Tetrahedron Vol. 42, No. 8, pp. 2351 to 2358, 1986
Printed in Great Britain.

0040-4020/86 $3.00+.00

HIGH-YIELDING SYNTHESES OF 4(5)-SUBSTITUTED IMIDAZOLES *VIA* ORGANOLITHIUM INTERMEDIATES. THE UTILITY OF SULPHONAMIDE N-PROTECTION AND SILICON-CONTAINING BLOCKING GROUPS

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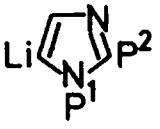
(*Received in UK* 3 *February* 1986)

Abstract - N-Protection of imidazole as its N,N-dimethylsulphonamido derivative, and blocking of the 2-position with the triethylsilyl group permits regioselective 5-metallation with sec-butyl-lithium. The resulting organolithium intermediates react with a range of electrophiles and the products are easily deprotected to give the 4(5)-substituted NH-free imidazoles in good to excellent yields. Isolation of the silicon-blocked intermediate is unnecessary and, indeed, is disadvantageous to final yields, making the procedure attractively economical of time.

I. INTRODUCTION

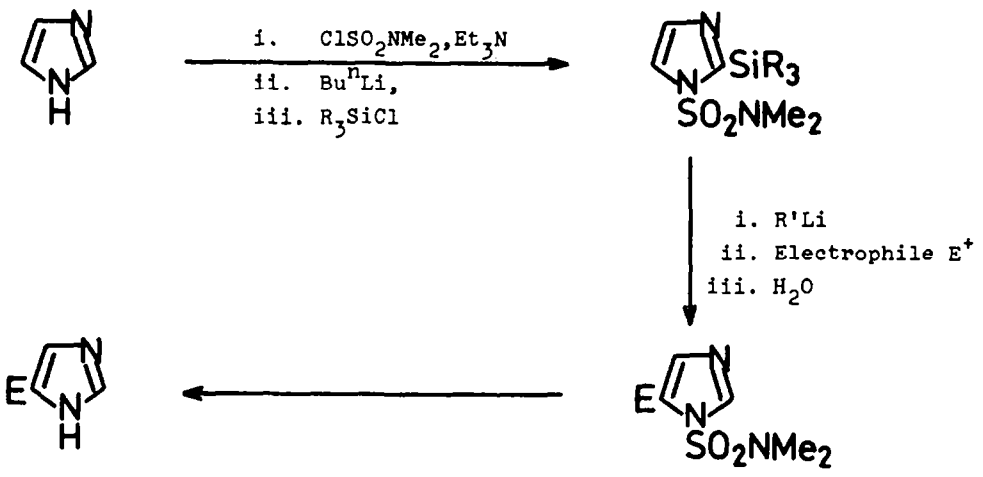
In our recent work on the lithiation of heteroaromatic systems[1] we have utilised both the technique of directed metallation and the strategy of blocking potentially reactive positions in these compounds with easily-removable silicon-containing groups. A related interest in the metallation of N-protected imidazoles[2] has led us to investigate the applicability of this methodology to the problem of the elaboration of the imidazole nucleus in the 4(5)-position *via* a lithio- intermediate of the general form (1), where P^1 and P^2 are removable protecting groups able to withstand the conditions for metallation at C-5. The results of these investigations are presented here.



(1)

N-Protected imidazoles undergo monolithiation readily at the 2-position[3] (typically with n-butyllithium at -78°C during 0.5h in an ethereal solvent). Under more forcing conditions, 2,5-dilithiation is possible[2] but attempts to induce subsequent, regioselective electrophilic attack at C-5 have met with only limited success. The claim that direct monolithiation has been achieved at C-5 in a compound unsubstituted at the 2-position is erroneous.[3] Halogen-metal exchange has been used to only a very limited extent in this connection,[3,4] transmetallation from a 5- into a 2-metallated species being a rapid process which diminishes the utility of this approach to 5-substituted derivatives. Several groups[4,5] have used thiophenyl blocking of the 2-position, alkoxymethyl-N-protection, and subsequent 5-metallation: the protecting groups are removed by treatment with aluminium amalgam and concentrated hydrochloric acid in 50% aqueous ethanol respectively.

