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Synthesis of activated 3-substituted indoles: an optimised one-pot procedure

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Abstract—3-Substituted-4,6-dimethoxyindoles can be synthesised in a one-pot procedure from 3,5-dimethoxyaniline and 2-haloketones in the presence of lithium bromide and sodium bicarbonate.

1. Introduction

The indole nucleus is present in a wide range of natural products, and consequently a variety of methods for the synthesis of indoles has been developed.[1,2] Amongst these numerous methods few practical and mild procedures are available for the construction of activated 3-substituted-4,6-dimethoxyindoles **6**, and in particular for 3-alkyl-4,6-dimethoxyindoles.[3–5] Indoles carrying this substitution pattern are of particular interest since they do not only activate C7 and C2, but also enhance the general reactivity of the indoles. An earlier study reported that 3-arylindoles can be synthesised via a modified Bischler procedure in four steps.[6,7] This approach involved condensation of 3,5-dimethoxyaniline **1** with phenacyl halides **2** (R = Ar) to afford arylamino ketones **3** which are consecutively protected giving the *N*-protected amido ketones **4**, prior to their cyclisation in acid yielding the *N*-protected indoles **5**. These are deprotected by base to yield the desired 3-arylindoles **6**. The *N*-protection is required to prevent Bischler rearrangement to give 2-arylindoles **7** instead.[6,8] This method has now been improved to provide a facile one-pot procedure that could also be extended to the preparation of 3-alkylindoles in good yields (Scheme 1).

2. Results and discussion

2.1. Scope of the four-step procedure

The modified Bischler synthesis has been successfully applied to 3,5-dimethoxyaniline and is an effective way for the preparation of 4,6-dimethoxyindoles with overall yields of 25–60% for aryl substituted indoles. Nevertheless, the presence of substituents carrying sensitive functions such as hydroxyl or ester groups contribute to a loss in yield, since chromatographic workup is needed for some of the intermediates prior to the next step in the reaction sequence. This also involves lengthy work-up, which adds to the accumulated reaction times needed for the four-step synthesis. Furthermore, there has been no general synthetic methodology for alkylindoles in this series.

After a close examination of the four-step synthesis the crucial step was identified as the formation of the anilino ketones **3**, where both the quality and quantity of the products were variable. Consequently, further investigations were undertaken to gain control over this step.

2.2. From a four-step procedure to a one-pot reaction

In order to synthesise 4,6-dimethoxy-3-methylindole **6a** via the modified Bischler procedure the reaction conditions in the first step had to be modified, eventually allowing the preparation of **6a** in 22% yield overall. Thus, in the crucial first step of its synthesis 1-chloroacetone **2a** was reacted with 3,5-dimethoxyaniline **1** in refluxing ethanol containing excess sodium bicarbonate and excess lithium bromide to produce the methyl anilinoketone **3a**, which ideally precipitated out of solution upon cooling affording the product in a variable yield of 30–67%. After a reaction period of only 3 h, the anilinoketone **3a** could be isolated in 70% yield, then cyclised using acetic anhydride to *N*-acetyl-4,6-dimethoxy-3-methylindole in 70% yield, and this could be hydrolysed with potassium hydroxide in ethanol to give indole **6a** in 90% yield. However, after longer reaction times

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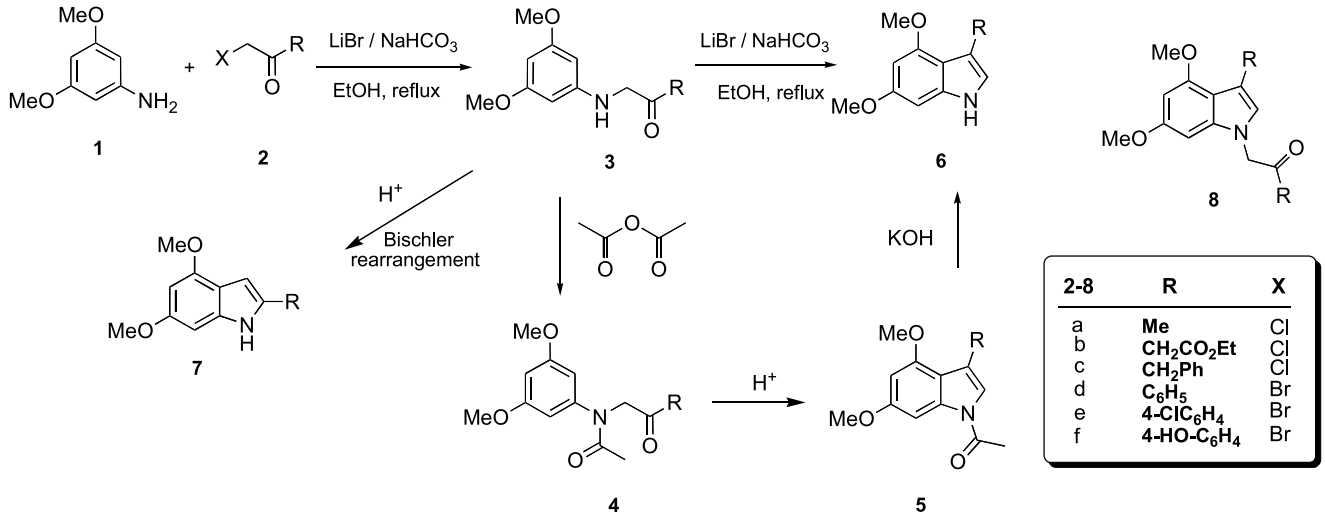

