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# The nitration of some 4,6-dimethoxyindoles

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**Abstract**—A range of 3-substituted-4,6-dimethoxyindoles bearing electron-withdrawing groups in either the 2- or 7-position, can be nitrated using nitric acid adsorbed on silica, to give 7-nitro and 2-nitro-indoles, respectively. A 1-cyano-indole gives regioselectively the 2-nitro-indole with loss of the cyano group.


## 1. Introduction

Indoles have long been known to be sensitive to acids and therefore their nitration requires care in the design of experimental conditions.[1–3] While the 3-position is the preferred site for electrophilic attack, in strong acid nitration occurs on the 3*H*-indolium salt to give the 5-nitroindole under the directing influence of the iminium moiety. However, the 3,6-dinitroindole can be obtained via the 3-nitroindole under more neutral conditions. The nitration of indoles containing hydrogen at C2 does not lead to well-defined products but usually gives only polymeric material presumably resulting from initial oxidative attack at C2 or at the 2,3-double bond.[4–7] While the nitration of 2-unsubstituted indoles in acidic conditions is unsuccessful, gramine and tryptophan undergo nitration with concentrated nitric acid in acetic acid.[8,9] The success of these nitrations has been attributed to protonation of the side chain amino group, with the resulting positive charge preventing oxidative attack through electrostatic repulsion. Indoles bearing a 3-aryl group can undergo nitration in that ring rather than the indole ring.[10] Also, *ipso*-nitration can occur at C3 with the displacement of acyl and hydroxymethyl groups.[11]

Recently, nitric acid absorbed onto silica has been used to mononitrate some activated indoles in reasonable chemical yields and with moderate regioselectivity, provided they also contained an electron-withdrawing group at N1 or C2.[12]

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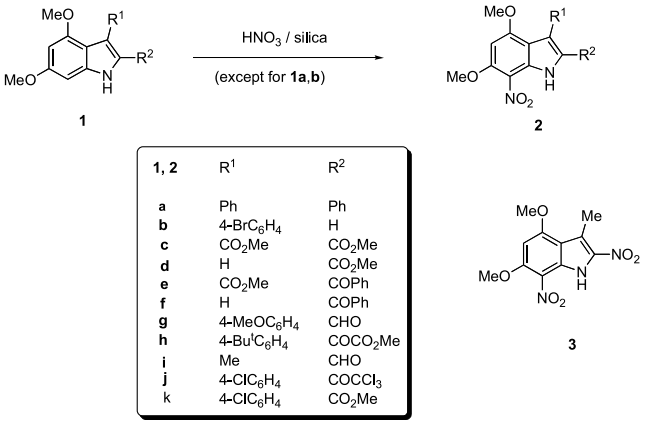
## 2. Results and discussion

We were interested in the nitration of 4,6-dimethoxyindoles for a variety of purposes, including their potential as a source of amino indoles. Initial studies involved 4,6-dimethoxy-2,3-diphenylindole **1a** and the 4′-bromophenyl analog **1b**. Investigated reaction conditions included a mixture of concentrated nitric and sulfuric acids at 0 °C, fuming nitric acid in tetrahydrofuran at −10 °C, copper(II) nitrate and acetic anhydride in tetrahydrofuran at 0 °C, concentrated nitric acid in acetic anhydride at −10 °C, and concentrated nitric acid supported on silica gel at room temperature: in all cases complex mixtures containing both mono- and poly-nitrated products were obtained. Clearly electron-withdrawing substituents were desirable and a survey was carried out on a range of such indoles, using the nitric acid on silica reagent. These reactions proceeded extremely quickly, usually in less than 10 s, at room temperature in dichloromethane, and gave good yields of mononitrated compounds. Some of the precursor indoles **1a**,[13] **1b**,[14,15] **1c**,[13] **1d**,[13] **1g**,[16] **1i**,[17] **4b**[16] and **6b**[15] have been reported previously, but details of the synthesis of **1e**, **1f**, **1g**, **1h**, **1j**, **4a**, **4b**, **4c**, **6a** and **6c** are provided here. Indoles **1e** and **1f** were prepared using the *N*-phenacyl isatin ring-opening and recyclisation strategy developed by Black and Wong.[18] The indole glyoxylic ester **1h** was obtained by the reaction of the new 3-(4-*tert*-butylphenyl)-4,6-dimethoxy-indole with oxalyl chloride followed by methanol, and indoles **1j** and **4c** by the reaction of 3-(4-chlorophenyl)-4,6-dimethoxyindole with trichloroacetyl chloride. Indoles **6** were formed by phenylsulfonylation, acetylation and cyanation, respectively, of the related indoles.

Thus the indoles **1c–j** with electron-withdrawing groups at C2 (and sometimes also C3) gave the 7-nitro compounds

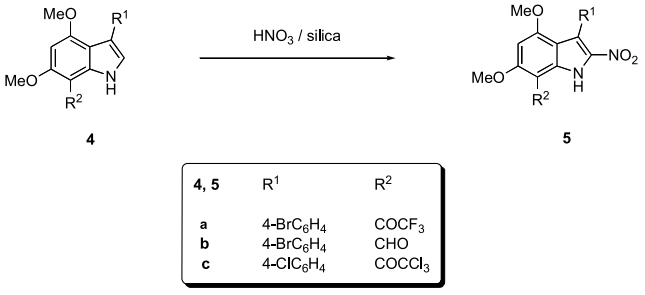



| 1, 2 | $R^1$ | $R^2$ |
|---|---|---|
| a | Ph | Ph |
| b | 4-$BrC_6H_4$ | H |
| c | $CO_2Me$ | $CO_2Me$ |
| d | H | $CO_2Me$ |
| e | $CO_2Me$ | COPh |
| f | H | COPh |
| g | 4-$MeOC_6H_4$ | CHO |
| h | 4-$Bu^tC_6H_4$ | $COCO_2Me$ |
| i | Me | CHO |
| j | 4-$ClC_6H_4$ | $COCCl_3$ |
| k | 4-$ClC_6H_4$ | $CO_2Me$ |

**Scheme 1.**

**2c**–**j**, respectively, in yields of 60–96%. Reaction of the 2-formyl-3-methyl indole **1i** produces not only the 7-nitro derivative **2i** in 68% yield, reaction for a longer time leads to the 2,7-dinitro-derivative **3** in 45% yield, through an *ipso*-substitution of the 2-formyl group (Scheme 1).

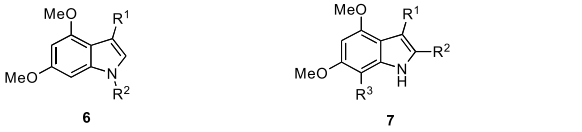
The presence of electron-withdrawing groups at C7, as in indoles **4a**–**c**, leads to formation of the 2-nitro-indoles **5a**–**c** respectively in 70–85%. Until recently 2-nitro-indoles were relatively unknown and only the 3-methyl- and 3-phenyl-2-nitro-indoles had been obtained in low yield and with undesirable 3-substitution.[19] 2-Nitroindoles have been synthesized directly through the thermolysis of β-substituted-*o*-azidostyrenes: 2-nitroindole itself was obtained in three steps from 2-nitrobenzaldehyde in 40% overall yield.[20,21] The ability to nitrate specifically at the 2-position is a new approach to 2-nitro-indoles that is extremely quick, clean and high yielding (Scheme 2).




| 4, 5 | $R^1$ | $R^2$ |
|---|---|---|
| a | 4-$BrC_6H_4$ | $COCF_3$ |
| b | 4-$BrC_6H_4$ | CHO |
| c | 4-$ClC_6H_4$ | $COCCl_3$ |

**Scheme 2.**

Indoles **6a**–**c**, substituted with electron-withdrawing groups at N1, reacted extremely rapidly with nitric acid on silica to give mixtures of mono- and dinitro-indoles, with consequent reduced yields of isolated products. $^1$H NMR spectra of the crude reaction mixtures indicated that partial hydrolysis of the N-substituent had occurred, and therefore complete removal of this substituent was effected by formal hydrolysis. It was difficult to characterize all of these products fully because of their variable stability. The *N*-phenylsulfonylindole **6a** gave a 75% yield of the rather unstable 2,7-dinitro-indole **7a**, while the *N*-acetylindole **6b** gave an approximately equal mixture of 2- and 7-nitro-indoles **7b** and **2b**, respectively, the former being less stable than the latter. Significantly, the *N*-cyanoindole **6c** showed a clear regiochemical preference for formation of the 2-nitro-indole **7c**, possibly as the result of hydrogen bonding of the cyano group on to free hydroxyl groups on the silica surface.