In the work presented here, we have attempted to capitalise upon the known[2,6] ease of cleavage of the imidazole C-2-Si bond and our previous observations[2] on



SCHEME 1

the utility of the dimethylsulphonamide function for N-protection in designing a route to 4(5)-substituted imidazoles involving minimal manipulation of intermediates. The strategy is outlined in Scheme 1. (Previous attempts to prepare an imidazole derivative, namely 1-ethoxymethyl-2-trimethylsilylimidazole, possessing N-1 and C-2 protecting groups removable in a 'one-pot' reaction failed.[4])

II. RESULTS AND DISCUSSION

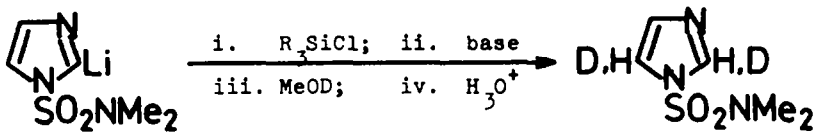
As in our earlier work,[2] the imidazole nitrogen was protected with the N,N-dimethylsulphonamido group the transformation from imidazole to the N-protected derivative (2) being achieved in essentially quantitative yield. This protecting group is resistant to the forcing conditions necessary for ring metallation, yet is easily removed with mild hydrolytic procedures (see below). The group has the additional advantage of facilitating ring metallation probably through the operation of both electronic and chelation effects.

Both trimethyl- and triethyl-silyl groups have been investigated for blocking of the 2-position. Although quantitative 2-lithiation of (2) with n-butyl-

(2) (3) (4)

lithium at -78°C in tetrahydrofuran (THF) for 0.5h may be demonstrated by work-up with MeOD and subsequent NMR analysis, use of chlorotrimethyl- or chlorotriethyl-silane (TMSCl or TESCl) as electrophile and subsequent product isolation always gave (3) or (4) contaminated with significant amounts of (2), probably as a consequence of their ease of hydrolysis over a wide pH range. The problem was easily circumvented by utilising (3) and (4) for further metallations without isolation, the excess of the trialkyl chlorosilane being simply removed by evaporation. In Table 1 are gathered together the results of a series of metallation studies carried out on (3) and (4) generated *in situ*.

TABLE 1 *in situ* 2-Protection and subsequent lithiation of N,N-dimethylimidazole-1-sulphonamide (2).



EXPT.	R_3SiCl:[a] SUBSTRATE RATIO	TIME (h)	TEMP. (°C)	BASE:[b] SUBSTRATE RATIO	TIME (h)	TEMP. (°C)	%DEUTERIATION[c] at 2-	at 5-
1	1.1A	16	20	1.2C	1	-78	35	63
2	1.1A	16	20	2.0C	1	-78	5	75
3	2.0A	2	-78	1.2C	1	-78	32	56
4	2.0A	2	-78	2.0C	1	-78	21	83
5	2.0B	16	20	2.0C	1	-78	0	82
6	2.0B	16	20	3.0C	1	-78	0	85
7	2.0B	16	20	1.1D	0.5	-78	0	63
8	2.0B	16	20	2.0D	0.5	-78	0	100

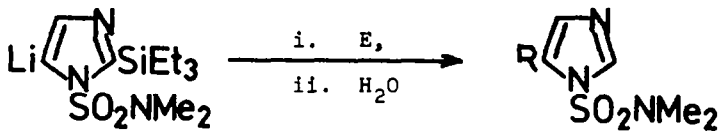
[a] A = TMSCl, B = TESCl; the solvent throughout is THF.

[b] C = lithium di-isopropylamide (LDA), D = sec-butyl-lithium.

[c] Estimated by quenching of the reaction mixtures with an excess of MeOD and integration of the ^1H N.M.R. signals.

