Brominated isoindolines: precursors to functionalised nitroxides

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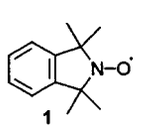
Received (in Cambridge) 3rd September 1998, Accepted 6th November 1998

A new, convenient method for the preparation of functionalised precursors to stable tetraalkylisoindoline nitroxides (aminoxyls) is presented. Simple treatment of 2-benzyl-1,1,3,3-tetramethylisoindoline **2** with Br_2 in CCl_4 gives rapid oxidative debenzylation, generating benzaldehyde and an unusual bromoamine, 2-bromo-1,1,3,3-tetramethylisoindoline **4**, in high yield. Treatment of the bromoamine **4** with $FeSO_4$–H_2SO_4 results in bromination of the aromatic ring in varying yield, while rapid treatment with peroxide–tungstate causes debromination, generating 1,1,3,3-tetramethylisoindoline **3**. Bromination of the isoindoline aromatic ring is more readily afforded by treatment of 2-benzyl-1,1,3,3-tetramethylisoindoline **2** with Br_2 and $AlCl_3$ in CCl_4, producing 2,5-dibromo-1,1,3,3-tetramethylisoindoline **7** and/or 2,5,6-tribromo-1,1,3,3-tetramethylisoindoline **6** in varying yields depending upon the exact reaction conditions. Rapid treatment with peroxide–tungstate generates the corresponding bromine substituted isoindolines, 5-bromo-1,1,3,3-tetramethylisoindoline **5** and 5,6-dibromo-1,1,3,3-tetramethylisoindoline **8**. Prolonged peroxide–tungstate treatment oxidises the substituted bromoamines to the corresponding nitroxides, 5-bromo-1,1,3,3-tetramethylisoindolin-2-yloxyl **9** and 5,6-dibromo-1,1,3,3-tetramethylisoindolin-2-yloxyl **10**. SQUID magnetic susceptibility measurements of crystalline **10** reveal strong antiferromagnetic interradical spin coupling. The crystal structures of **10**, 2-bromo-1,1,3,3-tetramethylisoindoline **4** and the hydrobromide dihydrate salt of 1,1,3,3-tetramethylisoindoline **3** (**3a**) have also been determined, with **10** displaying an interesting molecular packing arrangement.

Introduction

Aminoxyl radicals (nitroxides) containing a fused aromatic moiety are known to have many advantages[1–4] over the more accessible pyrrolidine and piperidine species. This is especially true of the tetraalkylisoindolin-2-yloxyl nitroxides (such as **1**) which have, however, been relatively under-utilised since the initial synthesis of the tetraethyl system[5–9] by Rozantsev *et al.* in the late 1960s. Isoindoline nitroxides are resistant to the ring-opening reactions which are significant decomposition pathways for the pyrrolidine and piperidine nitroxides.[10] These nitroxides also have excellent thermal and chemical stability in a wide variety of chemical environments, including basic and acidic solutions.



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The synthesis of isoindoline nitroxides can be readily adapted for the generation of ^2H and ^{15}N labelled derivatives.[11–13] Such compounds, with their specifically tailored spectroscopic characteristics may find application in spin-labelling, electron paramagnetic resonance imaging (EPRI) and magnetic resonance imaging (MRI). Indeed, preliminary studies indicate that isoindoline nitroxides possess isotropic EPR linewidths much smaller than those of pyrrolidine and piperidine nitroxides, and consequently show excellent promise as spin-labels.[14,15]

This work is concerned with the synthesis of new functionalised tetramethylisoindoline nitroxides. Since the first synthesis of this class of nitroxides[16,17] they have been primarily utilised in radical trapping techniques,[18–21] where the separation and characterisation of stable alkoxyamine radical adducts is facilitated by the inherent UV chromophore and symmetrical nature of the isoindoline system.

The application of tetramethylisoindoline nitroxides to areas outside of radical trapping has been hindered by a lack of structural variation, which has been limited to few nitrogenous moieties.[16] Recently, the application of isoindoline nitroxides has been advanced by the detailing of full NMR and EPR analyses[13,14] of **1** and its isotopically labelled ^{15}N and tetrakis-(trideuteriomethyl)[11] analogues, thereby permitting calculation of all hyperfine splitting constants and anisotropic *g*-factors of these compounds, and paving the way for their use in EPRI, MRI, spin-labelling and other spectroscopic techniques. This has led to the development of a simple EPR technique for the measurement of translational diffusion constants using the tetrakis(trideuteriomethyl) analogue[11] of **1** in conjunction with a deuterated 5-sulfonyl derivative.[22–24] Further work has involved the synthesis of various isotopically labelled 5-(*n*-alkyl)isoindoline nitroxides which show promise as spin-probes of lipid systems.[11,12]

While the potential of isoindoline nitroxides in imaging techniques and as spin probes/labels, as well as their usefulness in diffusion and EPR studies has been demonstrated, structural variation in the available nitroxides remains limited. The possibilities for functionalisation of the aromatic ring would permit synthesis of 'tailor-made' species for specific applications.[12]

We have successfully synthesised two novel bromo-substituted nitroxides (**9** and **10**), and their corresponding precursors, which may serve as further sources of functionalisation. Interestingly, the bromination procedure leads to the oxidative debenzylation of the nitroxide precursor 2-benzyl-1,1,3,3-tetramethylisoindoline **2** to give a novel isoindoline-based bromoamine **4**, with unusual chemical properties. These include isomerism in the presence of Fe^{II} salts and H_2SO_4 to form the

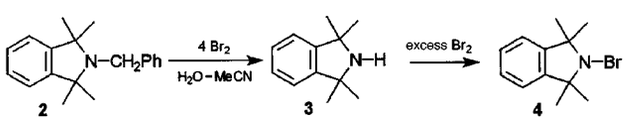
5-bromoisoindoline **5** in moderate yield, and the formation of salts of isoindoline **3** in solution when exposed to oxidisable substrates.