Scheme 1.

in the anilinoketone preparation and more appropriate stoichiometry, a major by-product appeared in the reaction mixture and was revealed by proton NMR spectroscopy to be the 3-methylindole **6a**. This was an interesting observation, since the cyclisation of amino ketones to indoles usually takes place under strongly acidic conditions. The absence of the corresponding 2-methylindole **7a** indicated that under the reaction conditions chosen no Bischler rearrangement could occur. With this information at hand the conditions could be adjusted to yield the indole **6a** in 74% yield, using molar equivalent amounts of all the reagents and reactants resulting in an efficient, shortened route to **6a**.

A similar observation was made for the reaction of 3,5-dimethoxyaniline **1** with ethyl 4-chloroacetoacetate **2b**. A reaction period of 3 h led to crude anilinoketone **3b**, which was converted with acetic anhydride to the *N*-acetyl compound **4b**, which was cyclised in trifluoroacetic acid to the *N*-acetylindole **5b** in an overall yield of 30%: hydrolysis with ethanolic potassium hydroxide gave indole **6b** in 70% yield. In contrast, a reflux period of 8 h in the initial step directly led to isolation of indole **6b** in 30% yield.

The one-pot method was also applied to the preparation of the 2-benzylindole **6c**, and the 3-arylindoles **6d–f**. Indole **6f** was also prepared by the stepwise process and intermediate compounds isolated and characterised.

Lithium bromide, being a crucial reagent, is assumed not only to exchange with the chloro group to facilitate the formation of the anilinoketone but also to act as a Lewis acid to allow cyclisation without rearrangement at neutral conditions and moderate temperatures.

Next, the scope and limitations of the lithium-mediated one-pot reaction were investigated. Depending on the reactivity of the desired substituent at C3 of the indole the conditions (temperature and ratio of the reactants and reagents) had to be slightly modified. Higher boiling solvents such as 1-propanol or ethylene glycol showed a significant decrease in the reaction times and increase in the yields, in examples incorporating less reactive, electron withdrawing aryl groups. A change of the ratio of the reactants and reagents would not only result in a shift of the equilibrium but also a change of pH, which plays an important role in the reaction. By use of excess amine **1** and/or sodium bicarbonate a basic pH is maintained throughout the reaction and this inhibits cyclisation and produces mostly the uncyclised intermediates **3**. If, on the other hand insufficient base is added to the reaction mixture to neutralise the released HBr completely, a moderate amount of the 2-arylindole **7** is produced. Therefore, it is important to maintain a neutral pH. An excess of the haloketone **2** had a positive effect on the rate and the yield of the reaction, but it also led to a new by-product, the *N*-substituted indole **8**. Because of this the excess of **2** was reduced to a minimum of 1.05 mequiv, giving good yields of **6**.

2.3. Comparison of the four-step procedure and the one-pot reaction

The lithium bromide templated one-pot synthesis can be alternatively used to synthesise a variety of different 3-substituted 4,6-dimethoxyindoles **6**. Depending on the reactivity of the substituent different alcohols had to be chosen as the solvent and also adjustments of the ratios of the reagents had to be made. Overall it was found to be a quicker, less labour-intensive and better yielding procedure than the four-step-procedure, especially for alkyl-substituted indoles as can be seen from Table 1.

3. Conclusions

The synthesis of activated indoles based on electron-rich arenes, e.g. dimethoxyanilines, can be achieved in a one-pot process by a direct cyclisation of an arylaminoketone, in the presence of lithium bromide and under essentially neutral conditions.

Table 1. Comparison of four-step and one-pot reaction

	Reaction time (h)		Overall yield (%)	
	Four-step	One-pot	Four-step	One-pot
6a	9[a]	6	22	74
6b	9[a]	9	14	30
6c	N/A	12	N/A	61
6d		18		65[b]
6e	23[a]	5	57	75[b]
6f	9.5[a]	12	26	29

[a] Plus four work-ups.
[b] Plus 5–10% of 2-substituted isomers **7** and 10–15% of *N*-substituted indoles **8**.

