Fairfull-Smith, Kathryn, Debele, Emmanuel, Allen, Jesse, Pfrunder, Michael, & McMurtrie, John
(2013)
Direct iodination of isoindolines and isoindoline nitroxides as precursors to functionalized nitroxides.
European Journal of Organic Chemistry, *2013*(22), pp. 4829-4835.

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https://doi.org/10.1002/ejoc.201300313

Direct Iodination of Isoindolines and Isoindoline Nitroxides as Precursors to Functionalized Nitroxides

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A new method for the direct aryl iodination of isoindolines and isoindoline nitroxides which utilizes periodic acid and potassium iodide in sulfuric acid is presented. Di-iodo functionalized tetramethyl and tetraethyl isoindolines and a di-iodo tetramethyl isoindoline nitroxide were prepared in high yield (70-82%). The analogous mono-iodo species were afforded in modest yield (34-48%). Iodinated nitrones were also obtained from a tetraethyl isoindoline nitroxide.

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        Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.xxxxxxxxx.

Introduction

Nitroxides (aminoxyls) are versatile stable free-radical containing compounds which are currently exploited in a variety of applications.[1,2] The isoindoline class of nitroxides, based on the structure of 1,1,3,3-tetramethylisoindolin-2-yloxyl **1**, are of particular interest due to their resistance to ring-opening reactions which are significant decomposition routes for pyrrolidine and piperidine based nitroxides (**2** and **3**).[3] The fused aromatic ring of isoindoline nitroxides provides additional advantages such as improved chemical and thermal stability in polymers[4,5] and superior electron paramagnetic resonance (EPR) linewidths.[6]
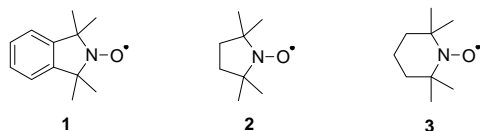

The uses for isoindoline based nitroxides are varied and include their application as spin traps,[7] antioxidants,[8,9] profluorescent probes[10] for imaging thermo-oxidative polymer degradation[11] or oxidative stress in biological systems,[12] probes for evaluating the oxidative potential of pollution,[13] alkoxyamines for polymeric radical exchange reactions,[14] spin labels for exploring the dynamic structure of nucleic acids[15] and prospective redox mediators for dye-sensitised solar cells.[16]

For applications outside of radical trapping, the isoindoline nitroxides utilized typically possess a functionalized aromatic ring, which allows the nitroxide moiety to be tailored for specific applications. A common precursor to functionalized isoindoline nitroxide structures are nitroxides bearing aryl halide substituents. The structural diversity of the halogen-substituted nitroxides can be readily expanded by aromatic substitution (for example, using palladium or copper catalysed coupling reactions)[17,18] to generate more complex structures. Due to the electron rich nature of the isoindoline system, the reactivity of the 5-iodo nitroxide **6** in cross coupling reactions is far superior to that of the brominated analogue.[19] Thus, there is a need for access to a range of iodinated isoindoline nitroxides in order to expand the scope for structural variations and broaden applications for this important class of compounds.

The current synthetic route used to prepare the 5-iodo nitroxide **6** involves a halogen exchange reaction which is achieved by lithiation of bromoamine **4** and treatment with iodine (Scheme 1).[11] Subsequent oxidation to the nitroxide is performed using hydrogen peroxide and a tungstate catalyst. This current strategy is limited in that it does not provide access to di-iodinated species nor can it be used to prepare iodinated analogues with bulkier ethyl groups surrounding the nitroxide radical (bromination of the *N*-benzyl-1,1,3,3-tetraethylisoindoline precursor is thought to cause ring opening).[20] Herein we describe a new direct route for the efficient mono- or di-iodination of isoindolines and isoindoline nitroxides using periodic acid and potassium iodide in concentrated sulfuric acid.
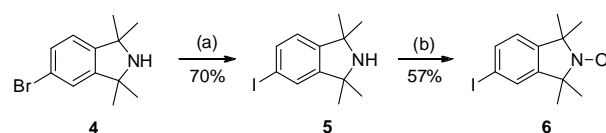
Scheme 1. Current synthetic route used to prepare **6**.[11] *Reagents and conditions:* (a)*(i) n*BuLi, THF, -78ºC, 15 min, *(ii)* I₂, THF, -78ºC to RT, *(iii)* NaHCO₃, H₂O₂, MeOH-DCM; 30 min; (b) NaHCO₃, Na₂WO₄.2H₂O, H₂O₂, MeOH, 3 days.

Results and Discussion

Aryl iodides can be prepared using many different methods;[21] however the low electrophilicity of molecular iodine makes direct iodination difficult, even in the presence of activating Lewis acids. The formation of HI can also cause problems if acid sensitive groups are present within the molecule. To circumvent these issues,

iodinations are often performed under oxidative conditions, where iodide ions (formed in the reaction) are reoxidised.[22] The use of *N*-iodosuccinimide (NIS) is a popular reagent for iodination but is generally limited to highly activated arenes. In our hands, 1,1,3,3-tetramethylisoindoline **7** was unreactive when treated with NIS and trifluoroacetic acid in chloroform.