The synthetic utility of the halogen substituent lends itself to further adaptation, but also demonstrates the effect of symmetry on the physical properties of the isoindoline system. The 5-bromo and 5,6-dibromo nitroxides (**9** and **8** respectively) exhibit significantly different physical properties, which can be related to the loss of symmetry in the mono-substituted compound. The 5-bromo compound **9** was crystallised with difficulty from acetonitrile to give crystals with poor morphology (mp 109 °C). The dibromo nitroxide **10** on the other hand gave crystals (mp 258 °C) which were suitable for single-crystal X-ray analysis. This showed an unusual helical crystal packing arrangement in a noncentrosymmetric crystal system, which suggested potential radical–spin interaction. Such interactions are typically antiferromagnetic but can become ferromagnetic to generate free-radical-based magnets, although limited to cryogenic temperatures. 2-(*p*-Nitrophenyl)-4,4,5,5-tetramethyl-1,3-imidazolin-3-oxide-1-oxyl[25] and 2,6-diazaadamantane-2,6-dioxyl[26] are some of the earliest examples. Nogami and coworkers investigated 165 kinds of 4-arylmethyleneamino-2,2,6,6-tetramethylpiperidin-1-yloxyls to find a correlation between the molecular and crystal structures and the magnetic properties. They concluded that the NO · · · aryl contact is a key to the occurrence of intermolecular ferromagnetic interaction.[27] We thus studied the temperature dependence of the paramagnetic susceptibility of **10** by superconducting quantum interference device (SQUID); a rather strong antiferromagnetic interradical coupling was found.

Results and discussion

Oxidative debenzylation of 2-benzyl-1,1,3,3-tetramethylisoindoline (2)

Treatment of the nitroxide precursor 2-benzyl-1,1,3,3-tetramethylisoindoline **2** with four equivalents of bromine resulted in oxidative cleavage of the benzyl group, producing benzaldehyde and 2-bromo-1,1,3,3-tetramethylisoindoline **4** in high yield (95%) (Scheme 1). Oxidative cleavage of tertiary amines



Scheme 1 Oxidative debenzylation of 2-benzyl-1,1,3,3-tetramethylisoindoline (**2**).

by halogens has been reported,[28] but the mechanism has received little attention. It appears that the initial action of Br_2 on **2** produces an imminium ion which is hydrolysed on work-up, giving 1,1,3,3-tetramethylisoindoline **3** and benzaldehyde. Treatment of **2** with one equivalent of Br_2 supports this hypothesis, producing a mixture of isoindoline **3**, benzaldehyde, and unreacted starting material. Bromoamine **4** is formed through rapid oxidation of **3** by excess Br_2. This is demonstrated independently by the treatment of **3** with Br_2, which gives rise to **4** in almost quantitative yield.

Crystals of **4**, obtained from methanol–water were suitable for structure determination by single crystal X-ray diffraction methods. Although the compound was found to sublime quite rapidly at room temperature in the X-ray beam, a low-temperature data set (110 K) was collected and provided the structure shown in Fig. 1. The compound shows no unusual structural features worthy of comment and exists in the solid state as unassociated molecules having no significant intermolecular contacts.

The dihydrate hydrobromide salt of isoindoline **3** (**3a**) was found to precipitate over a period of days from unresolved

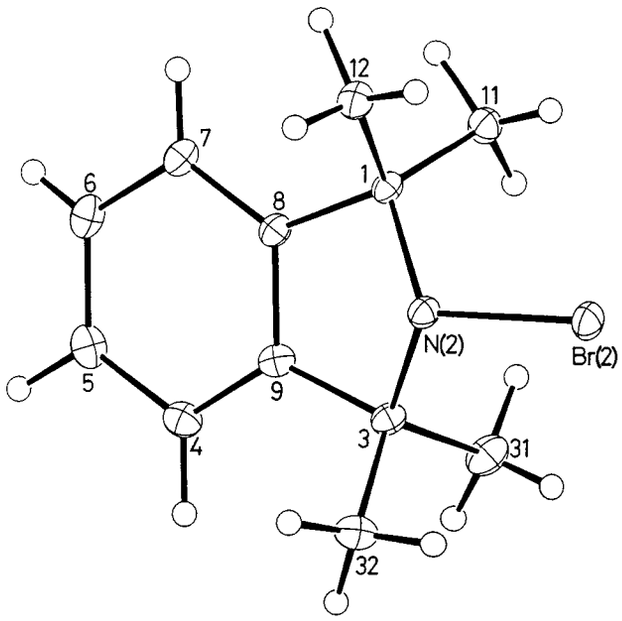


Fig. 1 Molecular configuration and atom numbering scheme for **4**. Unless otherwise indicated, atoms are carbon.