4. Experimental

4.1. General

Melting points were measured using a Mel-Temp melting point apparatus, and are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyser EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX300 (300 MHz) spectrometer. Mass spectra were recorded on either a Bruker FT-ICR MS (EI) or a Micromass ZQ2000 (ESI) at UNSW, or a Shimadzu LCMS QP 8000 (ESI) at the University of Otago, New Zealand. Infrared spectra were recorded with a Thermo Nicolet 370 FTIR Spectrometer using KBr discs. Ultraviolet–visible spectra were recorded using a Varian Cary 100 Scan Spectrometer. Column chromatography was carried out using Merck 230–400 mesh ASTM silica gel.

4.1.1. 4,6-Dimethoxy-3-methylindole (6a). *Method A (stepwise)*. A mixture of 3,5-dimethoxyaniline **1** (10.0 g, 65.3 mmol), chloroacetone **2a** (6.11 g, 66.0 mmol), sodium hydrogen carbonate (11.0 g, 130.6 mol) and lithium bromide (8.5 g, 98.0 mmol) in absolute ethanol (100 mL) was heated under reflux for 3 h with stirring. After cooling, the resulting precipitate was filtered off and washed with water to give 1-(3,5-dimethoxyphenylamino)-propan-2-one **3a** (9.6 g, 70%) as a white solid, mp 92–94 °C (ethanol) (Found: C, 63.2; H, 7.1; N, 6.7. $C_{11}H_{15}NO_3$ requires C, 63.1; H, 7.2; N, 6.7%). ν_{max}: 3400, 1720, 1620, 1590, 1510, 1510, 1480, 1266, 1210, 1170, 1160 cm^{-1}. λ_{max} (MeOH): 222 nm (ε 16,200 cm^{-1} M^{-1}), 236 (7500), 246 (8300). ^{1}H NMR spectrum ($CDCl_3$): δ 2.20 (s, 3H, Me), 3.32 (s, 6H, OMe), 3.93 (s, 2H, CH_2), 4.57 (bs, 1H, NH), 5.75 (d, J=2.0 Hz, 2H, H2, H6), 5.88 (t, J=2.0 Hz, 1H, H4). ^{13}C NMR spectrum ($CDCl_3$): δ 27.20 (Me), 54.06 (CH_2), 55.03 (OMe), 90.09 (C4), 91.64 (C2, C6), 148.70, 161.73 (C Ar), 203.80 (C=O). Mass spectrum (EI): *m/z* 210 (M+1, 15%), 209 (M, 60), 167 (20), 166 (100), 138 (20).

The anilino ketone **3a** (5.0 g, 23.9 mmol) was partially dissolved in acetic anhydride (10 mL) and stirred at room temperature for 3 h. Water (1 mL) was added and the solution was warmed to 50–60 °C. Water was then added slowly so that the temperature did not drop below 50 °C until the volume was tripled. Stirring was continued until the solution returned to room temperature. The solution was then extracted with ethyl acetate, the extract washed with water until neutral, saturated sodium hydrogen carbonate solution, saturated brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield an oil, which was dissolved in trifluoroacetic acid (20 mL). The solution was refluxed for 1 h after which ice/water was added and the resulting solid was filtered off. The precipitate was washed with water until neutral, dried and recrystallised from ethanol resulting in *N*-acetyl-4,6-dimethoxy-3-methylindole **5a** as a white solid (3.9 g, 70%), mp 144–145 °C (ethanol) (Found: C, 65.7; H, 6.3; N, 5.9. $C_{13}H_{15}NO_3 \cdot 0.25\ H_2O$ requires C, 65.7; H, 6.6; N, 5.9%). ν_{max}: 1750, 1710, 1660, 1560, 1500, 1270, 1200 cm^{-1}. ^{1}H NMR spectrum ($CDCl_3$): δ 2.35 (d, J=1.5 Hz, 3H, Me), 2.52 (s, 3H, CO*Me*), 3.84 and 3.86 (2s, 6H, OMe), 6.33 (d, J=2.0 Hz, 1H, H5), 6.85 (d, J=1.0 Hz, 1H, H2), 7.65 (d, J=2.0 Hz, 1H, H7). ^{13}C NMR spectrum ($CDCl_3$): δ 12.28 (Me), 23.95 (CO*Me*), 55.20 and 55.66 (OMe), 92.92 (C5), 95.12 (C7), 119.39 (C2), 114.60, 118.76, 137.82, 154.46, 159.46 (C Ar), 168.57 (C=O). Mass spectrum (EI): *m/z* 234 (M+1, 15%), 233 (M, 80), 191 (100), 190 (25), 176 (90).

