Azoles. Part 11.[1] Synthesis of imidazole-2(and -5)-carbaldehydes and derivatives of imidazo[1,2-*b*]isoquinoline; transmetallation of imidazol-5-yllithium compounds

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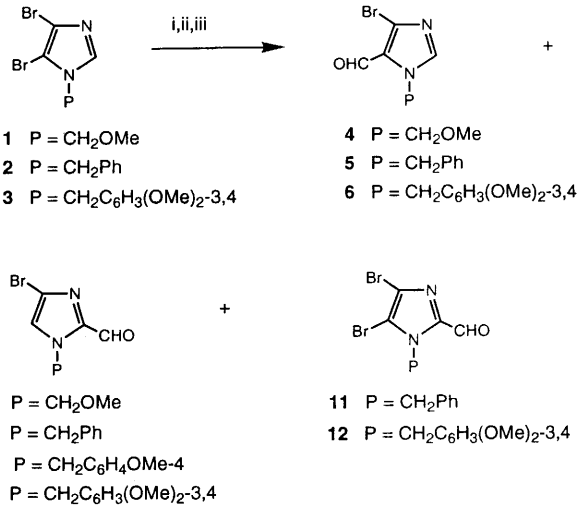
The transmetallations of 1-protected 4-bromoimidazol-5-yllithium derivatives have been studied using DMF as the quenching reagent. 4-Bromoimidazole-2-carbaldehydes are usually the major products and not the -5-carbaldehydes as reported previously. Various attempts to prevent or inhibit these transmetallations are described. Cyclisation of 4-bromo(and 4,5-dibromo)-1-(3,4-dimethoxybenzyl)imidazole-2-carbaldehyde and 1-(3,4-dimethoxybenzyl)benzimidazole-2-carbaldehyde in TFA gave the corresponding imidazo- or benzimidazo-[1,2-*b*]isoquinoline.

The provision of polyfunctionalised imidazoles for the synthesis of compounds with actual or potential biological activity, some naturally occurring, has recently attracted the attention of several groups.[2–26] A favoured approach to polyfunctionalised imidazoles involves halogen→metal exchange reactions of mono(or poly)-bromo-[2,3,6,12,17,18,27–30] or -iodo-imidazoles[5,7,9,10,27,28,31–34] (for reviews see refs. 35–38). Previously we[29,30,35–38] have described a strategy for the introduction of substituents into the imidazole ring by successive replacement of the bromine atoms in 1-protected 2,4,5-tribromoimidazoles in the order 2→5→4 using Br→Li exchange, a procedure adopted by others.[2,6,7] In particular, we are interested in obtaining 4-bromoimidazole-5-carbaldehydes for conversion into a number of bicyclic (and tricyclic) heterocycles, *e.g.* thienoimidazoles.[36,39] A problem with this approach is that imidazol-5-yllithium compounds[34–38,40] and their 4-lithiated analogues[31,32,34–38,40] equilibrate with the corresponding imidazol-2-yllithium derivatives, the latter faster than the former,[34] when position 2 of the imidazole ring is unsubstituted. In this paper we describe our experiences with such equilibration processes together with our attempts to prevent or inhibit them.

Imidazol-4(and 5)-ylmagnesium halides are much more stable than their lithiated analogues[5,10,27,28,33,38] but these too can undergo transmetallations, depending on solvent and 1-protecting group.[5,10,41] We will describe our experiences with imidazol-5-ylmagnesium bromides below and more fully in a future communication.

In 1987 we reported[29,30] that 1-protected 4,5-dibromoimidazoles react with 1 mol equiv. of butyllithium (in Et_2O at −78 °C) to give an imidazol-5-yllithium derivative which, on quenching with *N*,*N*-dimethylformamide (DMF), yields exclusively the corresponding 1-protected 4-bromoimidazole-5-carbaldehyde, *e.g.* **2**→**5** (Scheme 1). A further study of these reactions has shown that they are more complex than at first realised. Thus, the reaction between 1-benzyl-4,5-dibromoimidazole **2** with butyllithium, which has been repeated several times with DMF as the quenching reagent, is capricious, but after chromatographic separation of the products, the following compounds can be isolated (see Experimental section for details): 1-benzyl-4-bromoimidazole (0–12%),[29] 1-benzyl-4-bromoimidazole-5-carbaldehyde **5** (5–44% isolated yield), 1-benzyl-4-bromoimidazole-2-carbaldehyde **8** (35–45%) and 1-benzyl-4,5-dibromoimidazole-2-carbaldehyde **11** (17–40%)



1 P = CH_2OMe
2 P = CH_2Ph
3 P = $CH_2C_6H_3(OMe)_2$-3,4

4 P = CH_2OMe
5 P = CH_2Ph
6 P = $CH_2C_6H_3(OMe)_2$-3,4

7 P = CH_2OMe
8 P = CH_2Ph
9 P = $CH_2C_6H_4OMe$-4
10 P = $CH_2C_6H_3(OMe)_2$-3,4

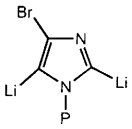
11 P = CH_2Ph
12 P = $CH_2C_6H_3(OMe)_2$-3,4

Scheme 1 *Reagents and conditions:* (i) BuLi, Et_2O, −78 °C; (ii) DMF; (iii) H_3O^+

(Scheme 1). 4,5-Dibromo-1-(3,4-dimethoxybenzyl)imidazole **3** reacted similarly but, in this case a mixture of the *two* isomeric aldehydes **6** (23%) and **10** (71% yield) was obtained. 4,5-Dibromo-1-(methoxymethyl)imidazole **1** gave mainly 4-bromo-1-(methoxymethyl)imidazole-2-carbaldehyde **7** (85% crude; 64% pure) which contained traces of the isomeric aldehyde **4** and what was believed to be 4-bromo-1-(methoxymethyl)-imidazole-2,5-dicarbaldehyde (ratio 95:5:5). The imidazole-5-carbaldehydes **5** and **6** have been characterised previously.[30] Imidazole-2-carbaldehydes were synthesised unambiguously for comparison purposes as described later.

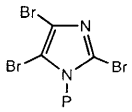
1-Benzyl-4,5-dibromoimidazole **2** reacted with 2.5 mol equiv. of ethylmagnesium bromide exclusively at position 5, as shown by hydrolysis of the resulting Grignard reagent, which gave a good yield of 1-benzyl-4-bromoimidazole[29] (by ^1H NMR spectroscopy). However, attempts to obtain the imidazole-5-carbaldehyde **5** by quenching the Grignard derivative with DMF (*cf.* ref. 27) failed.