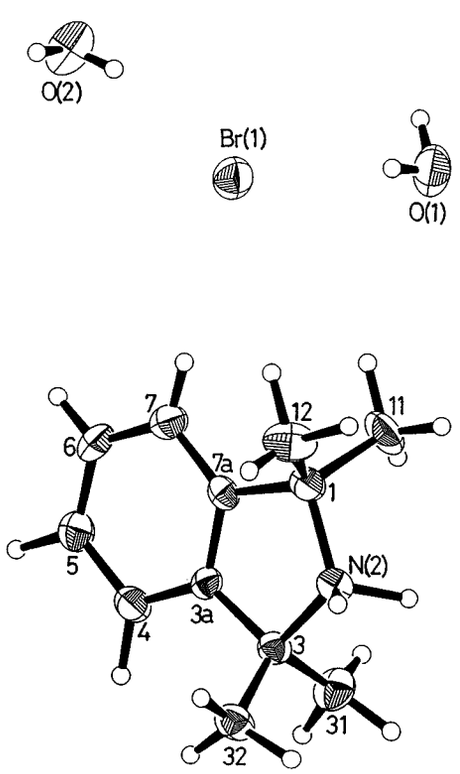


Fig. 2 Molecular configuration and atom numbering scheme for **3a**. Unless otherwise indicated, atoms are carbon.

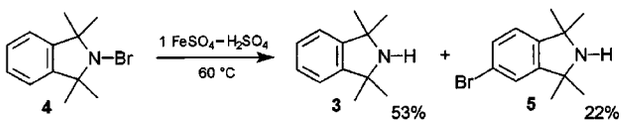
ether solutions of **3** and benzaldehyde. The formation of this reduced form of the bromoamine further suggests that **4** serves as a mild oxidant, converting benzaldehyde into benzoic acid.

Well-formed crystals of **3a** allowed a single crystal structure determination, giving the structure shown in Fig. 2, in which the isoindolinium cation forms a stable cation–anion association with the bromide ion. In addition, there are hydrogen bonding associations involving the indolinium protons and the lattice water molecules [O(1) and O(2)] [N(2) · · · O(1), 2.840(7) Å; N(2) · · · O(2), 2.806(7) Å], as well as bromide · · · water associations [Br · · · O(1), 3.345, 3.358(5) Å; Br · · · O(2), 3.331, 3.376(5) Å]. This is consistent with the general physical proper-

ties of the compound (high melting point, hardness and crystal stability).

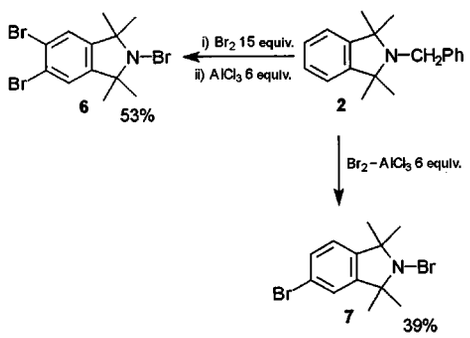
Bromination of the isoindoline ring

Treatment of bromoamine **4** with Fe^{II} in dilute H_2SO_4 was found to give the bromo-substituted isoindoline **5** in varying yield (up to 22%). The major product of the reaction, however, was the parent isoindoline **3** (up to 53%) (Scheme 2).



Scheme 2 Self-bromination of 2-bromo-1,1,3,3-tetramethylisoindoline (**4**).

Treatment of the nitroxide precursor **2** with Br_2 in the presence of $AlCl_3$ resulted in bromination of the aromatic ring at the 5- and/or 6- position (Scheme 3). Successful synthesis



Scheme 3 Bromination of the tetramethylisoindoline system.

of 2,5-dibromo-1,1,3,3-tetramethylisoindoline **7** and 2,5,6-tribromo-1,1,3,3-tetramethylisoindoline **6** was, however, strongly dependent upon the use of anhydrous, powdered $AlCl_3$ and strict control of the reaction conditions. Variation in reaction conditions resulted in the production of variable mixtures of all three bromoamines (**4**, **6** and **7**) the separation of which was problematic on a preparative scale. All three compounds exhibit essentially identical chromatographic retentions on silica and fractional crystallisation is difficult due to the low melting points of the compounds and their high solubility in common organic solvents.

Selective formation of **6** was afforded by treatment of **2** with 15 equivalents of Br_2, followed by addition of $AlCl_3$. Notably, the formation of the monobrominated product **7** was essentially negligible under these conditions as determined by NMR, suggesting that the 6-position is activated towards electrophilic substitution by the introduction of the first bromine substituent. This was reflected in the requirement for milder reaction conditions for selective synthesis of **7**.

Selective synthesis of **7** was favoured by the addition of **2** to a preformed $AlCl_3$–Br_2 complex, with a reduction in the number of equivalents of Br_2. The milder conditions however, also reduced the efficiency of the bromination such that a major side-product was the unsubstituted bromoamine **4**, which we were unable to separate from the desired product. Fortunately, resolution of the nitroxide derivatives of these compounds was successful.