The use of trimethylsilyl as the blocking group for the 2-position is unsatisfactory (experiments 1 - 4). The appreciable deuteriation levels found at this position in the product sulphonamide indicate significant competition by carbon-silicon bond cleavage during 5-metallation, even though the metallating agent is of low nucleophilicity (LDA). With triethylsilyl as the blocking group, however, [the required intermediate (4) being generated by treatment of 2-lithiated (2) with two molar equivalents of TESCl at 20°C for 16h] only 5-deuteriation was observed in the product sulphonamide. Presumably the steric bulk of the three ethyl groups is sufficient to discourage the competitive nucleophilic attack at silicon by the metallating agent. Even with a large excess of LDA as in experiment 6, however, quantitative 5-lithiation could not be attained, and attention was therefore turned to the carbon bases. In view of the demonstrated vulnerability of the carbon-silicon bond to nucleophilic cleavage, our choice centred on sec-butyl-lithium which, in the event, gave excellent results: use of two equivalents of this base afforded quantitative 5-lithiation (experiment 8).

The synthetical utility of this methodology for the preparation of 5-substituted imidazoles is illustrated in Scheme 2 by the results of work-up of the N-protected 5-lithio-2-triethylsilyl imidazole (5) with a range of electrophiles: yields are generally excellent. Interestingly, when benzophenone, carbon dioxide and N,N-dimethylchlorosulphonamide were used as electrophiles, both the triethylsilyl and the N-protecting groups were removed on dilute aqueous acidic work-up giving the 4(5)-substituted NH-free imidazoles in good yields (Scheme 3). For the first two of these electrophiles, neighbouring group participation by oxygen in the functionality introduced into the 5-position presumably lends anchimeric assistance to the removal of the N-protection (Scheme 4). The acceleration of the rates of hydrolysis of sulphonamides by

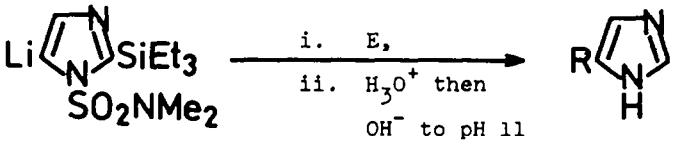


(5)

E	=	Me_2S_2	MeI	CH_2:$CHCH_2I$	TMSCl	$PhCH_2Br$	MeOD
R	=	MeS	Me	CH_2:$CHCH_2$	TMS	$PhCH_2$	D
Yield (%)	=	92	96	85	88	64[a]	89
Compound	=	(6)	(7)	(8)	(9)	(10)	(11)

[a] Isolated and characterised as the N-deprotected material (17).

SCHEME 2

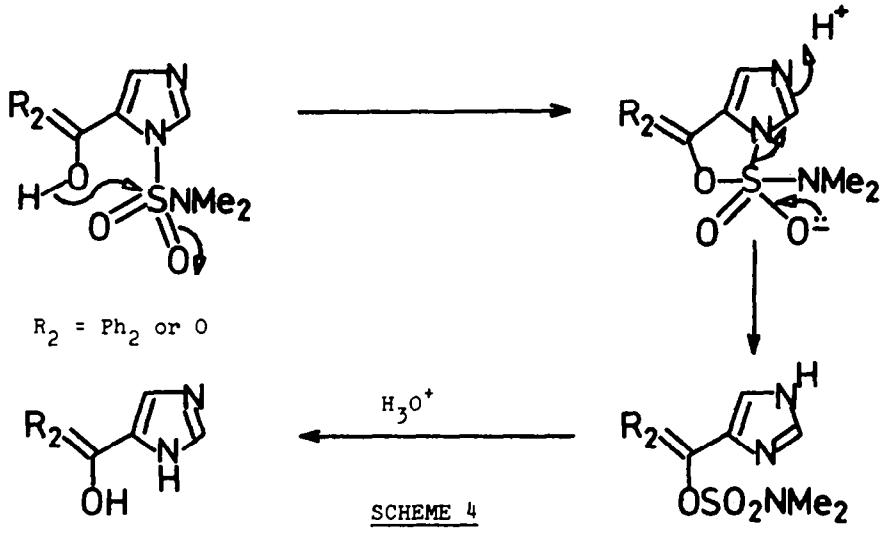


(5)

E	=	Ph_2CO	CO_2	$ClSO_2NMe_2$
R	=	$Ph_2C(OH)$	CO_2H	Cl
Yield (%)	=	78	74[a]	72
Compound	=	(12)	(13)	(14)

[a] Isolated and characterised as the ethyl ester (13a).

