Syntheses of Zindoxifene and Analogues by Titanium-Induced Oxo-Amide Coupling

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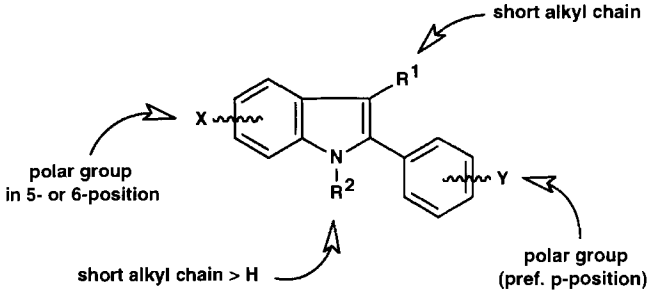
Highly reactive titanium on graphite is used to reductively cyclize electron-rich acylamino carbonyl compounds **7**, **8**, **12**, **14**, and **16** to the corresponding indole derivatives **9**, **10**, **13**, **15**, and **17**. Compound **9b** is a known precursor of the mammary tumor-inhibiting compound zindoxifene (**2**). The other products are new analogues of this anticancer drug, exhibiting the substitution pattern previously recognized to be essential for high pharmacological activity.

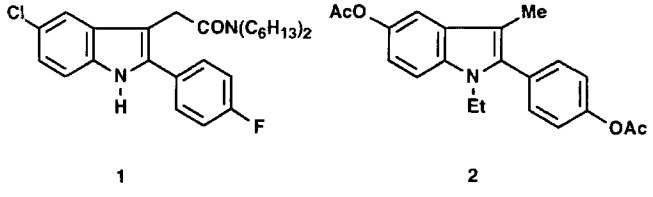
Many 2-phenylindole derivatives exhibit remarkable physiological activities. Among them 5-chloro-3-[(dihexylaminocarbonyl)methyl]-2-(4-fluorophenyl)indole (**1**) deserves particular attention, because it shows high affinity and selectivity for the mitochondrial DBI receptor (DBI = diazepam-binding inhibitor) and stimulates the production of neurosteroids at a <3 nM concentration[1]. Equally interesting is zindoxifene (**2**), the strongest cytostatic agent among a series of substituted 2-phenylindole derivatives and a potential drug for the treatment of estrogen-dependent malignancies such as mammary tumors[2]. The structure-activity profile of this class of compounds has been studied in detail and can be summarized as shown in Scheme 1. Short alkyl chains both at C-3 and at the indole nitrogen are necessary to fine-tune the lipophilicity of the drug, and polar substituents on the indole nucleus as well as on the 2-phenyl group are required for high pharmacological activity[2].

We have recently described a new indole synthesis based on the reductive coupling of acylamino carbonyl compounds by means of a low-valent titanium reagent (Scheme 2)[3]. This strategy has disproved the alleged inertness of amides in McMurry-type reactions[4] and should be well suited for the preparation of zindoxifene and analogues from simple precursors. In order to study the scope of this new approach and to obtain likewise potential drugs we synthesized a series of 2-phenylindole derivatives exhibiting all the structural features which are essential for pharmacological activity.

The preparation of zindoxifene (**2**) itself (Scheme 3) started from the commercially available 5-hydroxy-2-nitrobenzaldehyde (**3**). After methylation of the phenolic hydroxyl group, the aldehyde **4** was converted to the methyl ketone **5** by treatment with the aldehyde-selective Me-Ti(O*i*Pr)$_3$ reagent[5] followed by PDC oxidation of the resulting secondary alcohol. Subsequent hydrogenation of the nitro group and treatment of the resulting amine **6** with *p*-methoxybenzoyl chloride under standard conditions afforded the oxo-amide **7** as the required coupling precursor. Upon treatment with highly active titanium on graphite ($TiCl_3$: C_8K = 3:1)[6] as described recently[3], this compound smoothly cyclized to the indole **9a**[7] which can be *N*-alkylated in a one-pot procedure by adding an excess of NaH

Scheme 1. Structure-activity profile of substituted 2-phenylindole derivatives[2]





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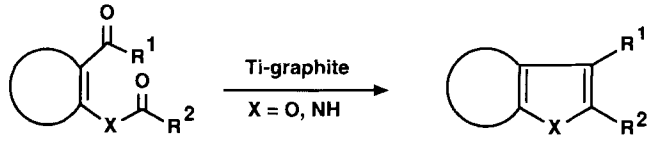
Scheme 2. Heterocycle synthesis by titanium-induced reductive coupling reactions[3]