Reduction of bromoamines to corresponding secondary amines

Treatment of each of the bromoamines (**4**, **6** and **7**) with H_2O_2 resulted in rapid reduction of the bromoamine to give the corresponding amines (**3**, **8** and **5** respectively) (Scheme 4). Oxidation of H_2O_2 initially caused vigorous effervescence due

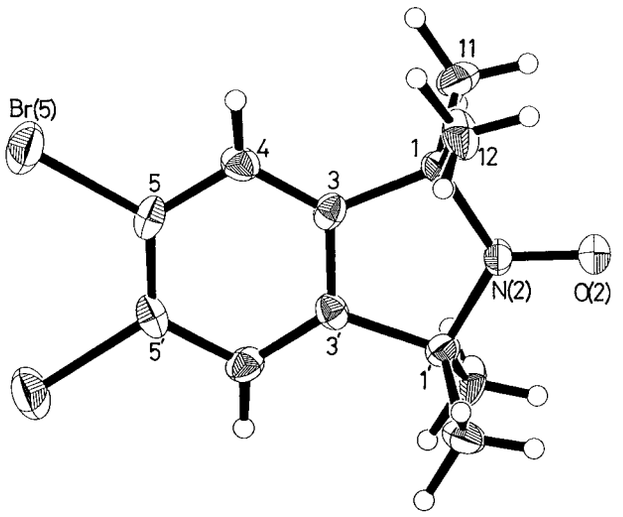
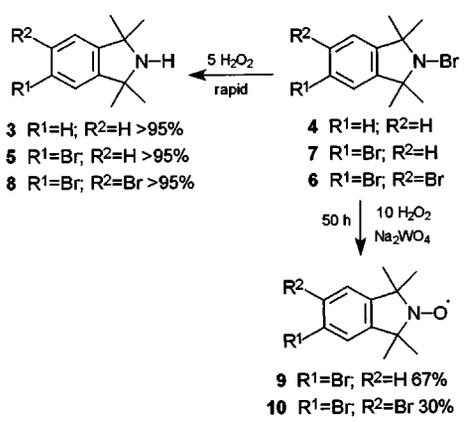


Fig. 3 Molecular configuration and atom numbering scheme for **10**. Unless otherwise indicated, atoms are carbon.



Scheme 4 Formation of nitroxides and amines from corresponding bromoamines.

to the production of O_2. The addition of bicarbonate facilitated complete reduction of the bromoamine, as the reaction was relatively sluggish and yields were reduced in its absence.

Further oxidation of the secondary amines to nitroxides by excess H_2O_2 is slow and was prevented by quenching the reaction mixture with 2 M NaOH within a few minutes of cessation of vigorous effervescence.

5-Bromo- and 5,6-dibromo-1,1,3,3-tetramethylisoindolin-2-yloxyl (9 and 10)

Oxidation of bromoamines **6** and **7** by H_2O_2 in the presence of $Na_2WO_4 \cdot 2H_2O$ gave the corresponding brominated nitroxides, **10** and **9**, in fair yield (Scheme 4). Initial addition of H_2O_2 produced vigorous effervescence as the bromoamines were reduced to the corresponding secondary amines (**8** and **5** respectively). Oxidation of the amines by excess H_2O_2 over the subsequent 50 hours gave the corresponding nitroxides, the identities of which were confirmed by gas chromatography–mass spectrometry and EPR, with each exhibiting a typical three-line nitroxide spectrum (Table 1).

Suitable crystals of **10** allowed a room-temperature, single-crystal structure determination to be completed, which confirmed the molecular structure of the nitroxide elucidated from the physical data. The molecules of **10** have two-fold rotational symmetry (Fig. 3) coincident with crystallographic symmetry, in the chiral space group $P4_12_12$. These consequently arrange helically down the 4_1 screw axis (Fig. 4), and although there are no significant nitroxide–nitroxide interactions, there is a weak intermolecular O · · · C (methyl) contact [O(2) · · · C(12), 3.39(1)

Table 1 EPR characteristics of brominated nitroxides **9** and **10**

Comp.	B_{res}/G	g	a_N /G	a_N /10^{-4} cm^{-1}
9	3381.07	2.0058	14.428	13.51
10	3380.69	2.0058	14.431	13.51

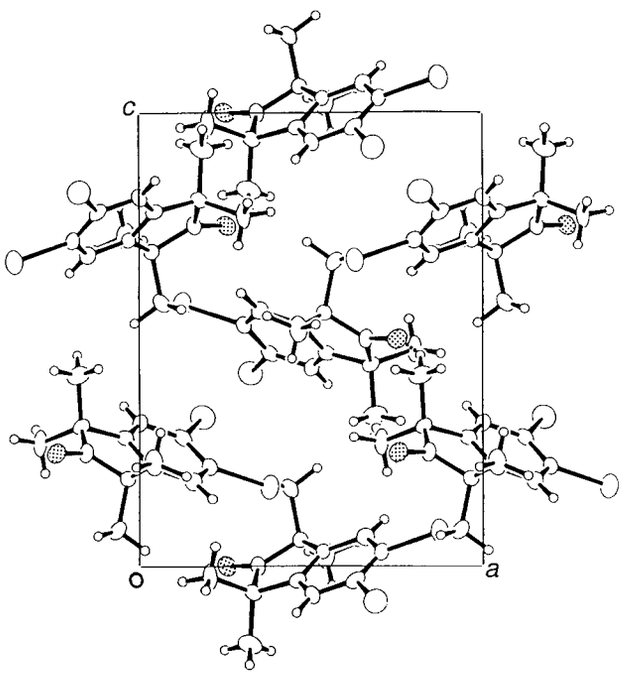


Fig. 4 Packing of molecules of **10** in the unit cell, viewed across the crystallographic 4_1 screw axis of the unit cell (*c* axis).

