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Polyfunctionalisation of Imidazole *via* Sequential Imidazolyl Anion Formation

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Abstract: A method for achieving the sequential functionalisation of the imidazole ring in the order C-5→C-4→C-2 is described. The chemistry proceeds *via* the regioselective formation of positionally stable imidazolyl anions which are reacted with electrophiles (aldehydes, alkyl halides, azides, formamides, isocyanates) to afford substituted imidazoles in 31-90% yield. © 1997 Elsevier Science Ltd.

A multifunctionalised imidazole ring is an important structural component of many biologically active molecules possessing properties of interest within the agrochemical and pharmaceutical industries. Examples include compounds exhibiting antiatherosclerotic,[1] antihypertensive,[2] antiinflammatory,[3,4] antimicrobial,[5] antioxidant,[6] antiprotozoal,[7] antipsychotic,[8] antitumoural,[9,10] antiulcerogenic,[11] cardiotonic,[12] fungicidal,[13,14] herbicidal,[15] hypocholesterolemic,[16] immunosuppressive,[17] and insecticidal[18] activities. As a consequence of this diverse biological activity the development of new imidazole chemistry is a topic of continuing interest, a recent example being the construction of combinatorial libraries containing highly substituted imidazoles.[19]

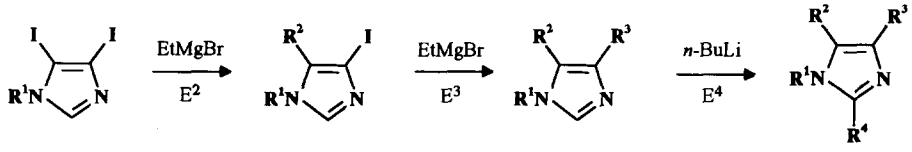
A potentially very versatile and attractive route for the synthesis of polyfunctionalised imidazoles is *via* the sequential formation of imidazole anions and their subsequent reactions with electrophiles. However, this approach is complicated by the tendency of imidazol-4-yl and -5-yl anions to undergo rapid equilibration to give imidazol-2-yl anions in the absence of blocking groups on C-2.[20,21,22] This problem can be overcome by functionalising the 2-position first and good methods exist for the sequential functionalisation of imidazole in the order C-2→C-5→C-4.[21,22,23] These methods involve the successive replacement of the halogens in protected trihaloimidazoles *via* metal-halogen exchange reactions performed at low temperature (-78°C). An interesting variant of this methodology utilises palladium(0) catalysed cross-coupling with arylboronic acids[24] to achieve polysubstitution. A method involving a combination of metallation and metal-halogen exchange to achieve trifunctionalisation has also been reported.[25]

We have previously reported that *N*-protected 4-iodoimidazoles undergo metal-halogen exchange in CH_2Cl_2 with EtMgBr at room temperature to yield positionally stable imidazol-4-yl magnesium halides.[26] This

methodology has found application in the synthesis of biologically interesting 4-substituted imidazoles, for example H_3 agonists and antagonists,[27] α_2-adrenergic agonists[28] and potential inhibitors of histidine biosynthesis.[29] In this paper we describe an extension of this work which enables the sequential functionalisation of imidazole in the order C-5→C-4→C-2. This ordering complements that achieved using the existing methods described above and in some cases has significant advantages. For example, the biologically important 4,5-disubstitution pattern[1,3,6,9,11,17] is available directly without the need for introducing and then removing blocking groups at C-2. In addition, a 2-amino substitutent as found in many imidazole alkaloids[4,5,10,14] or a 2-cyano group as found in certain fungicides,[13] is more conveniently introduced at the end of the functionalisation sequence than at the beginning.

RESULTS AND DISCUSSION

The objective of the work reported herein was to achieve sequential regioselective metal-halogen exchange reactions with an *N*-protected 4,5-diiodoimidazole, and then to metallate in the 2-position. Reaction of the imidazolyl anions thus generated with various electrophiles would then yield polyfunctionalised imidazoles as outlined in Scheme 1. In addition to our own results,[26] a key starting point for the present studies was a report by El Borai and Hassanein[30] describing the sequential metal-halogen exchange reactions of 4,5-diiodo-1-methylimidazole with EtMgBr in refluxing ether. After exchanging the ether for benzene, these workers then added treithyl orthoformate to give 5-diethoxymethyl-4-iodo-1-methylimidazole in 68% yield. Repeating the procedure gave 4,5-bis(diethoxymethyl)-1-methylimidazole in 39% overall yield. The absence of any isomerisation of the intermediate anions into the 2-position makes this report particularly noteworthy but despite the interest in the polyfunctionalisation of imidazole,[21-25] this result seems never to have been followed up. In particular, we were interested to investigate whether similar chemistry would work for 4,5-diiodoimidazoles with more easily removed *N*-protecting groups under our milder and simpler reaction conditions[26] and whether a wider variety of electrophiles could be employed. In addition we hoped to extend the methodology to include the synthesis of trifunctionalised imidazoles *via* metallation at the 2-position in a final step.



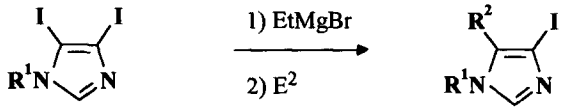
Scheme 1

The starting material for the current work was 4,5-diiodo-1-dimethylsulfamoylimidazole (**1**), which was prepared in two steps by diiodination of imidazole[31] followed by reaction with NaH and then dimethylsulfamoyl chloride.[13] It was hoped that the metal chelating properties of this protecting group would help to direct the metal-halogen exchange reaction to the 5-position and stabilise the resulting imidazol-5-yl anion.

