in the ratio 3 : 1; δ ($CDCl_3$) 2.87 (s, 6 H, NMe), 3.64 (t, 2 H, *J* 5.9 Hz, CH_2), 3.84 (t, 2 H, *J* 5.9 Hz, CH_2), 4.13 (br s, 1 H, OH), 6.96 (d, 1 H, *J* 1.8 Hz, imidazole 5-H), and 7.25 (d, 1 H, *J* 1.8 Hz, imidazole 4-H); *m/z* 219.0668 (M^+, 5%, $C_7H_{13}N_3SO_3$ requires 219.0678) and 108 (100).

Bis-[1-(N,N-*dimethylsulphamoyl*)*imidazol*-2-*yl*] *Ketone* (21) *and Methyl* 1-(N,N-*Dimethylsulphamoyl*)*imidazole*-2-*carboxylate*.—The sulphonamide (18) (1.21 g, 6.9 mmol) in THF (20 ml) was metallated ($a = 7.6$, $b = c = 0$, $d = 0.25$, $e = -78$) by Bu^{n}Li in hexane (5.5 ml) according to method A and quenched with methyl chloroformate (0.8 ml, 10.4 mmol). Stirring was continued for 12 h at room temperature after which the mixture was poured into H_2O (20 ml) and saturated with $NaHCO_3$. The usual work-up ($f = 5$, $g = 10$) gave a mixture (2.90 g), n.m.r. analysis of which indicated the presence of the ketone (21) (19%, 0.25 g) and the methyl ester (81%, 1.30 g). Column chromatography (SiO_2–EtOAc) yielded samples of the ketone (0.17 g); δ ($CDCl_3$) 4.00 (s, 12 H, NMe), 7.07 (d, 2 H, *J* 1.4 Hz, imidazole 5-H), and 7.44 (d, 2 H, *J* 1.4 Hz, imidazole 4-H), and the ester (0.79 g); m.p. 50—53 °C, δ ($CDCl_3$) 3.04 (s, 6 H, Me), 3.94 (s, 3 H, OMe), 7.10 (d, 1 H, *J* 1.7 Hz, imidazole 5-H), and 7.50 (d, 1 H, *J* 1.7 Hz, imidazole 4-H); δ_C ($CDCl_3$) 38.62 (q, NMe), 52.98 (q, OMe), 124.75 (d, imidazole C-5), 128.02 (d, imidazole C-4), 137.32 (s, imidazole C-2), and 158.24 p.p.m. (CO).

N,N-*Dimethyl*-2,5-*dimethylimidazole*-1-*sulphonamide* (22).—The sulphonamide (18) (1.33 g, 7.6 mmol) in DME (30 ml) was metallated ($a = 16.7$, $b = c = 0$, $d = 0.25$, $e = -5$) by Bu^{n}Li in hexane (12.12 ml) according to method A and quenched with iodomethane (1.3 ml, 20.9 mmol). Stirring was continued for 12 h at room temperature after which the solution was extracted with 2M-aqueous HCl (3 × 10 ml). The combined acidic solutions were washed with Et_2O (2 × 55 ml), basified with aqueous NaOH solution, and saturated with NaCl. The usual work-up ($f = 4$, $g = ca.$ 20) gave the *dimethyl derivative* (22) (0.81 g, 53%) which was purified by distillation under reduced pressure, b.p. 65 °C at 0.26 mmHg (Found: C, 41.3; H, 6.9; N, 20.8. $C_7H_{13}N_3SO_2$ requires C, 41.37; H, 6.45; N, 20.68%); δ ($CDCl_3$) 2.11 (s, 3 H, 5-Me), 2.53 (s, 3 H, 2-Me), 2.84 (s, 6 H, NMe), and 6.89 (s, 1 H, imidazole 4-H); *m/z* 203.0732 (M^+, 4%, $C_7H_{13}N_3SO_2$ requires 203.0729), 108 (29), and 44 (100).

2,5-*Bis*(2-*hydroxyethyl*)-N,N-*dimethylimidazole*-1-*sulphonamide and* 5-(2-*Hydroxyethyl*)-N,N-*dimethylimidazole*-1-*sulphonamide*.—The sulphonamide (18) (2.21 g, 12.6 mmol) in DME (60 ml) was metallated ($a = 27.8$, $b = c = 0$, $d = 0.25$, $e = -5$) by Bu^{n}Li in hexane (20.13 ml) according to method A and quenched with oxirane (*ca.* 4 ml, 72.6 mmol). Stirring was continued for 12 h at room temperature after which the solution was extracted with 2M-aqueous HCl (5 × 12 ml). The combined acidic extracts were washed with Et_2O (2 × 100 ml), basified with aqueous NaOH solution, and saturated with NaCl. The usual work-up ($f = 5$, $g = 40$) gave a mixture (1.19 g), n.m.r. analysis of which showed the presence of the 2,5-disubstituted derivative (61%); δ ($CDCl_3$) 7.06 (s, 1 H, imidazole 4-H) and 2.66—4.05 (m, 16 H, NMe and CH_2CH_2-OH), and the 5-monosubstituted derivative (39%); δ ($CDCl_3$) 7.11 (d, 1 H, *J* 1.1 Hz, imidazole 4-H), 7.86 (d, 1 H, *J* 1.1 Hz, imidazole 2-H), and 2.66—4.05 (m, 11 H, NMe and CH_2CH_2-OH).

N,N-*Dimethyl*-5-*methylimidazole*-1-*sulphonamide* (24) *and* N,N-*Dimethyl*-2,5-*dimethylimidazole*-1-*sulphonamide* (22).—The sulphonamide (18) (0.66 g, 3.8 mmol) in DME (15 ml) was metallated ($a = 8.35$, $b = c = 0$, $d = 0.25$, $e = -5$) by Bu^{n}Li in hexane (6.79 ml) according to method A and quenched with iodomethane (0.28 ml, 4.55 mmol). The reaction mixture was stirred for 0.5 h at −78 °C, H_2O (5 ml) was added, and the whole extracted with 2M-aqueous HCl (6 × 5 ml). The combined extracts were washed with Et_2O (3 × 2 ml) and basified to pH 11 with conc. aqueous NaOH solution. Saturation with NaCl and the usual work-up ($f = 6$, $g = 20$) gave a brown oil (0.30 g) which was purified by distillation under reduced pressure, b.p. 52—55 °C at 0.7 mmHg. N.m.r. analysis of the distillate indicated the presence of the 2,5-dimethyl compound (22) and the 5-methyl derivative (24); δ ($CDCl_3$) 7.81 (d, 1 H, *J* 1.1 Hz, imidazole 2-H), 6.95 (d, 1 H, *J* 1.1 Hz, imidazole 4-H), 2.80 (s, 6 H, NMe), and 2.23 (s, 3 H, CMe), in the ratio 5.6 : 1.*

A similar experiment, but with dimethyl sulphate as the electrophile, gave (22) and (24) in the ratio 1 : 1.1.

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