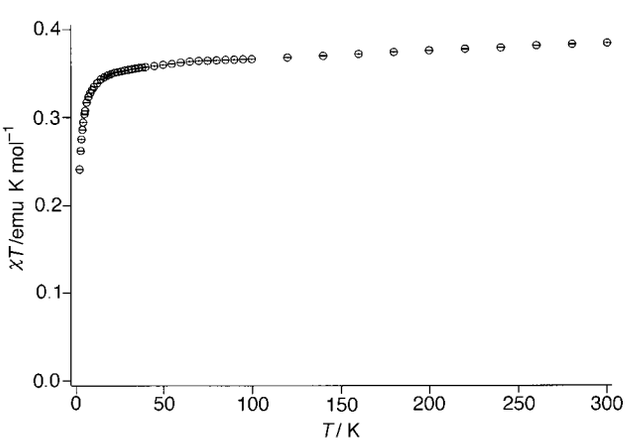


Fig. 5 Temperature dependence of the paramagnetic susceptibility of radical **10**.

Å]. This fact, together with the presence of acentric molecular packing, suggested the possibility of interradical magnetic interactions and prompted the measurement of the paramagnetic susceptibility of **10**.

Paramagnetic susceptibilities of radical 10

The interradical magnetic interactions in the unusual packing arrangement of the crystalline form of nitroxide **10** were investigated through the temperature dependence of its paramagnetic susceptibility χ in the temperature range 2–300 K at constant magnetic field (5000 G) on a Quantum Design MPMS-2 superconducting quantum interference device (SQUID) magnetometer/susceptometer. The data are presented in Fig. 5. Since it was not clear if the interradical interaction is stronger along the helical chain or between the chains, a mean-field theory for the interradical interaction was employed. A Curie–Weiss law, $\chi = C/(T - \theta)$, for the linear high-temperature data in the range 160–300 K gave $C = 0.3998$ emu K mol^{-1} and $\theta = -12.31$ K. Ferromagnetic interradical coupling was not found.

A most plausible origin for the antiferromagnetic interaction would be a through-space N–O · · · N–O interaction[29] (5.353(6) Å between the nearest neighbour nitroxides in the unit cell) and/or a through O · · · H_3C hydrogen bond-type interaction (O · · · C distance of 3.39(1) Å).

Experimental

NMR spectra were recorded on a Varian Unity 300 spectrometer. *J* Values are given in Hz. Gas chromatography-mass spectrometry was performed in EI mode on a Fisons Instruments MD800 gas chromatograph-mass spectrometer (GC-MS) equipped with a 60 m, 0.25 mm id, DB1 capillary column. EPR spectra were measured on a Bruker ESP 300E EPR spectrometer (X-band, ~9.2 GHz) using an EIP 548B microwave frequency counter and a Bruker O35M gaussmeter for microfrequency calibration. A fine microcrystalline sample of **10** (32.88 mg) was mounted in a gelatin capsule (4.5 × 11 mm, Japan Pharmacopoeia NO.) and its magnetic susceptibility was measured on a Quantum Design MPMS-2 superconducting quantum interference device (SQUID) magnetometer/susceptometer at 5000 G. Corrections for the diamagnetic contribution of the sample (-168×10^{-6} emu mol^{-1}) were made by using Pascal's constants. Those for the sample capsule were made directly by using the empty capsule. 2-Benzyl-1,1,3,3-tetramethylisoindoline (**2**) was synthesised as previously described.[17]

Oxidative debenzylation of 2-benzyl-1,1,3,3-tetramethylisoindoline (2)

Liquid Br_2 (2.40 cm^3, 46.8 mmol, 6 equiv.) was added dropwise to a stirring solution of 2-benzyl-1,1,3,3-tetramethylisoindoline (**2**) (2.00 g, 7.55 mmol) in CCl_4 (40 cm^3) resulting in the immediate deposition of a red oil on the sides of the vessel. After 15 min the reaction was basified by the careful addition of aqueous NaOH (2 M; 100 cm^3) and extracted with dichloromethane (3 × 50 cm^3). The combined organics were washed with water (50 cm^3), dried over Na_2SO_4 and evaporated under reduced pressure to give a golden oil which rapidly crystallised. Separation of the product mixture by column chromatography (SiO_2; 35–70 mesh; 1 : 3 : 96 AcOH–EtOAc–hexane) gave benzaldehyde and 2-bromo-1,1,3,3-tetramethylisoindoline **4**, which was recrystallised as pale yellow crystals from MeOH–H_2O (1.42 g, 74%), mp 53–54 °C (Found: C, 56.6; H, 6.4; N, 5.4. $C_{12}H_{16}BrN$ requires C, 56.7; H, 6.3; N, 5.5%); δ_H (299.949 MHz; $CDCl_3$) 1.48 (12H, s, CH_3), 7.17 (2H, dd, *J* 3.2 and 5.4, 5-H and 6-H), 7.27 (2H, dd, *J* 3.2 and 5.4, 4-H and 7-H); δ_C (75.430 MHz; $CDCl_3$) 28.2 (CH_3), 69.5 (C-1 and C-3), 121.6 (C-5 and C-6), 127.2 (C-4 and C-7), 144.2 (C-3a and C-7a).

An alternative synthesis of **4** was performed in aqueous solution. A solution of Br_2 in AcOH (1 M; 1.5 cm^3, 4 equiv.) was added dropwise to a stirring solution of **2** (100 mg, 377 μmol) in H_2O–MeCN (3 : 1; 4 cm^3) at room temperature. After 15 min the reaction was basified by the careful addition of NaOH (5 M) and extraction with dichloromethane (3 × 10 cm^3). The combined organics were washed with water (50 cm^3), dried over Na_2SO_4 and evaporated under reduced pressure to give a golden oil which rapidly crystallised. ^{1}H NMR showed the product to be a 5 : 3 mixture of **4** (90 mg, 95%) and benzaldehyde (23 mg, 57%).