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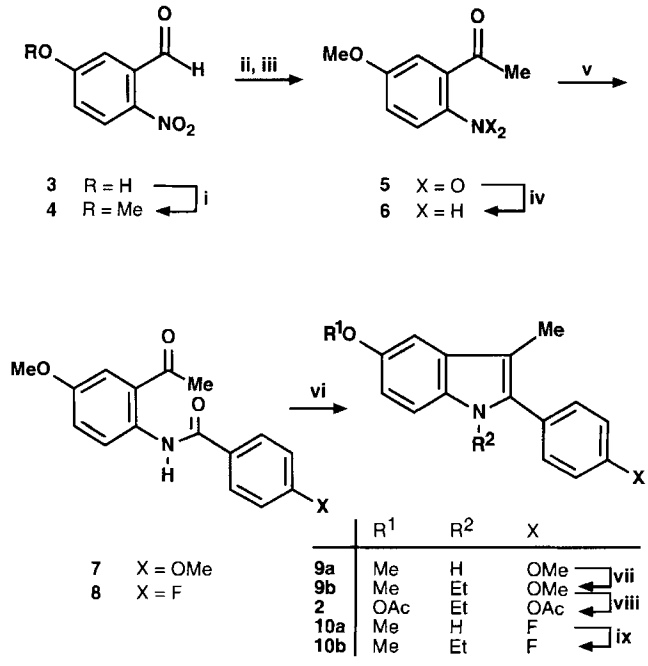
Scheme 3. Syntheses of zindoxifene (**2**) and its 4′-fluoro analogue. i, K_2CO_3, MeI, THF, 93%; ii, $MeTi(OiPr)_3$, THF −50 to 20°C, 88%; iii, PDC, CH_2Cl_2, 88%, iv, H_2 (1 atm), Pd/charcoal (5%), EtO, 97%; v, $pMeOC_6H_4COCl$ or pFC_6H_4COCl, CH_2Cl_2/pyridine, 77% (**7**) and 78% (**8**); vi, Ti-graphite ($TiCl_3$: C_8K = 3:1)[6], THF, reflux; vii, NaH, EtI, 20°C, 71% (both steps); viii, ref.[2a]; ix, NaH, EtI, 84% (both steps **8** → **10b**)

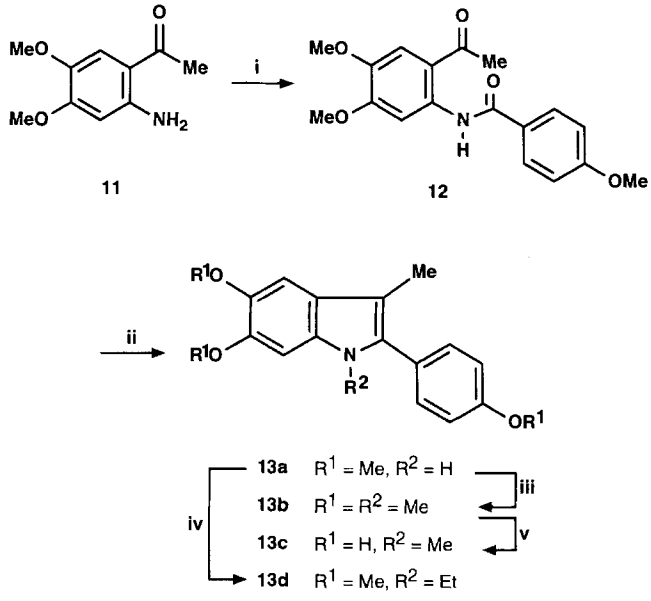


and ethyl iodide to the crude reaction mixture. Thus, indole **9b** was obtained in 38% overall yield from **3**. This compound shows interesting biological properties on its own and has previously been converted to zindoxifene (**2**) by standard protecting group manipulations[2a]. It is worth mentioning that this seven-step sequence has been carried out without a single chromatographic separation.

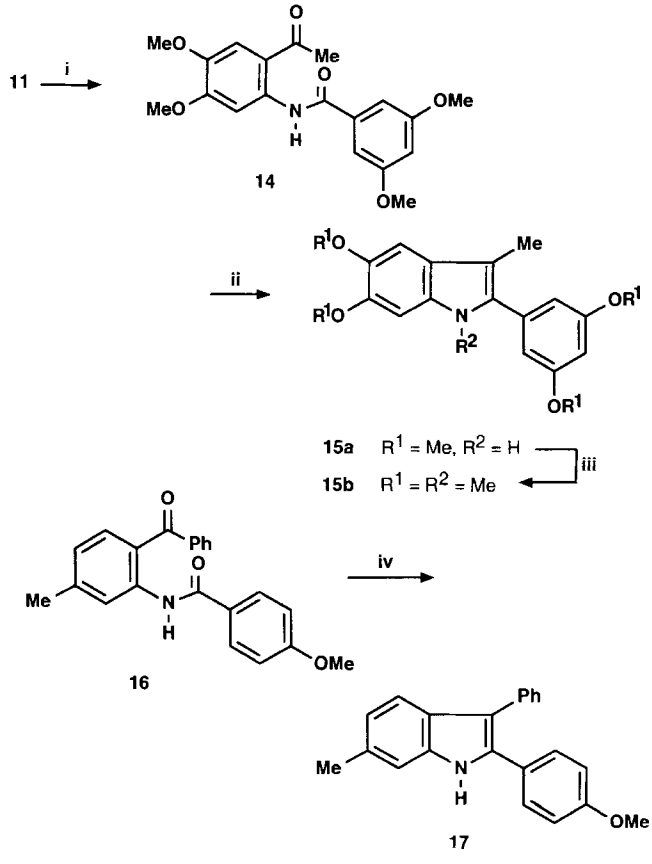
With amine **6** at hand, the preparation of zindoxifene analogues bearing functional groups other than OR on the 2-phenyl substituent is straightforward. Its treatment with e.g. *p*-fluorobenzoyl chloride, titanium-mediated coupling of the resulting oxo amide **8** to indole **10a** followed by its *N*-alkylation (EtI, NaH, **10a**→**10b**) proceeded without incident. Furthermore, simple recrystallization afforded an analytically pure sample of this new 4′-fluoro analogue of zindoxifene.