| 6 | $R^1$ | $R^2$ |
|---|---|---|
| a | Ph | $SO_2Ph$ |
| b | 4-$BrC_6H_4$ | $COCH_3$ |
| c | 4-$ClC_6H_4$ | CN |

| 7 | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| a | Ph | $NO_2$ | $NO_2$ |
| b | 4-$BrC_6H_4$ | $NO_2$ | H |
| c | 4-$ClC_6H_4$ | $NO_2$ | H |

In an attempt to slow down the nitration reactions, a nitrosation approach was investigated, as the nitrosonium cation is less reactive than the nitronium cation: any nitroso product could be subsequently oxidized to the related nitro compound. The reactions of indoles with nitrous acid and other nitrosating agents have been well studied.[1,22,23] Preferred attack is at C3 and the 3-nitroso-indole is usually isolated as its tautomeric isomer, the 3-oximino-3*H*-indole, which can be oxidized to the related 3-nitro-indole. The nitrosation of 3-aryl-4,6-dimethoxyindoles was examined under both acidic (sodium nitrite in acetic acid) and basic (*iso*-pentyl nitrate and potassium carbonate in dimethylformamide) conditions. The reaction failed completely under basic conditions, giving unchanged starting material. However, the reaction using acidic conditions furnished a complex mixture, which was suggested by $^1$H NMR spectroscopy to contain 7-substituted products, and by mass spectral analysis to contain both nitroso- and nitro-indole derivatives.

## 3. Conclusion

The use of nitric acid on silica is very effective for the nitration of 4,6-dimethoxyindoles bearing an electron-withdrawing group either at C2, C7 or N1. When such a group is positioned at C7, an entry to the very rare 2-nitro-indoles is provided.

## 4. Experimental

### 4.1. General information

Melting points (uncorrected) were measured using a Mel-Temp melting point apparatus. Microanalyses were performed by the Microanalysis Unit of the Australian National University, Canberra or the University of Otago, New Zealand. Infrared spectra were recorded as Nujol mulls on a Perkin–Elmer 298 or a Perkin–Elmer 580B spectrometer. Ultraviolet–visible spectra were recorded in methanol (unless otherwise stated) on a Hitachi UV-3200 spectrometer. $^1$H and $^{13}$C NMR spectra were obtained in the designated solvents on a Bruker AC300F (300 MHz) spectrometer or at 500 MHz with a Bruker AM-500 spectrometer. $^1$H NMR data are reported as follow: chemical shift measured in parts per million (ppm) downfield from TMS ($\delta$), multiplicity, observed coupling

constant ($J$) in Hertz (Hz), proton count. Multiplicities are reported as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), quintet (quin) and multiplet (m). $^{13}$C NMR chemical shifts are reported in ppm downfield from TMS and identifiable carbons are given. The EI and ES mass spectra were recorded on an AEI MS 12 mass spectrometer at 70 eV ionizing potential and 8000 V accelerating voltage with an ion source temperature of 210 °C. MALDI (matrix assisted laser desorption) mass spectra were recorded on a Finnigan MAT Lasermat 2000 for high molecular weight compounds. The principal ion peaks $m/z$ are reported together with their percentage intensities relative to the base peak (where possible). Kieselgel 60H (Merck, Art 7736) was employed for flash chromatography and thin-layer chromatography (TLC) was performed on DC Aluminium Foil Kieselgel $F_{254}$ (Merck, Art 5554). Preparative thin layer chromatography was performed on 3 mm plates using Merck silica gel 7730 $60GF_{254}$. Solvents and reagents were purified by literature methods. Petroleum ether refers to the hydrocarbon fraction of boiling range 60–80 °C. Compounds were detected by short and long ultraviolet light and with iodine vapor.

## 4.2. Preparation of indoles

**4.2.1. 4,6-Dimethoxy-1-(2-oxo-2-phenylethyl)indole-2,3-dione.** 4,6-Dimethoxyisatin (5.0 g, 24.1 mmol) was added to a solution of NaOH (1.0 g, 25 mmol) in methanol (150 mL) and the mixture was refluxed for 1 h. The methanol was evaporated and the reddish-purple residue was suspended in dry DMF (50 mL). A solution of phenacyl bromide (4.8 g, 24.1 mmol) in DMF (10 mL) was added and the reaction mixture was heated at 100 °C for 16 h. On cooling, the dark solution was poured onto a mixture of ice and 10% HCl (50 mL). The yellow precipitate was collected, dried and chromatographed with DCM. The title 1-phenacyl isatin was obtained as a yellow solid (3.9 g, 50%), mp 210–212 °C (from EtOH). (Found: C, 66.4; H, 4.6; N, 4.3. $C_{18}H_{15}NO_5$ requires C, 66.5; H, 4.7; N, 4.3%). $\nu_{max}$: 1745, 1715, 1700, 1635, 1600, 1440, 1390, 1215, 1170 cm$^{-1}$. $\lambda_{max}$: 215 nm ($\varepsilon$ 18,300 cm$^{-1}$ M$^{-1}$), 249 (25,200), 352 (13,300). $^1$H NMR spectrum ($CDCl_3$): $\delta$ 3.85, 3.96 (6H, 2s, OMe), 5.10 (2H, s, $CH_2$), 5.82 (1H, d, $J$=2.0 Hz, H5), 6.02 (1H, d, $J$=2.0 Hz, H7), 7.50–7.68 (3H, m, aryl), 7.99–8.02 (2H, m, aryl). $^{13}$C NMR spectrum ($CDCl_3$): $\delta$ 46.31 ($CH_2$), 56.08, 56.26 (OMe), 90.77 (C5), 91.96 (C7), 128.12, 128.98, 134.03 (aryl CH), 100.98, 134.03, 153.29, 160.17, 161.27 (aryl C), 170.03, 176.53, 191.22 (CO). Mass spectrum: $m/z$ 325 (M, 10%), 192 (60), 105 (100), 77 (40).

**4.2.2. 2-Benzoyl-4,6-dimethoxyindole-3-carboxylic acid.** 4,6-Dimethoxy-1-(2-oxo-2-phenylethyl)indole-2,3-dione (4.0 g, 12.3 mmol) was added to 20% aqueous NaOH (90 mL) and the mixture refluxed for 12 h. On cooling, the alkaline solution was diluted with water (300 mL), cooled in an ice bath and slowly acidified with conc. HCl. The precipitate was collected and dried to yield the title 2-benzoyl indole (3.0 g, 76%) as a light yellow solid, mp 206–207 °C. (Found: C, 66.0; H, 4.6; N, 4.2. $C_{18}H_{15}NO_5$ requires C, 66.4; H, 4.6; N, 4.3%). $\nu_{max}$: 3375, 3125, 1685, 1660, 1635, 1620, 1580, 1530, 1510, 1420, 1390, 1340, 1280, 1260, 1240, 1215, 1200, 1175, 1140 cm$^{-1}$. $\lambda_{max}$: 218 nm ($\varepsilon$ 16,000 cm$^{-1}$ M$^{-1}$), 256 (14,000), 351 (10,000). $^1$H NMR spectrum ($CDCl_3$): $\delta$ 3.38, 4.01 (6H, 2s, OMe), 6.37 (1H, d, $J$=2.0 Hz, H5), 6.53 (1H, d, $J$=2.0 Hz, H7), 7.35–7.53 (3H, m, aryl), 7.80–7.83 (2H, m, aryl), 10.08 (1H, bs, NH). $^{13}$C NMR spectrum ($CDCl_3$): $\delta$ 55.73, 56.26 (OMe), 87.81 (C5), 95.19 (C7), 128.36, 129.20, 133.24 (aryl CH), 110.85, 130.11, 137.07, 137.51, 137.89, 152.50, 159.62 (aryl C), 164.71, 190.40 (CO). Mass spectrum: $m/z$ 325 (M, 10%), 307 (10), 281 (70), 266 (20), 105 (100).