The *N*-acetylindole **5a** (2.0 g, 8.6 mmol) was partially dissolved in ethanol (50 mL). An excess of crushed potassium hydroxide was added to the above mixture and allowed to stir for 2 h. The resulting precipitate was filtered off and the solvent was removed from the filtrate, both solids were combined to yield 4,6-dimethoxy-3-methylindole **6a** as a light tan solid (1.5 g, 90%), mp 72–73 °C (lit.[5] mp 73–74 °C). ^{1}H NMR spectrum ($CDCl_3$): δ 2.46 (d, J=1.0 Hz, 3H, Me), 3.83 and 3.89 (2s, 6H, OMe), 6.21 (d, J=2.0 Hz, 1H, H5), 6.37 (d, J=1.0 Hz, 1H, H7), 6.67–6.68 (m, 1H, H2), 7.69 (bs, 1H, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 11.98 (Me), 55.12, 55.51 (OMe), 86.81 (C5), 91.22 (C7), 118.84 (C2), 112.02, 112.69, 138.00, 155.43, 157.36 (C Ar).

Method B (one-pot). 3,5-Dimethoxyaniline **1** (2.00 g, 13.1 mmol), chloroacetone **2a** (1.03 mL, 13.1 mmol), $NaHCO_3$ (1.09 g, 13.1 mmol) and LiBr (1.10 g, 13.1 mmol) were partially dissolved in EtOH (36 mL) and refluxed for 6 h. The solvent was evaporated and the crude residue extracted with CH_2Cl_2 (40 mL). The extract was washed with water (3×20 mL), dried ($MgSO_4$) and evaporated to give a yellow-green solid (2.62 g), which was purified by column chromatography (CH_2Cl_2/light petroleum, 9:1), yielding indole **6a** as a yellow solid (1.84 g, 74%), mp 72–74 °C (lit.[5] 73–74 °C).

4.1.2. Ethyl (4,6-dimethoxyindol-3-yl)acetate (6b). *Method A (stepwise)*. A mixture of 3,5-dimethoxyaniline **1** (5.00 g, 32.6 mmol), ethyl 4-chloroacetoacetate **2b** (5.4 g, 32.6 mmol), sodium hydrogen carbonate (5.5 g, 65.3 mmol) and LiBr (4.25 g, 44.0 mmol) in absolute ethanol (50 mL) was heated under reflux for 3 h with stirring. After cooling, water was added to the reaction mixture, which was extracted with dichloromethane, dried and concentrated to yield the crude amino ketone **3b** as a dark golden oil, which was then dissolved in acetic anhydride (10 mL) and stirred at room temperature for 3 h. Water (1 mL) was added and the solution was warmed to 50–60 °C. Water was then added slowly so that the temperature did not drop below 50 °C until the volume was tripled. Stirring was continued until the solution returned to room temperature. The solution was then extracted with ethyl acetate. The organic phase was washed with water until neutral, saturated sodium hydrogen carbonate solution, saturated brine solution and dried

(Na_2SO_4). The solvent was removed under reduced pressure to yield the crude protected anilinoketone, which was then dissolved in trifluoroacetic acid (10 mL). The solution was refluxed for 1 h after which ice/water was added and the resulting solid was filtered off and purified by chromatography (silica plug) and recrystallisation from ethanol to yield ethyl *N*-acetyl-4,6-dimethoxyindole-3-acetate **5b** as a light tan solid (3.00 g, 30%), mp 106–107 °C (ethanol). ν_{max}: 1730, 1695, 1600, 1590, 1570, 1410, 1280, 1200, 1160 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): δ 1.25 (t, J= 7.1 Hz, 3H, CH_2*Me*), 2.55 (s, 3H, CO*Me*), 3.79 (d, J= 3.3 Hz, 2H, CH_2), 3.80 and 3.84 (2s, 6H, OMe), 4.17 (q, J=7.1 Hz, 2H, *CH*$_2$Me), 6.31 (d, J=1.9 Hz, 1H, H5), 6.71 (s, 1H, H2), 7.63 (d, J=1.9 Hz, 1H, H7). Mass spectrum (EI): *m/z* 306 (M+1, 5%), 305 (M, 50), 263 (45), 190 (100).

