Supporting information-Part 1

A Traceless Approach for the Solid-Phase Parallel Synthesis of Trisubstitued Oxindoles

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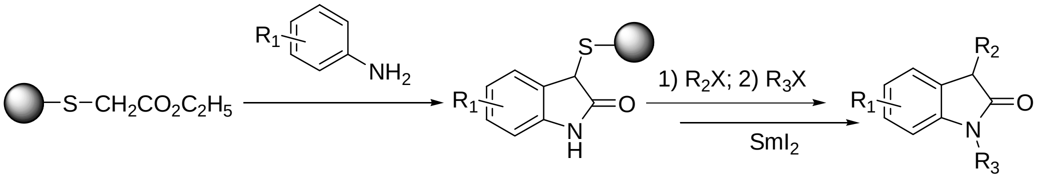

Experimental Section

Melting points are uncorrected. NMR spectra were recorded at 400MHz (^{1}H NMR) or 100MHz (^{13}C NMR) with $CDCl_3$ or DMSO-d_6 as solvent and TMS as the internal standard. J values are in Hertz and Chemical shifts are expressed in ppm downfield from internal TMS. DMF and DCM were distilled from CaH_2, THF was distilled from sodium and benzophenone before use. The other reagents were used directly without further purification. Column chromatography was performed on silica gel. LC-MS (ESI) spectra were recorded on a Thermo Finnigan LCQ Advantage mass Spectrophotometer 214 nm using a Betasil C_{18} (3 μm, 100 Å, 3×50 mm) column. The HPLC purity of the products was analyzed by Aligent 1100 Series. The following abbreviations were used to designate the multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet. Mercaptomethyl resin (100-200 mesh, cross-linked with 1% divinylbenzene, substitution: 1.0 mmol/g), was purchased from commercial sources.

Preparation of SmI_2 To a slurry of Sm powder (flame dried under Ar, 496 mg, 3.3 mmol) in THF (30 ml) was added I_2 (762 mg, 3.0 mmol) at room temperature. The reaction mixture was stirred for 2 h at room temperature under N_2 to prepare the SmI_2 (0.1 M in THF) reagent.

General procedure for preparation of resin-bound oxindole 5 To the mercaptomethyl resin **1** (600 mg, 100-200 mesh, 1% DVB, substitution: 1.0 mmol/g, sealed with polypropylene mesh packets) in DCM was added Et_3N (10 equiv, 0.2 M), $BrCH_2CO_2C_2H_5$ (10 equiv, 0.2 M). The mixture was shaken for 24 hours at room temperature, The resin was then washed with DMF (3 times), DCM (3 times), and MeOH (3 times). This procedure was repeated.

The resulting resin-bound compound **3** in DCM (30 ml) was added an aniline (10 equiv, 6 mmol) at room temperature. The above mixture was cooled to -78^{o}C. *t*-BuOCl (10 equiv, 6 mmol) in DCM (5 ml) was added dropwise over 30 min and the solution was stirred for 7 hours. Et_3N (10 equiv, 6 mmol) in DCM (5 ml) was added and the mixture was stirred for another 7 hours at -78°C. The reaction mixture was allowed to warm to room temperature. The resin was then washed with DMF (3 times), DMF/H_2O (5:1) (3 times), DMF/H_2O (2:1) (3 times), DMF/H_2O (5:1) (3 times), DMF (3 times), DCM (3 times), and MeOH (3 times). The resulting resin was treated with 10 ml 25% methanol solution of HCl in DCM (30 ml), the mixture was shaken for 15 hours at room temperature to afford resin-bound oxindole **5**. The resin was washed with DMF (3 times), DMF/H_2O (5:1) (3 times), DMF/H_2O (2:1) (3 times), DMF/H_2O (5:1) (3 times), DMF (3 times), DCM (3 times), and MeOH (3 times). The resin was then dried in vacuo.

General procedure for preparation of resin-bound oxindole 8 The resulting resin-bound oxindole **5** was swollen in DCM (40 ml) for 15 min and was cooled to 0°C, *m*-CPBA (6.67 equiv, 4 mmol) was added, the resulting mixture allowed to shake at room temperature for 45 minutes to afford resin-bound compound **7**. The resin was washed with DMF (3 times), DCM (3 times), and MeOH (3 times) and dried in vacuo.