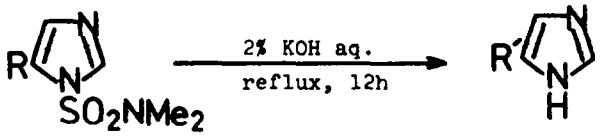
SCHEME 3



SCHEME 4

neighbouring hydroxyl groups is well-documented and has been studied extensively.[7] For the third electrophile (which was used in three molar excess), the ease of loss of the N-protecting group may be a consequence of activation *via* chlorination on the dimethylamino group or the basic imidazole nitrogen (or both), or simply of dipolar stabilisation of the transition state for sulphonamide hydrolysis by the chlorine introduced into the 5-position.

Although the chance observation of the ease of N-deprotection allowed us to achieve our intention of preparing 4(5)-substituted NH-free imidazoles in some instances, it is clear that the full synthetical potential of our strategy can only be realised if general methods for N-deprotection can be found. Studies on the parent sulphonamide (2) showed that quantitative deprotection is achievable with either 10% aqueous sulphuric acid or 2% aqueous potassium hydroxide, boiling under reflux for 12h. The latter conditions were applied to most of the compounds shown in Scheme 2 with results as summarised in Scheme 5. In view of



R	=	MeS	Me	$PhCH_2$	D	TMS
R'	=	MeS	Me	$PhCH_2$	H	H
Yield (%)	=	90	92	64	92	89
Compound	=	(15)	(16)	(17)	Imidazole	

SCHEME 5

the known[8] ease of ring-proton exchange of NH-free imidazoles, it is not surprising that the deuterium is lost from the 5-deuterio-N-dimethylsulphonamido derivative (11); loss of the trimethylsilyl group from (9) during hydrolysis is consistent with other observations on related systems.[9]

In conclusion, our results demonstrate the utility in imidazole chemistry of sulphonamide N-protection and silicon-blocking of the 2-position to achieve regioselective 5-metallation, with minimal isolation of intermediates. The 5-lithio-intermediates so prepared may be elaborated with a range of electrophiles and the blocking and protecting groups easily removed to give the 4(5)-substituted NH-free imidazoles in good to excellent yields.

III. EXPERIMENTAL

Procedures for analysis, purification and characterisation have been described in an earlier paper.[1] Tetrahydrofuran (THF) was dried and distilled prior to use from sodium-benzophenone, light petroleum and di-isopropylamine from CaH_2, and ethyl ethanoate was fractionally distilled. Reagents were stored under an atmosphere of argon and, where appropriate, over molecular sieves type 4A.

The concentrations of commercially available solutions of Bu^nLi and Bu^sLi were determined by means of the Gilman double-titration method.[10]

N,N-Dimethylimidazole-1-sulphonamide (2) was prepared by the method of Ngochindo and Chadwick.[2]

General Methods for Lithiation Studies of Table 1.

(A). 2-Lithio-N,N-dimethylimidazole-1-sulphonamide. - To a solution of sulphonamide (2) (1.0g, 5.71 mmol) in THF (30 ml) at -78°C was added Bu^nLi (6.28 mmol) in hexane and the reaction mixture stirred at -78°C for 30 minutes.

(B). *in situ* Generation of 2-protected imidazoles and their subsequent metallation. - To the 2-lithio-intermediate generated as in (A) was added the required trialkylchlorosilane and the reaction mixture was then stirred for the requisite time and temperature. The solvent and any excess of volatile reagents were then removed by evaporation under reduced pressure and gentle warming.

The residual oil was dissolved in THF (30 ml) and the solution cooled to -78°C. The required metallating agent was then added and the mixture left for the required time, before quenching with MeOD. The THF was removed by evaporation and the resulting solids were stirred with 2M-aqueous HCl (20 ml) for thirty minutes at 20°C. Basification to pH 11 with aqueous KOH solution (40% w/w), extraction with ethyl ethanoate (6 x 30 ml), drying ($MgSO_4$) and evaporation of the solvent gave the deuteriated imidazole.

