Synthesis and Reactions of Brominated 2-Nitroimidazoles

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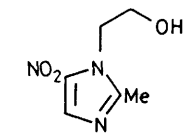
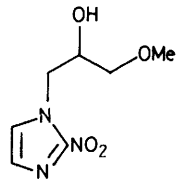
Various approaches to the synthesis of the hitherto-unknown 4(5)-bromo-2-nitroimidazole (**5**) are reported. Direct bromination of 2-nitroimidazole with *N*-bromosuccinimide gave the unreported 4,5-dibromo-2-nitroimidazole (**10**) in quantitative yield, but this could not be selectively debrominated to give compound (**5**). While 1-methyl-2-nitroimidazole readily gave 4-bromo-1-methyl-2-nitroimidazole (**15**) on bromination, this could not be demethylated to give (**5**), and bromination of various other N-protected 2-nitroimidazoles was also unsuccessful. Lithiation of 4-bromo-1-tritylimidazole (**21**) followed by quenching with propyl nitrate gave (after detritylation and methylation) a mixture of a dimer (**28**) and compound (**15**), indicating that the desired product (**5**) is produced in this reaction although it can only be isolated in derivatized form. The proposed route for formation of the dimer suggests a general reaction between 1-alkyl-4-bromo-2-nitroimidazoles and strong C- and N-nucleophiles, resulting in substitution at the 5-position.

Nitroimidazoles are an important class of biologically-active molecules. For example, metronidazole (**1**) and misonidazole (**2**) have found widespread use as antibacterial agents,[1] and misonidazole and related compounds have more recently been used as radiation sensitizers for hypoxic tumour cells.[2]

As part of a programme studying nitroaromatic mustards as hypoxia-selective drugs,[3,4] we required various brominated derivatives of 2-nitroimidazole, particularly 4(5)-bromo-2-nitroimidazole (**5**). Although both 2-halogeno-4(5)-nitroimidazoles (**3**) and 4(5)-halogeno-5(4)-nitroimidazoles (**4**) are known,[5,6] no 4(5)-halogeno-2-nitroimidazoles have been reported to date. This paper details the synthesis and chemistry of such compounds.



(**1**)



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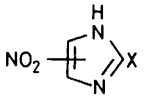
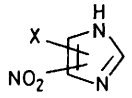


(**3**)

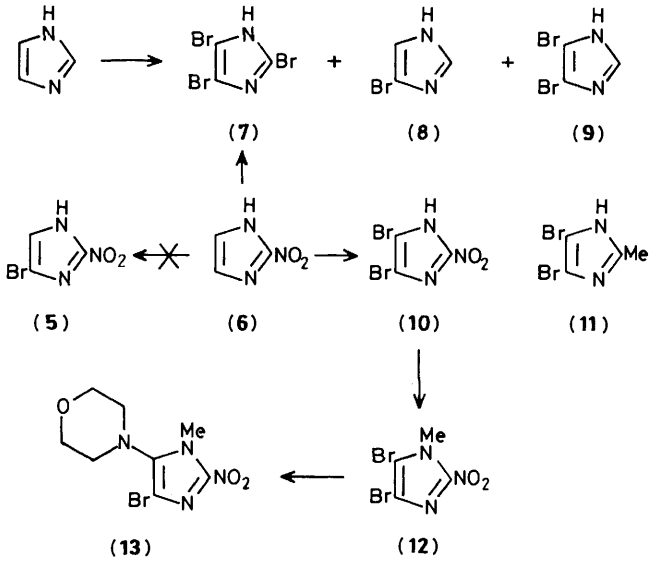


(**4**)

Initial attempts to prepare (**5**) focussed on the direct bromination of 2-nitroimidazole (**6**) itself. Bromination with bromine–acetic acid proceeded with nitro group replacement to give only 2,4,5-tribromoimidazole (**7**), as had been reported earlier.[7] However, bromination of (**6**) with 2 equiv. of *N*-bromosuccinimide (NBS) in DMF allowed isolation of the hitherto-unknown 4,5-dibromo-2-nitroimidazole (**10**) in near-quantitative yield. Nevertheless, the use of only one equivalent of NBS, even at low temperature, gave none of the desired 4(5)-bromo-2-nitroimidazole (**5**), but only the dibromo derivative (**10**) together with starting material.

Halogenation of imidazole itself with molecular bromine results in perbromination,[8] to give predominantly 2,4,5-tribromoimidazole (**7**), from which 4(5)-bromoimidazole (**8**) has to be obtained by reduction with Na_2SO_3. However, use of the less reactive NBS in DMF led to a mixture of the mono-, di-, and tribromoimidazoles (**7**)—(**9**) (Scheme 1), from which 4(5)-bromoimidazole (**8**) was obtained in 41% yield by simple crystallization of the reaction mixture.