As shown in Scheme 1, a polar substituent (preferably OMe, OH, OAc or halogen) in the 5- or 6-position is necessary for high pharmacological activity of the corresponding 2-phenyl indole derivatives[2]. To the best of our knowledge no compounds with such functional groups in both the 5- *and* the 6-position have been screened to date. Access to these potential drugs by using the titanium-mediated oxoamide cyclization technique, starting with commercially available 2-amino-4,5-dimethoxyacetophenone (**11**) is easy. Its reaction with *p*-methoxybenzoyl chloride in CH_2Cl_2/pyridine, followed by treatment of the resulting amide **12** with an excess of titanium-graphite under slightly modified

Scheme 4. Synthesis of 5,6-disubstituted zindoxifene analogues. i, $pMeOC_6H_4COCl$, CH_2Cl_2/pyridine, 75%; ii, Ti-graphite ($TiCl_3$:C_8K = 2:1)[8], DME, reflux, 66%; iii, NaH, MeI, THF, 90%; iv, NaH, EtI, THF, 76%; v, BBr_3, CH_2Cl_2, −60 to 20°C, 3 h, 83%



Scheme 5. i, 3,5-Dimethoxybenzoyl chloride, CH_2Cl_2/pyridine, 91%; ii, Ti-graphite ($TiCl_3$:C_8K = 3:1)[6], DME, 86%; iii, NaH, MeI, THF, 92%; iv, Ti-graphite ($TiCl_3$:C_8K = 2:1)[8], THF, 79%



conditions ($TiCl_3$:C_8K=2:1)[8] afforded the trimethoxyindole derivative **13a** (Scheme 4). *N*-Alkylation (MeI for **13a**→**13b**; EtI for **13a**→**13d**) and cleavage of the aryl ether groups with BBr_3 in CH_2Cl_2[9] proceeded smoothly. The same sequence employing 3,5-dimethoxybenzoyl chloride as the acylating agent led to the tetrasubstituted analogues **15** in good overall yield (Scheme 5). In order to complete this study the 2,3-diphenylindole **17** derivative was prepared by reductive cyclization of precursor **16** with the active titanium reagent.

As to the stability of the products, we found all polyalkoxylated indole derivatives obtained to be prone to oxidation on exposure to air, particularly when kept in solution. *N*-Alkylation retards this oxidative degradation.

In summary, we have shown that titanium-mediated indole formation[3] by reductive coupling works well with electron-rich acylamino carbonyl compounds and is perfectly compatible with alkoxy substituents in the substrates[10]. This allowed the ready preparation of the potential tumor-inhibiting drug zindoxifene and a variety of closely related analogues. Biological screening of the new compounds and further synthetic studies on the reductive indole synthesis are in progress.

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Experimental

Melting points: Gallenkamp apparatus or differential scanning calorimetry (DSC), uncorrected. – NMR: Bruker WH 400, MSL 300 or AC 200 at 400, 300, or 200 MHz (^1H) and 100, 75, and 50 MHz (^{13}C), respectively, in $CDCl_3$, TMS as internal standard unless stated otherwise. The multiplicity in the ^{13}C-NMR spectra refers to the geminal protons (DEPT). – MS: Varian CH-5 (70 eV). – IR: Nicolet FT-7199. – Elemental analyses: Dornis and Kolbe, Mülheim. – TLC: Polygram® Sil Gel/UV_{254} (Macherey, Nagel & Co). – Flash chromatography: Merck silica gel 60 (230–400 mesh) with toluene/ethyl acetate or hexane/ethyl acetate in the ratios indicated. – Graphite: Lonza KS 5-44, but other samples are equally suited[6]. $TiCl_3$ (99%, Aldrich). Anhydrous solvents are obtained by distillation over the given drying agents prior to use: THF (potassium/benzophenone), DME (Na/K alloy), CH_2Cl_2 (CaH_2), pyridine (MS 4 Å). All reactions are performed in predried glassware under argon using Schlenk techniques.

5-Methoxy-2-nitrobenzaldehyde (**4**): K_2CO_3 (9.09 g, 66 mmol) is added to 5-hydroxy-2-nitrobenzaldehyde (**3**) (10.96 g, 66 mmol) in THF (400 ml) causing immediate precipitation of the respective potassium phenolate. After stirring for 1 h MeI (60.58 g, 427 mmol) is added and the suspension refluxed for 24 h. The insoluble residues are filtered off, the filtrate is concentrated and the residue recrystallized from CH_2Cl_2 (slow cooling to −80°C) affording 7.50 g (64%) of analytically pure **4**. A second crop of the product (3.47 g, 29%) is obtained after evaporation of the solvent and sublimation of the residue (60–70°C bath temperature, 10^{-3} Torr); m.p. 82–83°C (ref.[11] 83°C). – IR (KBr): $\tilde{\nu}$ = 1690 cm^{-1}. – ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.97 (s, 3H, OMe), 7.17 (dd, *J* = 2.8/9 Hz, 1H, aromatic H), 7.32 (d, *J* = 2.8 Hz, 1H, aromatic H), 8.17 (d, *J* = 9 Hz, 1H, aromatic H), 10.46 (s, 1H, CHO). – ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 188.4 (s), 164.0 (s), 142.3 (s), 134.3 (s), 127.2 (d), 118.4 (d), 113.3 (d), 56.3 (q). – MS, *m/z* (%): 181 (100) [M^+], 151 (52), 134 (23), 123 (49), 108 (63), 106 (40), 95 (55), 92 (33), 80 (26), 63 (90).

