

Supporting Information

A novel alternative for the N–N bond formation through a PIFA-mediated oxidative cyclization and its application to the synthesis of indazol-3-ones

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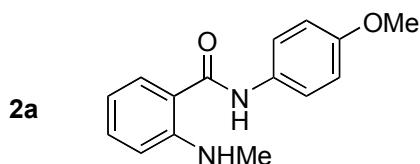
Supporting Information Available. Experimental details for compounds **2a-o** and ¹H NMR and ¹³C NMR spectra of all new compounds are included

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General Methods and Materials. All reagents were purchased and used as received. Melting points were measured using open glass capillaries and are uncorrected. Infrared spectra were recorded as KBr plates or as thin films and peaks are reported in cm⁻¹. Only representative absorptions are given. NMR spectra were recorded on a 250 instrument (250 MHz for ¹H and 62.83 MHz for ¹³C) at 20 °C. Chemical shifts (δ) were

measured in ppm relative to chloroform (δ = 7.26 for ^1H or 77.00 for ^{13}C) as internal standard. Coupling constants, J , are reported in hertz. DEPT experiments were used to assist with the assignation of the signals. HRMS spectra were recorded at the University of Vigo.

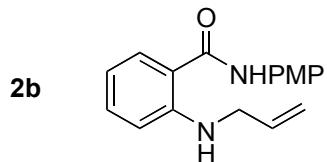
Typical procedure 1 for the synthesis of benzamides 2a-e, h-k, m-o. Synthesis of *N*-(4-methoxyphenyl)-2-methylaminobenzamide (2a).¹ A solution of AlMe₃ (9.0 mmol, 2.0 M in toluene) was added dropwise to a cooled (0 °C) suspension of *p*-anisidine (2.23 g, 18.1 mmol) in CH₂Cl₂ (50 mL). When the addition was complete, the reaction mixture was allowed to warm to room temperature and was stirred for 45 minutes until the gas evolution ceased. Then, a solution of commercially available methyl *N*-methylanthranilate (**1a**) (1.32 mL, 9.0 mmol) was added and the mixture was heated under reflux overnight. The reaction mixture was cooled to room temperature and was carefully quenched with 5% aq HCl (20 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3x15 mL). The combined organic extracts were washed with a saturated aqueous solution of NaHCO₃ (15 mL) and brine (15 mL). Then, the organic layer was dried over sodium sulfate, filtered and the solvent was evaporated at reduced pressure. The resulting residue was purified by crystallization from Et₂O to afford amide **2a** as a white solid (69% yield).



Mp 127-128 °C (Et₂O) (lit.¹ mp 122-123 °C); $^1\text{H-NMR}$ (CDCl₃) – 2.86 (s, 3H) 3.81 (s, 3H), 6.60-6.72 (m, 2H), 6.90 (d, $J=8.7$, 2H), 7.33-7.48 (m, 5H), 7.66 (bs, 1H); $^{13}\text{C-NMR}$ (CDCl₃) – 29.6, 55.4, 111.2, 114.0, 114.5, 115.2, 122.6, 127.2, 130.7, 133.0, 150.6, 156.5, 168.1; IR (KBr) 3378, 1631 cm⁻¹; MS (EI) m/z (%) 256 (M⁺, 29), 134 (100), 123 (88), 77 (25); HRMS calc. for C₁₅H₁₆N₂O₂ 256.1212, found 256.1208.

¹ Lee, C. -M. *J. Heterocycl. Chem.* **1964**, *1*, 235-8.

2-Allylamino-N-(4-methoxyphenyl)benzamide (2b). According to the general procedure 1 benzamide **2b** was obtained as a white solid from methyl *N*-allylantranilate (**1b**)² in 77% yield after purification by crystallization from Et₂O.