The bromine atoms of 4,5-dibromo-2-nitroimidazole (**10**) were unreactive towards reductive removal with Na_2SO_3 or $NaBH_4$, although such reactions are known to occur with both 2,4,5-tribromoimidazole (**7**)[8,9] and 4,5-dibromo-2-methylimidazole (**11**).[10] The compound was also unreactive towards bromine displacement by amines such as morpholine. However, the 1-methyl derivative (**12**) (prepared by methylation of (**10**) with Me_2SO_4 under basic conditions) reacted with morpholine at reflux temperature to give the 5-morpholino derivative (**13**) in 57% yield (Scheme 1). Assignment of the product as the 5- rather



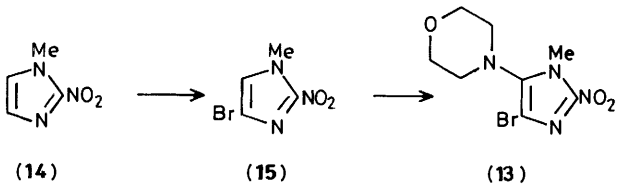
Scheme 1.

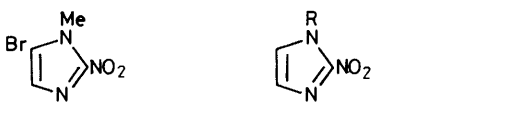
than the 4-morpholino isomer followed initially from the expected greater activation of the 5- than the 4-bromine atom of (**12**) by the 2-nitro group,[11] and was confirmed by preparation of the same compound by an independent, unequivocal route

(see later). Although halogen atoms in imidazoles are known to be activated towards nucleophilic displacement by adjacent nitro groups,[1,9,12] the present work is the first example of such activation by a 2-nitro group. As noted previously[13] for other 5-amino-substituted nitroimidazoles, compounds such as (**13**) were found to be somewhat unstable, decomposing over several weeks at room temperature.

In a further attempt to achieve monobromination of 2-nitroimidazole (**6**), the N-methyl derivative (**14**) was studied (Scheme 2). Bromination of (**14**) with NBS in DMF gave the bromide (**15**), whose structure was assigned initially as the 4-bromo compound rather than the isomeric (**16**) following literature precedents,[14] and from its n.m.r. spectrum. In particular, the ^{1}H n.m.r. spectrum displayed 4-bond coupling of 0.28 Hz between 5-H and the N-methyl group, as has been noted for other 4-substituted 1-methylimidazoles.[11] As expected for a 4-substituent, the bromine atom could not be displaced with morpholine. However, when (**15**) was treated with the more nucleophilic *N*-lithiomorpholide,[15] the morpholine adduct (**13**), identical with that prepared earlier from the dibromide (**12**), was isolated in 14% yield. Similar reaction of the dibromide (**12**) itself with *N*-lithiomorpholide also gave (**13**) in low yield. Treatment of 1-methyl-2-nitroimidazole (**14**)[16] under identical conditions resulted in no reaction, indicating the requirement for additional activation by the bromine substituent at the adjacent 4-position.

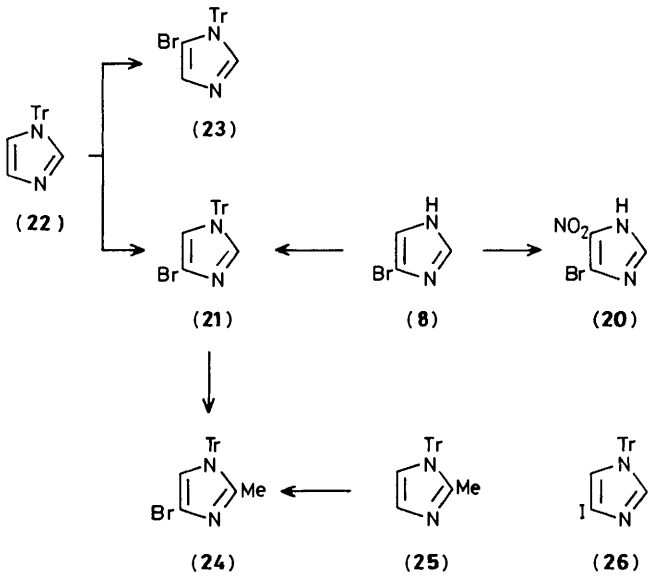
Attempts to demethylate the monobromide (**15**) to give the desired 4(5)-bromo-2-nitroimidazole (**5**) were unsuccessful. The use of more labile N-protecting groups such as trityl,[17] sulfamoyl,[18] or 2-[(trimethylsilyl)ethoxy]methyl (SEM)[19] in the bromination reaction were also unsuccessful. Direct bromination of the corresponding 1-protected compounds (**17**)—(**19**) did not proceed under moderate conditions, while the use of more vigorous conditions resulted in N-deprotection. The 2-nitro group markedly increases the lability of such N-protecting groups, while at the same time deactivating the imidazole ring towards electrophilic attack. Indirect bromination *via* lithio derivatives was also unsuccessful. Chadwick[18] and others[17,19,20] have used the above 1-protecting groups in the regioselective lithiation of imidazoles. Deprotonation proceeds preferentially at the 2-position, but if this is blocked, or if an excess of a suitably strong base is used, metallation may also occur at the 5-position. In the present work we were unable to deprotonate cleanly at the 5-position of the 1-protected 2-nitro compounds (**17**)—(**19**) using a variety of bases as strong as Bu^{t}Li or potassium di-isopropylamide,[21] with or without the addition of TMEDA or HMPA. At low temperatures no reaction occurred, while at higher temperatures there was extensive decomposition.