5-Methoxy-2-nitroacetophenone (**5**): To a stirred solution of **4** (6.54 g, 35 mmol) in THF (125 ml) is slowly added $MeTi(OiPr)_3$[5] (10.52 g, 44 mmol) at −50°C under Ar. Stirring is continued at that temp. for 4 h and at ambient temp. for 1 h. The orange solution is diluted with toluene, aqueous HCl is added (2 N, ≈ 50 ml), the organic phase is dried with Na_2SO_4, and the solvent evaporated. The remaining 1-(5-methoxy-2-nitrophenyl)ethanol (5.97 g, 88%, pale brown syrup) exhibits the following spectroscopic properties: IR: $\tilde{\nu}$ = 3400 cm^{-1} (OH). – ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.52 (s, 3H, Me), 3.07 (br. s, 1H, OH), 3.91 (s, 3H, OMe), 5.52 (q, 1H, *CH*Me), 6.84 (dd, 1H, aromatic H), 7.32 (d, 1H, aromatic H), 8.00 (d, 1H, aromatic H). – ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 163.8 (s), 144.9 (s), 140.3 (s), 127.4 (d), 112.9 (d), 111.9 (d), 65.7 (d), 55.8 (q), 21.4 (q). – MS, *m/z* (%): 197 (40) [M^+], 182 (25), 179 (41), 164 (36), 134 (70), 121 (27), 106 (31), 92 (28), 77 (42), 63 (34), 43 (100). – To a solution of this product in CH_2Cl_2 (200 ml) is added PDC (23.66 g, 63 mmol), the resulting suspension is refluxed for 6 h, filtered over a pad of silica, and the filtrate is concentrated. Thus, the title compound **5** is obtained in analytically pure form as pale yellow crystals (5.21 g, 88%); m.p. 66–67°C (ref.[12] 69–70°C). – IR (KBr): $\tilde{\nu}$ = 1700 cm^{-1}. – ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.50 (s, 3H, Me), 3.90 (s, 3H, OMe), 6.76 (d, *J* = 2.7 Hz, 1H, aromatic H), 6.97 (dd, *J* = 2.7/9 Hz, 1H, aromatic H), 8.12 (d, *J* = 9 Hz, 1H, aromatic H). – ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 200.0 (s), 164.3 (s), 141.3 (s), 138.0 (s), 126.9 (d), 114.7 (d), 111.9 (d), 56.1 (q), 30.2 (q). – MS, *m/z* (%): 195 (62) [M^+], 180 (100), 106 (21), 63 (37), 43 (81).

2-Amino-5-methoxyacetophenone (**6**): Compound **5** (5.20 g, 27 mmol), dissolved in EtOH (200 ml), is hydrogenated (1 atm) over Pd on charcoal (5%, 610 mg). After 3 h the hydrogen uptake (1.74 l) indicates complete conversion. The reaction mixture is filtered over a pad of silica and the filtrate concentrated affording **6** as a yellow syrup (4.25 g, 97%) [ref.[7] m.p. (of hydrochloride) 52–53°C]. – ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.52 (s, 3H, Me), 3.74 (s, 3H, OMe), 5.90 (br. s, 2H, NH_2), 6.58 (d, *J* = 9 Hz, 1H, aromatic H), 6.93 (dd, *J* = 3/9 Hz, 1H, aromatic H), 7.14 (d, *J* = 3 Hz, 1H, aromatic H). – ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 199.9 (s), 149.5 (s), 144.8 (s), 122.8 (d), 118.2 (d), 117.6 (s), 114.3 (d), 55.6 (q), 27.5 (q). – MS, *m/z* (%): 165 (96) [M^+], 150 (100), 122 (24), 52 (17), 43 (15).

5-Methoxy-2-[(4-methoxybenzoyl)amino]acetophenone (**7**): To a solution of **6** (1.19 g, 7.2 mmol) in CH_2Cl_2 (12 ml) and pyridine (6 ml) is added 4-methoxybenzoyl chloride (1.47 g, 8.6 mmol) dissolved in CH_2Cl_2 (5 ml). After stirring for 1 h at ambient temp., sat. aqueous $NaHCO_3$ (15 ml) is added, the mixture vigorously stirred for 2 h, the organic layer dried with Na_2SO_4, concentrated and the residue recrystallized from Et_2O/CH_2Cl_2 (8:1) by slowly cooling the solution to −80°C. Thus, the product is obtained as yellow crystals (1.66 g, 77%); m.p. 131.5–132.5°C (ref.[7] 132°C). – IR (KBr): $\tilde{\nu}$ = 3280, 3240 cm^{-1} (NH); 1670, 1650 cm^{-1} (C=O). – ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.66 (s, 3H, Me), 3.84, 3.92 (s, 3H each, OMe), 6.97 (d, *J* = 9 Hz, 2H, aromatic H), 7.15 (dd, *J* = 3.3/9.5 Hz, 1H, aromatic H), 7.38 (d, *J* = 3 Hz, 1H, aromatic H), 7.99 (d, *J* = 9 Hz, 2H, aromatic H), 8.88 (d, *J* = 9 Hz, 1H, aromatic H), 12.27 (br. s, 1H, NH). – ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 203.0 (s), 165.4 (s), 162.6 (s), 154.2 (s), 135.4 (s), 129.2 (2×, d), 127.4 (s), 123.0 (s), 122.2 (d), 120.4 (d), 116.8 (d), 113.9 (2×, d), 55.7 (q), 55.4 (q), 28.6 (q). – MS, *m/z* (%): 299 (35) [M^+], 135 (100), 107 (8), 92 (13), 77 (19).