Adaptations of the above oxidative debenzylation procedures were performed using one equivalent of Br_2. In both CCl_4 and aqueous solutions the crude product was found, by ^{1}H and ^{13}C

NMR, to contain a mixture of isoindoline **3**, benzaldehyde and starting material.

Exposure of **4** to oxidisable compounds (*e.g.* benzaldehyde) in solution over a period of several days resulted in the precipitation of a fine white crystalline material. This was recovered and recrystallised from MeCN, giving opaque white, or transparent prisms, which were identified by NMR and FT-IR as the hydrated hydrobromide salt of **3** (**3a**), mp 287–291 °C (decomp.) (Found: C, 49.0; H, 7.4; N, 4.7. $C_{12}H_{17}N{\cdot}HBr{\cdot}2H_2O$ requires C, 49.3; H, 7.6; N, 4.8%); ν_{max}/cm^{-1} 2800–2200br (N–H^+ str.), 2400–2550s (N–H^+ def.), 840s (NH_2^+ rock); δ_H (299.949 MHz; $CDCl_3$) 2.00 (12H, s, CH_3), 7.14 (2H, dd, *J* 3.0 and 5.7, 5-H and 6-H), 7.37 (2H, dd, *J* 3.0 and 5.7, 4-H and 7-H); δ_C (75.430 MHz; $CDCl_3$) 29.4 (CH_3), 68.8 (C-1 and C-3), 121.2 (C-5 and C-6), 129.2 (C-4 and C-7), 142.2 (C-3a and C-7a). X-Ray diffraction confirmed the identity of the compound as the dihydrate form of the hydrobromide salt of **3** (**3a**) (Fig. 2).

Independent synthesis of 2-bromo-1,1,3,3-tetramethylisoindoline (4)

A solution of Br_2 in CCl_4 (1.0 M; 2 cm^3, 2 mmol, 3.5 equiv.) was added dropwise to a stirring solution of isoindoline **3** (100 mg, 571 μmol) in CCl_4 (2 cm^3). The Br_2 colour faded rapidly and a red oil deposited on the sides of the flask. After 15 min the reaction mixture was basified with NaOH (2 M) and extracted with dichloromethane (3 × 10 cm^3). The combined organic components were washed with water, dried over Na_2SO_4 and the solvent removed under reduced pressure, giving the bromoamine **4** (137 mg, 94%), which was identified by ^1H and ^{13}C NMR.

Self-bromination of 2-bromo-1,1,3,3-tetramethylisoindoline (4)

$FeSO_4{\cdot}7H_2O$ (120 mg, 1 equiv.) was added to a hot (60 °C), stirring solution of **4** (100 mg, 394 μmol) in dil. H_2SO_4 (6 M; 3 cm^3). The solution initially became red–brown and then grew opaque. Over several minutes the colour deepened to dark brown and the suspension cleared. After 10 minutes the reaction mixture was basified with NaOH (5 M) and extracted with dichloromethane (3 × 20 cm^3). The combined organic components were washed with water and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a colourless oil, the major component of which was the isoindoline **3** (53% by ^1H NMR). The other product was identified as the bromo-substituted species **5** (22% by ^1H NMR).

2,5-Dibromo-1,1,3,3-tetramethylisoindoline (7)

Liquid Br_2 (1.5 cm^3, 29.3 mmol, 6 equiv.) was added with care to a cold (0 °C), stirring mixture of CCl_4 (25 cm^3) and anhydrous $AlCl_3$ (~6.5 g, 48.7 mmol, 10 equiv.). A solution of **2** (1.25 g, 4.72 mmol) in CCl_4 (25 cm^3) was added dropwise with the immediate deposition of a red oil.

After stirring at 0 °C for 1 hour the reaction mixture was basified with NaOH (5 M). The aqueous mixture was extracted with dichloromethane (3 × 50 cm^3) and the combined organic components washed with water and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave a crude mixture containing bromoamines **4** (230 mg, 19%) and **7** (610 mg, 39%) in a 1:2 molar ratio according to ^1H NMR; δ_H (299.949 MHz; $CDCl_3$) 1.43 (6H, s, CH_3), 1.44 (6H, s, CH_3), 7.02 (1H, d, *J* 8.1, 7-H), 7.28 (1H, d, *J* 1.7, 4-H), 7.37 (1H, dd, *J* 1.7 and 8.1, 6-H); δ_C (75.430 MHz; $CDCl_3$) 28.0 (CH_3), 28.2 (CH_3), 69.4 (C-1), 69.6 (C-3), 120.9 (C-5), 123.6 (C-6), 124.9 (C-7), 130.4 (C-4), 143.2 (C-7a), 146.4 (C-3a); *m/z* 253/255 (M^+, <1%), 238/240 (100), 223/225 (32). Separation of these compounds using chromatography proved impossible, but resolution was achieved after oxidation to the corresponding nitroxides, through fractional crystallisation.

2,5,6-Tribromo-1,1,3,3-tetramethylisoindoline (6)

A solution of **2** (0.50 g, 1.89 mmol) in CCl_4 (10 cm^3) containing pyridine (50 μl, 0.621 mmol, 0.33 equiv.) was cooled in an ice–H_2O bath. Liquid Br_2 (1.5 cm^3, 29.3 mmol, 15 equiv.) was added dropwise causing immediate deposition of a red oil. After stirring at 0 °C for 15 min, anhydrous $AlCl_3$ (~1.6 g, 12.0 mmol, 6.4 equiv.) was added to the solution. The reaction mixture was stirred for another 3.5 hours at 0 °C and then basified with NaOH (5 M). The aqueous mixture was extracted with dichloromethane (3 × 50 cm^3) and the combined organic components washed with water and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave a crude mixture containing benzaldehyde and bromoamine **6**.