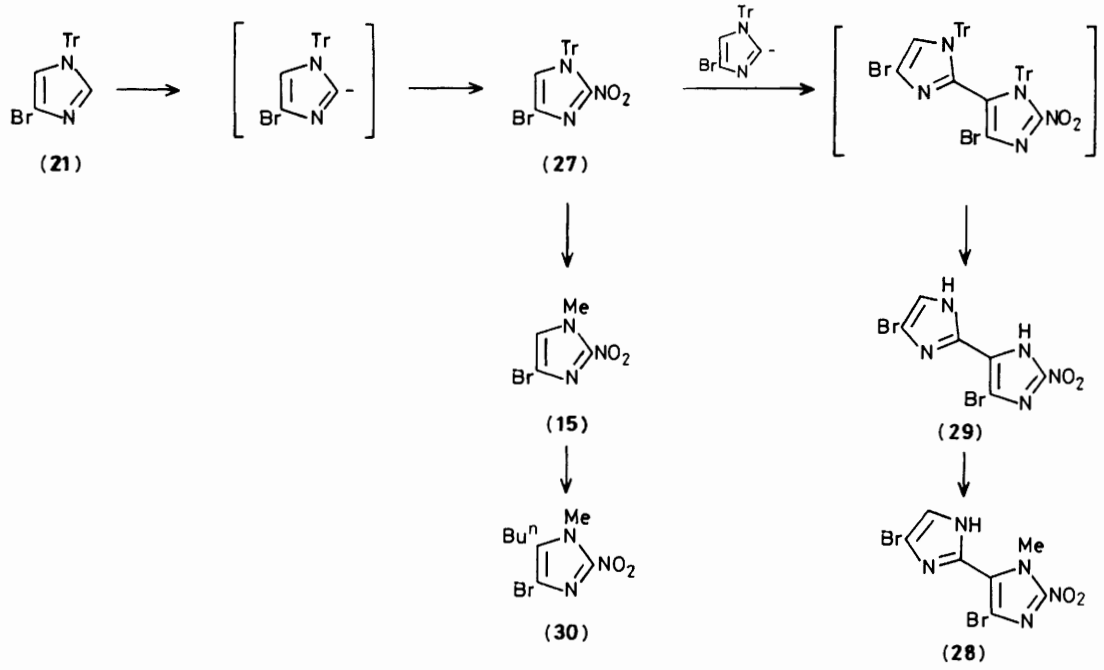
Scheme 2.

Final attempts to prepare 4(5)-bromo-2-nitroimidazole (**5**) involved the regioselective introduction of a nitro group into the 2-position of 4(5)-bromoimidazole derivatives[20] (Scheme 3). Nitration of 4(5)-bromoimidazole (**8**) under various conditions is known[22] to give only the 4-bromo-5-nitroimidazole (**20**). Kirk[17] has described a procedure for introduction of a nitro group into the 2-position of 1-tritylimidazoles by reaction of the 2-lithio derivative with propyl nitrate. Thus 4-bromo-1-tritylimidazole (**21**) was prepared by tritylation of 4(5)-bromoimidazole (**8**) under basic conditions. The same compound could also be prepared by bromination of 1-tritylimidazole (**22**), although in this case the product was contaminated with *ca.* 10% of the isomeric 5-bromo compound (**23**). Lithiation of the bromide (**21**) at 0 °C using butyl-lithium proceeded cleanly at the 2-position, as evidenced by the isolation of 4-bromo-2-methyl-1-tritylimidazole (**24**) upon quenching of the reaction with methyl iodide. Confirmation that C-2 deprotonation of (**21**) had occurred in preference to halogen–metal exchange at C-4 was obtained by the alternative preparation of (**24**) by bromination of the known[17] 2-methyl-1-tritylimidazole (**25**). Recently,[22] Iddon and Khan studied the halogen–metal exchange of polybromoimidazoles, and observed a reluctance of the 4-bromine atom to undergo exchange. Indeed, exchange at the 4-position was effected only after all other bromine atoms had been replaced by thioether groups. This is attributed to a destabilization of imidazole C-4 anions by the adjacent N-3 lone pair (the ALP effect as described by Kirk[23]). Interestingly, Kirk[23] has prepared 4-lithio-1-tritylimidazole by halogen–metal exchange of the 4-iodo compound (**26**), where iodine–lithium exchange was found to occur within seconds at 0 °C, although 3 equiv. of butyl-lithium were required to overcome the ALP effect.