2-[(4-Fluorobenzoyl)amino]-5-methoxyacetophenone (**8**): Prepared as described above by using **6** (2.16 g, 13 mmol) and 4-fluoro-

benzoyl chloride (2.53 g, 16 mmol) as substrates. Recrystallization by cooling a solution of the crude product in CH_2Cl_2 to −80°C affords the product as yellow crystals (2.92 g, 78%); m.p. 176−177°C, m.p. (DSC) 179°C. − IR (KBr): $\tilde{\nu}$ = 3220, 1670, 1648 cm^{-1} − ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.66 (s, 3H, Me), 3.82 (s, 3H, OMe), 7.15 (m, 3H, aromatic H), 7.39 (d, J = 3 Hz, 1H, aromatic H), 8.00−8.04 (m, 2H, aromatic H), 8.84 (d, J = 8.5 Hz, 1H, aromatic H), 12.34 (br. s, 1H, NH). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 203.0 (s), 165.1 ($^1J_{CF}$ = 252.9 Hz), 164.7 (s), 154.6 (s), 135.0 (s), 131.4 ($^4J_{CF}$ = 3.5 Hz), 129.7 ($^3J_{CF}$ = 8.7 Hz), 123.0 (s), 122.2 (d), 120.3 (d), 116.9 (d), 115.7 ($^2J_{CF}$ = 21.8 Hz), 55.7 (q), 28.5 (q). − MS, *m/z* (%): 287 (38) [M^+], 244 (17), 123 (100), 95 (35).

4,5-Dimethoxy-2-[(4-methoxybenzoyl)amino]acetophenone (**12**): To a solution of 2-amino-4,5-dimethoxyacetophenone (2.95 g, 15.2 mmol) in CH_2Cl_2 (30 ml) and pyridine (8 ml) is added 4-methoxybenzoyl chloride (3.21 g, 18.8 mmol) in CH_2Cl_2 (10 ml). After stirring for 1 h at room temp., sat. aqueous $NaHCO_3$ (20 ml) is added and the mixture vigorously stirred for 0.5 h. After separation and drying of the organic layer with Na_2SO_4 the solvents are evaporated, and the residue is recrystallized from hexane/ethyl acetate thus affording the title compound as pale yellow crystals (3.76 g, 75%); m.p. 156−157°C; m.p. (DSC) 159.5°C. − IR (KBr): $\tilde{\nu}$ = 3160, 3120, 1660, 1640, 1615 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.55 (s, 3H, Me), 3.79, 3.82, 3.95 (s, 3H each, OMe), 6.93 (d, J = 9 Hz, 2H, aromatic H), 7.19 (s, 1H, aromatic H), 7.96 (d, 2H, aromatic H), 8.68 (s, 1H, aromatic H), 12.81 (br. s, 1H, NH). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 200.9 (s), 165.5 (s), 162.5 (s), 154.6 (s), 143.2 (s), 138.4 (s), 129.2 (2×, d), 126.9 (s), 114.2 (s), 113.8 (2×, d), 113.5 (d), 103.1 (d), 56.1 (q), 56.0 (q), 55.3 (q), 28.2 (q). − MS, *m/z* (%): 329 (41) [M^+], 135 (100).

2-[(3,5-Dimethoxybenzoyl)amino]-4,5-dimethoxyacetophenone (**14**): Prepared as described above by using 2-amino-4,5-dimethoxyacetophenone (1.50 g, 7.68 mmol) and 3,5-dimethoxybenzoyl chloride (1.70 g, 8.47 mmol). The crude product is purified by flash chromatography with toluene/ethyl acetate (1:1) as eluent. Yellow crystals (2.50 g, 91%); m.p. 176−177°C. − ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.55 (s, 3H, Me), 3.81, 3.83, 3.96 (s, 3H each, OMe), 6.56 (t, ^4J = 1 Hz, 1H, aromatic H), 7.13 (d, ^4J = 1 Hz, 2H, aromatic H), 7.19 (s, 1H, aromatic H), 8.64 (s, 1H, aromatic H), 12.87 (br. s, 1H, NH). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 200.91, 165.76, 161.12, 154.81, 143.74, 138.15, 136.95, 114.69, 113.98, 105.25, 104.70, 103.50, 56.41, 56.24, 55.63, 28.31. − $C_{19}H_{21}NO_6$ (359.4): calcd. C 63.50, H 5.89, N 3.90; found C 63.42, H 5.98, N 3.99.

2-[(4-Methoxybenzoyl)amino]-4-methylbenzophenone (**16**): Prepared as described above by using 2-amino-4-methylbenzophenone (2.00 g, 9.47 mmol) and 4-methoxybenzoyl chloride (9.96 mmol). The crude product is purified by flash chromatography with toluene/ethyl acetate (4:1) as eluent. Colorless crystals (3.00 g, 92%); m.p. 93−95°C. − ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.41 (s, 3H, Me), 3.79 (s, 3H, OMe), 6.83−6.97 (m, 4H, aromatic H), 7.40−7.52 (m, 4H, aromatic H), 7.65 (d, J = 7 Hz, 1H, aromatic H), 8.04 (d, J = 8 Hz, 2H, aromatic H), 8.77 (s, 1H, aromatic H), 12.11 (br. s, 1H, NH). − ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 200.43, 165.69, 162.94, 146.44, 142.04, 139.57, 134.59, 133.04, 132.23, 129.84, 129.61, 128.48, 127.35, 123.01, 121.81, 120.65, 114.41, 55.79, 22.46. − $C_{22}H_{19}NO_3$ (345.4): calcd. C 76.50, H 5.55, N 4.06; found C 76.50, H 5.70, N 3.98.