The dilithiated species **13**, readily available from the corresponding tribromo compound **15**, is known[29] to give a good yield (72%) of the bis(methylsulfanyl) compound **17** with 2 mol equiv. of dimethyl disulfide. The dilithiated compound **14** was



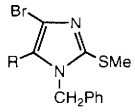
13 P = CH_2Ph

14 P = $CH_2C_6H_3(OMe)_2$-3,4



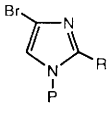
15 P = CH_2Ph

16 P = $CH_2C_6H_3(OMe)_2$-3,4



17 R = SMe

18 R = CHO



19 R = Br, P = $CH_2C_6H_3(OMe)_2$-3,4

20 R = Cl, P = CH_2Ph

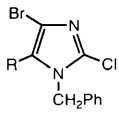
was prepared similarly from 2,4,5-tribromo-1-(3,4-dimethoxybenzyl)imidazole **16** and quenched with an excess of DMF. This reaction gave an inseparable mixture of products, apparently (shown by TLC and ^1H NMR spectroscopy) consisting of the dialdehyde (40–50%) together with the two isomeric monoaldehydes **6** and **10** (ratio 1:2), which was not examined further. Use of methyl formate or *N*-formylpiperidine as the quenching reagent gave a similar mixture of products.

Our next approach to the synthesis of imidazole-5-carbaldehydes was to protect C-2 of the imidazole ring with a removable protecting group. Initially, we chose bromine, which is removable with organolithium reagents,[35–38] and chlorine, which Begtrup and co-workers[42,43] have removed with nickel boride (from position 5) or sodium benzenethiolate in benzenethiol (from position 2) and Tanaka and co-workers[44–46] by hydrogenolysis with H_2 over Pd–C (from position 2). Recently, we[47] have removed chlorine in a 2-chlorothiazole *via* Cl→Li exchange and hydrolysis of the resulting 2-lithiated derivative.

2,4,5-Tribromo-1-(3,4-dimethoxybenzyl)imidazole **16** was converted into the 2,5-dilithiated derivative **14** with 2.1 mol equiv. of butyllithium (in Et_2O at −78 °C). **Careful** addition of 1 mol equiv. of water at this temperature, followed by warming up the mixture to −50 °C (which converts the mixture of monolithiated species into the more stable 2-isomer), then cooling it down again to −78 °C prior to the addition of 1 mol equiv. of bromine gave a good yield (64%) of 2,4-dibromo-1-(3,4-dimethoxybenzyl)imidazole **19** (*cf.* refs 28 and 32). 1-Benzyl-4-bromo-2-chloroimidazole **20** (50%) was prepared similarly from 1-benzyl-2,4,5-tribromoimidazole **15** using hexachloroethane to quench the monolithiated intermediate.

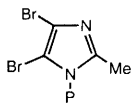
2,4-Dibromo-1-(3,4-dimethoxybenzyl)imidazole **19** was treated with lithium diisopropylamide (LDA) (in Et_2O at −78 °C) and the resulting reaction mixture quenched with water after 5 min or 30 min, which gave an approximately 50:50 mixture of starting material and 4,5-dibromo-1-(3,4-dimethoxybenzyl)imidazole **3**, as shown by ^1H NMR spectroscopic and TLC analysis of the crude product. No attempt was made to separate this mixture. Therefore, blocking C-2 with a bromine substituent does not prevent transmetallation from occurring.

By contrast, when 1-benzyl-4-bromo-2-chloroimidazole **20** was treated similarly with LDA and the reaction mixture quenched with deuterium oxide, ^1H NMR spectroscopic analysis of the crude product showed that conversion to the 5-lithiated derivative had been high and there was no evidence for the formation of products arising from transmetallation. Unfortunately, when DMF was used to quench the 5-lithiated derivative, conversion into 1-benzyl-4-bromo-2-chloroimidazole-5-carbaldehyde **21** was poor (*ca.* 50%) and starting material and by-products of unknown structure were



21 R = CHO

22 R = Br

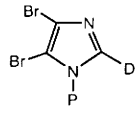


23 P = CH_2OMe

24 P = CH_2Ph

present also. We also synthesised 1-benzyl-4,5-dibromo-2-chloroimidazole **22** (64% yield) from the tribromo compound **15** and treated it successively with 1 mol equiv. each of butyllithium and DMF. No improvement in either the conversion or the quality of the imidazole-5-carbaldehyde **21** obtained was observed. In the synthesis of **22** from **15** using methyllithium a small amount (2%) of 1-benzyl-4,5-dibromo-2-methylimidazole **24** was formed by capture of the initially generated bromomethane with the imidazol-2-yllithium intermediate.[38]

In view of the well-known primary isotope effect exhibited by deuterium (*e.g.* in the 2-lithiation of thiophene,[48] k_H/k_D = 6.6 ± 0.3) we decided to investigate the Br→Li exchange reaction of the 1-protected 4,5-dibromo[2-$^2H_1$]imidazoles **25** and **26**. The starting materials were prepared in high yields by

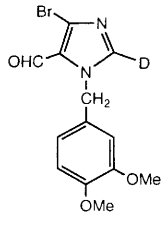


25 P = CH_2OMe

26 P = $CH_2C_6H_3(OMe)_2$-3,4

successive treatment of the corresponding 1-protected 2,4,5-tribromoimidazole with butyllithium[6] and deuterium oxide. Alternatively, compound **26** (70%) was obtained by successive treatment of the dibromoimidazole **3** with LDA and deuterium oxide. Previously, we[30] reported that butyllithium, unlike methyllithium, does not react regioselectively with some 1-protected 2,4,5-tribromoimidazoles (see also ref. 2). However, now we and others[6] have found that some 1-protected 2,4,5-tribromoimidazoles do react with butyllithium regioselectively with the bromine at C-2. Indeed sometimes, as in the reactions of compound **15** and its 1-methoxymethyl analogue, use of methyllithium results in the formation of the 2-methyl derivatives (*e.g.* **24** or **23**), formed through capture of the initially generated bromomethane by the respective imidazol-2-yllithium. The longer the reaction time, the more likely this is to happen.

When the 2-deuteriated compound **26** was treated successively



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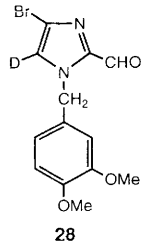

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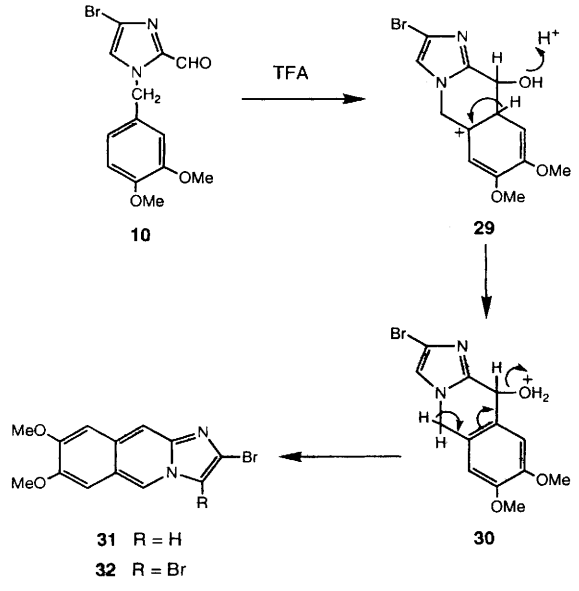
with butyllithium (in Et_2O at −78 °C) and DMF, it gave a mixture of the two aldehydes **27** and **28** (ratio 80:20 by ^1H NMR spectroscopic analysis of the crude product; ratio 85:15 isolated; actually compound **28** was contaminated with its 5-H analogue **10**) (*cf.* ratio 1:2 for aldehydes **6** and **10**) together with a substantial quantity (*ca.* 30%) of unidentified compounds. A similar result was obtained with the 2-deuteriated compound

25; in this case, however, formation of the 5-carbaldehyde (ratio 5-CHO:2-CHO = 2:1) was less favoured than in the reaction of the analogue **26** (ratio 5-CHO:2-CHO = 4:1).