**4.2.3. Methyl 2-benzoyl-4,6-dimethoxyindole-3-carboxylate (1e).** 2-Benzoyl-4,6-dimethoxyindole-3-carboxylic acid (2.0 g, 6.1 mmol) in diethyl ether (50 mL) was treated with an excess of diazomethane solution by slow addition over 30 min. The resulting solution was evaporated and the residue recrystallised from methanol to yield **1e** as a light yellow solid (2.1 g, 98%), mp 144–145 °C (from methanol). (Found: C, 67.3; H, 5.0; N, 4.1. $C_{19}H_{17}NO_5$ requires C, 67.3; H, 5.0; N, 4.1%). $\nu_{max}$: 3300, 1720, 1620, 1600, 1575, 1565, 1520, 1500, 1425, 1400, 1355, 1330, 1275, 1210 cm$^{-1}$. $\lambda_{max}$: 219 nm ($\varepsilon$ 18,000 cm$^{-1}$ M$^{-1}$), 257 (17,500), 353 (12,500). $^1$H NMR spectrum ($CDCl_3$): $\delta$ 3.27, 3.79, 3.84 (9H, 3s, OMe), 6.20 (1H, d, $J$=2.0 Hz, H5), 6.44 (1H, d, $J$=2.0 Hz, H7), 7.42–7.54 (3H, m, aryl), 7.76–7.79 (2H, m, aryl), 9.92 (1H, bs, NH). $^{13}$C NMR spectrum ($CDCl_3$): $\delta$ 51.66, 55.48, 55.60 (OMe), 85.92 (C5), 94.25 (C7), 128.29, 128.45, 132.15 (aryl CH), 111.74, 115.51, 131.30, 138.25, 138.74, 155.33, 161.04 (aryl C), 165.88, 187.86 (CO). Mass spectrum: $m/z$ 340 (M+1, 10%), 339 (M, 45), 278 (30), 105 (80), 77 (100).

**4.2.4. 2-Benzoyl-4,6-dimethoxyindole (1f).** 4,6-Dimethoxy-1-(2-oxo-2-phenylethyl)indole-2,3-dione (4.0 g, 12.3 mmol) was added to 20% aqueous NaOH (90 mL) and the mixture refluxed for 12 h. On cooling, the alkaline solution was diluted with water (300 mL) and extracted with chloroform. The extract was dried and concentrated to yield the pale yellow 2-benzoyl indole **1f** (2.8 g, 80%), mp 173–175 °C. (Found: C, 71.4; H, 5.6; N, 4.7. $C_{17}H_{15}NO_5$. 0.25 $H_2O$ requires C, 71.4; H, 5.5; N, 4.9%). $\nu_{max}$: 3310, 1635, 1615, 1590, 1570, 1510, 1490, 1390, 1290, 1220, 1200, 1150 cm$^{-1}$. $\lambda_{max}$: 219 nm ($\varepsilon$ 13,500 cm$^{-1}$ M$^{-1}$), 254 (13,500), 356 (17,500). $^1$H NMR spectrum ($CDCl_3$): $\delta$ 3.85, 3.91 (6H, 2s, OMe), 6.18 (1H, d, $J$=1.9 Hz, H5), 6.48 (1H, d, $J$=0.8 Hz, H3), 7.20 (1H, d, $J$=1.9 Hz, H7), 7.47–7.58 (3H, m, aryl), 7.95–7.97 (2H, m, aryl), 9.51 (1H, bs, NH). $^{13}$C NMR spectrum ($CDCl_3$): $\delta$ 55.31, 55.54 (OMe), 85.98 (C5), 92.86 (C7), 111.32 (C3), 128.29, 129.01, 131.88 (aryl CH), 114.40, 132.49, 138.18, 139.62, 155.51, 161.24 (aryl C), 186.06 (CO). Mass spectrum: $m/z$ 282 (M+1, 10%), 281 (M, 70), 266 (20), 238 (20), 149 (45), 105 (85), 77 (100).

**4.2.5. 4,6-Dimethoxy-3-(4-methoxyphenyl)indole-7-carbaldehyde, 4,6-dimethoxy-3-(4-methoxyphenyl)indole-2-carbaldehyde (1g) and 4,6-dimethoxy-3-(4-methoxyphenyl)indole-2,7-dicarbaldehyde.** To a stirred solution of 4,6-dimethoxy-3-(4-methoxyphenyl)indole (2.0 g, 7.1 mmol) in anhydrous chloroform (10 mL) at −50 °C was added dropwise an ice-cold solution of phosphoryl chloride (1.0 mL, 10.7 mmol) in DMF (2 mL). The mixture was stirred at this temperature for 1 h, then allowed to come to room temperature. Ice water (10 mL) was added and the

mixture stirred vigorously for 1 h, then made strongly alkaline with 10% NaOH and stirred vigorously for a further 4 h. The mixture was extracted with DCM (3×100 mL), the organic layer collected, dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude mixture was purified by column chromatography (DCM).

The first band gave 4,6-dimethoxy-3-(4-methoxyphenyl)-indole-7-carbaldehyde (1.1 g, 50%) as yellow needles, mp 199–201 °C (from DCM/petroleum ether). (Found: C, 69.2; H, 5.5; N, 4.5. $C_{18}H_{17}NO_4$ requires C, 69.4; H, 5.5; N, 4.5%). $\nu_{max}$: 3408, 1635, 1599, 1550, 1509, 1361, 1321, 1245, 1213, 1177, 1084, 981, 836 $cm^{-1}$. $\lambda_{max}$: 232 nm ($\varepsilon$ 2800 $cm^{-1}\,M^{-1}$), 258 (3500), 333 (1200), 368 (1000). $^1H$ NMR spectrum ($CDCl_3$): $\delta$ 3.88, 3.90, 3.99 (9H, 3s, OMe), 6.17 (1H, s, H5), 6.96 (2H, d, $J$=8.8 Hz, aryl), 7.06 (1H, d, $J$=2.5 Hz, H2), 7.53 (2H, d, $J$=8.8 Hz, aryl), 10.42 (1H, s, CHO), 10.52 (1H, s, NH). $^{13}C$ NMR spectrum ($CDCl_3$): 55.27, 55.35, 56.32 (OMe), 86.62, 113.19, 121.21, 130.47 (aryl CH), 104.45, 110.29, 118.42, 127.94, 137.62, 158.18, 161.42, 163.00 (aryl C), 188.25 (CHO). Mass spectrum: *m/z* 312 (M+1, 20%), 311 (M, 100), 296 (50), 97 (20), 69 (25), 57 (35).

The second band gave 4,6-dimethoxy-3-(4-methoxyphenyl)-indole-2-carbaldehyde **1g** (0.2 g, 10%) as yellow crystals, mp 215–216 °C (from DCM/petroleum ether). (Found: C, 69.2; H, 5.6; N, 4.4. $C_{18}H_{17}NO_4$ requires C, 69.4; H, 5.5; N, 4.5%). $\nu_{max}$: 3302, 1618, 1579, 1535, 1501, 1368, 1268, 1217, 1132, 802 $cm^{-1}$. $^1H$ NMR spectrum ($CDCl_3$): $\delta$ 3.74, 3.87, 3.88 (9H, 3s, OMe), 6.16 (1H, d, $J$=2.0 Hz, H5), 6.42 (1H, d, $J$=2.0 Hz, H7), 6.96 (2H, d, $J$=8.7 Hz, aryl), 7.48 (2H, d, $J$=8.7 Hz, aryl), 9.12 (1H, sb, NH), 9.50 (1H, s, CHO). $^{13}C$ NMR spectrum (DMSO-$d_6$): 55.32, 55.37, 55.59 (OMe), 86.62, 93.24, 113.06, 132.73 (aryl CH), 111.62, 124.95, 129.42, 131.30, 140.29, 156.67, 158.99, 161.06 (aryl C), 180.96 (CHO). Mass spectrum: *m/z* 312 (M+1, 20%), 311 (M, 100), 296 (20).

The third band gave 4,6-dimethoxy-3-(4-methoxyphenyl)-indole-2,7-dicarbaldehyde (0.5 g, 20%) as yellow crystals (Found: C, 67.4; H, 5.2; N, 4.1. $C_{19}H_{17}NO_5$ requires C, 67.3; H, 5.1; N, 4.1%). $\nu_{max}$: 3419, 1649, 1592, 1544, 1241, 1217, 990, 799, 608 $cm^{-1}$. $\lambda_{max}$: 248 nm ($\varepsilon$ 3150 $cm^{-1}\,M^{-1}$), 311 (1900), 348 (2250), 361 (2050), 373 (1850). $^1H$ NMR spectrum ($CDCl_3$): $\delta$ 3.86, 3.87, 3.83 (9H, 3s, OMe), 6.13 (1H, s, H5), 6.95 (2H, d, $J$=8.7 Hz, aryl), 7.42 (2H, d, $J$=8.7 Hz, aryl), 9.55 (1H, s, 2-CHO), 10.34 (1H, s, 7-CHO), 10.86 (1H, sb, NH). $^{13}C$ NMR spectrum (DMSO-$d_6$) 55.43, 56.59, 57.28 (OMe), 89.42, 113.38, 132.68 (aryl CH), 103.19, 111.19, 123.63, 129.12, 131.43, 137.68, 159.42, 163.76, 166.49 (aryl C), 181.24, 187.27 (CHO). Mass spectrum: *m/z* 340 (M+1, 20%), 339 (M, 100), 32 (25), 28 (100).