A high yielding octaiodination of an electron rich tetramethylfenestrindane has been reported by Kuck and Tellenbröker[23] using potassium iodide (KI) and periodic acid (H_5IO_6) in conc. sulfuric acid (H_2SO_4).[24] Under these conditions, H_5IO_6 reacts with H_2SO_4 and HI (formed from the reaction of KI with H_2SO_4) to produce $IOSO_3H$ (a source of strongly electrophilic iodonium ions, I^+).[22]

Using these conditions, we first attempted to prepare 5-iodo-1,1,3,3-tetramethylisoine **5** by reacting 1,1,3,3-tetramethylisoindoline **7** with 1.1 equivalents of I^+ (calculated using established stoichiometry).[22] After 3 hours, no starting material remained and a 7:3 ratio of mono-iodo product **5** and 5,6-diiodo-1,1,3,3-tetramethylisoine **8** was observed by ^1H NMR spectroscopy. The formation of a significant amount of di-iodo product **8** with the use of only 1.1 equivalents of I^+ suggests that once iodinated, the aromatic ring is not deactivated towards further substitution and di-iodination occurs. As the iodoamines **5** and **8** exhibited almost identical chromatographic rententions on silica, only a modest yield (34%) of pure **5** could be isolated (Scheme 2). The amount of di-iodo product **8** formed could be reduced when only 0.7 equivalents of I^+ were used, however more unreacted starting material **7** remained (the ratio of compounds **5**:**8**:**7** obtained was 13:1:6 by ^1H NMR spectroscopy). The di-iodo product **8** could be exclusively formed when 2.8 equivalents of I^+ was employed and was isolated in good yield (70%). No tri- or tetra-iodinated products were observed, even when 5.0 equivalents of I^+ was used.
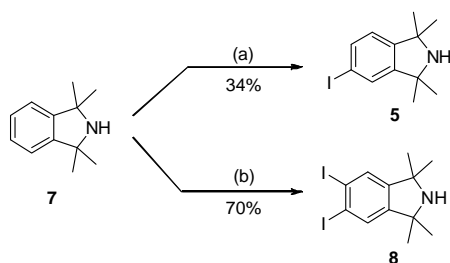
Scheme 2. Synthesis of iodoamines **5** and **8**. *Reagents and conditions:* (a) H_5IO_6 (0.27 equiv.), KI (0.83 equiv.), conc. H_2SO_4, 0ºC to RT, 3 hr; (b) H_5IO_6 (0.69 equiv.), KI (2.09 equiv.), conc. H_2SO_4, 0ºC to RT, 3 hr.

Following the successful preparation of iodo-substituted isoindolines **5** and **8**, we next attempted direct iodination of nitroxide **1**. Due to the paramagnetic broadening effect exhibited by nitroxides in ^1H NMR spectroscopy, the ratio of products obtained was analysed by analytical HPLC. The reaction of nitroxide **1** with 1 equivalent of I^+ (generated from H_5IO_6 and KI in H_2SO_4) gave mono-iodo nitroxide **6**, di-iodo nitroxide **9** and unreacted starting material **1** in a ratio of 54:32:3 respectively after stirring at room temperature for 3 hours. The best conversion to mono-iodo compound **6** was achieved when only 0.7 equivalents of I^+ were employed. Under these conditions the HPLC product ratio of **6**:**9**:**1** was found to be 14:5:1. Following careful separation by silica gel chromatography, the pure mono-iodo nitroxide **6** was isolated in modest yield (48%, Scheme 3).

The di-iodo nitroxide **9** could be selectively formed from nitroxide **1** in a high isolated yield (82%) when 3.6 equivalents of I^+ were used. Treatment of nitroxide **1** with 5 equivalents of I^+ did
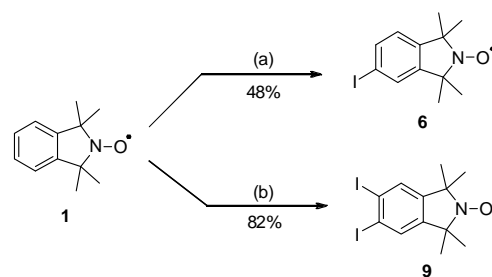
Scheme 3. Synthesis of iodo-substituted nitroxides **6** and **9**. *Reagents and conditions:* (a) H_5IO_6 (0.18 equiv.), KI (0.53 equiv.), conc. H_2SO_4, 0ºC to RT, 3 hr; (b) H_5IO_6 (0.9 equiv.), KI (2.7 equiv.), H_2SO_4, 3 hr.

not further improve the yield of **9**. The di-iodo compound **9** gave crystals which were suitable for single-crystal X-ray analysis (Figure 1). The crystal structure of **9** shares unit cell dimensions and crystal symmetry with structures of the similar molecules 5,6-dibromo-1,1,3,3-tetramethylisoin-2-yloxyl, 5,6-cyano- 1,1,3,3-tetramethylisoin-2-yloxyl and 5-bromo-6-cyano-1,1,3,3-tetramethylisoin-2-yloxyl.[25,26] The asymmetric unit comprises one half of the molecule which lies on a crystallographic 2-fold axis (the axis is coincident with the nitroxide N(1)–O(1) bond). Molecules arrange down a 4_3 screw axis, taking part in weak intermolecular hydrogen bonds of the form of Ar-H···O and C-H···O, with each O atom acting as acceptor for four interactions. Steric repulsion between I atoms appears to result in a slightly enlarged I···centroid···I angle of 63° (where the centroid is calculated from the position of the atoms of the 6-membered ring of the isoindoline moiety). The two rings of the isoindoline group deviate only 0.29° from co-planarity. The nitroxide N–O bond length of 1.272(4) Å is consistent with N–O bond lengths observed for 5-membered isoindoline type nitroxides.[27] Interestingly, the structure of **9** does not involve halogen bonds despite containing known donor (Ar-I) and acceptor (N-O) functionalities.[28,29]
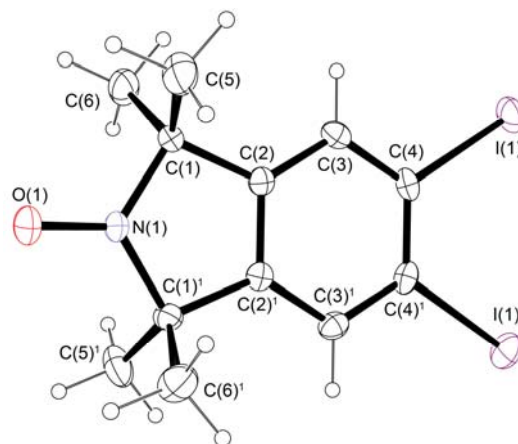
Figure 1. ORTEP depiction of the crystal structure of 5,6-diiodo-1,1,3,3-tetramethylisoin-2-yloxyl **9**.