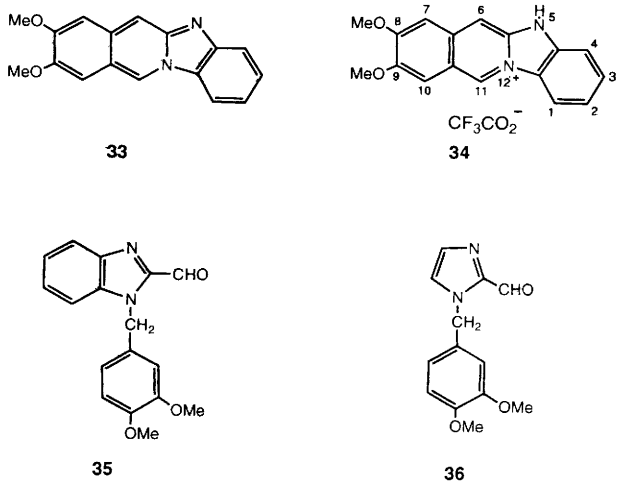
In order to study the compositions of the various mixtures of imidazole-2(and 5)-carbaldehydes obtained in this work (*e.g.* Scheme 1) and for the work which we describe later we prepared the 1-protected 4-bromoimidazole-2-carbaldehydes **8** (45%), **9** (65%) and **10** (62%) from the corresponding 2,4,5-tribromoimidazole through their reaction with 2.1 mol equiv. of butyllithium followed by careful addition of 1 mol equiv. of water to the resulting mixture, equilibration of the mixture of monolithiated compounds to the more stable 2-isomer (see before), and quenching the mixture with DMF. A sample of 4,5-dibromo-1-(3,4-dimethoxybenzyl)imidazole-2-carbaldehyde **12** (27.5%) was obtained from the corresponding tribromo compound **16** through its successive treatment with methyllithium [6] and DMF. In this case the low yield is probably due to the poor nucleophilicity of the imidazol-2-yllithium intermediate towards DMF and not due to capture of the initially generated bromomethane by this intermediate.

In an attempt to deprotect 4-bromo-1-(3,4-dimethoxybenzyl)-imidazole-2-carbaldehyde **10** with trifluoroacetic acid (TFA) we isolated a quantitative yield of the hydrotrifluoroacetate salt of 2-bromo-7,8-dimethoxyimidazo[1,2-*b*]isoquinoline, which gave the free base **31** (94%) with sodium hydrogen carbonate (Scheme 2). The hydrotrifluoroacetate salts of 2,3-dibromo-7,8-dimethoxyimidazo[1,2-*b*]isoquinoline **32** and 8,9-dimethoxybenzimidazo[1,2-*b*]isoquinoline **33** were prepared similarly in quantitative yield from compounds **12** and **35**, respectively. The former salt gave the free base **32** (97%) with sodium hydrogen carbonate whereas the latter salt **34** decomposed under these conditions. Compounds **31**, **32** and **34** are all high melting solids, which display a weak yellow–blue fluorescence in solution. They possess poor solubility in most solvents. These cyclisation reactions are an extension of the Bradsher reaction.[49] Partially saturated and *N*-substituted derivatives of the parent imidazo[1,2-*b*]isoquinoline skeleton are known already in the literature.[50 54] Compound **33** has been prepared by treatment of 2-(3,4-dimethoxybenzyl)benzimidazole with a phosphoryl chloride–DMF mixture (Vilsmeier–Haack conditions).[54]



Scheme 2

The bromine atoms in compounds **31** and **32** appear to contribute to their stability since treatment of 1-(3,4-dimethoxybenzyl)imidazole-2-carbaldehyde **36** with TFA (for 4 h at ambient temperature) gave an unstable mixture of two compounds (ratio *ca.* 1:1), one of which appeared from a ^{1}H NMR spectroscopic analysis to be 8,9-dimethoxyimidazo-[1,2-*b*]isoquinoline.



These heterocyclic Bradsher reactions proceed (Scheme 2) by initial protonation of the carbonyl oxygen followed by an intramolecular electrophilic substitution reaction, involving intermediates **29** and **30**. Cyclisation occurs *para* to a methoxy group and not at the alternative site. A 1-(3,4-dimethoxybenzyl) group appears to be essential for the success of these cyclisations. Thus, starting material was recovered from attempted cyclisation of 1-(4-methoxybenzyl)-4-bromoimidazole-2-carbaldehyde **9** in TFA at various temperatures. 1-(3,4-Dimethoxybenzyl)-4-bromoimidazole-5-carbaldehyde **6** and 1-benzyl-4-bromo-2-(methylsulfanyl)imidazole-5-carbaldehyde **18** [29] failed to cyclise.

Use of concentrated sulfuric acid in place of TFA as cyclising agent gave complex mixtures, in some cases containing starting material (by TLC). Boron trifluoride–diethyl ether (1 mol equiv.) was used also to successfully prepare compounds **31** and **32** and appeared more efficient (faster reactions) than TFA.

Experimental

IR spectra were recorded for liquid films or Nujol mulls between sodium chloride plates with a Perkin-Elmer 1710 FT spectrometer, ^{1}H NMR spectra were recorded with a Perkin-Elmer R32 (at 90 MHz) or Bruker AC300 FT instrument (at 300.13 MHz) with residual $CHCl_3$ as internal standard (δ 7.24 ppm) relative to tetramethylsilane; J values are given in Hz. Low resolution mass spectra (EI) were recorded with a Kratos MS30 and high-resolution mass spectra (EI) with a Kratos Concept 1S mass spectrometer (operating at approximately 70 eV). Molecular weights obtained by low-resolution (EI) mass spectrometry are given for the isotopes ^{79}Br and ^{35}Cl; the isotopic abundance ratios were as expected for the compounds containing these elements.

The Chromatotron® (Model 792T) was supplied by TC Research, Norwich, UK; 24 cm diameter plates were used for preparative separations, coated with a 4 mm layer of silica gel 60 PF-254 (Merck 7749) containing calcium sulfate. Camlab Polygram silica G/UV_{254} plates were used for TLC and flash chromatography [55] was carried out on silica gel 60 (Merck 9385), 40–63 μm (400–230 mesh).