Functionalisation of the Imidazole 5-Position

In order to effect the first metal halogen exchange reaction, a solution of the diiodo compound **1** in CH_2Cl_2 was treated with ethereal EtMgBr at ambient temperature as previously described for formation of imidazol-4-yl magnesium halides.[26] The reaction mixture was quenched by addition of an electrophile to yield the 5-substituted imidazoles **3-6** in 38-84% yield (Scheme 2. Table 1; entries 1-4). The anion reacted directly with acetaldehyde and phenyl isocyanate but reactions with benzyl bromides required prior addition of CuCN.2LiCl.[32] The isomeric 2-substituted imidazoles could not be detected in any of the reactions. However, when the reaction solvent was changed from CH_2Cl_2 to THF then 2-alkylated products were also formed. A similar effect of solvent on anion stability had been previously observed with *N*-sulfamoylated imidazol-4-yl magnesium halides.[26]

The use of different *N*-protecting groups was also investigated in order to broaden the scope of the methodology. In particular, the metal-halogen exchange chemistry of the benzyloxymethyl protected 4,5-diiodoimidazole **2** with EtMgBr has been investigated. Groziak *et al*[22] had previously studied the reaction of this molecule with *n*-BuLi and found that the imidazol-5-yl lithium anion was formed but isomerised to the imidazol-2-yl anion even at -78 °C. In contrast we have found the imidazol-5-yl magnesium species is positionally stable at ambient temperature and reacts cleanly with various electrophiles yielding the desired 5-substituted imidazoles **7-9** in 49-90% yield (Scheme 2. Table 1; entries 5-7). Unlike the magnesium anions derived from compound **1**, those derived from compound **2** are also stable in THF. Indeed, this is the preferred solvent for reactions with compound **2** due to the greater solubility of the imidazol-5-yl magnesium species in this solvent than in CH_2Cl_2. An attempt to further generalise the method to include 4,5-diiodo-1-triphenylmethylimidazole failed.

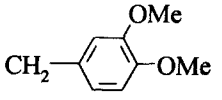
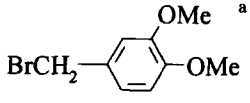
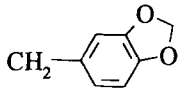
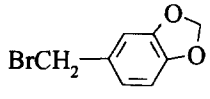
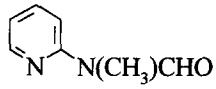


1 $R^1 = SO_2NMe_2$
2 $R^1 = CH_2OBn$

3-9

Scheme 2

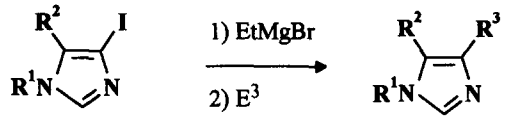
Table 1. Functionalisation of the Imidazole 5-Position.

starting material	product	R^1	R^2	electrophile (E^2)	isolated yield (%)
1	3	SO_2NMe_2	$CH(OH)CH_3$	MeCHO	84
1	4	SO_2NMe_2	CO.NHPh	PhNCO	42
1	5	SO_2NMe_2		 [a]	38
1	6	SO_2NMe_2		 [a]	46
2	7	CH_2OBn	$CH(OH)CH_3$	MeCHO	49
2	8	CH_2OBn	CHO		71
2	9	CH_2OBn	$CH_2CH{=}CH_2$	$BrCH_2CH{=}CH_2$ [a]	90

[a] CuCN.2LiCl added prior to the electrophile

Functionalisation of the Imidazole 4-Position

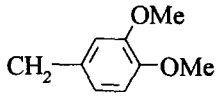
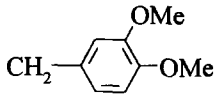
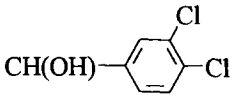
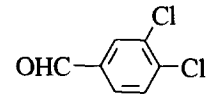
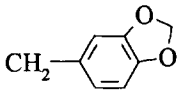
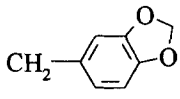
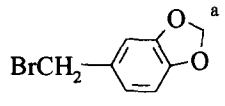
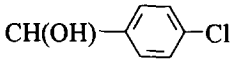
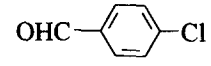
We next sought to effect functionalisation at the 4-position by treating a selection of the 4-iodo compounds **3-9** with EtMgBr at ambient temperature. The metal-halogen exchange and subsequent reaction with electrophiles proceeded smoothly for both *N*-sulfamoyl iodides (**5, 6**) and *N*-benzyloxymethyl iodides (**8a, 9**) to give the desired products **10-14** in 50-74% yield (Scheme 3. Table 2). When the electrophile is water, the product is an *N*-protected 5-monosubstituted imidazole (compound **10**). The preparation of this class of molecules *via* the current methodology is of comparable efficiency to other methods reported in the literature,[33,34] and may provide a useful alternative in some cases. With electrophiles other than water the products (compounds **11-14**) exhibit the biologically important 4,5-disubstitution patterns.[1,3,6,9,11,17] The imidazol-4-yl magnesium intermediate reacts directly with aldehydes (Table 2; entries 2, 4, 5) but addition of CuCN.2LiCl[32] was required to effect alkylation with a benzyl bromide (entry 3). The stability of the *N*-benzyloxymethyl imidazol-4-yl magnesium halides is especially noteworthy considering the exceedingly rapid isomerisation of the analogous lithium anions to the imidazol-2-yl lithium species.[22]



5, 6, 8a, 9 **10-14**

Scheme 3

Table 2. Functionalisation of the Imidazole 4-Position.