The expansion of the synthetic utility of tetraethyl-based nitroxides such as **14** is currently hindered by a lack of available methods to prepare aryl halide analogues in high yield. For this reason, we were keen to explore our new iodination methodology on tetraethyl-based isoindolines and their corresponding nitroxides. Using the previously optimised conditions for mono-iodination, tetraethyl isoindoline **10** was reacted with 0.7 equivalents of I^+ (generated from H_5IO_6 and KI in H_2SO_4) for 3 hours. Analysis of the product mixture by ^1H NMR spectroscopy revealed the

formation of mono-iodo product **11**, di-iodo product **13** and unreacted starting material **10** in a ratio of 6:1:1. Due to the polar nature of all products, attempts to separate the desired mono-iodo compound **11** using both normal and reversed phase chromatography were unsuccessful. Instead, oxidation of the mixture of secondary amines to their corresponding nitroxides was undertaken using *m*CPBA in DCM. Analysis of the resulting product mixture by analytical HPLC revealed the formation of the mono-iodo nitroxide **12**, the di-iodo nitroxide **15** and unsubstituted nitroxide **14** in a ratio of 16:1:4. At this stage, separation 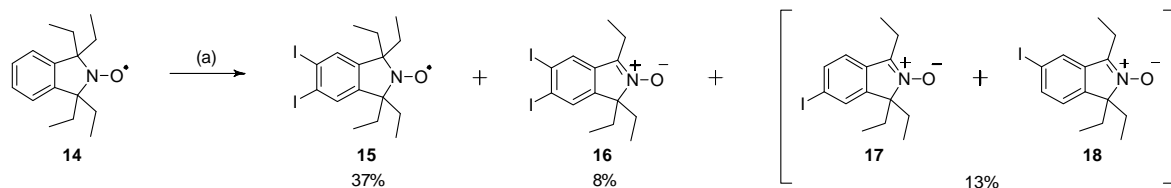of the desired nitroxide **12** was achieved in a 34% yield over 2 steps (Scheme 4). The di-iodo isoindoline **13** could be selectively produced in high yield (80%) from isoindoline **10** when 4 equivalents of I$^+$ were employed. This reaction could also be performed on a larger scale (2 grams) with only a small decrease in isolated yield (70%). Subsequent oxidation of amine **13** to the nitroxide **15** was achieved using *m*CPBA.
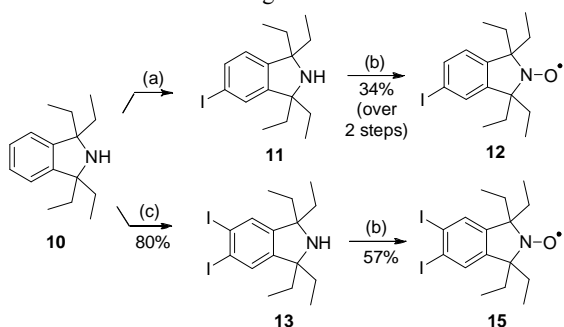
Scheme 4. Synthesis of iodoamines **11** and **13** and nitroxide **12**. *Reagents and conditions:* (a) H$_5$IO$_6$ (0.18 equiv.), KI (0.55 equiv.), conc. H$_2$SO$_4$, 0°C to RT, 3 hr; (b) *m*CPBA, DCM, 0°C to RT, 2 hr; (c) H$_5$IO$_6$ (0.9 equiv.), KI (2.7 equiv.), conc. H$_2$SO$_4$, 0°C to RT, 3 hr.

The treatment of nitroxide **1** with 5 equivalents of I$^+$ (generated from H$_5$IO$_6$ and KI in H$_2$SO$_4$) cleanly afforded the di-iodo nitroxide **9** in high yield. However, similar treatment of tetraethyl nitroxide **14** with 4 equivalents of I$^+$ gave the desired di-iodo nitroxide **15** in only modest yield (37%, Scheme 5) along with di-iodo nitrone **16** (8%) and mono-iodo nitrone regioisomers **17** and **18** (13%). These nitrone products most likely arise from the well established intramolecular decomposition of the corresponding oxoammonium ions[30] (which are formed under the oxidative iodination conditions). The nitrone products were not observed during the iodination of the tetramethyl nitroxide **1** because the decomposition is driven by the loss of ethene. Tetraethyl nitroxides are also more susceptible to oxidation than their tetramethyl counterparts.[31] The mono-iodination of nitroxide **14** was not attempted as nitrone by-products would presumably form and this product **12** can be more readily obtained by iodination and subsequent oxidation of the secondary amine **10** (Scheme 4).