Scheme 3.

4-Bromo-1-tritylimidazole (**21**) was treated with butyl-lithium and quenched with propyl nitrate, and the product was detritylated by acid treatment during work-up to give an orange solid, homogeneous by t.l.c. Immediate methylation of this material using Me_2SO_4–K_2CO_3 gave (by ^{1}H n.m.r. analysis) a 1.4:1 mixture of two products. The major component was separated by chromatography (in 37% yield) and found to be identical to 4-bromo-1-methyl-2-nitroimidazole (**15**) prepared earlier, indicating the presence of the sought-after 4(5)-bromo-2-nitroimidazole (**5**) in the original product mixture. The second component of the methylation reaction was unstable, and



Scheme 4.

decomposed during chromatography. However, when the methylation was carried out under neutral conditions (Me_2SO_4–dioxane), this compound was formed as almost the sole isolable product, together with less than 10% of (**15**) and some tarry material. Crystallization of the crude reaction mixture afforded pure material as an unstable yellow solid which was tentatively identified as the dimer (**28**) from ^1H n.m.r. and mass spectral data.

This compound is presumably formed by monomethylation of the more basic nitrogen of the dimer (**29**), which must be present in the original product mixture from the reaction of propyl nitrate with (**21**) (Scheme 4). Presumably, the initially-formed product (**27**) of the propyl nitrate quench reacts with unquenched 2-lithioimidazole in a similar reaction to that observed earlier between 4-bromo-1-methyl-2-nitroimidazole (**15**) and *N*-lithiomorpholide. If this mechanism is correct, then 1-alkyl-4-bromo-2-nitroimidazoles such as (**15**) should react with other strong carbon nucleophiles to give substitution products at the 5-position. In the event, reaction of 4-bromo-1-methyl-2-nitroimidazole (**15**) with butyl-lithium alone at −30 °C gave the 5-butylimidazole (**30**) in 18% yield, together with recovered starting material.

The ^1H n.m.r. spectrum of the freshly-prepared product from reaction of (**21**) with BuLi–propyl nitrate contained two singlets of equal intensity in the aromatic region (δ 7.37 and 7.14) suggesting that compounds (**5**) and (**29**) were present in approximately equal proportions. However, upon storage at room temperature the product darkened to a red glassy mass which was shown by ^1H and ^{13}C n.m.r. and mass spectral analysis to be oligomeric. Methylation of this aged material (Me_2SO_4–K_2CO_3) gave a mixture of many products, which was shown by ^1H n.m.r. analysis to contain the bromonitroimidazole (**15**), but only as a minor component.

Thus, while the desired 4(5)-bromo-2-nitroimidazole (**5**) has been identified, its instability and the difficulty in isolating it in pure form militate against its use as a synthetic intermediate.

Experimental

Analyses were carried out in the Microchemical Laboratory, University of Otago, Dunedin. M.p.s were determined on an Electrothermal apparatus using the supplied stem-corrected thermometer, and are as read. Routine n.m.r. spectra were obtained on a Bruker CW-60 spectrometer, while ^{13}C and long-range coupling studies were carried out on a Bruker AM-400 instrument. Mass spectra were determined on a Varian CH 7 11/250 spectrometer. To monitor the progress of reactions and the purity of products, t.l.c. on silica gel (Merck SiO_2, F_{254}) was used, visualizing with iodine.