The *N*-acetylindole **5b** (2.00 g, 6.6 mmol) was partially dissolved in ethanol (20 mL). Crushed KOH (0.26 g, 6.6 mmol) was added to the above mixture which was allowed to stir for 2 h. The resulting precipitate was filtered off to yield ethyl (4,6-dimethoxyindol-3-yl)acetate **6b** as a light tan solid (1.21 g, 70%), mp 105–106 °C (ethanol) (Found: C, 60.8; H, 6.1; N, 5.1. $C_{14}H_{17}O_4N.0.65\ H_2O$ requires C, 61.1; H, 6.7; N, 5.1%). ν_{max}: 3360, 1725, 1362, 1585, 1550, 1510, 1390, 1335, 1260, 1200 cm^{-1}. λ_{max}: 225 nm (ε 21,900 $cm^{-1}\ M^{-1}$), 269 (4900). ^1H NMR spectrum ($CDCl_3$): δ 1.27 (t, J=7.1 Hz, 3H, CH_2*Me*), 3.79 and 3.82 (2s, 6H, OMe), 3.87 (s, 2H, CH_2), 4.18 (q, J= 7.1 Hz, 2H, *CH*$_2$Me), 6.15 (d, J=1.5 Hz, 1H, H5), 6.36 (d, J=1.5 Hz, 1H, H7), 6.82 (d, J=1.5 Hz, 1H, H2), 7.97 (bs, 1H, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 14.25 (CH_2*Me*), 32.50 (*CH*$_2$Me), 54.96, 55.50 (OMe), 60.37 (CH_2), 86.75 (C5), 91.43 (C7), 120.29 (C2), 108.65, 111.91, 137.67, 154.72, 157.49 (C Ar), 172.92 (C=O). Mass spectrum (EI): *m/z* 264 (M+1, 5%), 263 (M, 40), 190 (100), 160 (35), 145 (30).

Method B (one-pot): A mixture of 3,5-dimethoxyaniline **1** (2.00 g, 13.1 mmol), ethyl-4-chloroacetoacetate **2b** (1.85 mL, 13.7 mmol), $NaHCO_3$ (1.10 g, 13.1 mmol) and LiBr (1.14 g, 13.1 mmol) was refluxed in EtOH (60 mL) for 8 h, the solvent evaporated and the crude residue extracted with CH_2Cl_2 (40 mL). The extract was washed with water (3×20 mL), dried ($MgSO_4$) and evaporated to give a brown-green solid, which was purified by column chromatography (CH_2Cl_2/MeOH, 98:2), yielding indole **6b** as a yellow solid (1.03 g, 30%), mp 102–104 °C.

4.1.3. 3-Benzyl-4,6-dimethoxyindole (6c). A suspension of 3,5-dimethoxyaniline **1** (1.73 g, 11.3 mmol), 1-chloro-3-phenylpropan-2-one **2c** (2.00 g, 11.9 mmol), $NaHCO_3$ (0.95 g, 11.3 mmol) and LiBr (0.98 g, 11.3 mmol) in 1-propanol (25 mL) was refluxed for 16 h. The mixture was cooled to room temperature and the precipitated salts filtered off. The remaining solution was concentrated to about one quarter of its volume and kept at room temperature for some time before filtration of the crude product. It was purified by column chromatography (CH_2Cl_2), yielding indole **6c** as a pale brown solid (1.85 g, 61%), mp 114–116 °C (Found: C, 76.5; H, 6.5; N, 5.2. $C_{17}H_{17}Cl_2NO_2$ requires C, 76.4; H, 6.4; N, 5.2%). ν_{max} (KBr): 3369, 1619, 1590, 1510, 1459, 1221, 1201, 1155, 1138, 1081, 938, 813, 740, 715 cm^{-1}. λ_{max} (CH_2Cl_2): 228 nm (ε 13,500), 271 (3800), 475 (600). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.82 (s, 6H, OMe), 4.24 (s, 2H, CH_2), 6.19 (d, J=1.5 Hz, 1H, H5), 6.40 (d, J= 1.9 Hz, 1H, H7), 6.53 (d, J=1.1 Hz, 1H, H2), 7.15–7.30 (m, 5H, Ph), 7.72 (s, 1H, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 32.9 (CH_2), 55.0 (OMe), 55.5 (OMe), 86.7 (C5), 91.5 (C7), 112.1, 116.6, 119.5 (C2), 125.4 (CH Ph), 128.0 (CH Ph), 128.8 (CH Ph), 138.0, 142.4, 155.2, 157.5. Mass spectrum (ES): *m/z* (%) 267.1 (100, M^+), 252.1 (39), 190.1 (49), 132.1 (20).