We have previously prepared the tetraethylisoindoline nitroxide **21** as a water soluble antioxidant for reducing oxidative stress in cellular systems.[20] The bulkier ethyl groups generate an antioxidant with improved activity as they render the nitroxide moiety more resistant to bio-reduction *in vivo*.[32] Compound **21** was previously accessed in 9 steps in 7.6% overall yield (the key transformation involved the oxidation of methyl groups attached to the aromatic ring). As large amounts of this compound are required for biological evaluations, we considered that utilization of the newly prepared di-iodo isoindoline **13** may present a more efficient synthetic route. A copper(I)-catalyzed cyanation of **13** was undertaken using K$_4$[Fe(CN)$_6$] in the presence of catalytic CuI and 1-butylimidazole to give dicyano isoindoline **19** in moderate yield (41%). Subsequent oxidation of **19** with *m*-CPBA afforded the corresponding nitroxide derivative **20** (68% yield), which could be hydrolysed using base to the desired nitroxide **21** in good yield (74%, Scheme 6). This alternative synthetic route, beginning from phthalic anhydride, uses 7 steps and, in our hands, gives the final nitroxide **21** in 6.3% overall yield. Thus, the two routes give comparable yields of **21** but the one utilizing di-iodo isoindoline **13** is more efficient as it requires two fewer steps.
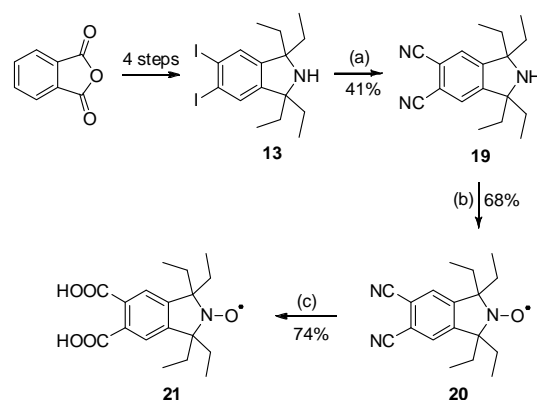
Scheme 6. Improved synthetic route to nitroxide **21**. *Reagents and conditions:* (a) K$_4$[Fe(CN)$_6$], CuI, 1-butylimidazole, 160°C, 4 d; (b) *m*CPBA, DCM, 0°C to RT, 14 hr; (c) KOH, EtOH/H$_2$O, 105°C, 2 d.

Conclusions

We have developed a new method for the direct aryl iodination of isoindolines and isoindoline nitroxides which employs periodic acid and potassium iodide in conc. sulfuric acid. This combination of reagents cleanly forms di-iodo products from amines **7** and **10** and nitroxide **1** in high yields (70-82%) but also gives iodinated nitrones when reacted with tetraethyl nitroxide **10**. Singly iodinated species were prepared from amines **7** and **10** and nitroxide **1** in modest yields (34-48%). For the first time, this method has given access to aryl iodide functionalised tetraethyl isoindolines and isoindoline nitroxides. The application of di-iodo isoindoline **13** as a viable precursor to a potential antioxidant with water solubility demonstrates the synthetic utility of the prepared compounds.

Scheme 5 Products isolated from the treatment of nitroxide **14** with H$_5$IO$_6$ and KI in H$_2$SO$_4$. *Reagents and conditions:* (a) H$_5$IO$_6$ (1.0 equiv.), KI (3.0 equiv.), conc. H$_2$SO$_4$, 0°C to RT, 3 hr.

Experimental Section

General Methods

All air-sensitive reactions were carried out under an atmosphere of ultra-high purity argon. 1,1,3,3-Tetramethylisoindoline **7**, 1,1,3,3-tetramethylisoindolin-2-yloxyl **1**, 1,1,3,3-tetraethylisoindoline **10** and 1,1,3,3-tetraethylisoindolin-2-yloxyl **14** were prepared using established literature procedures.[33-35] All other reagents were purchased from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer and referenced to the relevant solvent peak with coupling constants (J values) reported in Hz. Analytical HPLC was carried out on an a HPLC system using a Prep-C18 scalar column (4.6 ×150 mm, 10 μm) with a flow rate of 1 mL min^{-1}. ESI-high resolution mass spectra were obtained using a QTOF LC high resolution mass spectrometer which utilized electrospray ionisation (recorded in the positive mode). The mass-selective detector was optimised using calibration standards with reference masses at m/z 121.050873 and 922.009798. EI-high resolution mass spectra were recorded on a double focusing magnetic sector mass spectrometer in the positive mode. Fourier transform infrared (FTIR) spectra were recorded on a Fourier Transform Infrared Spectrometer equipped with a DTGS TEC detector and an ATR objective. Melting points were measured on a Variable Temperature Apparatus by the capillary method and are uncorrected. Single crystal X-ray diffraction data for **9** were collected at 173(2) K under the software control of CrysAlis CCD[36] on an Oxford Diffraction Gemini Ultra diffractometer using Mo-Kα radiation generated from a sealed tube. Data reduction was performed using CrysAlis RED.[36] Multi-scan empirical absorption corrections were applied using spherical harmonics, implemented in the SCALE3 ABSPACK scaling algorithm, within CrysAlis RED[36] and subsequent computations were carried out using the WinGX-32 graphical user interface.[37] The structure was solved by direct methods using SIR97[38] and refined with SHELXL-97.[39] Non-hydrogen atoms were modeled with anistropic thermal parameters while hydrogen atoms were modeled in calculated positions with thermal parameters determined using a riding model.