Bromination of 2-Nitroimidazole (**6**).—A solution of NBS (10.84 g, 0.061 mol) in DMF (50 ml) was added in one portion to a solution of 2-nitroimidazole (**6**) (3.35 g, 0.03 mol) in DMF (50 ml), and the mixture was allowed to stand at 20 °C for 45 min. The DMF was evaporated off under reduced pressure, and the residue was taken up in EtOAc and washed with brine (6 ×), aqueous Na_2SO_3 (2 ×), and water. The organic solution was dried and worked up to give an oil, which was chromatographed on silica gel. Elution with EtOAc gave 4,5-dibromo-2-nitroimidazole (**10**) (7.82 g, 97%), which crystallized from EtOAc–light petroleum as glistening yellow plates, m.p. 134—135 °C (Found: C, 13.3; H, 0.5; N, 15.2; Br, 58.75. $C_3HBr_2N_3O_2$ requires C, 13.29; H, 0.37; N, 15.51; Br, 59.00%); $\lambda_{max.}$(0.1M KOH) 386 nm; δ_C(CD_3SOCD_3–CD_3COCD_3) 146.33 (C-2), 113.29 (C-4, -5); *m/z* 273, 271, 269 ($M^{+\cdot}$, 20, 43, 22%), 243, 241, 239 (5, 12, 9), 216, 214, 212 (59, 100, 60), 200, 198, 196 (25, 51, 22), 172 (2), 146 (4), and 114 (5).

4,5-*Dibromo*-1-*methyl*-2-*nitroimidazole* (**12**).—A suspension of the dibromide (**10**) (2.00 g, 7.0 mmol), K_2CO_3 (2.03 g, 14 mmol), and Me_2SO_4 (0.69 ml, 7.2 mmol) in Me_2CO (80 ml) was heated under reflux in the absence of moisture for 18 h. After evaporation of the solvent under reduced pressure, the residue was partitioned between EtOAc and water, and the organic layer was worked up to give a yellow solid. Crystallization from EtOH gave the N-methyl compound (**12**) as fine yellow plates (1.36 g, 68%), m.p. 143—145 °C (Found: C, 16.95; H, 1.2; N, 15.0; Br, 56.05. $C_4H_3Br_2N_3O_2$ requires C, 16.86; H, 1.06; N, 14.75; Br, 56.09); δ_H($CDCl_3$) 4.11 (NMe); δ_C(CD_3COCD_3) 145.55 (C-2), 116.92 (C-5), 114.07 (C-4), and 37.91 (NMe).

4-*Bromo*-1-*methyl*-5-*morpholino*-2-*nitroimidazole* (**13**).—A solution of the dibromide (**10**) (0.20 g, 0.71 mmol) in morpholine (3 ml) was heated under reflux for 8 h and allowed to cool overnight. The excess of morpholine was evaporated off under reduced pressure, and the residue was triturated with EtOAc and chromatographed on silica gel. Elution with EtOAc–light *petroleum* (1:4) gave the morpholino compound (**13**) (0.11 g, 57%) as yellow plates, m.p. 66—68 °C (Found: C, 33.2; H, 3.75; N, 19.05. $C_8H_{11}BrN_4O_3$ requires C, 33.00; H, 3.81; N, 19.25); $\delta_H(CDCl_3)$ 3.93 (s, 3 H, Me), 3.87 (t, *J* 5 Hz, CH_2O), and 3.25 (t, 4 H, *J* 5 Hz, CH_2N).

Bromination of Imidazole.—A solution of NBS (11.44 g, 0.064 mol) in DMF (100 ml) was added dropwise over 1.5 h at 20 °C to a stirred solution of imidazole (4.00 g, 0.059 mol) in DMF (100 ml). After 48 h the solution was concentrated to dryness under reduced pressure, and the residue was dissolved in EtOAc and percolated through silica gel, eluting with more EtOAc, to give a solid which was triturated with hot $CHCl_3$. On cooling, 4(5)-bromoimidazole (**8**) (3.51 g, 41%) crystallized as white cubes, m.p. 125—126 °C (lit.,[8] m.p. 130—131 °C); $\delta_H(CD_3COCD_3)$ 7.62 (br s, 1 H, 2-H), and 7.12 (br s, 1 H, 4-H).

In a separate experiment on half the above scale, the solid from the initial EtOAc eluate was rechromatographed on silica gel. Elution with EtOAc–light petroleum (1:1) gave 2,4,5-tribromoimidazole (**7**) (3%), m.p. (AcOH) 219 °C (lit.,[8] m.p. 221 °C). Elution with EtOAc gave 4,5-dibromoimidazole (**9**) (6%), m.p. ($CHCl_3$) 215—220 °C (lit.,[8] m.p. 225 °C); $\delta_H(CD_3COCD_3)$ 7.77 (s, 2-H). Further elution with EtOAc gave 4(5)-dibromoimidazole (**8**) (32%).