Mp 107-108 °C (Et₂O); ¹H-NMR (CDCl₃) – 3.80-3.82 (m, 2H), 3.81 (s, 3H), 5.13-5.33 (m, 2H), 5.86-6.00 (m, 1H), 6.61-6.88 (m, 2H), 6.90-6.91 (m, 2H), 7.27-7.29 (m, 1H), 7.32-7.29 (m, 3H), 7.62 (bs, 1H), 7.71 (bs, 1H); ¹³C-NMR (CDCl₃) – 45.4, 55.4, 112.0, 114.0, 114.8, 115.3, 116.0, 122.7, 127.3, 130.7, 132.9, 134.6, 149.5, 156.5, 168.1; IR (KBr) 3342, 1631 cm⁻¹; MS (EI) *m/z* (%) 282 (M⁺, 2), 280 (26), 254 (29), 251 (24), 123 (24), 121 (100), 92 (27), 77 (67); HRMS calc. for C₁₇H₁₈N₂O₂ 282.1368, found 282.1362.

2-Benzylamino-N-(4-methoxyphenyl)benzamide (2c). According to the general procedure 1 benzamide **2c** was obtained as a white solid from commercially available methyl *N*-benzylantranilate (**1c**) in 67% yield after purification by crystallization from Et₂O.



Mp 112-114 °C (Et₂O); ¹H-NMR (CDCl₃) – 3.81 (s, 3H), 4.41 (d, *J*=5.5, 2H), 6.60-6.71 (m, 2H), 6.90 (d, *J*=8.7, 2H), 7.29-7.94 (m, 9H), 7.97 (bs, 1H), 7.99 (bs, 1H); ¹³C-NMR (CDCl₃) – 47.2, 55.3, 112.0, 114.0, 115.0, 115.2, 122.7, 126.9, 127.0, 127.3, 128.4, 130.6, 132.9, 138.8, 149.5, 156.4, 168.1; IR (KBr) 3343, 1637 cm⁻¹; MS (EI) *m/z* (%) 332 (M⁺, 6), 253 (11), 210 (34), 208 (30), 180 (10), 132 (25), 123 (100), 91 (36); HRMS calc. for C₂₁H₂₀N₂O₂ 332.1525, found 332.1523.

² Anderson, W. K.; Lai, G. *Synthesis* **1995**, 1287-1290.

N-(4-methoxyphenyl)-2-phenylaminobenzamide (2d). According to the general procedure 1 benzamide **2d** was obtained as a white solid from methyl *N*-phenylanthranilate (**1d**)³ in 68% yield after purification by crystallization from Et₂O.



Mp 140-142 °C (Et₂O); ¹H-NMR (CDCl₃) – 3.80 (s, 3H), 6.79-6.93 (m, 3H), 6.98-7.04 (m, 1H), 7.17-7.47 (m, 8H), 7.55-7.58 (m, 1H), 7.85 (bs, 1H), 9.16 (bs, 1H); ¹³C-NMR (CDCl₃) – 55.3, 114.0, 115.6, 118.1, 118.7, 120.5, 122.3, 122.8, 127.6, 129.2, 129.3, 132.3, 141.3, 145.3, 156.7, 167.8; IR (KBr) 3308, 1584 cm⁻¹; MS (EI) *m/z* (%) 318 (M⁺, 34), 196 (87), 195 (44), 167 (42), 123 (100); HRMS calc. C₂₀H₁₈N₂O₂ 318.1368, found 318.1371.

N-(4-methoxyphenyl)benzamide (2e).⁴ According to the general procedure 1 benzamide **2e** was obtained as a white solid from commercially available methyl anthranilate (**1e**) in 71% yield after purification by crystallization from Et₂O.