Synthesis of 5-iodo-1,1,3,3-tetramethylisoindoline 5

Potassium iodide (56 mg, 0.34 mmol) was added portionwise to a solution of periodic acid (26 mg, 0.11 mmol) in sulfuric acid (98%, 6 mL) at 0ºC. The resulting dark brown solution was stirred for 15 minutes and then 1,1,3,3-tetramethylisoindoline **7** (71 mg, 0.41 mmol) was added. The reaction was stirred for an additional 3 hours at 0ºC then carefully poured onto ice (50 mL) and basified with aqueous sodium hydroxide solution (10 M). The resulting solution was extracted with DCM (3 × 100 mL) and the combined organic layers were washed with saturated aqueous sodium thiosulphate solution (2 × 100 mL) and brine (2 × 100 mL) and dried using anhydrous sodium sulphate. Removal of the solvent *in vacuo* gave a crude product which was shown to contain 5-iodo-1,1,3,3-tetramethylisoindoline **5** and 5,6-diiodo-1,1,3,3-tetramethylisoindoline **8** in a 7:3 ratio by ^{1}H NMR spectroscopy. Purification of the crude mixture by silica gel chromatography (eluent 100% DCM to 100% Et$_2$O) gave **5**-iodo-1,1,3,3-tetramethylisoindoline **5** as a as a golden oil which slowly crystallised (57 mg, 39%). δ_H(400 MHz; CDCl$_3$; Me$_4$Si) 1.45 (12H, br s, 4 × CH$_3$), 1.61 (1H, br s, NH), 6.90 (1H, d, $J_{1,2}$ 8, Ar-H), 7.46 (1H, d, $J_{1,3}$ 1.6, Ar-H), 7.58 (1H, dd, $J_{1,2}$ 8, $J_{1,3}$ 1.6, Ar-H). EIMS (+ve mode) *m/z* 301 (M$^+$, 1%), 286 (M$^+$-CH$_3$, 100%), 271 (30%). The obtained ^{1}H NMR data was consistent with that previously reported.[11]

Synthesis of 5,6-diiodo-1,1,3,3-tetramethylisoindoline 8

Compound **8** was prepared using the procedure detailed above with potassium iodide (121 mg, 0.73 mmol), periodic acid (56 mg, 0.24 mmol), sulfuric acid (98%, 10 mL) and 1,1,3,3-tetramethylisoindoline **7** (61 mg, 0.35 mmol). The resulting crude product (139 mg) was purified by silca gel column chromatography (eluent DCM/Et$_2$O, 2:3) to afford 5,6-diiodo-1,1,3,3-tetramethylisoindoline **8** as a white powder (104 mg, 70%). M.p. 122-124ºC. δ_H(400 MHz; CDCl$_3$; Me$_4$Si) 1.44 (12H, s, 4 × CH$_3$), 1.60 (1H, s, NH), 7.64 (2H, s, Ar-H). δ_c(100 MHz; CDCl$_3$; Me$_4$Si) 31.6, 62.4, 105.6, 132.7, 151.4. HRMS (ES): calcd. for $[C_{12}H_{15}I_2N+H]^+$ 426.9294; found:427.9400. The sample was ≥ 98% pure following analysis by analytical HPLC (80% MeOH, 20% H$_2$O).

Synthesis of 5-iodo-1,1,3,3-tetramethylisoindolin-2-yloxyl 6

Compound **6** was prepared using the procedure detailed above with potassium iodide (137 mg, 0.83 mmol), periodic acid (65 mg, 0.277 mmol), sulfuric acid (98%, 8 mL) and 1,1,3,3-tetramethylisoindolin-2-yloxyl **1** (301 mg, 1.58 mmol). After stirring at 0ºC for 2.5 hours, the work-up detailed above was undertaken. The resulting crude product (393 mg) was shown to contain 5-iodo-1,1,3,3-tetramethylisoindolin-2-yloxyl **6**, 5,6-diiodo-1,1,3,3- tetramethylisoindolin-2-yloxyl **9** and 1,1,3,3-tetramethylisoindolin-2-yloxyl **1** in a 70:18:12 ratio by analytical HPLC. Purification of the crude mixture by silica gel chromatography (eluent 100% DCM) gave 5-iodo-1,1,3,3-tetramethylisoindolin-2-yloxyl **6** as a pale yellow solid (240 mg, 48%). M.p. 133-135ºC (Lit.[11] 132-135ºC). HRMS (EI): calcd. for $[C_{12}H_{15}INO]^+$ 316.0198; found:316.0204.

Synthesis of 5,6-diiodo-1,1,3,3-tetramethylisoindolin-2-yloxyl 9

Compound **9** was prepared using the procedure detailed above with potassium iodide (158 mg, 0.72 mmol), periodic acid (56 mg, 0.24 mmol), sulfuric acid (98%, 7 mL) and 1,1,3,3-tetramethylisoindolin-2-yloxyl **1** (51 mg, 0.267 mmol). After stirring at 0ºC for 2.5 hours, the work-up detailed above was undertaken. Purification of the crude mixture by silica gel column chromatography (eluent 100% DCM) gave 5,6-diiodo-1,1,3,3-tetramethylisoindolin-2-yloxyl **9** as a pale yellow solid (97 mg, 82%). M.p. 262-264ºC. Elemental analysis: calcd (%) for C$_{12}$H$_{14}$I$_2$NO: C 32.60, H 3.19, N 3.17; found C 32.57, H 3.09, N 3.12. HRMS (EI): calcd. for $[C_{12}H_{14}INO]^+$ 441.9165; found: 441.9159. Crystals suitable for x-ray diffraction were obtained by slow evaporation from DCM. The sample was ≥ 98% pure following analysis by analytical HPLC (80% MeOH, 20% H$_2$O).

Synthesis of 5-iodo-1,1,3,3-tetraethylisoindoline 11

Compound **11** was prepared using the procedure detailed above with potassium iodide (157 mg, 0.945 mmol), periodic acid (74 mg, 0.315 mmol), sulfuric acid (98%, 10 mL) and 1,1,3,3-tetraethylisoindoline **10** (400 mg, 1.73 mmol). The resulting crude product (460 mg) was shown to contain 5-iodo-1,1,3,3-tetraethylisoindoline **11**, 5,6-diiodo-1,1,3,3-tetraethylisoindoline **13** and 1,1,3,3-tetraethylisoindoline **10** in a 6:1:1 ratio by analytical HPLC. As these three products could not be separated using silica gel column chromatography, they were used in the next step without further purification.