Titanium-Induced Oxo-Amide Coupling Reactions and N-Alkylations

1-Ethyl-5-methoxy-2-(4-methoxyphenyl)-3-methylindole (**9b**): To a suspension of C_8K (4.69 g, 35 mmol)[6] in DME (40 ml) under Ar is added $TiCl_3$ (1.79 g, 12 mmol). The mixture is refluxed for 1.5 h, the oxo amide **7** (0.50 g, 1.7 mmol) is added and heating continued for another 60 min. The mixture is filtered through a short plug of silica, the insoluble residues are rinsed with DME in several portions. For analytical purposes an aliquot of the solution is concentrated affording 3-methyl-5-methoxy-2-(4-methoxyphenyl)indole (**9a**)[7] with the following spectral properties: ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.39 (s, 3H, Me), 3.85, 3.88 (s, 3H each, OMe), 6.84 (dd, J = 2.2/8.2 Hz, 1H, aromatic H), 6.99 (m, 2H, aromatic H), 7.02 (d, J = 2.5 Hz, 1H, aromatic H), 7.22 (d, J = 8.5 Hz, 1H, aromatic H), 7.47 (d, J = 8.8 Hz, 1H, aromatic H), 7.84 (br. s, 1H, NH). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.2 (s), 154.3 (s), 135.2 (s), 131.0 (s), 130.6 (s), 129.1 (2×, d), 126.1 (s), 114.4 (2×, d), 112.2 (d), 111.5 (d), 107.8 (s), 100.9 (d), 56.0 (q), 55.7 (q), 9.9 (q). − MS, *m/z* (%): 267 (100) [M^+], 252 (21), 224 (26). − The filtrate is concentrated to a volume of ≈ 30 ml, allowed to react with NaH (118 mg, 4.9 mmol) for 1 h prior to the addition of ethyl iodide (1 ml, 12 mmol). After stirring for 17 h at ambient temp., the solvent is removed in vacuo, the residue suspended in CH_2Cl_2 (30 ml), filtered and the filtrate concentrated. Recrystallization of the crude product from Et_2O (at −78°C) affords analytically pure **9b** as colorless crystals (350 mg, 71%); m.p. (DSC) 110.5°C (ref.[2a] 111−119°C). − ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.09 (t, 3H, CH_2CH_3), 2.11 (s, 3H, Me), 3.77, 3.78 (s, 3H each, OMe), 3.92 (q, 2H, CH_2CH_3), 6.88 (dd, J = 2.4/9 Hz, 1H, aromatic H), 7.00 (m, 2H, aromatic H), 7.03 (d, J = 2.6 Hz, 1H, aromatic H), 7.23 (d, J = 9 Hz, 1H, aromatic H), 7.32 (m, 2H, aromatic H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.3 (s), 154.1 (s), 138.0 (s), 131.6 (d), 131.3 (s), 129.1 (s), 124.9 (s), 113.8 (d), 111.4 (d), 110.1 (d), 108.3 (s), 100.8 (d), 56.0 (q), 55.2 (q), 38.6 (t), 15.4 (q), 9.3 (q). − MS, *m/z* (%): 295 (100) [M^+], 280 (30), 266 (4), 252 (6), 249 (5), 135 (7). − $C_{19}H_{21}NO_2$ (295.3): calcd. C 77.28, H 7.18, N 4.74; found C 76.86, H 7.25, N 4.92.

2-(4-Fluorophenyl)-5-methoxy-3-methylindole (**10a**): To a suspension of C_8K (6.66 g, 49 mmol)[6] in DME (75 ml) is added $TiCl_3$ (2.53 g, 16 mmol) under Ar. After heating for 1.5 h, oxo amide **8** (0.78 g, 2.7 mmol) is added, the mixture heated for 2 h, filtered through a short plug of silica, and the graphite rinsed with DME in several portions. The filtrate is worked up as described above, thus affording indole **10a** as colorless crystals (660 mg, 96%); m.p. (DSC) 133°C. − IR (KBr): $\tilde{\nu}$ = 3410 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.36 (s, 3H, Me), 3.86 (s, 3H, OMe), 6.84 (dd, J = 2.5/8.7 Hz, 1H, aromatic H), 7.00 (d, J = 2.5 Hz, 1H, aromatic H), 7.12 (m, 3H, aromatic H), 7.40−7.49 (m, 2H, aromatic H), 7.88 (br. s, 1H, NH). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 162.1 ($^1J_{CF}$ = 245.8 Hz), 154.1 (s), 134.1 (s), 131.0 (s), 130.3 (s), 129.5 ($^4J_{CF}$ = 3.5 Hz), 129.3 ($^3J_{CF}$ = 8 Hz), 115.7 ($^2J_{CF}$ = 20.9 Hz), 112.4 (d), 111.5 (d), 108.3 (s), 100.8 (d), 55.9 (q), 9.6 (q). − MS, *m/z* (%): 255 (100) [M^+], 240 (20), 212 (24). − HR-MS: calcd. $(C_{16}H_{14}FNO)^+$: 255.10716, found 255.10594.

1-Ethyl-2-(4-fluorophenyl)-5-methoxy-3-methylindole (**10b**): To a solution of **10a** (440 mg, 1.7 mmol) in DME (20 ml) is added NaH (128 mg, 5.3 mmol). After stirring for 1 h ethyl iodide (1 ml, 12 mmol) is added and stirring continued for another 4 h at ambient temp. Removal of the solvent in vacuo, suspending the residue in CH_2Cl_2 (20 ml), filtration, and evaporation of the solvent from the filtrate affords analytically pure **10b** as pale yellow crystals (430 mg, 88%); m.p. (DSC) 85°C. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.16 (t, 3H, CH_2CH_3), 2.19 (s, 3H, Me), 3.88 (s, 3H, OMe), 4.00 (q, 2H, CH_2CH_3), 6.90 (dd, J = 2.4/8.7 Hz, 1H, aromatic H), 7.04 (d, J = 2.4 Hz, 1H, aromatic H), 7.10−7.36 (m, 3H, aromatic H), 7.29−7.38 (m, 2H, aromatic H). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 162.7 ($^1J_{CF}$ = 245.8 Hz), 154.2 (s), 137.1 (s), 132.1 ($^3J_{CF}$ =