Light petroleum had a bp range of 60–80 °C, unless stated otherwise. Ether refers to diethyl ether. Solvents and reagents were dried by standard procedures. In all cases organic extracts

were combined, dried ($MgSO_4$), and evaporated under reduced pressure using a rotary evaporator. All reactions were carried out under dry nitrogen.

Mps were recorded in capillary tubes with a Gallenkamp mp apparatus and are uncorrected. Butterworth Laboratories Ltd. of Teddington provided the microanalytical data.

The following compounds were prepared by literature procedures: 2,4,5-tribromoimidazole,[56] 1-methoxymethyl-,[57] 1-benzyl- **15**,[57] 1-(4-methoxybenzyl)-,[57] and 1-(3,4-dimethoxybenzyl)-2,4,5-tribromoimidazole **16**,[57] 1-methoxymethyl- **1**,[30] 1-benzyl- **2**,[30] and 1-(3,4-dimethoxybenzyl)-4,5-dibromoimidazole **3**,[30] 4-bromo-1-(3,4-dimethoxybenzyl)imidazole-5-carbaldehyde **6**,[16] 1-benzyl-4-bromo-2-(methylsulfanyl)imidazole-5-carbaldehyde **18**,[29] and 3,4-dimethoxybenzyl chloride.[58]

CAUTION: 2,4,5-Tribromoimidazole and its 1-protected derivatives that are deprotected *in vivo* to give 2,4,5-tribromoimidazole are reported[59–62] to be neurotoxic.

1-(3,4-Dimethoxybenzyl)imidazole[63]

Imidazole (2.92 g, 42.9 mmol) was added to a stirred solution of 3,4-dimethoxybenzyl chloride (8.0 g, 42.9 mmol) in DMF (57 cm^3) at ambient temperature, followed by anhydrous sodium carbonate (5.45 g, 51.4 mmol) and the resulting mixture was stirred for 48 h. Then, it was filtered and evaporation of the solvent under reduced pressure gave a viscous brown oil which was dissolved in dichloromethane (75 cm^3). The solution was washed with deionised water (5 × 150 cm^3) and then the solvent was removed. The product (6.77 g) was flash chromatographed on silica (200 g). Dichloromethane–methanol (96.5 : 3.5; 50 cm^3 fractions) eluted the product (4.80 g, 51%) in fractions 10–16. It had mp 54–56 °C (lit.,[63] 39–41 °C) and was used without further purification; $\delta_H(CDCl_3)$ 3.81 (3 H, s, OMe), 3.85 (3 H, s, OMe), 5.03 (2 H, s, NCH_2) 6.62 (1 H, d, *J* 1.8, 2′-H), 6.72 (1 H, dd, *J* 10 and 1.8, 6′-H), 6.81 (1 H, d, *J* 10, 5′-H), 6.87 (1 H, br s, 5-H), 7.06 (1 H, s, 4-H) and 7.52 (1 H, br s, 2-H).

1-(3,4-Dimethoxybenzyl)benzimidazole (43%)[64] was prepared similarly and had mp 137.5–139 °C (from ethyl acetate) (lit.,[64] 68% and mp 140–141 °C); $\delta_H(CDCl_3)$ 3.77 (3 H, s, OMe), 3.85 (3 H, s, OMe), 5.27 (2 H, s, NCH_2), 6.68 (1 H, d, *J* 1.8, 2′-H), 6.74 (1 H, dd, *J* 8.2 and 1.8, 6′-H), 6.81 (1 H, d, *J* 8.2, 5′-H), 7.21–7.32 (3 H, m, ArH), 7.79–7.82 (1 H, m, ArH) and 7.91 (1 H, s, 2-H) (Found: C, 71.5; H, 6.0; N, 10.5%; M^+, 268. $C_{16}H_{16}N_2O_2$ requires C, 71.6; H, 6.0; N, 10.4%; *M*, 268).

Reaction of 1-benzyl-4,5-dibromoimidazole 2 with 1 mol equiv. of butyllithium (typical experiment)

Butyllithium in hexane (1.6 mol dm^{-3}; 11.8 cm^3, 18.9 mmol) was added during 5 min to a stirred solution of 1-benzyl-4,5-dibromoimidazole (5.0 g, 15.8 mmol) in dry ether (100 cm^3) at −75 °C, then dry DMF (3 cm^3, 2.83 g, 38.7 mmol) was added during 15 min whilst the temperature of the mixture was kept below −75 °C, and the resulting mixture was stirred at this temperature for a further 3–4 h. The cooling bath was removed and stirring continued at ambient temperature overnight. 10% Aqueous ammonium chloride (65 cm^3) was added whereupon extraction with ether (50 cm^3), neutralisation of the aqueous phase with hydrochloric acid (4 mol dm^{-3}), and repeated extraction with ether (2 × 50 cm^3), followed by distillation of the solvent from the dried ($MgSO_4$) combined ethereal extracts gave a semicrystalline oil (4.43 g). The products were separated using a Chromatotron® (see before) eluting with light petroleum–ethyl acetate (3 : 1) to give 1-benzyl-4-bromoimidazole-5-carbaldehyde **5** (1.75 g, 42%) [R_f = 0.3, mp 60–62 °C (lit.,[30] mp 59–60 °C), identical in all other respects (IR, ^1H NMR and mass spectra) with an authentic sample], 1-benzyl-4-bromoimidazole-2-carbaldehyde **8** (1.46 g, 35%) [R_f = 0.6, mp 67–69 °C, identical in all respects (mp and IR, ^1H NMR, and mass spectra) with the sample prepared as described later] and 1-benzyl-4,5-dibromoimidazole-2-carbaldehyde **11** (0.92 g, 17%) [R_f = 0.7, mp 91–92 °C (from aqueous methanol), ν_{max}/cm^{-1} 1690 (CO); $\delta_H(CDCl_3)$ 5.71 (2 H, s, NCH_2), 7.30 (5 H, m, ArH), 9.60 (1 H, s, CHO) (Found: C, 38.6; H, 2.4; N, 8.15%; M^+, 342. $C_{11}H_8Br_2N_2O$ requires C, 38.4; H, 2.3; N, 8.15%; *M*, 342].