Synthesis of 5-iodo-1,1,3,3-tetraethylisoindolin-2-yloyl 12 from 5-iodo,1,1,3,3-tetraethylisoindoline 11

*m*CPBA (0.68 g, 3.0 mmol, 77%) was added to a DCM (20 mL) solution of the above mixture (5-iodo-1,1,3,3-tetraethylisoindoline **11**, 5,6-diiodo-1,1,3,3-tetraethylisoindoline **13** and 1,1,3,3-tetraethylisoindoline **10** in a 6:1:1 ratio, 460 mg) at 0°C. The mixture was stirred at 0°C for 20 minutes and then allowed to warm to room temperature and stirred for a further 2 hours. The solution was diluted with water (20 mL) and the organic phase washed with aqueous sodium hydroxide solution (2 M, 3 × 50 mL) and brine (1 × 100 mL) and dried over anhydrous sodium sulfate. The solution was filtered and concentrated at reduced pressure. Purification by silica gel chromatography (100% DCM) gave 5-iodo-1,1,3,3-tetraethylisoindolin-2-yloyl **12** as a thick yellow oil (216 mg, 34% over 2 steps). IR (ATR) ν_{max} 2966, 2935 and 2877 (alkyl CH$_3$, CH$_2$), 1716 (C=O), 1595 (*C*=*C*-COO), 1459 and 1416 (aryl C-C), 1435 (N-O•), 815 cm^{-1} (C-I). HRMS (EI): calcd. for [C$_{16}$H$_{23}$INO]$^+$ 372.0824; found: 372.0827. The sample was ≥ 98% pure following analysis by analytical HPLC (95% MeOH, 5% H$_2$O).

Synthesis of 5,6-diiodo-1,1,3,3-tetraethylisoindoline 13

Compound **13** was prepared using the above procedure with potassium iodide (250 mg, 1.517mmol), periodic acid (119 mg, 0.506mmol), sulfuric acid (98%, 6 mL) and 1,1,3,3-tetraethylisoindoline **10** (120 mg, 0.562 mmol). After stirring at 0°C for 2 hours, the work-up detailed above was undertaken. Purification of the crude mixture by silica gel column chromatography (eluent 100% DCM) gave 5,6-diiodo-1,1,3,3-tetraethylisoindoline **13** as an off-white solid (216 mg, 80%). M.p. 80-81°C. Elemental analysis: calcd (%) for C$_{16}$H$_{23}$I$_2$N: C 33.75, H 3.54, N 3.28; found C 33.54, H 3.46, N 3.18. δ_H(400 MHz; CDCl$_3$; Me$_4$Si) 0.88 (12H, t, $J_{1,2}$ 7.4, 4 × CH$_3$), 1.55-1.73 (9H, m, 4 × CH$_2$, NH), 7.58 (2H, s, Ar-H). δ_c(100 MHz; CDCl$_3$; Me$_4$Si) 8.8, 33.5, 68.2, 105.2, 133.4, 150.2. HRMS (EI): calcd. for [C$_{16}$H$_{24}$I$_2$N]$^+$ 483.9920; found: 484.0022. The reaction gave a 70% isolated yield of 5,6-diiodo-1,1,3,3-tetraethylisoindoline **13** when 2 g of 1,1,3,3-tetraethylisoindoline **10** was used. The sample was ≥ 98% pure following analysis by analytical HPLC (95% MeOH, 5% H$_2$O).

Synthesis of 5,6-diiodo-1,1,3,3-tetraethylisoindolin-2-yloyl 15 from 1,1,3,3-tetraethylisoindolin-2-yloxyl 14

Potassium iodide (250 mg, 1.517 mmol, 0.975 mmol) was added portionwise to a solution of periodic acid (119 mg, 0.506 mmol, 0.325 mmol) in sulfuric acid (98%, 6 mL) at 0°C. The resulting dark brown solution was stirred for 15 minutes and then 1,1,3,3-tetraethylisoindolin-2-yloxyl **14** (120 mg, 0.562 mmol, 0.325 mmol) was added. The reaction was stirred for an additional 2 hours at 0°C then carefully poured onto ice (50 mL) and basified with aqueous sodium hydroxide solution (10 M). The resulting solution was extracted with DCM (3 × 100 mL) and the combined organic layers were washed with saturated aqueous sodium thiosulphate solution (2 × 100 mL) and brine (2 × 100 mL) and dried using anhydrous sodium sulphate. Removal of the solvent *in vacuo* and subsequent purification of the crude mixture by silica gel chromatography (eluent 100% chloroform) gave 5,6-diiodo-1,1,3,3-tetraethylisoindolin-2-yloyl **15** (59 mg, 37%) along with 5,6-diiodo-1,1,3-triethylisoindole-*N*-oxide **16** (14 mg, 8.4%) and a mixture of 5-iodo-1,1,3-triethylisoindole-*N*-oxide **17** and 6-iodo-1,1,3-triethylisoindole-*N*-oxide **18** (20.6 mg, 13%).

Data for 5,6-diiodo-1,1,3,3-tetraethylisoindolin-2-yloxyl 15

Yellow solid, M.p. 79-81°C. MS (EI) *m/z* 498 (M$^+$, 70). The sample was ≥ 98% pure following analysis by analytical HPLC (95% MeOH, 5% H$_2$O).

Data for 5,6-diiodo-1,1,3-triethylisoindole-*N*-oxide 16

White powder, M.p. 98-100°C. δ_H(400 MHz; CDCl$_3$; Me$_4$Si) 0.44 (6H, t, $J_{1,2}$ = 7.4, 2 × CH$_3$), 1.26 (3H, t, $J_{1,2}$ 7.4, CH$_3$), 1.81-1.92 (2H, m, CH$_2$), 2.11-2.21 (2H, m, CH$_2$), 2.81 (2H, q, $J_{1,2}$ 7.5, CH$_2$), 7.70 (1H, s, Ar-H), 7.85 (1H, s, Ar-H). δ_C(100 MHz; CDCl$_3$; Me$_4$Si) 7.3, 9.9, 16.8, 29.8, 83.8, 106.0, 107.2, 128.7, 131.2, 137.4, 141.8, 145.6. HRMS (EI) [C$_{14}$H$_{17}$I$_2$NO]$^+$: 469.9400, found 498.9487. The sample was ≥ 98% pure following analysis by analytical HPLC (95% MeOH, 5% H$_2$O).