starting material	product	R^1	R^2	R^3	electrophile (E^3)	isolated yield (%)
5	10	SO_2NMe_2		H	H_2O	74
5	11	SO_2NMe_2				50
6	12	SO_2NMe_2				74
8a [b]	13	CH_2OBn		$CH(OH)CH_3$	MeCHO	52
9	14	CH_2OBn	$CH_2CH{=}CH_2$			69

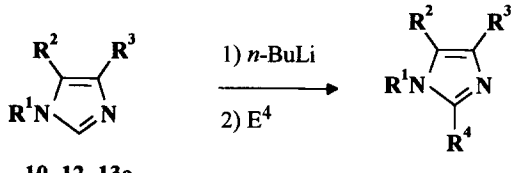
[a] CuCN.2LiCl added prior to the electrophile

[b] 8a is the ethylene acetal derivative of aldehyde **8**

Functionalisation of the Imidazole 2-Position

The final step in the current sequence required functionalisation of the imidazole 2-position *via* metalation. This reaction has been extensively studied[34-36] and we chose standard conditions utilising *n*-BuLi at -78 °C. Thus, deprotonation of imidazoles **10**, **12** and **13a** followed by addition of an electrophile gave the desired

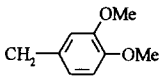
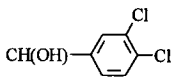
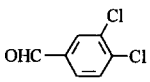
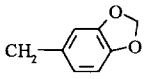
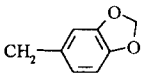
2-substituted products **15-17** in 31-55% yield (Scheme 4. Table 3). The 2-amino compound **16**, formed by employing azidobenzene as an electrophile and then hydrolysing the resulting 2-triazenoimidazole,[36] is a close analogue of the naturally occurring LTB_4 receptor antagonist, Leucettamine A.[4] The lower temperatures employed for the formation of the imidazol-2-yl anion makes this C-2 functionalisation much less convenient than the C-5 and C-4 metallation steps. However, recent work by others at Chesterford Park indicates that, at least in the case of *N*-sulfamoylated imidazoles, it may be possible to deprotonate the 2-position at -10 to 0 °C with LDA.[37]



10, 12, 13a **15-17**

Scheme 4

Table 3. Functionalisation of the Imidazole 2-Position.

starting material	product	R^1	R^2	R^3	R^4	electrophile (E^4)	isolated yield (%)
10	**15**	SO_2NMe_2		H			31
12	**16**	SO_2NMe_2			NH_2	PhN_3	51
13a [a]	**17**	CH_2OBn		CH(OH)Me	Me	MeI	55 [b]

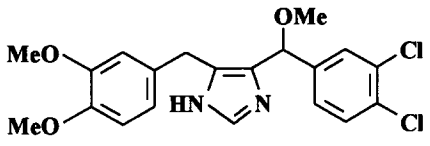
[a] **13a** is the O-trimethylsilyl derivative of **13**

[b] yield estimated by ^1H NMR

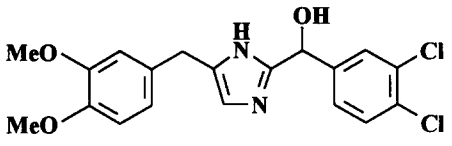
N-Deprotection

The dimethylsulfamoyl protecting group can be removed by hydrolysis under acidic or basic conditions or by treatment with $LiAlH_4$.[26,27,34] The benzlyoxymethyl protecting group is also easily removed by acid hydrolysis or by hydrogenolysis.[22,38] We have conducted a brief investigation into the *N*-deprotection of the *N*-sulfamoylated imidazoles **11, 15** and **16**. Thus, treatment of compound **11** or **15** with aqueous HCl in methanol yielded the NH-imidazoles **18** or **19** in 32% and 69% yield, respectively. It is interesting to note that

the hydroxyl group of **11** has been converted to a methoxyl group in **18** during the deprotection, possibly *via* a diazafulvene intermediate. Unfortunately, for reasons that remain unclear, we were unable to deprotect compound **16**.



18



19

Conclusion

Starting from a readily available *N*-protected 4,5-diiodoimidazole we have been able to achieve sequential functionalisation of the imidazole ring in the order C-5→C-4→C-2. The chemistry proceeds *via* the regioselective formation of the different imidazolyl anions which react with a wide variety of electrophiles in moderate to good yield (yields are all unoptimised). This has enabled the facile synthesis of 5-monosubstituted, 4,5- and 2,4(5)-disubstituted and 2,4,5-trisubstituted imidazoles. The procedure is experimentally simple and is well suited to the development of single-pot multistep synthetic sequences.

EXPERIMENTAL

Melting points were determined on a Buchi 510 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 682 spectrophotometer. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AC-300 spectrometer using residual protic solvent, $CHCl_3$ (δ7.25 ppm) or DMSO (δ2.50 ppm), as internal reference. Mass spectra were recorded using a VG Trio 2 spectrometer and accurate mass measurements were made using a VG 7070E spectrometer. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser. Vacuum flash chromatography[39] was performed on Fluka silica gel H using gradient elution. Solvent mixtures in which products were eluted are given in parenthesis. All experiments involving organometallic reagents or metal hydrides were carried out in oven dried glassware under a nitrogen atmosphere and using solvents dried over 0.4 nm molecular sieves prior to use. Other solvents and reagents were used as purchased.