Reaction of 4,5-dibromo-1-(3,4-dimethoxybenzyl)imidazole 3 with 1.2 mol equiv. of butyllithium

Butyllithium in hexane (1.51 mol dm^{-3}; 4.18 cm^3, 6.31 mmol) was added dropwise during 10 min to a stirred solution of 4,5-dibromo-1-(3,4-dimethoxybenzyl)imidazole **3** (1.98 g, 5.27 mmol) in dry THF (40 cm^3) at −78 °C. After a further 5 min had elapsed dry DMF (1.01 cm^3, 0.96 g, 13.15 mmol) was added dropwise during 15 min. The resulting mixture was stirred for a further 4 h at −78 °C, then for 16 h at ambient temperature. 20% Aqueous ammonium chloride (10 cm^3) was added followed by hydrochloric acid (4 mol dm^{-3}; *ca.* 2 cm^3) until the mixture was neutralised. The organic layer was separated and the aqueous phase extracted with dichloromethane (5 × 10 cm^3). The organic layer and extracts were combined, washed with water (3 × 10 cm^3), dried ($MgSO_4$), and removal of the solvents gave a brown oil (1.86 g), which was flash chromatographed on silica (50 g). Hexane–ethyl acetate (1 : 1; 12 cm^3 fractions) eluted 4-*bromo*-1-(3,4-*dimethoxybenzyl*)*imidazole*-2-*carbaldehyde* **10** (1.22 g, 71%) in fractions 8–14, mp 117–118.5 °C (twice from ethanol), ν_{max}/cm^{-1} 1683 (CO); $\delta_H(CDCl_3)$ 3.83 (3 H, s, OMe), 3.86 (3 H, s, OMe), 5.47 (2 H, s, NCH_2), 6.77–6.84 (3 H, m, ArH), 7.03 (1 H, s, 5-H) and 9.74 (1 H, s, CHO) (Found: C, 48.3; H, 3.9; N, 8.5%; M^+, 324. $C_{13}H_{13}BrN_2O_3$ requires C, 48.0; H, 4.0; N, 8.6%; *M*, 324); and 4-bromo-1-(3,4-dimethoxybenzyl)imidazole-5-carbaldehyde **6** (0.39 g, 23%), identical in all respects (mp and IR, ^1H NMR and mass spectra) with an authentic sample.[30]

Reaction of 4,5-dibromo-1-methoxymethylimidazole 1 with 1 mol equiv. of butyllithium

Butyllithium in hexane (1.50 mol dm^{-3}; 4.1 cm^3, 6.15 mmol) was added during 10 min to a stirred solution of 4,5-dibromo-1-methoxymethylimidazole **1** (1.65 g, 6.11 mmol) in dry THF (41 cm^3) at −78 °C, then dry DMF (0.94 mm^3, 0.897 mg, 12.3 mmol) was added and the mixture was allowed to warm up to 0 °C whereupon it was stirred for a further 90 min. 20% Aqueous ammonium chloride (15 cm^3) was added and extraction with dichloromethane (3 × 20 cm^3) gave a solid (1.37 g), which was submitted to dry column chromatography[65] on silica (15 g). Hexane–ethyl acetate (1 : 1; 45 cm^3 fractions) eluted a quantitative yield of crude 4-*bromo*-1-(*methoxymethyl*)-*imidazole*-2-*carbaldehyde* **7** (1.33 g, 85%) in fraction 2, mp 51–53 °C [from hexane–ethyl acetate (9 : 1); 12 cm^3] (863 mg, 64% after recrystallisation), ν_{max}/cm^{-1} 1687 (CO); $\delta_H(CDCl_3)$ 3.35 (3 H, s, OMe), 5.70 (2 H, s, NCH_2), 7.31 (1 H, s, 5-H) and 9.72 (1 H, s, CHO) (Found: C, 33.0; H, 3.2; N, 12.7%; M^+, 218. $C_6H_7BrN_2O_2$ requires C, 32.9; H, 3.2; N, 12.8%; *M*, 218). The crude product **7** was shown by ^1H NMR spectroscopy and TLC to contain traces of two other products (ratio *ca.* 95 : 5 : 5) believed to be 4-bromo-1-(methoxymethyl)imidazole-5-carbaldehyde **4** and 4-bromo-1-(methoxymethyl)imidazole-2,5-dicarbaldehyde, respectively.

2,4-Dibromo-1-(3,4-dimethoxybenzyl)imidazole 19

Butyllithium in hexane (1.50 mol dm^{-3}; 5.97 cm^3, 8.96 mmol) was added during 20 min to a stirred solution of 2,4,5-tribromo-1-(3,4-dimethoxybenzyl)imidazole **16** (1.94 g, 4.27 mmol) in dry THF (27 cm^3) at −78 °C. Then dry THF (2.5 cm^3) containing deionised water (76.8 mm^3, 4.27 mmol) was syringed into the mixture during 10 min, after which the temperature of the mixture was raised to −50 °C, then lowered again to −78 °C.

Bromine (252 mm^3, 0.786 g, 4.91 mmol) in hexane (2.5 cm^3) was added during 10 min and the cooling was discontinued after a further 1.5 h. Work-up, as described before, gave a pale yellow oil (1.74 g) which solidified. The *product* **19** (1.035 g, 64% after recrystallisation) had mp 116–118 °C [from hexane–ethanol (2:1)]; $\delta_H(CDCl_3)$ 3.84 (3 H, s, OMe), 3.86 (3 H, s, OMe), 4.97 (2 H, s, NCH_2) 6.68 (1 H, d, *J* 1.8, 2′-H), 6.74 (1 H, dd, *J* 8.5 and 1.8, 6′-H), 6.83 (1 H, d, *J* 8.5, 5′-H) and 6.85 (1 H, s, 5-H) (Found: C, 38.6; H, 3.2; N, 7.3%; M^+, 374. $C_{12}H_{12}Br_2N_2O_2$ requires C, 38.3; H, 3.2; N, 7.45%; *M*, 374).

1-Benzyl-4-bromo-2-chloroimidazole 20

Using the procedure described in the preceding experiment for the synthesis of compound **19**, 1-benzyl-2,4,5-tribromoimidazole **15** (2.97 g, 7.52 mmol) in THF (38 cm^3) was treated successively with butyllithium in hexane (1.47 mol dm^{-3}; 10.75 cm^3, 15.8 mmol), water (136 mm^3, 7.55 mmol) in THF (6 cm^3), and hexachloroethane (1.96 g, 8.3 mmol) in THF (6 cm^3), to give a crude product (1.56 g) which was flash chromatographed on silica (70 g). Hexane–ethyl acetate (9:1; 40 cm^3 fractions) eluted the *title compound* **20** (1.024 g, 50%) in fractions 7–11, as a yellow oil; $\delta_H(CDCl_3)$ 5.03 (2 H, s, NCH_2), 6.82 (1 H, s, 5-H), 7.08–7.20 (2 H, m, ArH) and 7.26–7.40 (3 H, m, ArH) (Found: M^+, 269.9547. $C_{10}H_8BrClN_2$ requires *M*, 269.9560).