5-Methylthio-N,N-dimethylimidazole-1-sulphonamide (6). - To the 2-lithio-intermediate generated as in general method (A) (5.71 mmol) was added triethylchlorosilane (1.92 ml, 11.42 mmol). The mixture was stirred at 20°C for 16h, after which time the solvent and any excess of chlorosilane were removed by evaporation under reduced pressure with gentle heating. THF (30 ml) was added to the resulting oil, and the solution was cooled to -78°C. Bu^sLi (11.42 mmol) in cyclohexane solution was added and the mixture stirred at -78°C for thirty minutes yielding the 5-lithio-intermediate. Dimethyldisulphide (1.62 ml, 18 mmol), was then added and the mixture allowed to warm to 20°C. Stirring was continued for 12h. The solvents were removed by evaporation and the residue was stirred with 2M aqueous HCl (50 ml) for thirty minutes. The solution was washed with light petroleum (2 x 10 ml), basified to pH 11 with aqueous KOH solution (40% w/w) and extracted with diethyl ether (6 x 30 ml). Drying ($MgSO_4$) of the combined ethereal extracts and evaporation of the solvent yielded the crude product which was distilled under reduced pressure, b.p. 170°C at 0.3 mmHg to give pure 5-methylthio-N,N-dimethylimidazole-1-sulphonamide (6) as a clear oil (1.16g, 92%) (Found: C, 32.5; H, 5.2; N, 18.8. $C_6H_{11}N_3O_2S_2$ requires C, 32.58; H, 5.01; N, 19.00%); δ ($CDCl_3$), 8.00 (1H, d, J 1.0 Hz, imidazole 2-H), 7.10 (1H, d, J 1.0 Hz, imidazole 4-H), 2.98 (6H, s, NCH_3), 2.42 (3H, s, SCH_3); m/z 221 (M^+, 81%), and 113 (100).

5-Methyl-N,N-dimethylimidazole-1-sulphonamide (7). - To the 5-lithio-intermediate (5.71 mmol) generated as above for (6) was added methyl iodide (0.87 ml, 14.0 mmol) at -78°C. The mixture was stirred at 20°C for 4h and concentrated by evaporation yielding a thick oil, which was stirred with 2M aqueous HCl (50 ml) for 2h at 20°C. Work-up as for (6), extraction with ethyl ethanoate (6 x 30 ml), drying of the extracts ($MgSO_4$) and evaporation of the solvents gave the crude product as an oil, which was distilled under reduced pressure, b.p. 160°C at 0.25 mmHg to yield pure 5-methyl-N,N-dimethylimidazole-1-sulphonamide (7) as a clear oil (1.04g, 96%) pure by g.l.c. analysis; δ ($CDCl_3$), 7.86 (1H, d, J 1.1 Hz, imidazole 2-H), 6.79 (1H, d, J 1.1 Hz, imidazole 4-H), 2.87 (6H, s, NCH_3), 2.36 (3H, s, CH_3); m/z 189.0572 (M^+, 29%, $C_6H_{11}N_3O_2S$ requires 189.0572) and 108 (100).

Prop-2-enyl-N,N-dimethylimidazole-1-sulphonamide (8). - To the 5-lithio-intermediate generated as above for (6) (5.71 mmol) at -78°C was added allyl iodide (2.01 ml, 22 mmol) and the mixture was stirred at -78°C for thirty minutes and at 20°C for 12h. The solvents were then removed by evaporation and the residues were treated as in the preparation of (7). Evaporation of solvents from the resulting organic solution yielded the product prop-2-enyl-N,N-dimethylimidazole-1-sulphonamide (8) contaminated with 15% of starting sulphonamide (2) from which it was inseparable by p.t.l.c. and distillation; δ ($CDCl_3$), 7.82 (1H, s, imidazole 2-H), 6.79 (1H, s, imidazole 4-H), 5.91 (1H, m, J 17.6, 11.0, 6.6 Hz, -CH=), 5.13 (2H, m, J 17.6, 11.0 Hz, $=CH_2$), 3.50 (2H, d, J 6.6 Hz, CH_2-), 2.91 (6H, s, NCH_3); m/z 215 (M^+, 17%) and 108 (100).