The resin-bound oxindole **7** was swollen in DMF (40 ml) for 15 min, K_2CO_3 (10 equiv, 6 mmol) and an alkyl halide (10 equiv, 6 mmol) were added and the resulting mixture was shaken at room temperature for 22 hours to afford resin-bound oxindole **8**. The resin was washed with DMF (3 times), DMF/H_2O (5:1) (3 times), DMF/H_2O (2:1) (3 times), DMF/H_2O (5:1) (3 times), DMF (3 times), DCM (3 times), and MeOH (3 times). The resin then was dried in vacuo.

General procedure for preparation of resin-bound oxindole 10 The resulting resin-bound oxindole **8** was swollen in THF (40 ml) for 15 min, NaH (10 equiv, 6 mmol) and CH_3I (10 equiv, 6 mmol) were added. The reaction mixture was shaken at room temperature for 40 hours to afford resin-bound oxindole **10**. The resin was washing with THF (3 times), THF/H_2O (5:1) (3 times), THF/H_2O (2:1) (3 times), THF/H_2O (5:1) (3 times), THF (3 times), DCM (3 times), and MeOH (3 times). The resin then was dried in vacuo.

General procedure for cleavage of resin-bound oxindoles 5, 8, and 10 The resulting resin-bound oxindole **5**, **8**, or **10** was added to the freshly prepared SmI_2 (0.1 M in THF, 30ml, 5 equiv) at room temperature. After being stirred for 3 hours at room temperature under N_2, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (8ml). The tea-bag resin was taken off and washed with EtOAc (2×10 ml). The combined solution was concentrated in vacuo, and then was extracted with EtOAc (3×10 ml). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and filtered. After being concentrated in vacuo, the residue was purified by flash chromatography on silica gel (ethyl acetate/cyclohexane 1/3 for **5a-5j**; 1/4 for **8a-8d**; 1/5 for **10a-10b**) to afford the desired product oxindoles **6a-6j**, **9a-9d**, or **11a-11b**.

oxindole (6a): White solid. Mp: 115-116.5^{o}C (lit.[1] 116-117^{o}C). ^{1}H NMR (400MHz, $CDCl_3$) δ 9.45 (1H, s), 7.22-6.89 (4H, m), 3.53 (2H, s). ^{13}C NMR (100MHz, $CDCl_3$) δ 178.3, 142.7, 127.9, 125.3, 124.5, 122.2, 109.9, 36.3. LC-MS (ESI) *m/z*: 134.1 ($M+H^+$).

7-methyl-oxindole (6b): Light brown solid. Mp: 207.5-209^{o}C (lit.[1] 206-207^{o}C). ^{1}H

NMR (400MHz, $CDCl_3$) δ 9.91 (1H, s), 7.06-6.91 (3H, m), 3.55 (2H, s), 2.32 (3H, s). ^{13}C NMR (100MHz, $CDCl_3$) δ 178.8, 141.7, 129.1, 124.9, 122.2, 121.8, 119.5, 36.8, 16.5. LC-MS (ESI) *m/z*: 148.2 ($M+H^+$).

5-methyl-oxindole (6c): White solid. Mp: 172.5-174°C (lit.[1] 171.5-174°C). ^{1}H NMR (400MHz, $CDCl_3$) δ 9.76 (1H, s), 7.0 (1H, s), 6.96 (1H, d, J = 7.9 Hz), 6.75 (1H, d, J = 7.9 Hz), 3.41 (2H, s), 2.28 (3H, s). ^{13}C NMR (100MHz, $CDCl_3$) δ 176.5, 140.3, 130.2, 127.2, 124.8, 124.4, 108.6, 35.6, 20.3. LC-MS (ESI) *m/z*: 148.2 ($M+H^+$).

5-trifluoromethyl-oxindole (6d): Light yellow solid. Mp: 188-200°C. ^{1}H NMR (400MHz, DMSO-d_6) δ 10.71 (1H, s), 7.53-6.96 (3H, m), 3.57 (2H, s). ^{13}C NMR (100MHz, DMSO-d_6) δ 176.3, 147.3, 126.8, 126.1, 125.1, 123.4, 121.8, 121.2, 109.0, 35.5. LC-MS (ESI) *m/z*: 201.4 (M^+).