1-Benzyl-4,5-dibromo-2-chloroimidazole 22

Methyllithium in ether (0.67 mol dm^{-3}; 10.55 cm^3, 7.07 mol) was treated with 1-benzyl-2,4,5-tribromoimidazole **15** (2.66 g, 6.73 mmol) in THF (45 cm^3) at −78 °C and the resulting mixture was quenched with hexachloroethane (1.67 g, 7.05 cm^3) in THF (5 cm^3). Work-up in the usual way gave a yellow oil (2.80 g) which produced a solid on trituration with hexane. The crude product was flash chromatographed on silica (100 g). Hexane–ethyl acetate (92:8; 45 cm^3 fractions) eluted the *title compound* **22** (1.51 g, 64%) in fractions 8–13 as a colourless solid, mp 61–62 °C [from aqueous ethanol (15:85); 8 cm^3]; $\delta_H(CDCl_3)$ 5.18 (2 H, s, NCH_2), 7.12–7.19 (2 H, m, ArH) and 7.28–7.40 (3 H, m, ArH) (Found: C, 34.6; H, 1.8; N, 7.9%; M^+, 348. $C_{10}H_7Br_2ClN_2$ requires C, 34.3; H, 2.0; N, 8.0%; *M*, 348) and (in fractions 15–17) 1-*benzyl*-4,5-*dibromo*-2-*methylimidazole* **24** contaminated, as shown by TLC and mass and ^1H NMR spectroscopy, with 1-benzyl-4,5-dibromo- **2**, 1-benzyl-4-bromo-2-chloro- **20** and 1-benzyl-4-bromo-2-chloro-5-methylimidazole. The last product was rechromatographed on silica (10 g) eluting with hexane–ethyl acetate (9:1; 5 cm^3 fractions) to give the pure compound (45 mg, 2%) as a white solid, mp 94–96 °C (from ethanol); $\delta_H(CDCl_3)$ 2.08 (3 H, s, Me), 5.10 (2 H, s, NCH_2), 7.02–7.05 (2 H, m, ArH) and 7.29–7.40 (3 H, m, ArH) (Found: C, 40.2; H, 2.7; N, 7.9%; M^+, 328. $C_{11}H_{10}Br_2N_2$ requires C, 40.0; H, 3.05; N, 8.5%; *M*, 328).

1-Methoxymethyl-4,5-dibromo[2-$^2H_1$]imidazole 25

Using the same method as described before for the synthesis of 1-benzyl-4,5-dibromo-2-chloroimidazole **22** but using butyllithium in place of methyllithium and quenching the intermediate 2-lithium compound with deuterium oxide gave a pale yellow solid (obtained from 5.0 g, 14.35 mmol, 2,4,5-tribromo-1-methoxymethylimidazole). This was dissolved in ethyl acetate, the solution was filtered through silica (20 g), and evaporation of the solvent gave a colourless product (4.07 g). The crude product in hot hexane (7.0 cm^3)–ethyl acetate (2.5 cm^3) was seeded, more hexane (6.5 cm^3) was added and the *product* **25** (2.91 g, 75%) crystallised as a colourless solid, mp 69–71 °C; $\delta_H(CDCl_3)$ 3.31 (3 H, s, OMe) and 5.23 (2 H, s, NCH_2); δ_C 56.49 (OMe), 77.43 (CH_2), 103.77 (C-5), 118.05 (C-4) and 137.68 (C-2; as a 1:1:1 triplet) (Found: C, 22.2; H, 2.05; N, 10.25%; M^+, 269. $C_5H_5Br_2DN_2O$ requires C, 22.2; H, 1.9; N, 10.3%; *M*, 269).

4,5-Dibromo-1-(3,4-dimethoxybenzyl)[2-$^2H_1$]imidazole 26

(*a*) Starting with 2,4,5-tribromo-1-(3,4-dimethoxybenzyl)-imidazole **16** (2.71 g, 5.96 mmol) in THF (50 cm^3) and using the same procedure as that described before for the synthesis of 1-benzyl-4,5-dibromo-2-chloroimidazole **22** except that the intermediate 2-lithium compound was generated using butyllithium and quenched with deuterium oxide (1.08 cm^3, 1.2 g, 60.0 mmol) a crude product (2.01 g) was obtained which was flash chromatographed on silica (90 g). Hexane–ethyl acetate (1:1; 40 cm^3 fractions) eluted the *title compound* **26** (1.55 g, 69%) in fractions 22–32, as a colourless solid, mp 113.5–115 °C [from ethanol (5 cm^3)]; $\delta_H(CDCl_3)$ 3.83 (3 H, s, OMe), 3.86 (3 H, s, OMe), 5.01 (2 H, s, NCH_2), 6.68 (1 H, d, *J* 1.8, 2′-H), 6.72 (1 H, dd, *J* 9.0 and 1.8, 6′-H) and 6.82 (1 H, d, *J* 9.0, 5′-H); δ_C 50.86 (CH_2), 55.86 (2 × OMe), 103.87 (C-5), 111.31, 110.62, 117.21 (C-4), 120.26, 126.47, 137.13 (C-2; as a 1:1:1 triplet), 149.24 and 149.36 (Found: C, 38.4; H, 3.0; N, 7.3%; M^+, 375. $C_{12}H_{11}Br_2DN_2O_2$ requires C, 38.2; H, 2.9; N, 7.4%; *M*, 375).

(*b*) The same product **26** (70%; deuterium incorporation 86% in this case) was prepared also from 4,5-dibromo-1-(3,4-dimethoxybenzyl)imidazole **3** (1.41 g) *via* its metallation with 1.1 mol equiv. of LDA followed by quenching the mixture with deuterium oxide and work-up as described in (*a*).

Reaction of 4,5-dibromo-1-(3,4-dimethoxybenzyl)[2-$^2H_1$]imidazole 26 with butyllithium

Butyllithium in hexane (1.59 mmol dm^{-3}; 1.1 cm^3, 1.75 mmol) was added during 10 min to a stirred solution of 4,5-dibromo-1-(3,4-dimethoxybenzyl)[2-$^2H_1$]imidazole **26** (0.65 g, 1.72 mmol) in THF (16 cm^3) at −78 °C followed, after a further 5 min, by the addition of DMF (335 mm^3, 0.317 g, 4.34 mmol) during 15 min. The resulting mixture was stirred at −78 °C for a further 4 h, then allowed to warm up to ambient temperature and stirred for a further 16 h. Work-up in the usual way gave a brown semicrystalline material which was flash chromatographed on silica (28 g). Hexane–ethyl acetate (1:1; 9 cm^3 fractions) eluted: (in fractions 8–14) 4-*bromo*-1-(3,4-*dimethoxybenzyl*)[2-$^2H_1$]*imidazole*-5-*carbaldehyde* **27** (226 mg, 40%) as a colourless solid, mp 161.5–162 °C (from ethanol), ν_{max}/cm^{-1} 1671 (CO); $\delta_H(CDCl_3)$ 3.84 (3 H, s, OMe), 3.86 (3 H, s, OMe), 5.39 (2 H, s, NCH_2), 6.78–6.84 (3 H, m, ArH) and 9.76 (1 H, s, CHO); δ_C 50.77 (CH_2), 55.82 (2 × OMe), 111.23 (C-2′/5′), 120.76 (C-6′), 126.25 (C-5), 126.75 (C-1′), 130.68 (C-4), 141.61 (C-2; as a 1:1:1 triplet), 149.26 (C-3′/4′) and 179.47 (CHO) (Found: C, 47.9; H, 3.8; N, 8.4%; M^+, 325. $C_{13}H_{12}BrDN_2O_3$ requires C, 47.9; H, 3.7; N, 8.6%; *M*, 325); and (in fractions 4 and 5) 4-bromo-1-(3,4-dimethoxybenzyl)imidazole-2-carbaldehyde **10** (38 mg, 7%), with a deuterium incorporation at C-5 (*i.e.* compound **28**) of only 25%, identical with an authentic sample, mp 117–118 °C (from ethanol), ν_{max}/cm^{-1} 1683 (CO).