4,5-Diiodoimidazole

4,5-Diiodoimidazole was prepared using a modification of the method described by Iddon *et al*[31] for the preparation of 2,4,5-triiodoimidazole. A solution of iodine (255 g, 0.88 mol) and KI (281.5 g, 1.7 mol) in water (750 ml) was instilled into a stirred solution of imidazole (34 g, 0.5 mol) in aqueous 4M NaOH (1.5 l) at r.t. over 45 min. After stirring for a further 5 hrs the reaction mixture was adjusted to pH 8 with glacial acetic acid. The resulting precipitate was collected by filtration, dried *in vacuo* over P_2O_5 and triturated with EtOAc to give 4,5-diiodoimidazole (87.5 g, 0.27 mol, 55%) mp 180-181 °C dec. (Lit.[31] mp 191-192 °C dec.).

1-Dimethylsulfamoyl-4,5-diiodoimidazole (1)

Sodium hydride (60% oil dispersion, 4.4 g, 110 mmol) was added in portions to a stirred solution of 4,5-diiodoimidazole (32 g, 100 mmol) in dry DMF (150 ml) with cooling (ice/water) over 10 min. After a further 10 min the reaction mixture was allowed to warm to r.t. and stirred for 1.5 hr. The grey anion solution was then re-cooled (ice/water) and dimethylsulfamoyl chloride (11.8 ml, 110 mmol) was added dropwise. The reaction mixture was allowed to warm to r.t. over 1 hr and after 16 hrs was poured onto crushed ice. The precipitated crude product was collected by filtration, washed with water, dried *in vacuo* over P_2O_5 and crystallised from EtOAc-$^iPr_2O$ to yield the diiodo compound **1** (30.1 g, 71 mmol, 71%) mp 119-121 °C. A sample prepared by recrystallisation for elemental analysis had mp 126.5-128 °C. IR (KCl) ν_{max} 3120 (m), 2902 (m), 1465 (s), 1430 (s), 1385 (s), 1190 (s), 1135 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.02 (6H, s), 8.04 (1H, s); MS m/z (EI) 427 (M^+, 27%), 319 (6), 108 (100); Anal. calcd for $C_5H_7I_2N_3O_2S$: C, 14.06; H, 1.65; N, 9.84. Found: C, 14.01; H, 1.56; N, 9.94%.

1-(Dimethylsulfamoyl-4-iodoimidazol-5-yl)ethanol (3)

A 3.0 M solution of EtMgBr in ether (0.172 ml, 0.52 mmol) was instilled into a solution of diiodo compound **1** (0.20 g, 0.47 mmol) in dry CH_2Cl_2 (2.0 ml) at r.t. over 5 min. The resulting suspension was stirred at r.t. for 30 mins and then ethanal (80 µl, 1.41 mmol) was added. After stirring for a further 2.5 hrs the mixture was diluted with CH_2Cl_2 (5 ml) and poured into half saturated NH_4Cl solution (10 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by vacuum flash chromatography (1:1 EtOAc/hexanes) to yield the carbinol **3** as an off-white solid (0.137 g, 0.40 mmol, 84%) mp 191-193 °C dec. IR (KCl) ν_{max} 3115 (m), 2980 (m), 1470 (m), 1035 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (3H. d. *J*=7.5 Hz), 2.72 (1H, d, *J*=10 Hz, Exch. with D_2O), 2.95 (6H, s), 5.29 (1H, m), 7.82 (1H, s); MS m/z (EI) 345 (M^+, 18%), 330 (25), 221 (92), 108 (100); Anal. calcd. for $C_7H_{12}IN_3O_3S.0.1H_2O$: C, 24.23; H, 3.54; N, 12.11. Found: C, 23.81; H, 2.96; N, 11.98%

1-Dimethylsulfamoyl-4-iodo-5-phenylcarbamoylimidazole (4)

A 3.0 M solution of EtMgBr in ether (0.86 ml, 2.58 mmol) was instilled into a solution of the diiodo compound **1** (1.0 g, 2.34 mmol) in dry CH_2Cl_2 (10 ml) at r.t. over 8 mins. The resulting suspension was stirred at r.t. for 30 mins and then phenyl isocyanate (0.255 ml, 2.35 mmol) was added. The reaction mixture was stirred at r.t. for 18 hrs and then worked up as described above for compound **3**. The crude product was crystallised from toluene to yield the amide **4** as pale yellow needles (0.33 g, 0.79 mmol, 34%) mp 136-138 °C. The mother liquors were concentrated *in vacuo* and purified by vacuum flash chromatography (3:2 EtOAc/hexanes) to yield a further quantity of the amide **4** (0.08 g, 0.19 mmol, 8%) IR (KCl) ν_{max} 3246 (m), 3010 (m), 1650 (s), 1542 (m), 1434 (m), 1264 (s) cm^{-1}. ^1H NMR (DSMO-d_6) 2.77 (6H, s), 7.08 (1H, t, *J*=7 Hz), 7.32 (2H, t, *J*=7 Hz), 7.78 (2H, d, *J*=7 Hz), 7.95 (1H, s), 9.82 (1H, s); MS m/z (EI), 313 (MH^+-Me_2NSO_2, 17%), 221 (14), 93 (100); HRMS(EI) calcd for $C_{10}H_8IN_3O$ (MH^+-Me_2NSO_2): 312.9712. Found: 312.9723.