8.2 Hz), 131.5 (s), 129.1 (s), 128.5 ($^4J_{CF}$ = 3.5 Hz), 115.6 ($^2J_{CF}$ = 22.4 Hz), 111.8 (d), 110.3 (d), 108.8 (s), 101.0 (d), 56.2 (q), 38.9 (t), 15.5 (q), 9.5 (q). – MS, *m/z* (%): 283 (100) [M^+], 268 (47), 253 (6), 240 (10). – HR-MS: calcd. $(C_{18}H_{18}FNO)^+$: 283.13729, found 283.13724. – $C_{18}H_{18}FNO$ (283.1): calcd. C 76.31, H 6.39, F 6.71, N 4.94; found C 75.71, H 6.53, F 6.92, N 5.06.

5,6-Dimethoxy-2-(4-methoxyphenyl)-3-methylindole (**13a**): To a suspension of C_8K (4.72 g, 35 mmol)[6] in DME (80 ml) is added $TiCl_3$ (2.70 g, 17.5 mmol) under Ar and the resulting suspension refluxed for 1.5 h to ensure complete reduction. Oxo amide **12** (955 mg, 2.9 mmol) is added and refluxing continued until TLC shows complete conversion of the substrate (≈ 2 h). The mixture is filtered over a pad of silica, which is subsequently rinsed with DME in several portions. Workup of the filtrate as described above affords the title compound as colorless crystals (570 mg, 66%); m.p. 158–160°C. – IR (KBr): $\tilde{\nu}$ = 3420 cm^{-1}. – ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.37 (br. s, 3H, Me), 3.85, 3.90, 3.97 (s, 3H each, OMe), 6.88 (s, 1H, aromatic H), 7.00 (d, *J* = 9 Hz, 1H, aromatic H), 7.45 (d, 1H, aromatic H), 7.84 (br. s, 1H, NH). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 162.0, 150.3, 147.9, 145.7, 134.3, 130.4, 130.0, 124.7, 114.1, 105.6, 104.8, 84.4, 56.6, 56.2, 55.6, 25.9. – MS, *m/z* (%): 297 (100) [M^+], 282 (36), 239 (17). – $C_{18}H_{19}NO_3$ (297.3): calcd. C 72.71, H 6.44, N 4.71; found C 72.56, H 6.80, N 4.83.

5,6-Dimethoxy-2-(4-methoxyphenyl)-1,3-dimethylindole (**13b**): To a solution of **13a** (100 mg, 0.336 mmol) in THF (3 ml) under Ar are added NaH (60% in mineral oil, 27 mg, 0.67 mmol) and MeI (143 mg, 1.01 mmol) with stirring. Standard extractive workup after a reaction time of 30 min, followed by flash chromatography (toluene/ethyl acetate, 4:1) affords the product as colorless crystals (94 mg, 90%), m.p. 162–165°C (dec.). – ^1H NMR ($CDCl_3$, 75 MHz): δ = 2.26 (s, 3H, Me), 3.58 (s, 3H, NMe), 3.90, 3.99, 4.00 (s, 3H, OMe), 7.02–7.05 (m, 3H, aromatic H), 7.28–7.33 (m, 3H, aromatic H). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.22, 147.16, 145.05, 136.34, 131.84, 124.94, 121.41, 113.93, 107.88, 101.30, 93.50, 56.79, 56.64, 55.43, 31.11, 9.56. – MS, *m/z* (%): 311 (100) [M^+], 297 (11), 296 (56), 253 (19), 238 (3), 224 (2), 210 (2), 133 (2). – $C_{19}H_{21}NO_3$ (311.4): calcd. C 73.29, H 6.80, N 4.50; found C 73.16, H 6.72, N 4.56.

5,6-Dihydroxy-2-(4-hydroxyphenyl)-1,3-dimethylindole (**13c**): To a stirred solution of substrate **13b** (100 mg, 0.321 mmol) in CH_2Cl_2 (5 ml) is added BBr_3 (1 M in CH_2Cl_2, 2.10 ml, 2.10 mmol) at –60°C under Ar. The mixture is allowed to warm to ambient temp. and stirred for another 3 h. Slow addition of $NaHCO_3$ (saturated in H_2O, 10 ml), extraction of the aqueous phase with ethyl acetate (60 ml in three portions), drying of the extract (Na_2SO_4), and evaporation of the solvent from the combined organic layers followed by flash chromatography of the residue affords the title compound as colorless crystals (72 mg, 83%); m.p. 170–171°C. – ^1H NMR ([D_6]acetone, 300 MHz): δ = 2.15 (s, 3H, Me), 3.48 (s, 3H, NMe), 6.98–7.25 (AB, *J* = 8 Hz, 4H, aromatic H), 7.53, 7.58 (s, 1H each, aromatic H). – ^{13}C NMR ([D_6]acetone, 75 MHz): δ = 157.66, 143.42, 140.77, 136.76, 133.04, 132.46, 124.59, 122.59, 116.04, 107.22, 103.96, 96.23, 31.07, 9.72. – $C_{16}H_{15}NO_3$ (269.3): calcd. C 71.36, H 5.61, N 5.20; found C 71.45, H 5.72, N 5.02.