1-Benzyl-4-bromoimidazole-2-carbaldehyde 8

Using the same procedure as that described before for the synthesis of 2,4-dibromo-1-(3,4-dimethoxybenzyl)imidazole **19** except that the mixture was quenched finally with DMF instead of bromine, 1-benzyl-2,4,5-tribromoimidazole **15** (3.38 g, 8.56 mmol) in THF (71 cm^3) was treated successively with butyllithium in hexane (1.45 mol dm^{-3}; 12.4 cm^3, 17.98 mmol), water (154 mm^3, 8.56 mmol) in THF (6 cm^3) and DMF (1.66 cm^3, 1.57 g, 21.4 mmol). Work-up as described before gave a yellow–brown oil (2.45 g) which was flash chromatographed on silica (65 g). Hexane–ethyl acetate (85:15; 45 cm^3 fractions) eluted the *title compound* **8** (1.03 g, 45%) in fractions 6–8, as a yellow oil which solidified, mp 65–67 °C [twice from hexane (7 cm^3)–tetrachloromethane (1 cm^3)], ν_{max}/cm^{-1} 1690 (CO); $\delta_H(CDCl_3)$ 5.56 (2 H, s, NCH_2), 7.06 (1 H, s, 5-H), 7.18–7.26 (2 H, m, ArH), 7.31–7.39 (3 H, m, ArH) and 9.73 (1 H, s, CHO) (Found: C, 49.8;

H, 3.4; N, 10.4%; M^+, 264. $C_{11}H_9BrN_2O$ requires C, 49.8; H, 3.4; N, 10.6%; *M*, 264).

The following compounds were prepared similarly: 4-*bromo*-1-(4-*methoxybenzyl*)*imidazole*-2-*carbaldehyde* **9** (65%) [the crude product was flash chromatographed on silica; hexane–ethyl acetate (65:35) eluted a yellow oil which solidified], mp 70–71 °C (from ethanol), ν_{max}/cm^{-1} 1689 (CO); $\delta_H(CDCl_3)$ 3.78 (3 H, s, OMe), 5.48 (2 H, s, NCH_2), 6.87 (2 H, d, *J* 9.0, 2′/6′-H), 7.02 (1 H, d, *J* 0.9, 5-H), 7.19 (2 H, d, *J* 9.0, 3′/5′-H) and 9.73 (1 H, d, *J* 0.9, CHO) (Found: C, 49.0; H, 3.55; N, 9.4%; M^+, 294. $C_{12}H_{11}BrN_2O_2$ requires C, 48.8; H, 3.8; N, 9.5%; *M*, 294); 4-bromo-1-(3,4-dimethoxybenzyl)imidazole-2-carbaldehyde **10** (62%) [the crude product was flash chromatographed on silica; hexane–ethyl acetate (66:34) eluted the product as white crystals], mp 117–118.5 °C (from ethanol), identical in other respects (TLC and IR and ^1H NMR spectra) with the sample prepared as described before.

4,5-Dibromo-1-(3,4-dimethoxybenzyl)imidazole-2-carbaldehyde 12

2,4,5-Tribromo-1-(3,4-dimethoxybenzyl)imidazole **16** (4.96 g, 10.9 mmol) in THF (75 cm^3) was treated successively with methyllithium in ether (0.65 mol dm^{-3}; 16.8 cm^3, 10.9 mmol) and DMF (2.1 cm^3, 2.0 g, 27.4 mmol) using the method described before for the synthesis of 1-benzyl-4,5-dibromo-2-chloroimidazole **22**. Work-up gave the crude product (1.7 g) which was recrystallised from ethanol (12 cm^3), to give the *title compound* **12** (1.21 g, 27.5%) as a pale-yellow solid, mp 129–131 °C, ν_{max}/cm^{-1} 1690 (CO); $\delta_H(CDCl_3)$ 3.82 (3 H, s, OMe), 3.83 (3 H, s, OMe), 5.60 (2 H, s, NCH_2), 6.75–6.84 (3 H, m, ArH) and 9.59 (1 H, s, CHO) (Found: C, 38.9; H, 2.9; N, 6.8%; M^+, 402. $C_{13}H_{12}Br_2N_2O_3$ requires C, 38.6; H, 3.0; N, 6.9%; *M*, 402).

1-(3,4-Dimethoxybenzyl)benzimidazole-2-carbaldehyde 35

1-(3,4-Dimethoxybenzyl)benzimidazole (4.56 g, 17.00 mmol) was dissolved in dry THF (113 cm^3) and treated with butyllithium in hexane (1.44 mol dm^{-3}; 12.0 cm^3, 17.3 mmol), followed by addition of DMF (3.29 cm^3, 3.11 g, 42.6 mmol) in a similar manner as described above. After 1 h at 0 °C work-up gave the crude *product* **35** (4.84 g) which was recrystallised from ethyl acetate (25 cm^3). The pale-yellow product **35** (3.27 g, 65%) had mp 123–124 °C, ν_{max}/cm^{-1} 1695 (CO); $\delta_H(CDCl_3)$ 3.77 (3 H, s, OMe), 3.81 (3 H, s, OMe), 5.77 (2 H, s, NCH_2), 6.69–6.77 (3 H, m, 2′/5′/6′-H), 7.38–7.50 (3 H, m, 5/6/7-H), 7.93 (1 H, d, *J* 9.0, 4-H) and 10.14 (1 H, s, CHO) (Found: C, 68.9; H, 5.4; N, 9.3%; M^+, 296. $C_{17}H_{16}N_2O_3$ requires C, 68.9; H, 5.4; N, 9.45%; *M*, 296).