5-(3,4-Dimethoxybenzyl)-1-dimethylsulfamoyl-4-iodoimidazole (5)

A 3.0 M solution of EtMgBr in ether (10.3 ml, 30.9 mmol) was instilled into a solution of the diiodo compound **1** (12.0 g, 28.1 mmol) in dry CH_2Cl_2 (100 ml) at r.t. The resulting suspension was stirred at r.t. for 30 mins and then a 1.0 M solution of CuCN.2LiCl[32] in dry THF (25.3 ml, 25.3 mmol) was added, followed by 3,4-dimethoxybenzyl bromide (5.84 g, 25.3 mmol) in dry CH_2Cl_2 (10 ml). The yellow reaction solution was stirred at r.t. for 20 hrs and poured into half saturated NH_4Cl containing 2% concentrated NH_3 (100 ml). The mixture was stirred for 20 mins, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by vacuum flash chromatography (1:1 EtOAc/hexanes) to yield the iodoimidazole **5** (4.32 g, 9.58 mmol, 38%) mp 134.5-138 °C; IR (KCl) ν_{max} 3108 (m), 2931 (m), 1516 (s), 1465 (s), 1388 (s), 1143 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.58 (6H, s), 3.85 (6H, s), 4.16 (2H, s), 6.72 (3H, m), 7.93 (1H, s); MS m/z (EI) 451 (M^+, 100%), 343 (29), 215 (88); HRMS(EI) calcd for $C_{14}H_{18}IN_3O_4S$: 451.006. Found: 451.0039.

1-Dimethylsulfamoyl-4-iodo-5-(3,4-methylenedioxybenzyl)imidazole (6)

A 3.0 M solution of EtMgBr in ether (12.9 ml, 38.6 mmol) was instilled into a solution of diiodo compound **1** (15.0 g, 35.1 mmol) in dry CH_2Cl_2 (140 ml) at r.t. The resulting suspension was stirred at r.t. for 30 mins and then a 1.0 M solution of CuCN.2LiCl[32] in dry THF (32 ml, 32 mmol) was added, followed by 3,4-methylenedioxybenzyl bromide[40] (6.8 g, 31.6 mmol) in dry CH_2Cl_2 (20 ml). The yellow reaction solution was stirred at r.t. for 65 hrs and then worked up as described for compound **5**. Vacuum flash chromatography (1:1 EtOAc/hexanes) yielded the iodoimidazole **6** as a pale yellow crystalline solid (6.28 g, 14.4 mmol, 46%) mp 136.5-137.5 °C; IR ν_{max} (KCl) 3110 (m), 2910 (m), 1490 (s), 1390 (s), 1150 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.62 (6H, s), 4.12 (2H, s), 5.94 (2H, s), 6.66 (3H, m), 7.92 (1H, s); MS m/z (EI) 435 (M^+, 9%), 327 (22), 301 (25), 108 (100); Anal. calcd for $C_{13}H_{14}IN_3O_4S$; C, 35.87; H, 3.24; N, 9.65. Found: C, 35.83; H, 3.19; N, 9.32%.

1-(1-Benzyloxymethyl-4-iodoimidazol-5-yl)ethanol (7)

A 3.0 M solution of EtMgBr in ether (0.87 ml, 2.61 mmol) was instilled into a solution of diiodo compound **2**[22] (1.0 g, 2.27 mmol) in dry THF (9 ml) at r.t. The resulting solution was stirred at r.t. for 30 mins and then ethanal (0.25 ml, 4.45 mmol) was added. After stirring at r.t. for a further 1 hr the mixture was worked up as described for compound **3**. Vacuum flash chromatography (1:1 EtOAc/hexanes) yielded the carbinol **7** as a colourless glass (0.40 g, 1.12 mmol, 49%); IR (KCl) ν_{max} 3360 (s), 3100 (m), 2980 (m), 1490 (m), 1455 (m), 1195 (m), 1115 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59 (3H, d, *J*=7.5 Hz), 2.39 (1H, d, *J*=6.5 Hz, Exch. with D_2O), 4.55 (2H, s), 5.10 (1H, m), 5.39 (1H, d, *J*=10 Hz), 5.61 (1H, d, *J*=10 Hz), 7.35 (5H, m), 7.48 (1H, s); MS m/z (EI) 358 (M^+, 3%), 313 (12), 92 (100); HRMS (EI) calcd for $C_{13}H_{15}IN_2O_2$: 358.0150. Found: 358.0164.

1-Benzyloxymethyl-4-iodoimidazole-5-carboxaldehyde (8)

A 3.0 M solution of EtMgBr in ether (1.31 ml, 3.93 mmol) was instilled into a solution of the diiodo compound **2**[22] (1.5 g, 3.4 mmol) in dry THF (15 ml) at r.t. The resulting solution was stirred at r.t. for 30 mins and then *N*-methyl-*N*-2-pyridylformamide (0.45 ml, 3.74 mmol) was added. After stirring at r.t. for a further 2 hrs the mixture was worked up as described for compound **3**. Vacuum flash chromatography (2:3 EtOAc/hexanes) yielded the aldehyde **8** as a pale yellow oil (0.823 g, 2.4 mmol, 71%). This material had identical ^1H NMR and MS spectra to those previously reported by Groziak and Wei.[22]

5-Allyl-1-benzyloxymethyl-4-iodoimidazole (9)

A 3.0M solution of EtMgBr in ether (3.67 ml, 11 mmol) was instilled into a solution of the diiodo compound **2**[22] (4.4 g, 10 mmol) in dry THF (45 ml) at r.t. The resulting solution was stirred at r.t. for 30 mins and then a 1.0 M solution of CuCN.2LiCl[32] in dry THF (9 ml, 9 mmol) was added. The reaction mixture was cooled to -30 °C and allyl bromide (0.78 ml, 9 mmol) was added. The temperature was allowed to increase to 0 °C and then after stirring for 4 hrs the reaction was worked up as described for compound **5**. Vacuum flash chromatography (1:1 EtOAc/hexanes) yielded the allyl imidazole **9** as an oil (3.19 g, 9 mmol, 90%); IR (Film) ν_{max} 3085 (m), 2910 (m), 1640 (m), 1490 (s), 1360 (m), 1215 (s), 1095 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.24 (2H, d, *J*=5 Hz), 4.26 (2H, s), 5.06 (2H, m), 5.29 (2H, s), 5.83 (1H, m), 7.34 (5H, m), 7.52 (1H, s); MS m/z (EI) 354 (M^+, 5%), 92 (100); HRMS (EI) calcd for $C_{14}H_{15}IN_2O$: 354.0261. Found: 354.0245.