5-bromo-oxindole (6e): White solid. Mp: 215-217°C. ^{1}H NMR (400MHz, DMSO-d_6) δ 10.23 (1H, s), 7.30-6.75 (3H, m), 3.46 (2H, s). ^{13}C NMR (100MHz, DMSO-d_6) δ 175.3, 142.0, 129.4, 126.7, 126.4, 112.7, 110.2, 35.2. LC-MS (ESI) *m/z*: 212.0 (M^+).

5-fluoro-oxindole (6f): Light purple solid. Mp: 143-144°C. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.76 (1H, s), 6.95-6.79 (3H, m), 3.49 (2H, s). ^{13}C NMR (100MHz, $CDCl_3$) δ 177.0, 159.6, 157.2, 139.0, 126.7, 113.7, 113.6, 112.1, 111.8, 109.9, 36.4. LC-MS (ESI) *m/z*: 152.1 ($M+H^+$).

4-bromo-oxindole and 6-bromo-oxindole (6g): White solid. As a mixture without being separated. ^{1}H NMR (400MHz, DMSO-d_6) δ 10.62 (1H, s), 10.49 (1H, s), 7.16-7.09 (4H, m), 6.93-6.80 (2H, m), 3.44 (4H, s). ^{13}C NMR (100MHz, DMSO-d_6) δ

176.6, 175.2, 145.8, 145.3, 130.0, 126.9, 126.5, 125.6, 124.1, 124.0, 120.3, 118.4, 112.2, 108.7, 37.4, 35.8. LC-MS (ESI) *m/z*: 213.1 (M+H$^+$).

5-carboethoxy-oxindole (6h): White solid. Mp: 189-190.5ºC (lit.[2] 190-192ºC). ^{1}H NMR (400MHz, DMSO-d_6) δ 10.37 (1H, s), 7.91 (1H, d, *J* = 8.9 Hz), 7.86 (1H, s), 6.93 (1H, d, *J* = 8.2 Hz), 4.33 (2H, q). 3.50 (2H, s), 1.38 (3H, t). ^{13}C NMR (100MHz, DMSO-d_6) δ 176.5, 165.7, 147.4, 129.6, 124.9, 124.6, 123.1, 108.5, 59.9, 35.3, 13.7. LC-MS (ESI) *m/z*: 206.2 (M+H$^+$).

4-chloro-7-methyl-oxindole (6i): White solid. Mp: 243-245ºC. ^{1}H NMR (400MHz, DMSO-d_6) δ 10.61 (1H, s), 7.02 (1H, d, *J* = 8.3 Hz), 6.88 (1H, d, *J* = 8.3 Hz), 3.49 (2H, s), 2.17 (3H, s). ^{13}C NMR (100MHz, DMSO-d_6) δ 175.5, 143.4, 130.3, 126.0, 123.4, 120.7, 117.5, 35.5, 16.0. LC-MS (ESI) *m/z*: 182.2 (M+H$^+$).

5, 7-dichloro-oxindole (6j): White solid. Mp: 245-247ºC. ^{1}H NMR (400MHz, DMSO-d_6) δ 10.52 (1H, s), 7.18 (1H, s), 7.11 (1H, s), 3.55 (2H, s). ^{13}C NMR (100MHz, DMSO-d_6) δ 174.7, 139.4, 127.2, 126.4, 125.8, 122.2, 113.8, 35.9. LC-MS (ESI) *m/z*: 202.0 (M$^+$).

3-allyl-5-bromo-oxindole (9a): Light yellow solid. Mp: 97-99ºC. ^{1}H NMR (400MHz, CDCl$_3$) δ 8.93 (1H, s), 7.38 (1H, s), 7.34 (1H, d, *J* = 8.2 Hz), 6.78 (1H, d, *J* = 8.2 Hz), 5.78-5.70 (1H, m), 5.16-5.08 (2H, m), 3.52 (1H, t, *J* = 6.2 Hz), 2.83-2.78 (1H, m), 2.62-2.57 (1H, m). ^{13}C NMR (100MHz, CDCl$_3$) δ 179.3, 140.6, 133.3, 131.3, 130.9, 127.6, 118.6, 114.9, 111.2, 45.8, 34.5. LC-MS (ESI) *m/z*: 252.1 (M$^+$).