Data for 5-iodo-1,1,3-triethylisoindole-*N*-oxide 17 and 6-iodo-1,1,3-triethylisoindole-*N*-oxide 18:

Inseparable mixture. Yellow oil. Products formed in a 3:2 ratio by ^{1}H NMR analysis; **major isomer:** δ_H(400 MHz; CDCl$_3$; Me$_4$Si) 0.38-0.48 (m, 2 × CH$_3$), 1.23-1.32 (m, CH$_3$), 1.83-1.95 (m, CH$_2$), 2.11-2.24 (m, CH$_2$), 2.80-2.90 (m, CH$_2$), 6.96 (1H, d, $J_{1,2}$ 8.3, Ar-H), 7.67-7.71 (2H, m, Ar-H); **minor isomer**: δ_H(400 MHz; CDCl$_3$; Me$_4$Si) 0.38-0.48 (m, 2 × CH$_3$), 1.23-1.32 (m, CH$_3$), 1.83-1.95 (m, CH$_2$), 2.11-2.24 (m, CH$_2$), 2.80-2.90 (m, CH$_2$), 7.12 (1H, d, $J_{1,2}$ 8.1, Ar-H), 7.54 (1H, d, $J_{1,2}$ = 1.4, Ar-H), 7.73 (1H, dd, $J_{1,2}$ 8.1, $J_{1,3}$ 1.3, Ar-H). δ_C(100 MHz; CDCl$_3$; Me$_4$Si) 7.2, 9.9, 16.9, 29.9, 30.0, 83.6, 83.9, 92.8, 93.2, 120.0, 122.5, 127.5, 129.7, 135.2, 135.9, 137.9, 140.0, 142.7, 146.1, 146.9. HRMS (EI) [C$_{14}$H$_{18}$INO]$^+$: 344.0433, found 344.0525. The sample was ≥ 98% pure following analysis by analytical HPLC (95% MeOH, 5% H$_2$O).

Synthesis of 5,6-diiodo-1,1,3,3-tetraethylisoindolin-2-yloxyl 15 from 5,6-diiodo-1,1,3,3-tetraethylisoindoline 13

*m*CPBA (0.65 g, 2.85 mmol, 77%) was added to a DCM (30 mL) solution of 5,6-diiodo-1,1,3,3-tetraethylisoindoline **13** (0.60 g, 1.24 mmol) at 0°C. The mixture was stirred at 0°C for 20 minutes and then allowed to warm to room temperature and stirred for a further 2 hours. The solution was diluted with water (25 mL) and the organic phase washed with aqueous sodium hydroxide solution (2 M, 3 × 50 mL) and brine (1 × 75 mL) and dried over anhydrous sodium sulfate. The solution was filtered and concentrated *in vacuo*. Purification by silica gel chromatography (100% chloroform) gave 5,6-diiodo-1,1,3,3-tetraethylisoindolin-2-yloxyl **15** as a yellow solid (0.352 g, 57%). The obtained data was consistent with that shown above.

Synthesis of 5,6-dicyano-1,1,3,3-tetraethylisoindoline 19

5,6-Diiodo-1,1,3,3-tetraethylisoindoline **13** (2.80 g, 5.80 mmol) was dissolved in toluene (12 mL) and transferred to a pressure tube. K$_4$[Fe(CN)$_6$] (914 mg, 2.50 mmol), CuI (112.8 mg, 592 µmol) and *n*-butylimidazole (1.52 mL, 11.6 mmol) were then added. Argon was bubbled through the orange/yellow solution for 20 minutes before the pressure tube was sealed. The orange/yellow solution was heated for 4 d at 160°C, resulting in a colour change to a dark green solution. After 4 d, analysis by TLC (DCM/ether 50:1) showed that all starting product had been consumed. The mixture was allowed to cool to room temperature, diluted with H$_2$O (100 mL) and extracted with EtOAc (4 × 100 mL). During the extraction the solution required some sonication in order for clear layers to form. The solvent was removed under reduced pressure and the crude product was dried under high vacuum to give a dark green oil (6.20 g). The crude was purified by silica gel column chromatography (DCM/diethyl ether 50/1) to give a pale yellow solid (1.67 g) which was shown by ^{1}H NMR spectroscopy to be a mixture of monoiodo/monocyano product (53%) and the desired dicyano product **19** (47%). A series of four recrystallisations were conducted on the product using hexane to give a pure sample of **19**

as shiny white needle-like crystals (0.67 g, 41% yield). M. p. 90-93°C. FTIR (ATR): cm^{-1} = 3000-3500 (br, w) [R$_2$N-H], 2968, 2924, 2874, 2852 (m) [Ar-H], 2231 (m) [R-C≡N]. δ_H(400 MHz; CDCl$_3$; Me$_4$Si) 0.87 (12H, br t, $J_{1,2}$ 7.6, 4 × CH$_3$), 1.57 (1H, s, NH), 1.60-1.80 (8H, m, 4 × CH$_2$), 7.47 (2H, s, Ar-H). δ_C(100 MHz; CDCl$_3$; Me$_4$Si) 8.7, 33.5, 69.1, 114.4, 115.9, 127.8, 154.1. HRMS (ESI) [C$_{18}$H$_{24}$N$_3$]$^+$: 282.1970, found 282.2017. The sample was ≥ 98% pure following analysis by analytical HPLC (70% MeOH, 30% H$_2$O).