Bromoamine **6** was purified by column chromatography (SiO_2; 35–70 mesh; 1:3:96 AcOH–EtOAc–hexane), and recrystallised from MeOH–H_2O, forming yellow needles (413 mg, 53%), mp 110–112 °C (Found: C, 35.2; H, 3.4; N, 3.3. $C_{12}H_{14}Br_3N$ requires C, 35.0; H, 3.4; N, 3.4%); δ_H (299.949 MHz; $CDCl_3$) 1.43 (12H, s, CH_3), 7.39 (2H, s, 4-H and 7-H); δ_C (75.430 MHz; $CDCl_3$) 28.0 (CH_3), 69.4 (C-1 and C-3), 123.2 (C-5 and C-6), 127.0 (C-4 and C-7), 145.3 (C-3a and C-7a); *m/z* 331/333/335 (M^+, <1%), 316/318/320 (100), 301/303/305 (23).

Reduction of bromoamines to corresponding secondary amines

Each of the bromoamines **4**, **6** and **7** was reduced rapidly by treatment with H_2O_2 to give the corresponding amine (**3**, **8** and **5** respectively). A representative procedure for reduction of **4** is detailed below.

A solution of bromoamine **4** (200 mg, 0.79 mmol) in MeOH (2 cm^3) containing $NaHCO_3$ (100 mg, 1.19 mmol, 1.5 equiv.) and a catalytic amount of $Na_2WO_4{\cdot}H_2O$ (~20 mg, 61 μmol) was treated with H_2O_2 (30%; 500 μl, 4.4 mmol, 5.6 equiv.), producing vigorous effervescence which quickly subsided. The reaction mixture was immediately quenched and basified with 2 M NaOH, and extracted with dichloromethane. The organic components were washed with H_2O, dried over Na_2SO_4, and the solvent removed under reduced pressure, leaving a colourless oil which crystallised to give isoindoline **3** (135 mg, 98%), mp 36–38 °C (lit.,[17] 36–38 °C); δ_H (299.949 MHz; $CDCl_3$,) 1.46 (12H, s, CH_3), 2.00 (1H, br, NH), 7.12 (2H, dd, *J* 3.2 and 5.4, 5-H and 6-H), 7.24 (2H, dd, *J* 3.2 and 5.4, 4-H and 7-H); δ_C (75.430 MHz; $CDCl_3$) 32.0 (CH_3), 62.6 (C-1 and C-3), 121.5 (C-5 and C-6), 127.0 (C-4 and C-7), 148.5 (C-3a and C-7a); *m/z* 175 (M^+, 1%), 160 (100), 145 (36).

This procedure was adapted appropriately for the reduction of bromoamines **6** and **7**. The addition of a small volume of MeCN to the solvent was necessary to facilitate solution of the organic reagents. Isoindolines **5** and **8** were identified by NMR and GC-MS but not characterised further, as they were not major synthetic targets.

Isoindoline **5**: δ_H (299.949 MHz; $CDCl_3$) 1.43 (6H, s, CH_3), 1.45 (6H, s, CH_3), 1.87 (1H, br, NH), 6.98 (1H, d, *J* 7.8, 7-H), 7.23 (1H, d, *J* 2.0, 4-H), 7.34 (1H, dd, *J* 2.0 and 7.8, 6-H); δ_C (75.430 MHz; $CDCl_3$) 31.7 (CH_3), 62.5 (C-1), 62.6 (C-3), 121.3 (C-5), 123.0 (C-6), 124.7 (C-7), 130.1 (C-4), 147.8 (C-7a), 151.2 (C-3a); *m/z* 253/255 (M^+, 1%), 238/240 (100), 223/225 (29), 159 (13), 115 (20).

Isoindoline **8**: mp 76–77 °C; δ_H (299.949 MHz; $CDCl_3$) 1.42 (12H, s, CH_3), 1.87 (1H, br, NH), 7.34 (2H, s, 4-H and 7-H); δ_C (75.430 MHz; $CDCl_3$) 31.5 (CH_3), 62.4 (C-1 and C-3), 122.8 (C-5 and C-6), 126.8 (C-4 and C-7), 150.2 (C-3a and C-7a); *m/z* 331/333/335 (M^+, 1%), 316/318/320 (100), 301/303/305 (22), 239/237 (7), 158 (21), 142 (23), 115 (16).

5-Bromo- and 5,6-dibromo-1,1,3,3-tetramethylisoindolin-2-yloxyl (9 and 10)

A 1:2 mixture of **6** and **7** (134 mg, 373 μmol) was dissolved in MeOH (1.20 cm^3) containing the minimum amount of MeCN

(50 μl) necessary for dissolution of the substrates. $NaHCO_3$ (50 mg, 595 μmol, 1.6 equiv.) and $Na_2WO_4 \cdot 2H_2O$ (20 mg, 60 μmol) were added to the solution, followed by H_2O_2 (30%; 420 μl, 3.71 mmol, 10 equiv.). After the initial vigorous effervescence subsided the solution was stirred at room temperature for 50 hours.