**4.2.6. Methyl [3-(4-*tert*-butylphenyl)-4,6-dimethoxyindol-7-yl] glyoxylate and methyl [3-(4-*tert*-butylphenyl)-4,6-dimethoxyindol-2-yl] glyoxylate (1h).** 3-(4-*tert*-Butylphenyl)-4,6-dimethoxyindole (1.0 g, 3.2 mmol) was dissolved in anhydrous diethyl ether (30 mL). Oxalyl chloride (0.39 mL, 4.0 mmol) was added in one portion. The mixture was stirred for 3 h at room temperature. The resulting orange-red precipitate was filtered off. This solid was then added to a solution of excess methanol in diethyl ether (20 mL). The mixture was stirred for 1 h. Water was then added and the mixture extracted with DCM. The organic layer was washed until neutral, then dried ($MgSO_4$). The solvent was removed under reduced pressure to give ester **1h** as a light yellow solid (45 mg, 35%), mp 177–178 °C (from methanol). (Found: C, 70.0; H, 6.4; N, 3.3. $C_{23}H_{25}NO_5$ requires C, 69.9; H, 6.4; N, 3.5%). $\nu_{max}$: 3320, 3260, 1755, 1630, 1600, 1570, 1520, 1490, 1340, 1310, 1280, 1240, 1210, 1200, 1160, 1130, 1070 $cm^{-1}$. $\lambda_{max}$: 214 nm ($\varepsilon$ 31,800 $cm^{-1}\,M^{-1}$), 259 (22,500), 348 (24,000). $^1H$ NMR spectrum ($CDCl_3$): $\delta$ 1.36 (9H, s, $Bu^t$), 3.21, 3.64, 3.85 (9H, 3s, OMe), 6.10 (1H, d, $J$=1.9 Hz, H5), 6.41 (1H, d, $J$=1.9 Hz, H7), 7.37, 7.40 (4H, 2dd, $J$=14.0, 8.7 Hz, aryl), 9.47 (1H, bs, NH). $^{13}C$ NMR spectrum ($CDCl_3$): $\delta$ 31.24 ($CH_3$-$Bu^t$), 34.55 (C-$Bu^t$), 51.85, 55.15, 55.54 (OMe), 85.58 (C5), 93.54 (C7), 123.93, 130.65 (aryl CH), 113.37, 127.39, 130.21, 130.59, 140.09, 150.38, 157.20, 162.29 (aryl C), 164.43, 177.56 (CO). Mass spectrum: *m/z* 396 (M+1, 30%), 395 (M, 90), 338 (20), 280 (100), 265 (25).

The filtrate containing 2-indol-7-ylglyoxyloyl chloride was evaporated under pressure. The residue was re-dissolved in diethyl ether (10 mL) and excess methanol was added. The mixture was allowed to stir for 1 h. The resulting precipitate was dissolved in DCM, washed with water until neutral, and dried to yield the methyl-[3-(4-*tert*-butylphenyl)-4,6-dimethoxyindol-7-yl]-glyoxylate as a yellow solid (38 mg, 30%), mp 196–197 °C (from methanol). (Found: C, 69.6; H, 6.2; N, 3.3. $C_{23}H_{25}NO_5$ requires C, 69.9; H, 6.4; N, 3.5%). $\nu_{max}$: 3390, 1725, 1620, 1590, 1570, 1550, 1540, 1500, 1430, 1350, 1320, 1310, 1260, 1210, 1170, 1150, 1120, 1085, 1060 $cm^{-1}$. $\lambda_{max}$: 211 nm ($\varepsilon$ 23,500 $cm^{-1}\,M^{-1}$), 256 (24,000), 340 (12,300). $^1H$ NMR spectrum ($CDCl_3$): $\delta$ 1.37 (9H, s, $Bu^t$), 3.94 (9H, s, OMe), 6.17 (1H, s, H5), 7.11 (1H, d, $J$=2.3 Hz, H2), 7.47, 7.64 (4H, 2dd, $J$=33.5, 8.3 Hz, aryl), 10.53 (1H, bs, NH). $^{13}C$ NMR spectrum ($CDCl_3$): $\delta$ 31.34 ($CH_3$-$Bu^t$), 34.39 (C-$Bu^t$), 52.13, 55.48, 57.09 (OMe), 87.22 (C5), 121.82 (C2), 124.85, 128.95 (aryl CH), 100.67, 110.80, 119.03, 132.05, 138.34, 148.90, 162.03, 162.35 (aryl C), 166.44, 184.62 (CO). Mass spectrum: *m/z* 396 (M+1, 10%), 395 (M, 50), 336 (100).

**4.2.7. 3-(4-Chlorophenyl)-4,6-dimethoxy-7-trichloroacetylindole (4c) and 3-(4-chlorophenyl)-4,6-dimethoxy-2-trichloroacetylindole (1j).** Trichloroacetyl chloride (2.0 mL, 17.9 mmol) was added dropwise to a solution of 3-(4-chlorophenyl)-4,6-dimethoxyindole (1.0 g, 3.5 mmol) in chloroform (20 mL). After completion of the addition, the solution was refluxed under $N_2$ overnight. The mixture was allowed to cool to room temperature, then water (20 mL) was added. The organic layer was extracted with DCM (2× 20 mL) and the organic layer was dried ($MgSO_4$), the solvent evaporated off under reduced pressure. Column chromatography of the residue (DCM/petroleum ether) gave the orange **4c** as the first fraction (1.0 g, 66%), mp 178 °C (DCM/petroleum ether). (Found: C, 50.0; H, 3.0; N, 3.1. $C_{18}H_{13}Cl_4NO_3$ requires C, 49.9; H, 3.0; N 3.2%). $\nu_{max}$: 3380, 1610, 1580, 1560, 1340, 1245, 1215, 1080 $cm^{-1}$. $\lambda_{max}$: 212 nm ($\varepsilon$ 14,000 $cm^{-1}\,M^{-1}$), 256 (12,600), 343 (8000). $^1H$ NMR spectrum ($CDCl_3$): $\delta$ 3.43, 3.99 (6H, 2s, OMe), 6.23 (1H, s, H5), 7.08 (1H, d, $J$=2.0 Hz, H2),

7.35–7.48 (4H, m, aryl), 10.29 (1H, sb, NH). $^{13}$C NMR spectrum ($CDCl_3$): $\delta$ 55.45, 55.62 (OMe), 87.69 (C5), 121.84 (C2), 127.79, 130.74, (aryl CH), 98.65 ($CCl_3$), 110.80, 118.53, 132.05, 133.81, 139.78, 160.38, 161.39 (aryl C), 182.36 (CO). Mass spectrum: *m/z* 435 (M+2, $Cl^{37/37}$, 7%), 433 (M, $Cl^{35/35}$, 15), 316 (33), 314 (100).

The second fraction produced the yellow **1j** (0.30 g, 17%), mp 214 °C (DCM/petroleum ether). (Found: C, 49.9; H, 2.9; N, 3.3. $C_{18}H_{13}Cl_4NO_3$ requires C, 49.9; H, 3.0; N, 3.2%). $\nu_{max}$: 3400, 1670, 1615, 1570, 1380, 1350, 1250, 1210, 1150 cm$^{-1}$. $\lambda_{max}$: 210 nm ($\varepsilon$ 21,200 cm$^{-1}$ M$^{-1}$), 281 (14,300), 360 (9600). $^1$H NMR spectrum ($CDCl_3$): $\delta$ 3.63, 3.88 (6H, 2s, OMe), 6.13 (1H, d, $J$=2.0 Hz, H5), 6.45 (1H, d, $J$=2.0 Hz, H7), 7.36 – 7.48 (4H, m, aryl), 8.95 (1H, sb, NH). $^{13}$C NMR spectrum ($CDCl_3$): $\delta$ 55.26, 55.70 (OMe), 87.57 (C5), 93.96 (C7), 127.34, 131.63, (aryl CH), 113.20, 120.67, 132.41, 132.86, 133.31, 139.13, 156.62, 161.47 (aryl C), 96.25 ($CCl_3$), 170.64 (CO). Mass spectrum: *m/z* 435 (M+2, $^{37/37}$Cl, 10%), 433 (M, $^{35/35}$Cl, 25), 314 (35), 279 (90), 264 (50), 150 (100).