5-(3,4-Dimethoxybenzyl)-1-dimethylsulfamoylimidazole (10)

A 3.0 M solution of EtMgBr in hexane (0.5 ml, 1.5 mmol) was instilled into a solution of the iodo compound **5** (0.5 g, 1.11 mmol) in dry CH_2Cl_2 (5 ml) at r.t. The resulting suspension was stirred at r.t. for 1 hr and then water (2 ml) was added. After stirring for a further 15 mins the reaction mixture was worked up as described for compound **3**. Vacuum flash chromatography (2:1 EtOAc/hexane) yielded the benzylimidazole **10**

(0.268 g, 0.82 mmol, 74%) mp 126-127 °C; IR (KCl) ν_{max} 2935 (m), 1515 (s), 1466 (s), 1375 (s), 1142 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.80 (6H, s), 3.88 (3H, s), 3.91 (3H, s), 4.06 (2H, s), 6.68 (1H, s), 6.80 (3H, m), 7.92 (1H, s); MS m/z (EI). 325 (M^+, 43%), 217 (100); HRMS (EI) calcd for $C_{14}H_{19}N_3O_4S$: 325.1096. Found: 325.1113.

4-(3,4-Dichloro-α-hydroxybenzyl)-5-(3,4-dimethoxybenzyl)-1-dimethylsulfamoylimidazole (11)

A 3.0 M solution of EtMgBr in ether (0.813 ml, 2.44 mmol) was instilled into a solution of the iodo compound **5** (1.0 g, 2.22 mmol) in dry CH_2Cl_2 (10 ml) at r.t. The resulting suspension was stirred at r.t. for 20 mins and then 3,4-dichlorobenzaldehyde (1.16 g, 6.65 mmol) in dry CH_2Cl_2 (2 ml) was added. After stirring at r.t. for 16 hrs the reaction mixture was worked up as described for compound **3**. Vacuum flash chromatography (1:1 EtOAc/ hexanes) yielded the carbinol **11** (0.55 g, 1.10 mmol, 50%) mp 123.5-125.5 °C; IR (KCl) ν_{max} 3000 (m), 2880 (m), 1509 (s), 1464 (m), 1257 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65 (6H, s), 3.74 (3H, s), 3.86 (3H, s), 4.18 (2H, m), 5.58 (1H, bs), 6.50 (1H, d, *J*=9 Hz), 6.60 (1H, s), 6.73 (1H, d, *J*=9 Hz), 7.18 (1H, dd, *J*=1 and 9 Hz), 7.34 (2H, m), 7.94 (1H, s); MS m/z (EI) 499 (M^+, 25%), 391 (85), 218 (100); HRMS (EI) calcd for $C_{21}H_{23}Cl_2N_3O_5S$: 499.0735. Found: 499.0751.

1-Dimethylsulfamoyl-4,5-bis(3,4-methylenedioxybenzyl)imidazole (12)

A 3.0 M solution of EtMgBr in ether (5.1 ml, 15.3 mmol) was instilled into a solution of the monoiodo compound **6** (6.0 g, 13.8 mmol) in dry CH_2Cl_2 (60 ml) at r.t. The resulting suspension was stirred at r.t. for 30 mins and then a 1.0 M solution of CuCN.2LiCl[32] in dry THF (13 ml, 13 mmol) was added, followed by 3,4-methylenedioxybenzyl bromide[40] (2.8 g, 13 mmol) in dry CH_2Cl_2 (10 ml). The yellow reaction solution was stirred at r.t. for 70 hrs and then worked up as described for compound **5**. Vacuum flash chromatography (9:1 Et_2O/hexanes) yielded the dibenzylimidazole **12** as a pale yellow solid (4.25 g, 9.59 mmol, 74%) mp 74.5-76 °C; IR (KCl) ν_{max} 3130 (m), 2900 (m), 1490 (s), 1440 (s), 1390 (s), 1245 (s), 1170 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.62 (6H, s), 3.74 (2H, s), 4.14 (2H, s), 5.94 (2H, s), 5.96 (2H, s), 6.51 (2H, m), 6.68 (4H, m), 7.92 (1H, s); MS m/z (EI) 433 (M^+, 23%), 335 (100), 213 (50), 135 (52); Anal. calcd for $C_{21}H_{21}N_3O_6S.0.3H_2O$: C, 56.19; H, 4.85; N, 9.36. Found: C, 56.18; H, 5.00; N, 9.27%.