4-*Bromo*-1-*methyl*-2-*nitroimidazole* (**15**).—NBS (6.62 g, 0.037 mol) was added to a solution of 1-methyl-2-nitroimidazole[25] (**14**) (4.30 g, 0.034 mol) in DMF (100 ml), and the solution was kept at 20 °C for 48 h and poured into water. Extraction with EtOAc and the usual work-up gave the bromide (**15**), which crystallized from EtOAc–hexane as cream plates (5.99 g, 85%), m.p. 144—146 °C (Found: C, 23.25; H, 2.0; N, 20.5; Br, 39.05. $C_4H_4N_3BrO_2$ requires C, 23.31; H, 1.96; N, 20.40; Br, 38.80%); $\delta_H(CD_3COCD_3)$ 7.60 (s, 1 H, 5-H) and 4.15 (s, 3 H, Me). At 400 MHz, the signal at δ 4.15 appeared as a doublet (*J* 0.28 Hz), decoupled by irradiation at δ 7.60; $\delta_C(CDCl_3)$ 146.31 (C-2), 126.45 (C-5), 114.89 (C-4), and 37.32 (NMe).

Reaction of the 4-*Bromoimidazole* (**15**) *with* N-*Lithiomorpholide.*—Butyl-lithium (0.85 ml of a 1.37M solution in hexane, 1.16 mmol) was added dropwise to a solution of morpholine (0.10 ml, 1.16 mmol) in THF (5 ml) at −78 °C. After 15 min a solution of the bromide (**15**) (0.20 g, 0.97 mmol) in THF (2 ml) was added, and the solution was stirred at −78 °C for a further 15 min and then allowed to come to 20 °C over 2 h. The mixture was poured into water, extracted with EtOAc, and worked up to give an oil which was chromatographed on silica gel. Elution with EtOAc–light petroleum (1:4) gave starting material (48 mg), followed by 4-bromo-1-methyl-5-morpholino-2-nitroimidazole (**13**) (40 mg, 14%), identical R_F, n.m.r. data, and m.p. to the material prepared from the dibromide (**12**). Reaction of the dibromide (**12**) with *N*-lithiomorpholide also gave the product (**13**) in a similar yield.

1-(N,N-*Dimethylsulphonamido*)-2-*nitroimidazole* (**18**).—*N,N*-Dimethylsulphamoyl chloride (2.08 ml, 0.019 mol) was added under nitrogen to a solution of 2-nitroimidazole (**6**) (2.00 g, 0.018 mmol) and Et_3N (2.96 g, 0.021 mol) in CH_2Cl_2 (50 ml), and the mixture was stirred at 20 °C for 24 h. After washing with water and saturated aqueous $NaHCO_3$, the organic solution was chromatographed on alumina. Elution with EtOAc–light petroleum (1:1) gave the imidazole (**18**) (1.94 g, 49%) as an unstable solid, which crystallized from $CHCl_3$–light petroleum containing a trace of Et_3N as fine needles, which slowly decomposed when heated above 210 °C; $\delta_H(CD_3COCD_3)$ 7.41 (d, 1 H, *J* 1.3 Hz, 5-H), 7.03 (d, 1 H, *J* 1.3 Hz, 4-H), and 3.08 (s, 6 H, NMe_2).

2-*Nitro*-1-[2-(*trimethylsilyl*)*ethoxymethyl*]*imidazole* (**19**).—Sodium hydride (0.46 g of a 60% dispersion in mineral oil, 0.011 mol) was washed several times under nitrogen with light petroleum and covered with THF (10 ml). A suspension of 2-nitroimidazole (**6**) (1.00 g, 8.85 mmol) in DMF (25 ml) was added dropwise, and the slurry was stirred at 20 °C for 10 min and then cooled to 0 °C. 2-(Trimethylsilyl)ethoxymethyl chloride (1.88 ml, 0.011 mol) was added dropwise and the mixture was stirred at 0 °C for a further 30 min and then at 20 °C for 1 h. The solution was poured into brine and extracted with EtOAc, and the organic layer was washed with brine (3 ×), saturated $NaHCO_3$, and water and worked up to give an oil which was chromatographed on silica gel. Elution with EtOAc–light petroleum (1:4) gave the N-SEM protected imidazole (**19**) (1.26 g, 58%), which crystallized from light petroleum as cream plates, m.p. 43 °C (Found: C, 44.35; H, 7.0; N, 17.35. $C_9H_{17}N_3O_3Si$ requires C, 44.35; H, 7.04; N, 17.28); $\delta_H(CD_3COCD_3)$ 7.23 (br s, 1 H, 5-H), 7.15 (br s, 1 H, 4-H), 5.77 (s, 2 H, NCH_2O), 3.63 (t, 2 H, *J* 8 Hz, CH_2N), 0.92 (t, 2 H, *J* 8 Hz, CH_2Si), and 0.00 (s, 9 H, $SiMe_3$).