4.1.4. 2-4,6-Dimethoxy-3-phenylindole (6d) and 2-(4,6-di-methoxy-3-phenylindol-1-yl)-1-phenylethanone (8d). A mixture of 3,5-dimethoxyaniline **1** (1.0 g, 6.53 mmol), 2-bromoacetophenone **2d** (1.62 g, 8.16 mmol), LiBr (0.57 g, 6.53 mmol) and $NaHCO_3$ (0.55 g, 6.53 mmol) in 1-propanol (25 mL) was refluxed overnight. The solvent was removed in vacuo, the residue extracted into CH_2Cl_2 (25 mL) and washed with water (3×15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. The resulting product mixture was separated by column chromatography on silica gel (CH_2Cl_2) yielding compound **8d** as yellow crystals (0.36 g, 15%) in the first band, mp 54–56 °C. (Found: C, 77.8; H, 5.8; N, 3.6. $C_{24}H_{21}NO_3$ requires C, 77.6; H, 5.7; N, 3.8%). ν_{max} (KBr): 3427, 1699, 1600, 1501, 1450, 1340, 1219, 1201, 1144, 1060, 757, 690 cm^{-1}. λ_{max} (CH_2Cl_2): 237 nm (ε 38,000), 248 (10,000). ^1H NMR (300 MHz, $CDCl_3$): δ 3.80 (s, 6H, OMe), 5.36 (s, 2H, CH_2), 6.25 (s, 1H, H5), 6.29 (s, 1H, H7), 6.88 (s, 1H, H2), 7.23–7.28 (m, 1H, Ph), 7.34–7.39 (m, 2H, Ph), 7.47–7.53 (m, 2H, Ph), 7.62–7.64 (m, 3H, Ph), 7.98–8.00 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.4 (CH_2), 55.1 (OMe), 55.6 (OMe), 85.3 (C7), 92.2 (C5), 110.9, 118.7, 125.0 (C2), 125.6 (CH Ph), 127.4 (CH Ph), 128.0 (CH Ph), 128.9 (CH Ph), 129.5 (CH Ph), 133.9 (CH Ph), 134.7, 135.8, 139.1, 155.1, 157.7, 192.9 (CO). Mass spectrum (ES): *m/z* (%) 371.1 (47, M^+), 266.1 (100), 250.1 (36).

The second band eluted from the column yielded **6d** as a brown powder (1.08 g, 65%), mp 57–59 °C (lit.[7] 58 °C). ^1H NMR (300 MHz, $CDCl_3$): δ 3.86 (s, 6H, OMe), 6.34 (d, J= 2.0 Hz, 1H, H5), 6.45 (d, J=2.0 Hz, 1H, H7), 6.97 (d, J= 2.1 Hz, 1H, H2), 7.32–7.72 (m, 5H, Ph), 8.07 (br s, 1H, NH).

4.1.5. 3-(4-Chlorophenyl)-4,6-dimethoxyindole (6e) and 1-(4-chlorophenyl)-2-[3-(4-chlorophenyl)-4,6-di-methoxy-indol-1-yl]ethanone (8e). A mixture of 3,5-dimethoxyaniline **1** (1.0 g, 6.53 mmol), 2-bromoacetophenone **2e** (1.9 g, 8.14 mmol), LiBr (0.57 g, 6.53 mmol) and $NaHCO_3$ (0.55 g, 6.53 mmol) in 1-propanol (25 mL) was refluxed overnight. The solvent was evaporated in vacuo, the residue extracted into CH_2Cl_2 (25 mL) and washed with water (3× 15 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting product mixture was separated by column chromatography on silica gel (CH_2Cl_2/light petroleum, 7:3) yielding indole **8e** as yellow crystals (0.35 g, 0.80 mmol, 12%) in the first band, mp 74–76 °C. (Found: C, 65.5; H, 4.4; N, 3.2. $C_{24}H_{19}Cl_2NO_3$ requires C, 65.5; H, 4.4; N, 3.2%). ν_{max} (KBr): 3406 (br), 2933, 2838 (w), 1700, 1588, 1545, 1335, 1217 (s), 1146, 1092, 1060, 834 cm^{-1}. λ_{max} (CH_2Cl_2): 248 nm (ε 34,000). ^1H NMR spectrum

(300 MHz, DMSO-d_6): δ 3.71 (s, 3H, OMe), 3.75 (s, 3H, OMe), 5.83 (s, 2H, CH_2), 6.24 (d, $J=1.5$ Hz, 1H, H5), 6.62 (d, $J=1.5$ Hz, 1H, H7), 7.19 (s, 1H, H2), 7.36 (d, $J=8.7$ Hz, 2H, Ar), 7.51 (d, $J=8.7$ Hz, 2H, Ar), 7.67 (d, $J=8.7$ Hz, 2H, Ar), 8.09 (d, $J=8.7$ Hz, 2H, Ar). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 52.5 (CH_2), 55.1 (OMe), 55.6 (OMe), 85.0 (C5), 92.3 (C7), 117.8, 124.7 (C2), 127.5 (CH Ar), 129.3 (CH Ar), 129.4 (CH Ar), 130.1, 130.6 (CH Ar), 131.5, 132.8, 134.1, 139.0, 140.6, 155.0, 157.9, 191.7 (CO). Mass spectrum (ES): *m/z* (%) 440.95 (36), 438.96 (50, M^+), 302.05 (35), 300.06 (100).