1-Benzyloxymethyl-4-(1-hydroxyethyl)imidazole-5-carboxaldehyde Ethylene Acetal (13)

The aldehyde **8** was converted to 1-benzyloxymethyl-4-iodoimidazole-5-carboxaldehyde ethylene acetal (**8a**) as described by Groziak and Wei.[22] A 3.0 M solution of EtMgBr in ether (0.69 ml, 2.1 mmol) was instilled into a solution of the iodoimidazole **8a** (0.70 g, 1.81 mmol) in dry THF (7 ml) at r.t. The resulting solution was stirred at r.t. for 30 mins and then ethanal (0.20 ml, 3.62 mmol) was added. The reaction mixture was stirred for a further 1 hr at r.t. and then worked up as described for compound **3**. Vacuum flash chromatography (15% EtOH in EtOAc) yielded the carbinol **13** as a colourless oil (0.275 g, 0.90 mmol, 50%);

IR (Film) ν_{max} 3300 (m), 3100 (m), 2980 (m), 1505 (m), 1465 (m), 1230 (m), 1080 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57 (3H, d, *J*=6 Hz), 2.73 (1H, bs, exch. with D_2O), 4.05 (4H, m), 4.49 (2H, s), 5.03 (1H, m), 5.40 (2H, s), 6.11 (1H, s), 7.33 (5H, m), 7.54 (1H, s); MS m/z (FAB) 305 (MH^+, 100%); HRMS (FAB) calcd for $C_{16}H_{20}N_2O_4$: 305.1501. Found: 305.1528.

5-Allyl-1-benzyloxymethyl-4-(4-chloro-α-hydroxybenzyl)imidazole (14)

A 3.0 M solution of EtMgBr in ether (1.04 ml, 3.11 mmol) was instilled into a solution of the iodoimidazole **9** (1.0 g, 2.8 mmol) in dry THF (10 ml) at r.t. The resulting solution was stirred for 30 mins and then 4-chlorobenzaldehyde (0.44 g, 3.11 mmol) was added. The reaction mixture was stirred for a further 16 hrs and then worked up as described for compound **3**. Vacuum flash chromatography (2% EtOH in EtOAc) yielded the carbinol **14** (0.71 g, 1.93 mmol, 69%); IR (KCl) ν_{max} 3380 (m), 3085 (m), 2940 (m), 1640 (m), 1495 (s), 1370 (m), 1100 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.39 (2H, d, *J*=4 Hz), 4.42 (2H, s), 4.91 (1H, d, *J*=15.5 Hz), 5.08 (1H, d, *J*=10.5 Hz), 5.26 (2H, s), 5.76 (2H, m), 7.33 (9H, m), 7.51 (1H, s); MS m/z (EI) 368 (M^+, 2%) 91 (100); HRMS (EI) calcd. for $C_{21}H_{21}ClN_2O_2$: 368.1291. Found: 368.1283.

2-(3,4-Dichloro-α-hydroxybenzyl)-5-(3,4-dimethoxybenzyl)-1-dimethylsulfamoylimidazole (15)

A 2.5 M solution of *n*-BuLi in hexane (1.04 ml, 2.62 mmol) was instilled into a solution of the imidazole **10** (0.71 g, 2.18 mmol) in dry THF (15 ml) at -78 °C. The resulting solution was stirred at -78 °C for 30 mins and then 3,4-dichlorobenzaldehyde (0.572 g, 3.27 mmol) in dry THF (3 ml) was added. The reaction mixture was allowed to warm to r.t. and after 16 hrs was worked up as described for compound **3**. Vacuum flash chromatography (7:3 EtOAc/hexanes) yielded the carbinol **15** as a glass (0.335 g, 0.67 mmol, 31%); IR (KCl) ν_{max} 2938 (m), 2833 (m), 1509 (s), 1464 (m), 1382 (s), 1257 (s), 1150 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.72 (6H, s), 3.88 (3H, s), 3.92 (3H, s), 4.01 (2H, s), 4.28 (1H, d, *J*=9 Hz, Exch. with D_2O), 6.15 (1H, d, *J*=9 Hz), 6.54 (1H, s), 6.72 (1H, d, *J*=8 Hz), 6.84 (1H, d, *J*=8 Hz), 7.23 (1H, dd, *J*=1.5 and 8.5 Hz), 7.41 (1H, d, *J*=8.5 Hz), 7.49 (1H, d, *J*=1.5 Hz); MS m/z (EI) 499 (M^+, 27%), 391 (52), 373 (38), 217 (100); HRMS (EI) calcd for $C_{21}H_{23}Cl_2N_3O_5S$: 499.0735. Found: 499.0762.

2-Amino-1-dimethylsulfamoyl-4,5-bis(3,4-methylenedioxybenzyl)imidazole (16)

A 2.5 M solution of *n*-BuLi in hexane (1.08 ml, 2.70 mmol) was instilled into a solution of the imidazole **12** (1.0 g, 2.26 mmol) in dry THF (5 ml) at -78 °C. The resulting red solution was stirred at -78°C for 40 mins and then azidobenzene (0.30 g, 2.48 mmol) in dry THF (0.5 ml) was added. The reaction mixture was allowed to warm to r.t. and after 16 hrs was diluted with CH_2Cl_2 (20 ml) and poured into saturated $NaHCO_3$ (20 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated. The resulting crude 2-triazenoimidazole (1.30 g) was dissolved in MeOH (4.5 mol) and 6M HCl (9 ml) was added. The mixture was heated at reflux for 16 hrs and

worked up as described above. Vacuum flash chromatography (7:3 EtOAc/hexanes) yielded the 2-aminoimidazole **16** as a glass (0.53 g, 1.16 mmol, 51%); IR (KCl) ν_{max} 3460 (m), 3250 (m), 3060 (m), 2890 (m), 1650 (m), 1480 (s), 1440 (s), 1240 (s), 1035 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.67 (6H, s), 3.65 (2H, s), 4.00 (2H, s), 5.38 (2H, s, Exch. with D_2O), 5.92 (2H, s), 5.94 (2H, s),6.57-6.75 (6H, m); MS m/z (EI) 458 (M^+, 18%), 350 (30), 189 (100), 135 (36); Anal. calcd for $C_{21}H_{22}N_4O_6S$: C, 55.01; H, 4.83; N, 12.21. Found: C, 54.96; H, 5.01; N, 11.98%.