4-*Bromo*-1-*tritylimidazole* (**21**).—(*a*) *N*-Bromosuccinimide (1.89 g, 0.011 mol) was added to a solution of 1-tritylimidazole[24] (**22**) (3.00 g, 9.66 mmol) in DMF (100 ml), and the mixture was stirred at 20 °C for 20 h and then poured into water. Extraction with EtOAc and usual work-up gave the bromide (**21**), contaminated with *ca.* 10% of the 5-bromo isomer (**23**) (^1H n.m.r. analysis). Crystallization from 95% EtOH gave pure 4-bromo-1-tritylimidazole (**21**) as coarse rods (2.81 g, 75%), m.p. 248—250 °C (Found: C, 67.9; H, 4.35; N, 7.2; Br, 20.55. $C_{22}H_{17}BrN_2$ requires C, 67.88; H, 4.40; N, 7.19; Br, 20.53%); $\delta_H(CDCl_3)$ 7.45—7.00 (m, 16 H, ArH and 2-H), and 6.80 (d, 1 H, *J* 1.8 Hz, 5-H).

(*b*) To a solution of chlorotriphenylmethane (30.0 g, 0.11 mol) and 4(5)-bromoimidazole (**8**) (14.3 g, 0.01 mol) in CH_2Cl_2 (200 ml) was added Et_3N (17.7 ml, 0.13 mol). The solution was kept at 20 °C for 20 h then diluted with CH_2Cl_2. The organic layer was washed with water and worked-up to give an oil which was chromatographed on silica gel. Elution with EtOAc–light petroleum (1:9) gave a forerun of triphenylmethanol, followed by 4-bromo-1-tritylimidazole (**21**) (25.4 g, 67%), m.p. 242—246 °C, identical with the above product.

4-*Bromo*-2-*methyl*-1-*tritylimidazole* (**24**).—(*a*) Butyl-lithium (0.35 ml of a 1.37M solution in hexane, 0.47 mmol) was added dropwise at 0 °C under nitrogen to a solution of the bromoimidazole (**21**) (0.17 g, 0.43 mmol). After 45 min at 0 °C, iodomethane (54 μl, 0.86 mmol) was added in one portion, and the mixture was stirred at 20 °C for an additional 1 h and then poured into water. Extraction with EtOAc gave a solid which was chromatographed on silica gel. Elution with EtOAc–light petroleum (1:9) gave 4-bromo-2-methyl-1-tritylimidazole (**24**) (0.11 g, 63%), which crystallized from aqueous EtOH as cubes containing a small quantity of triphenylmethanol, resulting from detritylation during crystallization, m.p. 215—220 °C (Found: C, 69.4; H, 4.95; N, 6.45. $C_{23}H_{19}BrN_2 \cdot 0.1Ph_3COH$ requires C, 69.65; H, 4.84; N, 6.52%); $\delta_H(CDCl_3)$ 7.5—7.0 (m, 15 H, ArH), 6.66 (s, 1 H, 5-H), and 1.63 (s, 3 H, CH_3). EtOAc–light petroleum (3:7) eluted 2-methyl-1-tritylimidazole (**24**) (28 mg, 20%), which crystallized from aqueous EtOH as coarse rods, m.p. 210—214 °C (lit.,[17] m.p. 217—218.5 °C); $\delta_H(CDCl_3)$

7.5—7.0 (m, 15 H, ArH), 6.84 (d, 1 H, *J* 1.6 Hz, 4-H), 6.64 (d, 1 H, *J* 1.6 Hz, 5-H), and 1.63 (s, 3 H, CH_3).

(*b*) NBS (64 mg, 0.36 mmol) and 2-methyl-1-tritylimidazole[17] (**25**) (0.10 g, 0.33 mmol) were mixed in DMF (5 ml), and the solution was kept at 20 °C for 72 h and then poured into water. Extraction with EtOAc and usual work-up gave a solid which was chromatographed on silica gel. Elution with EtOAc–light petroleum (1:4) gave 4-bromo-2-methyl-1-tritylimidazole (**24**) (85 mg, 64%), identical with the compound produced above.