1-(3,4-Dimethoxybenzyl)imidazole-2-carbaldehyde 36

To a stirred solution of 1-(3,4-dimethoxybenzyl)imidazole (1.85 g, 8.48 mmol) in THF (57 cm^3) at 0 °C was added during 20 min butyllithium in hexane (1.48 mol dm^{-3}; 5.84 cm^3, 8.64 mmol), followed by DMF (1.63 cm^3, 1.55 g, 21.2 mmol) and the resulting mixture was stirred at 0 °C for a further 1 h when cooling was discontinued and the mixture was allowed to stir for a further 30 min. Work-up in the usual way gave a yellow oil (2.20 g) which solidified on being kept at 5 °C overnight. Flash chromatography of the resulting solid on silica (50 g), eluting with hexane–ethyl acetate (25:75; 25 cm^3 fractions) gave (in fractions 10–19) the pure *product* **36** (1.85 g, 89%) mp 60–61 °C [from hexane (4 cm^3)–ethyl acetate (4 cm^3); the solution was cooled, then seeded, and supersaturated with hexane by addition of a further 12 cm^3], ν_{max}/cm^{-1} 1683 (CO); $\delta_H(CDCl_3)$ 3.82 (3 H, s, OMe), 3.85 (3 H, s, OMe), 5.51 (2 H, s, NCH_2), 6.75–6.82 (3 H, m, ArH), 7.10 (1 H, s, 5-H or 4-H), 7.26 (1 H, s, 4-H or 5-H) and 9.84 (1 H, s, CHO) (Found: C, 63.3; H, 5.7; N, 11.1%; M^+, 246. $C_{13}H_{14}N_2O_3$ requires C, 63.4; H, 5.7; N, 11.4%; *M*, 246).

2-Bromo-7,8-dimethoxyimidazo[1,2-*b*]isoquinoline 31

(*a*) A solution of 4-bromo-1-(3,4-dimethoxybenzyl)imidazole-2-carbaldehyde **10** (1.05 g, 3.23 mmol) in trifluoroacetic acid (TFA) (11 cm^3) was kept at ambient temperature for 2 h, then the solvent was removed from the resulting clear yellow solution under reduced pressure and the yellow crystalline residue (1.52 g) was dissolved in dichloromethane (90 cm^3). The fluorescent solution was washed with saturated aqueous sodium hydrogen carbonate (50 cm^3) and the aqueous layer was extracted with dichloromethane (3 × 20 cm^3). The organic layer and extracts were combined, washed with deionised water (20 cm^3), dried ($MgSO_4$), and the solvent was removed under reduced pressure to give the *product* **31** (0.93 g, 94%) as a curry-yellow powder, mp 219–220 °C (with decomposition); $\delta_H(CDCl_3)$ 3.94 (3 H, s, OMe), 3.96 (3 H, s, OMe), 6.73 (1 H, s, ArH), 6.83 (1 H, s, ArH), 7.64 (1 H, s, ArH), 7.72 (1 H, s, ArH) and 8.48 (1 H, s, ArH) (Found: C, 50.7; H, 3.4; N, 9.0%; M^+, 306.0008. $C_{13}H_{11}BrN_2O_2$ requires C, 50.8; H, 3.6; N, 9.1%; *M*, 306.0004). Attempted recrystallisation of this product from ethanol (*ca.* 50 cm^3) was capricious and resulted in a lower yield (0.74 g) of a darker product. Its ^1H-decoupled ^{13}C NMR spectrum showed 13 singlets, 2 overlapping at δ_C 55.49 (2 × OMe) and 11 between δ_C 101.34 and 151.33 ppm.

(*b*) The same product **31** was obtained in the same yield by adding boron trifluoride–diethyl ether (1 mol equiv.) to a stirred solution of the starting material **10** in dichloromethane (concentration 0.3 mol dm^{-3} of **10** in CH_2Cl_2). After 10 min the resulting mixture was worked up as described in (*a*).

2,3-Dibromo-7,8-dimethoxyimidazo[1,2-*b*]isoquinoline 32

Using method (*a*) 4,5-dibromo-1-(3,4-dimethoxybenzyl)imidazole-2-carbaldehyde **12** (0.70 g, 1.74 mmol) was converted into the *title compound* **32** (crude yield 0.65 g, 97%), mp 236–237 °C (with decomposition) [from acetonitrile (150 cm^3) (0.54 g, 81% after recrystallisation)]; $\delta_H(CDCl_3)$ 3.99 (3 H, s, OMe), 4.01 (3 H, s, OMe), 6.90 (1 H, s, ArH), 6.94 (1 H, s, ArH), 7.84 (1 H, s, ArH) and 8.53 (1 H, s, ArH) (Found: C, 40.7; H, 2.3; N, 7.2%; M^+, 384. $C_{13}H_{10}Br_2N_2O_2$ requires C, 40.45; H, 2.6; N, 7.3%; *M*, 384). The ^1H-decoupled ^{13}C NMR spectrum displayed 13 singlets, 2 around δ_C 56 (2 × OMe) and 11 between δ_C 91.25 and 151.96 ppm.

Use of boron trifluoride–diethyl ether, as described in (*b*) before, gave an identical result.

8,9-Dimethoxybenzimidazo[1,2-*b*]isoquinolin-12-ium trifluoroacetate 34 [54]

Using procedure (*a*) (and omitting the sodium hydrogen carbonate wash procedure), as described before, 1-(3,4-dimethoxybenzyl)benzimidazole-2-carbaldehyde **35** (0.12 g, 0.40 mmol) was converted into the *title compound* **34** in a quantitative yield. The crude product (0.165 g) was triturated with ether (10 cm^3) and dried, mp 227–228 °C (with decomposition); ν_{max}/cm^{-1} 1684 (CO) and 3435 (N^+H); $\delta_H([^2H_6]DMSO)$ 3.99 (3 H, s, OMe), 4.03 (3 H, s, OMe), 7.46 (1 H, s, ArH), 7.63 (1 H, s, ArH), 7.64 (1 H, t, *J* 8.0, ArH), 7.80 (1 H, t, *J* 8.0, ArH), 7.88 (1 H, d, *J*, 8.0, 4-H), 8.25 (1 H, s, ArH), 8.56 (1 H, d, *J* 8.0, 1-H), 10.25 (1 H, s, 11-H) and 14.03 (1 H, br s, NH) (recorded with a freshly prepared sample). Recrystallisation [from ethanol (6 cm^3)] gave a product (0.151 g, 96%) whose ^1H NMR spectrum showed evidence of decomposition. Attempts to prepare the free base **33** with an aqueous sodium hydrogen carbonate wash failed. The ^1H-decoupled ^{13}C NMR spectrum (of a freshly prepared sample) displayed 17 singlets, 2 around δ_C 56 (2 × OMe) and 15 between δ_C 102.64 and 155.90 ppm. Because of the instability of this compound **34** it was not possible to obtain good microanalytical data (Found: $M^+ - CF_3CO_2H$, 278. $C_{19}H_{15}F_3N_2O_4$ requires $M - CF_3CO_2H$, 278).

Acknowledgements

We thank The Danish Research Academy and Rhône-Poulenc for financial support (to A. K. P.), Drs David W. Hawkins and Michael P. L. Caton (of Rhône-Poulenc), and Professor Dr Mikael Begtrup (of The Royal Danish School of Pharmacy, University of Copenhagen) for their interest in our work, Mrs Ruth Howard for recording low-resolution mass spectra, Mrs Valerie Boote (University of Manchester) for recording the high-resolution mass spectral data, Dr M. A. Stuckey for recording ^{1}H and ^{13}C NMR spectra at 300 MHz, and Mrs Sandra Hickman for help in preparing the manuscript.

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Paper 5/01303H
Received 3rd *March* 1995
Accepted 15th *March* 1995