1-Benzyloxymethyl-4-(1-hydroxyethyl)-2-methylimidazole-5-carboxaldehyde Ethylene Acetal (17)

Chlorotrimethylsilane (0.435 ml, 1.37 mmol) was instilled into a cooled solution (ice/water bath) of the carbinol **13** (0.38 g, 1.25 mmol) in CH_2Cl_2 (4 ml) and Et_3N (0.435 ml, 3.12 mmol). 4-Dimethylaminopyridine (8 mg, 0.06 mmol) was added and the mixture allowed to warm to r.t. and was stirred for 2 days. The red reaction mixture was poured into saturated $NaHCO_3$ solution (20 ml) and extracted with EtOAc (2 x 25 ml). The combined organic extracts were washed with saturated brine (20 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Vacuum flash chromatography (3:2 EtOAc/hexanes) yielded 1-benzyloxymethyl-4-(1-trimethylsilyloxyethyl)-imidazole-5-carboxaldehyde ethylene acetal (**13a**) (0.30 g, 0.80 mmol, 64%). IR (Film) ν_{max} 2970 (m), 1500 (m), 1255 (m), 1080 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (9H, s), 1.56 (3H, d, *J*=7 Hz), 4.01 (4H, m), 4.50 (2H, s), 5.06 (1H, q, *J*=7 Hz), 5.42 (2H, s), 6.27 (1H, s), 7.32 (5H, m), 7.56 (1H, s); MS m/z (FAB) 377 (MH^+, 75%), 287 (100); HRMS (FAB) calcd. for $C_{19}H_{28}N_2O_4Si$: 377.1897. Found: 377.1898.

A 2.5 M solution of *n*-BuLi in hexane (0.13 ml, 0.33 mmol) was instilled into a solution of the silyl ether **13a** (0.10 g, 0.274 mmol) in dry THF (3 ml) at -78 °C. The resulting solution was stirred at -78 °C for 10 mins and then methyl iodide (0.05 ml, 0.82 mmol) was added. The reaction mixture was allowed to warm to r.t., stirred for 2 hrs and worked up as described for compound **13a** above. Vacuum flash chromatography (1% Et_3N and 5% acetone in EtOAc) yielded an inseparable 5:1 mixture of carbinols **17** and **13** (0.057 g, 0.18 mmol, 66% ; yield of **17** corrected for presence of **13** is 55%); IR (Film) ν_{max} 3300 (m), 2980 (m), 1520 (m), 1455 (m), 1415 (m), 1360 (m), 1075 (s) cm^{-1}; ^1H NMR ($CDCl_3$; data for **17** only) δ 1.52 (3H, d, *J*=6.5 Hz), 2.40 (3H, s), 3.08 (1H, bs, Exch. with D_2O), 3.98 (4H, m), 4.54 (2H, s), 4.95 (1H, q, *J*=6.5 Hz), 5.37 (2H, s), 6.00 (1H, s), 7.31 (5H, m); MS m/z (FAB) 319 (MH^+, 32%) 149 (100); HRMS (FAB) calcd. for $C_{17}H_{22}N_2O_4$: 319.1658. Found: 319.1707.

4-(3,4-Dichloro-α-methoxybenzyl)-5-(3,4-dimethoxybenzyl)imidazole (18)

An aqueous 6 M solution of HCl (4 ml) was added to a solution of the carbinol **11** (0.20 g, 0.40 mmol) in MeOH (2 ml). The solution was heated at reflux for 16 hrs, cooled to r.t. and basified by addition of saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 x 30 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Vacuum flash chromatography (2% EtOH in EtOAc) yielded the free NH imidazole **18** (0.050 g, 0.13

mmol, 32%) mp 99-102 °C; IR (KCl) ν_{max} 3000 (m), 2930 (m), 1509 (s), 1464 (m), 1257 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.30 (3H, s), 3.79 (3H, s), 3.87 (3H, s), 3.92 (2H, s), 5.33 (1H, s), 6.60 (1H, s), 6.66 (1H, d, *J*=9 Hz), 6.79 (1H, d, *J*=9 Hz), 7.20 (1H, m), 7.41 (2H, m), 7.53 (1H, s); MS m/z (EI) 406 (M^+, 45%), 391 (85), 374 (56), 343 (100); HRMS (EI) calcd. for $C_{20}H_{20}Cl_2N_2O_3$: 406.0851. Found: 406.0836.

2-(3,4-Dichloro-α-hydroxybenzyl)-4-(3,4-dimethoxybenzyl)imidazole (19)

An aqueous 6M solution of HCl (5 ml) was added to a solution of the carbinol **15** (0.26 g, 0.52 mmol) in MeOH (2.5 ml). The mixture was heated at reflux for 28 hrs, cooled to r.t. and worked up as described for compound **18**. Vacuum flash chromatography (2-3% EtOH in EtOAc) yielded the free NH imidazole **19** (0.14 g, 0.36 mmol, 69%) mp 73-76 °C; IR ($CHCl_3$) ν_{max} 3300 (m), 2843 (m), 1516 (s), 1466 (s), 1261 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.72 (2H, s), 3.76 (3H, s), 3.81 (3H, s), 5.70 (1H, s), 6.51 (1H, s), 6.71 (3H, m), 7.13 (1H, dd, *J*=1 and 9 Hz), 7.35 (1H, d, *J*=9 Hz), 7.48 (1H, d, *J*=1 Hz); MS m/z (EI) 392 (M^+, 100%), 374 (19); HRMS (EI) calcd. for $C_{19}H_{18}Cl_2N_2O_3$: 392.0694. Found: 392.0655.

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