The second band eluted from the column yielded indole **6e** a pale yellow solid (1.40 g, 75%), mp 188–190 °C (lit.[7] 185–187 °C). ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 3.80 (s, 3H, OMe), 3.85 (s, 3H, OMe), 6.27 (d, $J=1.9$ Hz, 1H, H5), 6.49 (d, $J=1.9$ Hz, 1H, H7), 6.99 (d, $J=2.6$ Hz, 1H, H2), 7.32 (d, $J=8.6$ Hz, 2H, Ar), 7.53 (d, $J=8.6$ Hz, 2H, Ar), 8.08 (br s, 1H, NH).

4.1.6. 4,6-Dimethoxy-3-(4-hydroxyphenyl)indole (6f). *Method A (stepwise).* A mixture of 3,5-dimethoxyaniline **1** (10.0 g, 66.6 mmol), 4-hydroxyacetophenone[9] **2f** (15.0 g, 69.0 mmol) and $NaHCO_3$ (5.6 g, 66.6 mmol) in MeOH (160 mL) was refluxed for 3 h. A yellow precipitate was obtained after cooling to room temperature and was filtered off and washed with water (30 mL). Recrystallisation from EtOH yielded 2-(3,5-dimethoxyphenylamino)-1-(4-hydroxyphenyl)ethanone **3f** as a white powder (10.4 g, 36.2 mmol, 56%), mp 166–168 °C. (Found: C, 66.6; H, 6.1; N, 4.9. $C_{16}H_{17}NO_4$ requires C, 66.9; H, 6.0; N, 4.9%). ν_{max} (KBr): 3456, 3405, 1667, 1626, 1579, 1518, 1315, 1254, 1209, 1195, 1168, 1158, 1072, 961, 809, 799, 676, 591 cm^{-1}. λ_{max} (MeOH): 219 nm (ε 32,500), 278 (18,600). ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 3.63 (s, 6H, OMe), 4.49 (d, $J=5.3$ Hz, 2H, CH_2), 5.69–5.74 (m, 2H, NH and H4′), 5.87 (d, $J=1.5$ Hz, 2H, H2′ and H6′), 6.86 (d, $J=9.3$ Hz, 2H, ArOH), 7.94 (d, $J=9.3$ Hz, 2H, ArOH), 10.37 (br s, 1H, OH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): 49.8 (CH_2), 55.2 (OMe), 89.3, 91.8 (CH), 115.7 (CH), 127.0, 130.8 (CH), 150.3, 161.5 (CH), 162.7, 194.8 (CO). Mass spectrum (EI): *m/z* (%) 287 (25, M^+), 166 (100), 122 (42).

A solution of anilinoketone **3f** (10.0 g, 34.8 mmol) in acetic anhydride (50 mL) was stirred at room temperature for 3 h, after which water (10 mL) was added, the solution heated to 50–60 °C and kept at this temperature, while more water (150 mL) was added. The mixture was cooled to room temperature, extracted with EtOAc (40 mL), and washed with water (2×25 mL), saturated aqueous $NaHCO_3$ (2×25 mL) and brine (2×25 mL). The organic layer was dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Recrystallisation from EtOH yielded 2-(*N*-acetyl-3,5-dimethoxyphenylamino)-1-(4-hydroxyphenyl) ethanone **4f** as a white solid (9.5 g, 28.8 mmol, 82%), mp 186–188 °C. (Found: C, 65.5; H, 6.0; N, 4.1. $C_{18}H_{19}NO_5$ requires C, 65.6; H, 5.8; N, 4.3%). ν_{max} (KBr): 3178, 1696, 1608, 1578, 1425, 1341, 1242, 1192, 1156, 1154, 1078, 981, 849, 702, 561 cm^{-1}. λ_{max} (MeOH): 218 nm (ε 22,000), 278 (18,000). ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 1.89 (s, 1H, COMe), 3.72 (s, 6H, OMe), 4.98 (s, 2H, CH_2), 6.46 (s, 1H, H4′), 6.53 (s, 2H, H2′ and H6′), 6.84 (d, $J=8.7$ Hz, 2H, ArOH), 7.83 (d, $J=8.7$ Hz, 2H, ArOH), 10.43 (br s, 1H, OH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 22.3 (Me), 55.7 (CH_2), 55.8 (OMe), 99.8 (CH), 106.4 (CH), 115.7 (CH), 126.8, 130.8 (CH), 145.6, 161.1, 162.8, 169.5, 192.5. Mass spectrum (EI): *m/z* (%) 329 (7, M^+), 208 (17), 166 (100), 121 (93).