Synthesis of 5,6-dicyano-1,1,3,3-tetraethylisoindolin-2-yloxyl 20

5,6-Dicyano-1,1,3,3-tetraethylisoindoline **19** (0.64 g, 2.2 mmol) was dissolved in DCM (30 mL), cooled to 0°C and treated with *m*-chloroperbenzoic acid (1.29 g, 5.73 mmol). The reaction mixture was stirred overnight (~14 h) while gradually allowing it to return to room temperature. Complete consumption of the starting product was verified by TLC (100% DCM) and the reaction mixture was carefully basified with 5 M aq. NaOH solution. The product was extracted with DCM (2 × 50 mL) and then washed with 5M aq. NaOH solution (2 × 50 mL). The organic layer was washed with brine, dried over Na$_2$SO$_4$ and the solvent was removed by rotary evaporation to give a yellow solid which was recrystallised (MeCN) to give 5,6-dicyano-1,1,3,3-tetraethylisoindolin-2-yloxyl **20** as shiny yellow crystals (0.43 g, 68% yield). M. p. 112-114°C. FTIR (ATR) = 3026, 2970, 2840, 2880 (m) [Ar-H], 2232 cm^{-1} (m) [R-C≡N]. HRMS (ESI) [C$_{18}$H$_{22}$N$_3$NaO]$^+$: 319.1661, found 319.1654. The sample was ≥ 98% pure following analysis by analytical HPLC (70% MeOH, 30% H$_2$O).

Synthesis of 5,6-dicarboxy-1,1,3,3-tetraethylisoindolin-2-yloxyl 21

A suspension of 5,6-dicyano-1,1,3,3-tetraethylisoindolin-2-yloxyl **20** (0.37 g, 1.2 mmol) in H$_2$O/EtOH (5 mL/1 mL) was treated with KOH (0.37 g, 6.6 mmol), heated to 105°C and stirred at this temperature for 2 d. The reaction mixture was then allowed to cool to room temperature and washed with EtOAc (10 mL). The aqueous layer was then acidified with 5 M aq. HCl solution (20 mL, to pH 1), then extracted with EtOAc (5 × 25 mL), dried with Na$_2$SO$_4$ and evaporated under reduced pressure to give a yellow solid. The crude product was recrystallised using H$_2$O/MeCN (8 mL/2 mL) to give 5,6-dicarboxy-1,1,3,3- tetraethylisoindolin-2-yloxyl **21** as shiny yellow needle-like crystals (0.31 g, 74% yield). M. p. 181-183°C (Lit.[20] 186-188°C). FTIR (ATR) = 2600-3200 (br, m) [COOH], 2976, 2938, 2879 (m) [Ar-H], 1700 cm^{-1} (s) [COOH]. HRMS (ESI) [C$_{18}$H$_{24}$NNaO$_5$]$^+$: 357.1552, found 357.1549.

Crystal data and refinement details for 5,6-diiodo-1,1,3,3-tetramethylisoin-2-yloxyl 9:

C$_{12}$H$_{14}$I$_2$N$_1$O$_1$, M = 442.04, tetragonal, $P4_32_12$, a = 9.9777(1) Å, c = 13.7730(3) Å, V = 1367.18(4) Å^3, D_c = 2.148 g cm^{-3}, Z = 4, crystal size 0.32 × 0.22 × 0.07 mm, yellow plate, 173(2) K, λ(Mo-Kα) = 0.71073, T(Empirical)$_{min,max}$ = 0.21, 1, $2\theta_{max}$ = 57.7, hkl range −13 to 13, −13 to 13, −15 to 18, N = 10315, N_{ind} = 1702 (R_{merge} = 0.033), N_{obs} = 1627 ($I > 2\sigma(I)$), N_{var} = 1651, residuals $R1(F, 2\sigma)$ = 0.018, $wR2(F^2$, all) = 0.043, GoF(all) = 1.040, $\Delta\rho_{min,max}$ = −0.69, 0.32 e Å^{-3}. The refinement residuals are defined as $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ for $F_o > 2\sigma(F_o)$ and $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_c^2)^2]\}9^{1/2}$ where $w = 1/[\sigma^2(F_o^2) + (0.025P)^2 + 0.4P]$, $P = (F_o^2 + 2F_c^2)/3$. The CIF file has been deposited with the Cambridge Structural Database (CCDC reference number 918603) and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Supporting Information (see footnote on the first page of this article): (1) ^{1}H NMR and ^{13}C NMR spectra for compounds **8, 13, 16-19**; (2) HPLC chromatograms for compounds **8, 9, 12, 13, 15-20**; (3) CIF file for x-ray crystal structure of compound **9.**

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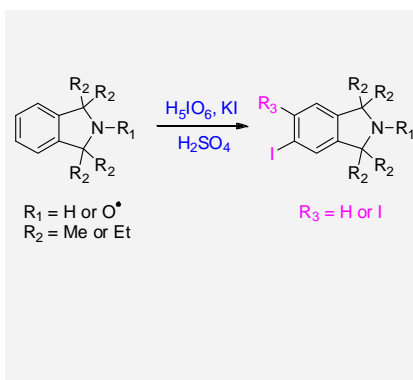[39] G. M. Sheldrick *Acta Cryst.* **2008**, *A64*, 112.

Entry for the Table of Contents

A new method which allows direct aryl iodination of isoindolines and isoindoline nitroxides using periodic acid and potassium iodide in sulphuric acid is reported.

R_1 = H or O•
R_2 = Me or Et

R_3 = H or I

**Kathryn E. Fairfull-Smith*,
Emmanuel A. Debele, Jesse P. Allen,
Michael C. Pfrunder and John C.
McMurtrie** …….. Page No. – Page No.

The Direct Iodination of Isoindolines and Isoindoline Nitroxides as Precursors to Functionalised Nitroxides