1-Ethyl-5,6-dimethoxy-2-(4-methoxyphenyl)-3-methylindole (**13d**): NaH (240 mg, 10 mmol) is added to a solution of indole **13a** (560 mg, 1.9 mmol) in THF (20 ml). After stirring for 2 h at ambient temperature, EtI (1.2 ml, 15 mmol) is introduced and stirring continued for another 2 h. The solvent is removed in vacuo and the residue suspended in CH_2Cl_2 (50 ml). Filtration and evaporation of the solvent from the filtrate affords analytically pure **13d** as colorless crystals (470 mg, 76%); m.p. (DSC) 124–125°C. – ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.19 (s, 3H, CH_2CH_3), 2.20 (s, 3H, Me), 3.86, 3.96, 3.97 (s, 3H each, OMe), 4.00 (q, 2H, CH_2CH_3), 6.84 (s, 1H, aromatic H), 6.96–7.05 (m, 3H, aromatic H), 7.26–7.34 (m, 2H, aromatic H). – ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 159.0 (s), 146.9 (s), 144.9 (s), 135.9 (s), 131.6 (2×, d), 130.4 (s), 125.0 (s), 121.7 (s), 113.8 (2×, d), 108.1 (s), 101.0 (d), 93.4 (d), 56.5 (2×, q), 55.2 (q), 38.6 (t), 15.3 (q), 9.3 (q). – MS, *m/z* (%): 325 (100) [M^+], 310 (65), 282 (8), 267 (14). – $C_{20}H_{23}NO_3$ (325.4): calcd. C 73.82, H 7.13, N 4.30; found C 73.54, H 7.43, N 4.30.

(3,5-Dimethoxyphenyl)-5,6-dimethoxy-3-methylindole (**15a**): To a suspension of C_8K (4.2 g, 31 mmol)[6] in DME (50 ml) is added $TiCl_3$ (1.58 g, 10.2 mmol), and the resulting suspension is refluxed for 1.5 h. Oxo amide **14** (310 mg, 0.9 mmol) in DME (15 ml) is added and heating continued until TLC shows complete conversion of the substrate (0.5 h). The suspension is filtered over a plug of silica, the graphite washed with ethyl acetate (50 ml in several portions), the combined filtrates are concentrated, and the residue is subjected to column chromatography affording **15a** as colorless crystals (240 mg, 86%); m.p. 141–142°C. – ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.46 (s, 3H, Me), 3.84, 3.85, 3.88, 3.97 (s, 3H each, OMe), 6.45 (s, 1H, aromatic H), 6.71 (s, 2H, aromatic H), 6.84 (s, 1H, aromatic H), 7.02 (s, 1H, aromatic H), 8.06 (br. s, 1H, NH). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 161.24, 147.72, 145.30, 135.66, 132.91, 130.45, 123.14, 108.96, 105.81, 101.21, 99.11, 94.71, 56.67, 56.40, 55.56, 10.14. – MS, *m/z* (%): 327 (100) [M^+], 312 (33), 284 (3), 269 (11), 164 (3), 148 (2). – $C_{19}H_{21}NO_4$ (327.4): calcd. C 69.71, H 6.47, N 4.28; found C 69.65, H 6.60, N 4.20.

2-(3,5-Dimethoxyphenyl)-5,6-dimethoxy-1,3-dimethylindole (**15b**): To a solution of **15a** (500 mg, 1.5 mmol) in THF (25 ml) is added NaH (0.7 g, 3.0 mmol). After stirring for 30 min at 0°C methyl iodide (230 mg, 1.6 mmol) is added through a syringe and the resulting mixture stirred at ambient temp. for 5 h. Quenching with water (50 ml), followed by extractive workup (ethyl acetate) and flash chromatography affords the title compound as colorless crystals (480 mg, 92%); m.p. 153–155°C. – ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.31 (s, 3H, Me), 3.63 (s, 3H, NMe), 3.86, 3.87, 3.99, 4.00 (s, 3H each, OMe), 6.54, 6.55, 6.56, 6.85, 7.06 (s, 1H each, aromatic H). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 160.83, 147.48, 145.21, 136.47, 134.54, 132.09, 121.43, 109.01, 108.46, 101.40, 99.82, 93.51, 56.85, 56.69, 55.63 (2×), 31.40, 9.76. – MS, *m/z* (%): 341 (100) [M^+], 327 (11), 326 (56), 298 (6), 283 (17). – $C_{20}H_{23}NO_4$ (341.4): calcd. C 70.36, H 6.79, N 4.10; found C 70.20, H 6.80, N 4.19.

2-(4-Methoxyphenyl)-6-methyl-3-phenylindole (**17**): Obtained by reaction of substrate **16** (722 mg, 2.09 mmol) with titanium graphite ($TiCl_3$:C_8K = 2:1)[8] (10.2 mmol) in THF (50 ml) for 8 h as described above. Standard workup followed by flash chromatography affords product **17** as pale yellow oil, which crystallizes upon standing at room temp. Colorless crystals (518 mg, 79%); m.p. 210–212°C. – ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.59 (s, 3H, Me), 3.87 (s, 3H, OMe), 6.91 (d, *J* = 7.5 Hz, 1H, aromatic H), 7.13 (d, *J* = 8 Hz, 1H, aromatic H), 7.21 (s, 1H, aromatic H), 7.39–7.61 (m, 8H, aromatic H), 7.73 (d, *J* = 8 Hz, 1H, aromatic H), 8.09 (br. s, 1H, NH). – ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 159.29, 136.50, 133.69, 130.29, 129.56, 128.68, 126.19, 125.60, 122.29, 119.32, 114.34, 111.07, 55.37, 21.89. – MS, *m/z* (%): 313 (100) [M^+], 296 (12), 277 (2), 263 (2). – $C_{22}H_{19}NO$ (313.4): calcd. C 84.31, H 6.11, N 4.47; found C 84.37, H 6.14, N 4.40.

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