A solution of *N*-acetylanilino ketone **4f** (5.0 g, 15.2 mmol) in TFA (25 mL) was stirred at room temperature for 1.5 h. A green ppt formed after quenching with ice/water (100 mL), which was filtered off and washed with water until rinsings were neutral. Recrystallisation from EtOH yielded *N*-acetyl-4,6-dimethoxy-3-(4-hydroxyphenyl)indole **5f** as a pale grey solid (3.89 g, 12.5 mmol, 83%), mp 210–212 °C. ν_{max} (KBr): 3252, 1681, 1574, 1508, 1426, 1310, 1208, 1167, 1042, 966, 825, 688 cm^{-1}. λ_{max} (MeOH): 209 nm (ε 41,500), 252 (31,600), 319 (7100). (Found: C, 69.2; H, 5.6; N, 4.5. $C_{18}H_{17}NO_4$ requires C, 69.4; H, 5.5; N, 4.5%). ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 2.61 (s, 1H, COMe), 3.71 (s, 3H, OMe), 3.79 (s, 3H, OMe), 6.46 (d, $J=1.9$ Hz, 1H, H5), 6.75 (d, $J=8.3$ Hz, 2H, ArOH), 7.35 (d, $J=8.3$ Hz, 2H, ArOH), 7.47 (s, 1H, H2), 7.63 (d, $J=1.9$ Hz, 1H, H7), 9.34 (s, 1H, OH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 24.4 (CO*Me*), 55.6 (OMe), 55.8 (OCH_3), 93.2 (C5), 95.5 (C7), 112.3, 114.8 (CH Ar), 122.0 (C2), 123.0, 125.1, 130.8 (CH Ar), 137.8, 154.2, 156.8, 159.2, 170.0 (CO). Mass spectrum (EI): *m/z* (%) 311 (18, M^+), 269 (20), 254 (40), 69 (50), 43 (100).

A suspension of *N*-acetylindole **5f** (3.40 g, 10.9 mmol) and KOH (2.5 g, 44.6 mmol) in MeOH (55 mL) was stirred for 3 h, followed by the addition of aqueous HCl solution (5 M, 8–10 mL) until no further precipitation was observed. The salts were filtered off, the solvent removed under reduced pressure, the remaining mixture diluted with CH_2Cl_2 (50 mL), and washed with water (3×20 mL). The organic layer was dried with $MgSO_4$ and the solvent removed in vacuo. The crude product was flash chromatographed (CH_2Cl_2/MeOH, 96:4) and recrystallised in EtOH to yield indole **6f** as a pale yellow solid (2.01 g, 7.47 mmol, 69%), mp 212–214 °C.

Method B (one-pot). A mixture of 3,5-dimethoxyaniline **1** (1.02 g, 6.66 mmol), 4-hydroxyphenacylbromide **2f** (1.50 g, 6.98 mmol), $NaHCO_3$ (0.56 g, 6.66 mmol) and LiBr (0.58 g, 6.66 mmol) in 1-propanol (20 mL) was refluxed for 12 h. The mixture was cooled to room temperature and the precipitated salts filtered off. The remaining solution was concentrated to about one quarter of its volume and kept at room temperature for 3 h, after which the crude product was filtered off. It was purified by column chromatography (CH_2Cl_2/MeOH, 96:4), yielding indole **6f** as pale brown needles (0.52 g, 29%), mp 210–212 °C. ν_{max} (KBr): 3443, 3334, 1541, 1501, 1320, 1199, 1161, 1149, 1041, 838, 811, 550 cm^{-1}. λ_{max} (MeOH): 231 nm (ε 27,000), 261 (13,500). (Found: C, 70.4; H, 5.7; N, 5.1. $C_{16}H_{15}NO_3\cdot(1/4)H_2O$ requires C, 70.2; H, 5.7; N, 5.1%). ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 3.70 (s, 3H, OMe), 3.74 (s, 3H, OMe), 6.14 (d, $J=1.9$ Hz, 1H, H5), 6.47 (d, $J=1.9$ Hz, 1H, H7), 6.69 (dd, $J=6.4$, 1.9 Hz, 2H, Ar), 7.00 (d, $J=2.3$ Hz, 1H, H2), 7.29 (dd, $J=6.4$, 1.9 Hz, 2H, Ar), 9.09 (br s, 1H, OH), 10.89 (br s, 1H, NH); ^{13}C-NMR spectrum (75 MHz, DMSO-d_6): δ 55.2 (OMe), 55.5 (OMe), 87.6 (C5),

91.8 (C7), 110.2, 114.7 (CH Ar), 117.3, 120.8 (C2), 127.6, 130.3 (CH Ar), 138.8, 154.6, 155.5, 156.8. Mass spectrum (EI): *m*/*z* (%) 269 (100, M^+), 254 (48), 211 (20).

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