The reaction mixture was diluted with H_2O (10 cm^3) and extracted with dichloromethane (3 × 25 cm^3). The combined organic components were washed with dilute H_2SO_4 (1 M) and finally with brine. Evaporation of the organic phase under reduced pressure produced a mass of yellow–orange crystals which was repeatedly triturated with cold hexane, leaving **10** undissolved. This was recrystallised from MeCN to give bright orange crystals (13 mg, 30%), mp 258 °C (decomp.) (Found: C, 41.4; H, 4.1; N, 4.0. $C_{12}H_{14}Br_2NO$ requires C, 41.4; H, 4.1; N, 4.0%); *m*/*z* 346/348/350 (M^+, 72%), 331/333/335 (47), 316/318/320 (68), 301/303/305 (57), 222/224 (42), 143 (100), 128 (88), 115 (73); *g* 2.0058, a_N 14.428 G.

Evaporation of the triturant under reduced pressure gave the hexane soluble component, **9**, which was recrystallised from MeCN giving poorly-shaped yellow platelets (45 mg, 67%), mp 109 °C (Found: C, 53.6; H, 5.6; N, 5.1. $C_{12}H_{15}BrNO$ requires C, 53.6; H, 5.6; N, 5.2%); *m*/*z* 268/270 (M^+, 66%), 253/255 (66), 238/240 (73), 223/225 (57), 144 (100), 128 (84), 115 (61); *g* 2.0058, a_N 14.431 G.

Crystallography

Crystal data for (3a). $C_{12}H_{22}BrNO_2$, $M = 292.2$, monoclinic, space group $P2_1/n$ (variant of $P2_1/c$, No. 14), $a = 9.862(2)$, $b = 12.495(3)$, $c = 11.898(4)$ Å, $\beta = 91.45(2)°$, $V = 1465.7(6)$ Å^3, $F(000) = 608$, $D_c(Z = 4)$ 1.324 g cm^{-3}, μ(Mo-Kα) 28.0 cm^{-1}, T 295(1) K, crystal size 0.38 × 0.26 × 0.25 mm.

Crystal data for (4). $C_{12}H_{16}BrN$, $M = 254.2$, monoclinic, space group $P2_1/n$ (variant of $P2_1/c$, No. 14), $a = 6.1366(6)$, $b = 13.4524(9)$, $c = 14.156(1)$ Å, $\beta = 99.433(4)°$, $V = 1152.8(2)$ Å^3, $F(000) = 520$, $D_c(Z = 4)$ 1.464 g cm^{-3}, μ(Cu-Kα) = 45.3 cm^{-1}, T 130.0(1) K, crystal size 0.36 × 0.36 × 0.07 mm.

Crystal data for (10). $C_{12}H_{14}Br_2NO$, $M = 348.1$, tetragonal, space group $P4_12_12$ (No. 92), $a = 9.9675(7)$, $c = 13.353(1)$ Å, $V = 1326.6(1)$ Å^3, $F(000) = 684$, $D_c(Z = 4)$ 1.743 g cm^{-3}, μ(Mo-Kα) 61.1 cm^{-1}, T 295(1) K, crystal size 0.42 × 0.20 × 0.20 mm.

Data collection, structure solution and refinement. X-Ray diffraction data for **3a** and **10** were collected at ambient temperature on a Rigaku AFC7R diffractometer by using graphite monochromatised Mo-Kα X-radiation (λ 0.71069 Å) from a 12 kW rotating anode source. Data for **4** were collected at low temperature (130 K: Oxford Cryostream cooled) on an Enraf-Nonius CAD-4f four-circle diffractometer by using nickel filtered Cu-Kα X-radiation (λ 1.54180 Å). Minor decay in the intensities of three standards monitored throughout the respective data collection periods [maximum, 3% for **4**] indicated negligible crystal decomposition but was allowed for by using a linear isotropic correction. Of 3625 reflections (3430 unique: $2\theta_{max}$ 55°) [for **3a**], 2543 reflections (2350 unique: $2\theta_{max}$ 150°) [for **4**], and 956 unique reflections ($2\theta_{max}$ 55°) [for **10**], 1152, 2123 and 374 respectively with $I > 2\sigma(I)$ (**2**) or $I > 3\sigma(I)$ (**3a** and **10**) were considered observed and were used in the expression of conventional refinement residuals.† Data were corrected for Lorentz and polarisation effects and for extinction, with either analytical absorption corrections being applied [for **4**] (Gaussian[30]) [max./min. transmission factors 0.71, 0.27], or semi-empirical corrections (psi scans) [for **3a** and **10**]. The structures were solved by direct methods (SHELXS-86,[31] SIR92,[32] DIRDIF-94[33]) and refined using full-matrix least-squares refinement (SHELXL-93[34] or TeXsan[35]), with anisotropic thermal parameters for all non-hydrogen atoms, giving residuals† R, wR_2 (or R_w) and S respectively of 0.038, 0.035 (R_w), 1.78 [for **3a** {on (F_o)}], 0.056, 0.147 (wR_2), 1.02 [for **4** {on (F_o)^2}], and 0.028, 0.023 (R_w), 1.31 [for **10** (on F_o)]. Hydrogen atoms were located either by difference methods or were included in the refinements at calculated positions with positional and thermal parameters either fixed or riding.

Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 2*, available *via* the RSC web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 188/148.

† $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w(F_o)^2]^{\frac{1}{2}}$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{\frac{1}{2}}$.

Acknowledgements

The authors acknowledge the financial support of the Centre for Instrumental and Developmental Chemistry of the Queensland University of Technology and the Australian Research Council.

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Paper 8/06884D