5-Trimethylsilyl-N,N-dimethylimidazole-1-sulphonamide (9). - To the 5-lithio-intermediate (5.71 mmol) generated as above was added trimethylchlorosilane (1.90 ml, 15 mmol) at -78°C. Stirring was continued at -78°C for thirty

minutes and for 3h at 20°C. The solvents were removed by evaporation to give an oil which was treated as in the preparation of (7). Removal of solvent by evaporation from the resulting solution yielded a thick oil which was distilled under reduced pressure, b.p. 235°C at 1.0 mmHg, to give pure 5-trimethylsilyl-N,N-dimethylimidazole-1-sulphonamide (9) (1.19g, 88%) as a waxy, white, solid, m.p. 35 - 36°C (Found: C, 38.8; H, 6.8. $C_8H_{17}N_3O_2Si$ requires C, 38.84; H, 6.93%); δ ($CDCl_3$), 7.99 (1H, s, imidazole 2-H), 7.11 (1H, s, imidazole 4-H), 2.85 (6H, s, $N-CH_3$), 0.34 (9H, s, $SiCH_3$); m/z 247 (M^+, 6%) and 232 (100).

4(5)-Benzylimidazole (17). - To the 5-lithio-intermediate generated as in the preparation of (6) (5.71 mmol) was added benzyl bromide (2.4 ml, 20 mmol) at -78°C. Stirring was continued at -78°C for thirty minutes and at 20°C for 12h. The usual work-up and extraction procedure yielded 5-benzyl-N,N,dimethylimidazole-1-sulphonamide (10) as an oil; δ ($CDCl_3$), 8.01 (1H, s, imidazole 2-H), 7.79 - 7.33 (5H, m, C_6H_5), 6.8 (1H, s, imidazole 4-H), 4.19 (2H, s, CH_2Ph), 2.74 (6H, s, NCH_3); m/z 265 (M^+, 10%) and 157 (100), which was heated under reflux in aqueous KOH solution (2% w/w, 150 ml) for 12h. Removal of water and trituration of the solids with THF (200 ml) followed by drying ($MgSO_4$) and evaporation gave crude 4(5)-benzylimidazole (17)[11] which was distilled under reduced pressure, b.p. 110°C at 0.1 mmHg, to give the pure imidazole derivative (0.58g, 64%), m.p. 55 - 56°C (lit.,[11] 84 - 85°C); δ ($CDCl_3$), 7.36 (1H, s, imidazole 2-H), 7.32 - 6.92 (5H, m, C_6H_5), 6.67 (1H, s, imidazole 4(5)-H), 3.87 (2H, s); m/z 158.0844 (M^+, 100%, $C_{10}H_{10}N_2$ requires 158.0844).

4(5)-Imidazolyldiphenyl methanol (12). - To the 5-lithio-intermediate (5.71 mmol) generated as in the preparation of (6) was added benzophenone (2.73g, 15 mmol) in THF (10 ml) at -78°C. Stirring was continued for thirty minutes at -78°C and at 20°C for 4h. The solvents were then removed by evaporation and the residue was treated as in the preparation of (7). Evaporation of the solvent from the resulting solution afforded the crude product, which was recrystallized from C_6H_{12}/ethyl ethanoate to yield pure 4(5)-imidazolyldiphenyl methanol (12)[12] (1.11g, 78%), m.p. 171 - 172°C (lit.,[12] 173 - 174°C) (Found: C, 76.5; H, 5.6; N, 11.1. $C_{16}H_{14}N_2O$ requires C, 76.80; H, 5.60; N, 11.20%); δ (CD_3OD), 7.54 (1H, s, imidazole 2-H), 7.39 - 7.06 (10H, m, C_6H_5), 6.48 (1H, s, imidazole 4(5)-H); m/z 250 (M^+, 2%) and 232 (100).