3-benzyl-5-fluoro-oxindole (9b): Light yellow solid. Mp: 194-196ºC. ^{1}H NMR (400MHz, DMSO-d_6) δ 10.05 (1H, s), 7.11-6.91 (7H, m), 6.59-6.56 (1H, m), 4.12

(1H, t), 3.27(1H, dd, J = 13.2 Hz, 4.9 Hz), 3.01 (1H, dd, J = 13.2 Hz, 8.7 Hz). ^{13}C NMR (100MHz, DMSO-d_6) δ 178.6, 159.1, 157.2, 137.7, 134.7, 130.0, 127.5, 126.4, 113.1, 112.9, 112.2, 109.9, 46.3, 34.2. LC-MS (ESI) *m/z*: 242.2 (M+H$^+$).

5-carboethoxy-3-(4-bromobenzyl)-oxindole (9c): White solid. Mp: 168-169°C. ^{1}H NMR (400MHz, DMSO-d_6) δ 10.72 (1H, s), 7.78 (1H, d, J = 8.8 Hz), 7.48 (1H, s), 7.40 (2H, d, J = 8.0 Hz), 7.07 (2H, d, J = 7.6 Hz), 6.82 (1H, d, J = 8.8 Hz), 4.22 (2H, q), 3.88(1H, t), 3.32 (1H, dd, J = 13.6 Hz, 4.8 Hz), 2..96 (1H, dd, J = 13.6 Hz, 7.6 Hz), 1.27 (3H, t). ^{13}C NMR (100MHz, DMSO-d_6) δ 178.6, 166.0, 147.6, 137.5, 131.9, 131.3, 130.5, 129.2, 125.6, 122.9, 120.0, 109.3, 60.6, 46.3, 34.7, 14.5. LC-MS (ESI) *m/z*: 375.3 (M+H$^+$).

3-benzyl-5, 7-dichloro-oxindole (9d): Light yellow solid. Mp: 195-196°C. ^{1}H NMR (400MHz, DMSO-d_6) δ 10.90 (1H, s), 7.32 (1H, s), 7.24-7.11 (5H, m), 6.97 (1H, s), 3.98 (1H, t), 3.34 (1H, dd, J = 13.6 Hz, 5.2 Hz), 3.04(1H, dd, J = 13.6 Hz, 6.8 Hz). ^{13}C NMR (100MHz, DMSO-d_6) δ 178.0, 139.9, 137.7, 132.7, 129.6, 128.5, 127.3, 126.9, 125.8, 123.7, 114.2, 47.8, 34.9. LC-MS (ESI) *m/z*: 293.2 (M+H$^+$).

3-allyl-5-fluoro-1-methyl-oxindole (11a): Light yellow solid. Mp: 46-47°C. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.05-6.95 (2H, m), 6.74-6.71 (1H, m), 5.79-5.69 (1H, m), 5.13-5.05(2H, m), 3.49-3.46 (1H, m), 3.19 (3H, s), 2.84-2.80 (1H, m), 2.57-2.51 (1H, m). ^{13}C NMR (100MHz, $CDCl_3$) δ 176.7, 160.2, 157.8, 140.3, 133.6, 130.2, 118.3, 114.1, 113.9, 112.4, 112.2, 108.1, 45.4, 34.7, 26.2. LC-MS (ESI) *m/z*: 206.2 (M+H$^+$).

3-benzyl-1-methyl-5-trifluoromethyl-oxindole (11b): White solid. Mp: 113-115°C. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.49 (1H, d, J = 8.2 Hz), 7.27-7.10 (5H, m), 6.96 (1H, s), 6.78 (1H, d, *J* = 8.2 Hz), 3.72 (1H, dd, *J* = 4.8 Hz, 8.9 Hz), 3.49 (1H, dd, *J* = 4.8 Hz, 13.7 Hz), 3.16(3H, s), 2.91 (1H, dd, *J* = 8.9 Hz, 13.7 Hz). ^{13}C NMR (100MHz, $CDCl_3$) δ 176.8, 147.2, 137.1, 129.3, 128.8, 128.4, 126.9, 125.7, 124.7, 124.4, 124.1, 123.8, 123.0, 121.6, 120.3, 107.5, 46.9, 36.7, 26.2. LC-MS (ESI) *m/z*: 306.2 ($M+H^+$).

References

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