**4.2.8. 3-(4-Bromophenyl)-4,6-dimethoxyindole-7-carbaldehyde (4b).** To a stirred solution of 3-(4-bromophenyl)-4,6-dimethoxyindole (1.50 g, 6.8 mmol) in anhydrous chloroform (10 mL) at −15 °C was added dropwise an ice cold solution of phosphoryl chloride (0.63 mL, 6.8 mmol) in DMF (1.5 mL). The mixture was stirred at this temperature for 1 h, then allowed to come to room temperature. Ice water (10 mL) was added and the mixture stirred vigorously for 1 h, then made strongly alkaline with 10% NaOH and stirred vigorously for a further 4 h. The mixture was extracted with DCM (3×100 mL), the organic layer collected, dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was column chromatographed (DCM) to give **4b** as yellow crystals (1.14 g, 70%), mp 218–220 °C (from DCM/petroleum ether). (Found: C, 57.0; H, 4.2; N, 3.7. $C_{17}H_{14}BrNO_3$ requires C, 56.7; H, 3.9; N, 3.9%). $\nu_{max}$: 3400, 1640, 1590, 1350, 1330, 1210, 1090, 980, 800 cm$^{-1}$. $\lambda_{max}$: 233 nm ($\varepsilon$ 2250 cm$^{-1}$ M$^{-1}$), 252 (2250), 267 (1500), 332 (1250), 363 (1000). $^1$H NMR spectrum ($CDCl_3$): $\delta$ 3.93, 4.00 (6H, 2s, OMe), 6.20 (1H, s, H5); 7.09 (1H, d, $J$= 2.2 Hz, H2); 7.44 (2H, d, $J$=8.6 Hz, aryl); 7.49 (2H, d, $J$= 8.6 Hz, aryl); 10.39 (1H, s, CHO); 10.54 (1H, sb, NH). $^{13}$C NMR spectrum ($CDCl_3$): 55.44, 56.40 (OMe), 86.82, 121.83, 130.76, 131.03 (aryl CH), 104.50, 109.96, 117.73, 120.03, 134.42, 137.77, 161.27, 163.13 (aryl C), 188.37 (CHO). Mass spectrum: *m/z* 362 (M+1, $^{81}$Br, 20%), 361 (M, $^{81}$Br, 100), 360 (M+1, $^{79}$Br, 22), 359 (M, $^{79}$Br, 100), 265 (35).

### 4.3. Preparation of nitric acid on silica gel

Silica gel (60H, Merck, 60 g) was added to nitric acid (8 M, 140 mL) and the resulting suspension stirred at room temperature for 2 h. The suspension was filtered and the silica gel allowed to dry in air for one week, then stored in an airtight container. The nitric acid content of the gel was determined by titration to be approximately 20%.

### 4.4. General procedure for the nitration of C-substituted indoles

To a solution of indole (100 mg) in DCM (20 mL) was added $HNO_3$ supported on silica gel (0.50 g). The mixture was quickly shaken for 10 seconds and immediately filtered. The solvent was removed and the residue recrystallised from methanol.

**4.4.1. Dimethyl-4,6-dimethoxy-7-nitroindole-2,3-dicarboxylate (2c).** Indole **1c** (100 mg, 0.34 mmol) gave the yellow nitrated indole **2c** (110 mg, 96%), mp 267–268 °C (from methanol). (Found: C, 49.6; H, 4.0; N, 8.1. $C_{14}H_{14}N_2O_8$ requires C, 49.7; H, 4.2; N, 8.3%). $\nu_{max}$: 3460, 1740, 1710, 1630, 1590, 1555, 1520, 1500, 1450, 1420, 1345, 1320, 1290, 1250, 1225, 1200, 1120 cm$^{-1}$. $\lambda_{max}$: 205 nm ($\varepsilon$ 18,700 cm$^{-1}$ M$^{-1}$), 229 (22,300), 295 (14,700), 356 (13,200). $^1$H NMR spectrum ($CDCl_3$): $\delta$ 3.94, 3.97, 4.03, 4.09 (12H, 4s, OMe), 6.27 (1H, s, H5), 10.52 (1H, sb, NH). $^{13}$C NMR spectrum ($CDCl_3$): $\delta$ 52.43, 52.71, 56.45, 57.31 (OMe), 88.99 (C5), 111.22, 115.35, 123.71, 124.92, 131.76, 159.16, 159.68 (aryl C), 160.03, 165.43 (CO). Mass spectrum: *m/z* 339 (M+1, 10%), 338 (M, 100), 306 (50), 275 (35), 248 (65), 215 (40), 202(40).

**4.4.2. Methyl-4,6-dimethoxy-7-nitroindole-2-carboxylate (2d).** Indole **1d** (100 mg, 0.43 mmol) gave the yellow nitrated indole **2d** (95 mg, 80%), mp 230–231 °C (from methanol). (Found: C, 50.3; H, 4.3; N, 9.8. $C_{12}H_{12}N_2O_6\cdot 0.25H_2O$ requires C, 50.6; H, 4.4; N, 9.8%). $\nu_{max}$: 3485, 1710, 1620, 1580, 1535, 1510, 1310, 1300, 1250, 1220, 1170, 970 cm$^{-1}$. $\lambda_{max}$: 209 nm ($\varepsilon$ 12,000 cm$^{-1}$ M$^{-1}$), 225 (13,700), 292 (13,000), 356 (9000). $^1$H NMR spectrum (DMSO-$d_6$): $\delta$ 3.86, 4.06, 4.08 (9H, 3s, OMe), 6.59 (1H, s, H5), 7.19 (1H, d, $J$=2.6 Hz, H3), 10.94 (1H, sb, NH). $^{13}$C NMR spectrum (DMSO-$d_6$): $\delta$ 52.39, 57.12, 58.03 (OMe), 90.25 (C5), 107.17 (C3), 79.53, 113.45, 126.74, 132.64, 158.40, 160.09 (aryl C), 160.84 (CO). Mass spectrum: *m/z* 281 (M+1, 10%), 280 (M, 100), 248 (55), 218 (40), 201 (15), 190 (25).

**4.4.3. Methyl-2-benzoyl-4,6-dimethoxy-7-nitroindole-3-carboxylate (2e).** Indole **1e** (100 mg, 0.29 mmol) gave the yellow nitrated indole **2e** (102 mg, 90%), mp 188–190 °C (from methanol). (Found: C, 58.8; H, 4.1; N, 7.3. $C_{19}H_{16}N_2O_7$. 0.25 $H_2O$ requires C, 58.7; H, 4.3; N, 7.2%). $\nu_{max}$: 3430, 3410, 1730, 1635, 1620, 1590, 1575, 1540, 1490, 1395, 1300, 1275, 1255, 1240, 1210, 1190, 1175 cm$^{-1}$. $\lambda_{max}$: 208 nm ($\varepsilon$ 31,500 cm$^{-1}$ M$^{-1}$), 245 (25,000), 337 (21,800). $^1$H NMR spectrum (DMSO-$d_6$): $\delta$ 3.36, 4.02, 4.07 (9H, 3s, OMe), 6.65 (1H, s, H5), 7.51–7.56 (2H, m, aryl), 7.64–7.73 (3H, m, aryl), 11.92 (1H, sb, NH). $^{13}$C NMR spectrum (DMSO-$d_6$): $\delta$ 51.96, 57.26, 58.08 (OMe), 91.28 (C5), 129.04, 129.11, 133.64 (aryl CH), 79.53, 110.50, 113.24, 131.80, 135.61, 137.69, 157.93, 159.98 (aryl C), 164.19, 187.23 (CO). Mass spectrum: *m/z* 385 (M+1, 15%), 384 (M, 100), 352 (20), 385 (25), 323 (25).

**4.4.4. (4,6-Dimethoxy-7-nitroindol-2-yl)-phenylmethanone (2f).** Indole **1f** (100 mg, 0.36 mmol) gave the yellow nitrated indole **2f** (87 mg, 75%), mp 239–240 °C (from methanol). $\nu_{max}$: 3460, 1620, 1575, 1565, 1515, 1410, 1310, 1290, 1250, 1215, 1190, 1170, 1110 cm$^{-1}$. $\lambda_{max}$: 309 nm ($\varepsilon$ 22,500 cm$^{-1}$ M$^{-1}$), 230 (17,500), 241 (16,900), 336 (21,800). $^1$H NMR spectrum ($CDCl_3$): $\delta$ 4.08, 4.11 (6H, 2s, OMe), 6.26 (1H, s, H5), 7.22 (1H, d, $J$=2.6 Hz, H3), 7.49–7.64 (3H, m, aryl), 7.93–7.96 (2H, m, aryl), 10.73 (1H,

sb, NH). $^{13}$C NMR spectrum ($CDCl_3$): $\delta$ 56.18, 57.36 (OMe), 88.39 (C5), 110.68 (C3), 128.51, 129.05, 132.43 (aryl CH), 114.36, 133.76, 133.99, 137.64, 159.48, 159.48, 160.95 (aryl C), 185.60 (CO). Mass spectrum: *m/z* 327 (M+1, 15%), 326 (M, 100), 250 (35), 207 (20).