4(5)-*Bromo*-2-*nitroimidazole* (**5**).—Butyl-lithium (17.7 ml of a 1.43M solution in hexane, 0.025 mol) was added dropwise under N_2 to a solution of 4-bromo-1-tritylimidazole (**21**) (8.20 g, 0.021 mol) in THF (150 ml). After 1 h at 0 °C, propyl nitrate (2.7 ml, 0.027 mol) was added and the brown solution was stirred at 20 °C for 2 h. MeOH (90 ml) and conc. HCl (20 ml) was added and the solution was stirred overnight and then concentrated to dryness under reduced pressure. The residue was partitioned between EtOAc and water and the organic portion was chromatographed on silica gel. Elution with EtOAc gave triphenylmethanol, followed by a hygroscopic yellow powder (1.96 g), m.p. >230 °C (decomp.) containing the bromoimidazole (**5**) and a compound, tentatively identified as the dimer (**29**); $\delta_H(CD_3COCD_3)$ 7.37, 7.14 (2 s, 1 H each) and 4.60 (br, H_2O and NH). On storage at room temperature for several months the product polymerized to a brittle orange-red solid, m.p. >320 °C.

Methylation of 4(5)-*Bromo*-2-*nitroimidazole*.—(*a*) *Basic conditions*. The mixture containing the bromide (**5**) (0.58 g, 3.02 mmol), Me_2SO_4 (0.34 ml, 3.62 mmol) and K_2CO_3 (0.83 g, 6.04 mmol) in Me_2CO (30 ml) was heated under reflux with stirring for 30 min, and then evaporated to dryness. The residue was partitioned between EtOAc and water, and the organic layer was worked up to give a 1.4:1 mixture of the compounds (**15**) and (**28**). Chromatography on silica gel and elution with EtOAc–light petroleum (1:4) gave 4-bromo-1-methyl-2-nitroimidazole (**15**) (0.23 g, 37%), which crystallized from EtOAc–light petroleum as cream plates, m.p. 142—145 °C, and was identical in all respects with the material obtained by bromination of 1-methyl-2-nitroimidazole.

(*b*) *Neutral conditions*. A solution of the mixture containing the bromide (**3**) (0.60 g, 3.12 mmol) and Me_2SO_4 (0.44 ml, 4.69 mmol) in dioxane (20 ml) was heated under reflux in an atmosphere of N_2 for 7 h. The liquid was decanted from a tarry residue and poured into brine. Extraction with EtOAc gave an oil, comprising *ca.* 5:95 mixture of compounds (**15**) and (**28**). Crystallization from CH_2Cl_2–light petroleum gave the dimer (**28**) (0.17 g) as unstable orange needles, m.p. 240—245 °C (decomp.); $\delta_H(CD_3COCD_3)$ 7.28 (s, 1 H, 5-H), 4.13 (s, 3 H, NMe), and 3.30 (br, 1 H, NH); *m/e* 353, 351, 349 ($M^{+\bullet}$, 100%), 307, 305, 303 ($M^{+\bullet} - NO_2$, 16), 266, 264, 262 (30), 226, 224, 222 (14), 225, 223 ($M^{+\bullet} - NO_2 - Br$, 22), 211, 209 (13), 145 ($M^{+\bullet} - NO_2 - 2Br$, 11), 118 (21), 91 (13), 77 (20), and 42 (20).

4-*Bromo*-5-*butyl*-1-*methyl*-2-*nitroimidazole* (**30**).—Butyl-lithium (0.66 ml of a 1.45M solution in hexane, 0.95 mmol) was added at −30 °C to a solution of the bromoimidazole (**15**) (0.164 g, 0.79 mmol) in THF (8 ml). After 1 h at this temperature, water was added and the mixture was extracted with EtOAc and worked-up to give an oil. Chromatography on silica, eluting with 20% EtOAc–light petroleum, gave the butylimidazole (**30**) (38.1 mg, 18%) as a yellow oil; $\delta_H(CDCl_3)$ 4.53 (s, 3 H, NMe), 3.23 (t, 2 H, *J* 7.5 Hz, $CH_2C{=}C$), 2.11 (m, 2 H, CH_2), 1.96 (m, 2 H, CH_2), and 1.52 (t, 3 H, *J* 7.3 Hz, CH_3); $\delta_C(CDCl_3)$ 143.75 (C-2), 137.22 (C-5), 115.24 (C-4), 34.90 (NMe), 30.23 (C-1′), 23.91 (C-2′), 22.24 (C-3′), and 13.63 (C-4′); *m/z* 263, 261 ($M^{+\bullet}$, 13%), 220, 218 (21), 182 ($M^{+\bullet}$ − Br, 16), 140 (20), 129 (100), 109 (13), 98 (8), 93 (10), 68 (15), 58 (30), and 42 (20) (Found: $M^{+\bullet}$, 263.006 39, 261.010 47 (mass spectrum). $C_8H_{12}BrN_3O_2$ requires 263.009 24, 261.011 29).

Further elution with EtOAc–light petroleum gave starting material (**15**) (27.6 mg, 17%).

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