Ethyl 4(5)-imidazolecarboxylate (13a). The 5-lithio-intermediate generated as above for (6) was poured onto a slurry of crushed, solid, CO_2 and diethyl ether. After evaporation of the solvents, the resulting solids were stirred with 2M aqueous HCl (100 ml) for 1h at 20°C. The resulting solution was washed with light petroleum (2 x 10 ml), basified to pH 11 with aqueous KOH solution (40% w/w) and boiled under reflux for 3h. The mixture was acidified to pH 6.5 with concentrated aqueous HCl, the water was removed and the residue was heated under reflux in absolute alcohol with acid catalysis (2 drops of concentrated H_2SO_4) for 6h. The solution was neutralized ($NaHCO_3$) the alcohol was removed and the resulting solids were suspended in water (20 ml). Basification ($NaHCO_3$) to pH 9, extraction with ethyl ethanoate (6 x 30 ml), drying ($MgSO_4$) and evaporation of the solvent afforded the crude ethyl ester. Recrystallization from C_6H_{12}/ethyl ethanoate gave the pure ester[13] (0.59g, 74%), m.p. 157 - 160°C (lit.,[13] 160 - 162°C) as a white solid; δ ($CDCl_3$), 7.81 (1H, s, imidazole 2-H), 7.76 (1H, s, imidazole 4(5)-H), 4.33 (2H, q, J 6.3 Hz, CH_2), 1.30 (3H, t, J 6.3 Hz, CH_3); m/z 140 (M^+, 35%), and 95 (100).

4(5)-Chloroimidazole (14). - To the 5-lithio-imidazole generated as for (6) above (5.71 mmol) at -78°C was added dimethylsulphamoyl chloride (1.84 ml, 17.14 mmol) and the mixture stirred for thirty minutes at -78°C and at 20°C for 2h. The solvents were removed by evaporation and the residue was stirred with 2M aqueous HCl (100 ml) for 1h at 20°C. The resulting solution was washed

with light petroleum (2 x 10 ml) and basified to pH 11 with aqueous KOH solution (40% w/w). Extraction of the aqueous layer with ethyl ethanoate (6 x 30 ml) and drying of the organic extracts ($MgSO_4$) gave the crude product (14)[14] as a tan solid. Recrystallization from C_6H_{12}/CH_2Cl_2/ethyl ethanoate gave pure 4(5)-chloroimidazole (14)(0.42g, 72%), m.p. 120 - 121°C (lit.,[14] 117 - 118°C); δ ($CDCl_3$), 7.54 (1H, s, imidazole 4(5)-H), 6.98 (1H, s, imidazole 2-H); m/z 104 (M^+, 32%) and 102 (M^+, 100).

4(5)-Methylthio-imidazole (15). - The methylthiosulphonamide derivative (6) (0.8g, 3.62 mmol) was boiled under reflux with aqueous KOH solution (2% w/w, 20 ml) for 12h. The water was removed under reduced pressure, the residue was triturated with ethyl ethanoate (200 ml) and the organic extract dried ($MgSO_4$). Evaporation of the solvent and distillation under reduced pressure, b.p. 160°C at 0.22 mmHg, gave pure 4(5)-methylthio-imidazole[15] (0.37g, 90%) as a white solid, m.p. 86 - 87°C (lit.,[15] 87°C) (Found: C, 42.5; H, 5.4; N, 24.6. $C_4H_6N_2S$ requires C, 42.10; H, 5.30; N, 24.55%); δ ($CDCl_3$), 7.72 (1H, s, imidazole 2-H), 7.08 (1H, s, imidazole 4(5)-H), 2.39 (3H, s, SCH_3).

4(5)-Methylimidazole (16). - The methylsulphonamide derivative (7) (1.0g, 5.29 mmol) was boiled under reflux for 12h with aqueous KOH solution (2% w/w, 50 ml). The resulting solution was acidified to pH 2 (concentrated aqueous HCl), washed with light petroleum (2 x 10 ml), and basified to pH 11 with aqueous KOH solution (40% w/w). The water was removed under reduced pressure to give a solid which was triturated with ethyl ethanoate. Drying of the organic extract ($MgSO_4$) and evaporation of the solvent gave the crude product which was distilled under reduced pressure, b.p. 110°C at 0.15 mmHg, to give pure 4(5)-methylimidazole (16) (0.40g, 92%), m.p. 52 - 53°C (lit.,[16] 54.2°C); δ ($CDCl_3$), 7.54 (1H, s, imidazole 2-H), 6.76 (1H, s, imidazole 4(5)-H), 2.26 (3H, s, CH_3); m/z 82 (M^+, 100%).

Acknowledgement AJC is indebted to the S.E.R.C. for a studentship.

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