**4.4.5. 4,6-Dimethoxy-3-(4-methoxyphenyl)-7-nitroindole-2-carbaldehyde (2g).** Indole **1g** (100 mg, 0.32 mmol) gave the yellow nitrated indole **2g** (103 mg, 90%), mp 272–274 °C (from methanol). (Found: C, 59.3; H, 4.6; N, 7.9. $C_{18}H_{16}N_2O_6$. 0.5 $H_2O$ requires C, 59.2; H, 4.7; N, 7.7%). $\nu_{max}$: 3450, 1650, 1620, 1580, 1570, 1550, 1510, 1490, 1440, 1420, 1340, 1300, 1260, 1230, 1210, 1180 cm$^{-1}$. $\lambda_{max}$: 204 nm ($\varepsilon$ 15,900 cm$^{-1}$ M$^{-1}$), 249 (16,000), 325 (11,400), 377 (9500). $^1$H NMR spectrum ($CDCl_3$): $\delta$ 3.89, 4.10 (9H, 2s, OMe), 6.23 (1H, s, H5), 6.98, 7.42 (4H, 2dd, $J$=34.3, 8.7 Hz, aryl), 9.57 (1H, s, CHO), 10.65 (1H, sb, NH). $^{13}$C NMR spectrum ($CDCl_3$): $\delta$ 55.34, 55.94, 57.33 (OMe), 88.54 (C5), 113.19, 132.39 (aryl CH), 112.44, 112.97, 118.63, 123.33, 130.26, 131.97, 134.11, 159.76, 162.42 (aryl C), 181.35 (CO). Mass spectrum: *m/z* 357 (M+1, 20%), 356 (M, 100).

**4.4.6. Methyl [3-(4-*tert*-butylphenyl)-4,6-dimethoxy-7-nitroindol-2-yl] glyoxylate (2h).** Indole **1h** (100 mg, 0.25 mmol) gave the yellow nitrated indole **2h** (111 mg, 84%), mp 284–285 °C (from methanol). (Found: C, 62.7; H, 5.4; N, 6.3. $C_{23}H_{24}N_2O_7$ requires C, 62.7; H, 5.5; N, 6.4%). $\nu_{max}$: 3450, 1740, 1630, 1580, 1560, 1520, 1510, 1490, 1440, 1420, 1340, 1320, 1290, 1230, 1210, 1150 cm$^{-1}$. $\lambda_{max}$: 206 nm ($\varepsilon$ 8000 cm$^{-1}$ M$^{-1}$), 245 (5900), 339 (6000). $^1$H NMR spectrum ($CDCl_3$): $\delta$ 1.29 (9H, s, Bu$^t$), 3.74, 3.85, 4.04 (9H, 3s, OMe), 6.23 (1H, s, H5), 7.20, 7.35 (4H, 2dd, $J$=48.7, 8.7 Hz, aryl), 9.08 (1H, sb, NH). $^{13}$C NMR spectrum ($CDCl_3$): $\delta$ 31.21 ($CH_3$-Bu$^t$), 34.61 (C-Bu$^t$), 52.05, 55.94, 57.26 (OMe), 88.52 (C5), 124.17, 130.48 (aryl CH), 113.04, 118.33, 128.29, 128.89, 129.96, 134.11, 151.10, 160.12, 162.53 (aryl C), 163.54, 177.43 (CO). Mass spectrum: *m/z* 441 (M+1, 15%), 440 (M, 85), 343 (25), 325 (100), 307 (25).

**4.4.7. 4,6-Dimethoxy-3-methyl-7-nitroindole-2-carbaldehyde (2i).** Indole **1i** (100 mg, 0.46 mmol) gave the yellow nitrated indole **2i** (78 mg, 60%), mp 243–245 °C (from methanol). $\nu_{max}$: 3440, 3370, 3320, 1650, 1640, 1615, 1570, 1550 1450, 1430, 1410, 1300, 1280, 1220, 1200, 970 cm$^{-1}$. $\lambda_{max}$: 207 nm ($\varepsilon$ 16,600 cm$^{-1}$ M$^{-1}$), 230 (17,000), 323 (18,900), 360 (16,400). $^1$H NMR spectrum (DMSO-$d_6$): $\delta$ 2.63 (3H, s, $CH_3$), 4.04, 4.06 (6H, 2s, OMe), 6.47 (1H, s, H5), 9.99 (1H, s, CHO), 11.13 (1H, sb, NH). $^{13}$C NMR spectrum (DMSO-$d_6$): $\delta$ 10.93 ($CH_3$), 57.18, 57.97 (OMe), 89.81 (C5), 113.57, 124.13, 131.85, 133.39, 159.45, 163.02 (aryl C), 182.45 (CHO). Mass spectrum: *m/z* 265 (M+1, 15%), 264 (M, 100), 246 (30), 188 (50), 173 (40).

**4.4.8. 4,6-Dimethoxy-3-methyl-2,7-dinitroindole (3).** To a solution of indole **1i** (100 mg, 0.46 mmol) in DCM (20 mL) was added $HNO_3$ supported on silica gel (0.50 g). The mixture was stirred for 10 min and then filtered. The solvent was removed and the residue triturated in methanol to give the yellow dinitrated indole **3** (58 mg, 45%), mp 274–276 °C. (Found: C, 47.3; H, 4.0; N, 14.7. $C_{11}H_{11}N_3O_6$ requires C, 47.0; H, 3.9; N, 14.9%). $\nu_{max}$: 3400, 1620, 1580, 1530, 1500, 1420, 1390, 1340, 1310, 1280, 1240, 1200 cm$^{-1}$. $\lambda_{max}$: 204 nm ($\varepsilon$ 9500 cm$^{-1}$ M$^{-1}$), 234 (7100), 363 (8500). $^1$H NMR spectrum (DMSO-$d_6$): $\delta$ 2.72 (3H, s, $CH_3$), 4.06, 4.07 (6H, 2s, OMe), 6.54 (1H, s, H5), 11.41 (1H, sb, NH). Mass spectrum: *m/z* 282 (M+1, 20%), 281 (M, 50), 263 (50), 251 (100), 234 (20).

**4.4.9. 3-(4-Chlorophenyl)-4,6-dimethoxy-7-nitro-2-trichloroacetylindole (2j).** The title compound was prepared from 2-trichloroacetylindole **1j** (0.20 g, 0.46 mmol) and conc. $HNO_3$ supported on silica gel (0.80 g). The nitro compound **2j** (0.16 g, 72%) was obtained as a yellow solid, mp 202 °C (DCM/petroleum ether). (Found: C, 44.7; H, 2.5; N, 5.9. $C_{18}H_{12}Cl_4N_2O_5$. 0.3 $H_2O$ requires C, 44.8; H, 2.6; N, 5.8%). $\nu_{max}$: 3410, 1700, 1620, 1560, 1530, 1350, 1290, 1220, 1200, 980, 845 cm$^{-1}$. $\lambda_{max}$: 242 nm ($\varepsilon$ 28,400 cm$^{-1}$ M$^{-1}$), 202 (24,900), 294 (12,600), 369 (12,500). $^1$H NMR spectrum ($CDCl_3$): $\delta$ 3.80, 4.11 (6H, 2s, OMe), 6.21 (1H, s, H5), 7.31–7.40 (4H, m, aryl), 11.29 (1H, sb, NH). $^{13}$C NMR spectrum ($CDCl_3$): $\delta$ 56.09, 57.46 (OMe), 88.91 (C5), 127.67, 131.41 (aryl CH), 95.49 ($CCl_3$), 112.73, 118.22, 122.21, 127.58, 131.88, 133.45, 133.89, 160.52, 162.14 (aryl C), 171.15 (CO). Mass spectrum: *m/z* 480 (M+2, $^{37/37}$Cl, 7%), 478 (M, 10), 375 (98), 361 (30), 359 (100).

**4.4.10. Methyl 3-(4-chlorophenyl)-4,6-dimethoxy-7-nitroindole-2-carboxylate (2k).** The mixture of indole **2j** (670 mg, 1.40 mmol) in methanol (20 mL) was treated with triethylamine (4 drops), then heated under reflux for 1 h. The mixture was allowed to cool to room temperature and the resulting precipitate was filtered, washed with methanol and dried to give the ester **2k** (430 mg, 78%) as a yellow solid, mp 240 °C (methanol/DCM). (Found: C, 55.4; H, 3.9; N, 7.0. $C_{18}H_{15}ClN_2O_6$ requires C, 55.3; H, 3.9; N, 7.2%). $\nu_{max}$: 3460, 1700, 1680, 1580, 1325, 1285, 1225, 1200, 980, 800 cm$^{-1}$. $\lambda_{max}$: 242 nm ($\varepsilon$ 62,800 cm$^{-1}$ M$^{-1}$), 203 (61,600), 368 (28,000), 294 (27,000). $^1$H NMR spectrum ($CDCl_3$): $\delta$ 3.79, 3.80, 4.09 (9H, 3s, OMe), 6.20 (1H, s, H5), 7.34 (4H, s, aryl), 10.64 (1H, sb, NH). $^{13}$C NMR spectrum ($CDCl_3$): $\delta$ 51.97, 55.87, 57.33 (OMe), 88.55 (C5), 127.20, 132.05 (aryl CH), 112.84, 122.71, 124.50, 127.09, 131.75, 132.47, 133.39, 159.02, 160.77 (aryl C), 161.72 (CO). Mass spectrum: *m/z* 392 (M+2, $^{37/37}$Cl, 7%), 390 (M, $^{35/35}$Cl, 21), 358 (20).

**4.4.11. 1-[3-(4-Bromophenyl)-4,6-dimethoxy-2-nitroindol-7-yl]-2,2,2-trifluoroethanone (5a).** Indole **4a** (100 mg, 0.23 mmol) gave the yellow nitrated indole **5a** (94 mg, 85%), mp 232–234 °C (from methanol). (Found: C, 45.8; H, 2.6; N, 5.6. $C_{18}H_{12}N_2O_5BrF_3$ requires C, 45.7; H, 2.6; N, 5.9%). $\nu_{max}$: 3390, 1720, 1630, 1600, 1580, 1490, 1440, 1420, 1400, 1360, 1320, 1300, 1230, 1200, 1190, 1170, 1160, 1120 cm$^{-1}$. $\lambda_{max}$: 232 nm ($\varepsilon$ 23,800 cm$^{-1}$ M$^{-1}$), 351 (16,900). $^1$H NMR spectrum ($CDCl_3$): $\delta$ 3.82, 4.05 (6H, 2s, OMe), 6.20 (1H, s, H5), 7.47, 7.64 (4H, 2dd, $J$=78.4, 8.2 Hz, aryl) 11.30 (1H, sb, NH). $^{13}$C NMR spectrum ($CDCl_3$): $\delta$ 55.91, 56.67 (OMe), 88.99 (C5), 130.57, 131.84 (aryl CH), 99.26, 104.96, 111.74, 118.72, 119.00, 122.45, 127.14, 129.89, 131.56, 164.57 (aryl C), 165.73 (CO). Mass spectrum: *m/z* 475 (M+2, 10%), 474 (M+1, 95), 472 (85), 458 (20), 442 (20), 403 (100), 403 (90), 392 (35), 149 (75).

**4.4.12. 3-(4-Bromophenyl)-4,6-dimethoxy-2-nitroindole-7-carbaldehyde (5b).** Indole **4b** (100 mg, 0.28 mmol) gave the yellow nitrated indole **5b** (90 mg, 80%), mp 288–290 °C (from methanol). (Found: C, 50.4; H, 3.3; N, 3.9. $C_{17}H_{13}N_2O_5Br$ requires C, 50.4; H, 3.2; N, 6.9%). $\nu_{max}$: 3400, 3355, 1650, 1600, 1575, 1530, 1510, 1485, 1450, 1400, 1360, 1290, 1230, 1220 $cm^{-1}$. $\lambda_{max}$: 205 nm ($\varepsilon$ 16,100 $cm^{-1}$ $M^{-1}$), 240 (19,900). $^1H$ NMR spectrum ($CDCl_3$): $\delta$ 3.80, 4.04 (6H, 2s, OMe), 6.18 (1H, s, H5), 7.47, 7.64 (4H, 2dd, $J$=70.8, 8.2 Hz, aryl), 10.35 (1H, s, CHO), 11.21 (1H, sb, NH). $^{13}C$ NMR spectrum ($CDCl_3$): $\delta$ 55.70, 56.41 (OMe), 88.32 (C5), 130.48, 131.97 (aryl CH), 103.53, 118.66, 122.28, 126.46, 130.21, 132.25, 134.26, 163.47, 166.41 (aryl C), 187.56 (CHO). Mass spectrum: *m/z* 407 (M+2, 15%), 406 (M+1, 100), 404 (100), 376 (20), 374 (25), 368 (20).

**4.4.13. 3-(4-Chlorophenyl)-4,6-dimethoxy-2-nitro-7-trichloroacetylindole (5c).** To a solution of 7-trichloroacetylindole **4c** (0.13 g, 0.3 mmol) in DCM (10 mL) was added conc. $HNO_3$ supported on silica gel (0.50 g). The mixture was stirred for 10 min. After completion of the reaction, the silica was filtered off. The filtrate was concentrated and the residue chromatographed (DCM/petroleum ether) to give compound **5c** (0.10 g, 70%) as a yellow solid, mp 243 °C (from DCM/petroleum ether). (Found: C, 45.2; H, 2.3; N, 5.1. $C_{18}H_{12}Cl_4N_2O_5$. $0.1H_2O$ requires C, 45.1; H, 2.6; N, 5.8%). $\nu_{max}$: 3400, 1650, 1580, 1485, 1290, 1235, 1220, 1160, 980, 840, 800, 720 $cm^{-1}$. $\lambda_{max}$: 227 nm ($\varepsilon$ 20,900 $cm^{-1}$ $M^{-1}$), 203 (16,400). $^1H$ NMR spectrum ($CDCl_3$): $\delta$ 3.80, 4.04 (6H, 2s, OMe), 6.21 (1H, s, H5), 7.36 – 7.41 (4H, m, aryl), 11.03 (1H, sb, NH). $^{13}C$ NMR spectrum ($CDCl_3$): $\delta$ 55.90 (OMe), 89.25 (C5), 127.73, 131.72 (aryl CH), 97.78, 98.23, 112.20, 119.20, 129.71, 134.23, 135.51, 136.68, 163.67, 163.90 (aryl C), 165.49 (CO). Mass spectrum: *m/z* 478 (M, 3%), 361 (30), 359 (100).

## 4.5. Preparation of N-substituted indoles

**4.5.1. 4,6-Dimethoxy-3-phenyl-1-phenylsulfonylindole (6a).** 4,6-Dimethoxy-3-phenylindole (5.84 g, 23 mmol) in anhydrous THF (100 mL) and the solution cooled in an ice-ethanol bath. *n*-Butyllithium (1.6 M, 15.9 mL, 24.4 mmol) was added dropwise over 5 min and the solution stirred under $N_2$ for 1 h. Phenylsulfonyl chloride (4.10 g, 23 mmol) was added slowly over 5 min and the mixture stirred at room temperature for 2 h. The reaction mixture was poured into ice water (200 mL) and extracted with diethyl ether (3× 100 mL). The organic extract was dried ($MgSO_4$), concentrated and the residue purified by column chromatography (DCM/hexane) to give **6a** as a white powder (6.85 g, 76%), mp 157–159 °C. (Found: C, 67.1; H, 5.0; N, 3.5. $C_{22}H_{19}NO_4S$ requires C, 67.2; H, 4.9; N, 3.6%). $\nu_{max}$: 1590, 1340, 1200, 1180, 1170, 1140, 1100, 810, 800, 750, 720, 680 $cm^{-1}$. $\lambda_{max}$: 230 nm ($\varepsilon$ 15,900), 246 (14,300), 287 (3500), 304 (1900). $^1H$ NMR spectrum ($CDCl_3$): $\delta$ 3.72, 3.90 (6H, 2s, OMe), 6.35 (1H, d, $J$=2.1 Hz, H5), 7.22 (1H, d, $J$=2.1 Hz, H2), 7.23–7.56 (9H, m, H7 and aryl), 7.91–7.94 (2H, m, aryl). $^{13}C$ NMR spectrum ($CDCl_3$): $\delta$ 55.18, 55.83 (OMe), 89.87 (C5), 95.24 (C7), 121.54 (C2), 126.80, 127.07, 127.64, 129.31, 129.55, 133.86 (aryl CH), 113.03, 124.70, 133.86, 137.53, 138.09 (aryl C), 154.70, 159.25 (C4, C6). Mass spectrum: *m/z* 394 (M+1, 4%), 393 (M, 15), 253 (20), 252 (100).

**4.5.2. 3-(4-Chlorophenyl)-4,6-dimethoxy-indole-1-carbonitrile (6c).** The 3-(4-chlorophenyl)-4,6-dimethoxyindole (1.0 g, 3.5 mmol) was added to a suspension of sodium hydride (1.1 equiv) in DMF (10 mL) at room temperature under $N_2$. *p*-Nitrophenylisocyanate (0.69 g, 4.2 mmol) was added slowly to the sodium salt of the indole and the mixture was further stirred at room temperature for 1 h. Water was added and extraction with ethyl acetate, followed by drying and evaporation of the solvent yielded the cyanoindole **6c** (0.93 g, 85%) as white crystals, mp 214–215 °C (from methanol). (Found: C, 65.1; H, 4.1; N, 8.9. $C_{17}H_{13}N_2O_2Cl$ requires C, 65.3; H, 4.2; N, 9.0%). $\nu_{max}$: 3130, 2215, 1615, 1590, 1560, 1550, 1500, 1450, 1430, 1300, 1260, 1240, 1200 $cm^{-1}$. $\lambda_{max}$: 210 nm ($\varepsilon$ 21,800 $cm^{-1}$ $M^{-1}$), 245 (27,000). $^1H$ NMR spectrum ($CDCl_3$): $\delta$ 3.77, 3.89 (6H, 2s, OMe), 6.38 (1H, d, $J$=2.1 Hz, H5), 6.70 (1H, d, $J$=2.1 Hz, H7), 6.98 (1H, s, H2), 7.35, 7.46 (4H, dd, $J$=33.3, 8.2 Hz, aryl). $^{13}C$ NMR spectrum ($CDCl_3$): $\delta$ 55.34, 55.88 (OMe), 87.28 (C5), 95.90 (C7), 107.47 (CN), 120.43 (C2), 127.94, 130.70 (aryl CH), 110.12, 123.96, 131.39, 133.46, 139.65, 155.15, 160.15 (aryl C). Mass spectrum: *m/z* 314 (M+2, 35%), 312 (M, 100), 262 (30).

## 4.6. General procedure for the nitration of N-substituted indoles

To a solution of indole (100 mg) in dichloromethane (20 mL) was added $HNO_3$ supported on silica gel (0.50 g). The mixture was quickly shaken for 10 s and immediately filtered. The solvent was removed and the residue was run on preparative TLC plates with DCM to separate out the different bands. The crude nitrated indole fractions were then hydrolysed in methanol with excess NaOH. Each fraction was again run on a preparative TLC plate with DCM to yield the deprotected nitrated indole products.

**4.6.1. 4,6-Dimethoxy-2,7-dinitro-3-phenylindole (7a).** Indole **6a** (100 mg, 0.25 mmol) gave the yellow nitrated indole **7a** (65 mg, 75%), mp 221–223 °C. $\nu_{max}$: 3420, 1620, 1605, 1570, 1555, 1515, 1490, 1430, 1410, 1355, 1330, 1310, 1280, 1270, 1220, 1195, 1170 $cm^{-1}$. $\lambda_{max}$: 207 nm ($\varepsilon$ 16,000 $cm^{-1}$ $M^{-1}$), 242 (11,800), 357 (11,300). $^1H$ NMR spectrum ($CDCl_3$): $\delta$ 3.78, 4.11 (6H, 2s, OMe), 6.24 (1H, s, H5), 7.42 (5H, s, aryl) 10.97 (1H, sb, NH). $^{13}C$ NMR spectrum ($CDCl_3$): $\delta$ 55.97, 57.29 (OMe), 89.28 (C5), 127.39, 128.22, 130.02 (aryl CH), 111.76, 130.21, 130.54, 144.21, 149.70, 153.13, 160.20, 162.69 (aryl C). Mass spectrum: *m/z* 344 (M+1, 15%), 343 (100), 313 (25), 267 (20), 105 (85), 77 (90).

**4.6.2. 3-(4-Bromophenyl)-4,6-dimethoxy-2-nitroindole (7b).** Indole **6b** (100 mg, 0.27 mmol) gave the yellow nitrated indole **7b** (35 mg, 35%), mp 211–213 °C $\nu_{max}$: 3390, 1620, 1570, 1520, 1490, 1420, 1340, 1290, 1250, 1210, 1180, 1150, 1120 $cm^{-1}$. $\lambda_{max}$: 215 nm ($\varepsilon$ 25,300 $cm^{-1}$ $M^{-1}$), 261 (13,500), 385 (10,800). $^1H$ NMR spectrum ($CDCl_3$): $\delta$ 3.64, 3.87 (6H, 2s, OMe), 6.17 (1H, d, $J$=2.1 Hz, H5), 6.38 (1H, d, $J$=2.1 Hz, H7), 7.30, 7.52 (4H, 2dd, $J$=57.9, 8.7 Hz, aryl) 9.25 (1H, sb, NH). $^{13}C$ NMR spectrum ($CDCl_3$): $\delta$ 55.16, 55.64 (OMe), 85.50 (C5), 94.48

(C7), 130.27, 132.10 (aryl CH), 111.99, 119.81, 122.06, 130.69, 134.67, 135.81, 157.23, 162.69 (aryl C). Mass spectrum: *m/z* 379 (M+2, 10%), 378 (M+1, 100), 376 (90), 346 (40), 315 (30), 253 (25).

**4.6.3. 3-(4-Bromophenyl)-4,6-dimethoxy-7-nitroindole (2b).** Indole **6b** (100 mg, 0.27 mmol) also gave the yellow nitrated indole **2b** (40 mg, 40%), mp 218–220 °C. (Found: C, 50.2; H, 3.6; N, 7.2. $C_{16}H_{13}N_2O_4Br$. 0.25 $H_2O$ requires C, 50.3; H, 3.6; N, 7.4%). $\nu_{max}$: 3420, 1610, 1570, 1550, 1535, 1500, 1450, 1440, 1360, 1350, 1320, 1300, 1280, 1250, 1230, 1210 $cm^{-1}$. $\lambda_{max}$: 213 nm ($\varepsilon$ 23,000 $cm^{-1}$ $M^{-1}$), 263 (14,800), 283 (7400). $^1H$ NMR spectrum ($CDCl_3$): $\delta$ 3.93, 4.08 (6H, 2s, OMe), 6.26 (1H, s, H5), 7.13 (1H, d, $J$= 2.6 Hz, H2), 7.38–7.51 (4H, m, aryl), 10.31 (1H, sb, NH). $^{13}C$ NMR spectrum ($CDCl_3$): $\delta$ 55.59, 57.22 (OMe), 88.26 (C5), 121.80 (C2), 130.64, 131.04 (aryl CH), 118.98, 120.44, 130.64, 131.80, 133.34, 133.60, 156.84, 160.23 (aryl C). Mass spectrum: *m/z* 379 (M+2, 35%), 377 (M, 100), 347 (25).

**4.6.4. 3-(4-Chlorophenyl)-4,6-dimethoxy-2-nitroindole (7c).** Indole **6c** (100 mg, 0.32 mmol) gave the yellow nitrated indole **7c** (53 mg, 50%), mp 216–217 °C. (Found: C, 57.2; H, 3.9; N, 8.3. $C_{16}H_{13}N_2O_4Cl \cdot 0.25H_2O$ requires C, 57.0; H, 4.0; N, 8.3%). $\nu_{max}$: 3370, 1620, 1590, 1580, 1570, 1535, 1520, 1490, 1455, 1440, 1385, 1335, 1280, 1270, 1240, 1200, 1170, 1140, 1120 $cm^{-1}$. $\lambda_{max}$: 220 nm ($\varepsilon$ 15,700 $cm^{-1}$ $M^{-1}$), 260 (18,900), 385 (15,700). $^1H$ NMR spectrum ($CDCl_3$): $\delta$ 3.64, 3.87 (6H, 2s, OMe), 6.16 (1H, d, $J$=1.6 Hz, H5), 6.38 (1H, d, $J$=1.6 Hz, H7), 7.35, 7.42 (4H, m, aryl), 9.26 (1H, sb, NH). $^{13}C$ NMR spectrum ($CDCl_3$): $\delta$ 55.15, 55.64 (OMe), 85.51 (C5), 94.48 (C7), 127.34, 131.82 (aryl CH), 112.06, 119.84, 130.19, 133.76, 135.82, 153.86, 157.23, 162.69 (aryl C). Mass spectrum: *m/z* 334 (M+1, 35%), 333 (M, 20), 332 (100), 302 (50), 271 (45).

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