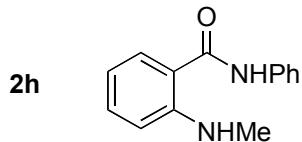


Mp 122-123 °C (Et₂O) (lit.⁴ 123-125 °C); ¹H-NMR (CDCl₃) – 3.79 (s, 3H), 5.32 (bs, 2H), 6.63-6.70 (m, 2H), 6.87 (d, *J*=8.7, 2H), 7.19-7.26 (m, 1H), 7.41-7.45 (m, 3H), 7.80 (bs, 1H); ¹³C-NMR (CDCl₃) – 55.4, 114.1, 116.2, 116.7, 117.4, 122.6, 127.1, 130.7, 132.5, 149.0, 156.5, 167.5; IR (KBr) 3283, 1637 cm⁻¹; MS (EI) *m/z* (%) 242 (M⁺, 45), 123 (82), 120 (100), 92 (33); HRMS calc. for C₁₄H₁₄N₂O₂ 242.1055, found 242.1054.

³ Gujadur, R.; Venkataraman, D.; Kintigh, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791-4793.

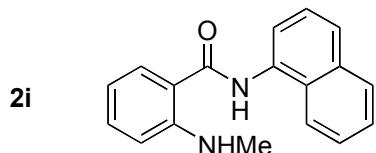
⁴ Waisser, K.; Machacek, M.; Dostal, H.; Gregor, J.; Kubicova, L.; Klimesova, V.; Kunes, J.; Palat, K.; Hladuvkova, J.; Kaustova, J.; Möllmann, U. *Collect. Czech. Chem. Commun.* **1999**, 1902-1924.

2-Methylaminobenzanilide (2h).⁵ According to the general procedure 1 benzanilide **2h** was obtained as a white solid from commercially available methyl *N*-methylantranilate (**1a**) and aniline in 88% yield after purification by crystallization from Et₂O.



Mp 121-122 °C (Et₂O) (lit.⁵ 124-125 °C); ¹H-NMR (CDCl₃) – 2.87 (s, 3H), 6.62-6.74 (m, 2H), 7.12-7.18 (m, 1H), 7.38-7.57 (m, 6H), 7.76 (bs, 1H); ¹³C-NMR (CDCl₃) – 29.5, 111.1, 114.4, 115.0, 120.5, 124.2, 127.3, 128.8, 133.1, 137.7, 150.6, 168.2; IR (KBr) 3367, 1637 cm⁻¹; MS (EI) *m/z* (%) 226 (M⁺, 33), 134 (100), 93 (32), 77 (21); HRMS calc. for C₁₄H₁₄N₂O 226.1106, found 226.1105.

2-Methylamino-*N*-(1-naphthyl)benzamide (2i). According to the general procedure 1 benzamide **2i** was obtained as a white solid from commercially available methyl *N*-methylantranilate (**1a**) and 1-naphthylamine in 91% yield after purification by crystallization from Et₂O.

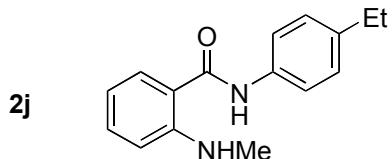


Mp 185-187 °C (Et₂O); ¹H-NMR (CDCl₃) – 2.88 (d, *J*=4.8, 3H), 6.68-6.77 (m, 2H), 7.40-7.54 (m, 5H), 7.66-7.77 (m, 2H), 7.84-7.92 (m, 3H), 8.11 (bs, 1H); ¹³C-NMR (CDCl₃) – 29.6, 111.5, 114.6, 121.1, 121.7, 125.6, 126.1, 126.2, 126.4, 127.4, 128.0, 128.7, 132.5, 133.5, 134.2, 151.1, 168.8; IR (KBr) 3300, 1627 cm⁻¹; MS (EI) *m/z* (%) 276 (M⁺, 11), 143 (45), 134 (100), 77 (26); HRMS calc. for C₁₈H₁₆N₂O 276.1263, found 276.1262.

***N*-(4-ethylphenyl)-2-methylaminobenzamide (2j).** According to the general procedure 1 benzamide **2j** was obtained as a white solid from commercially available methyl *N*-

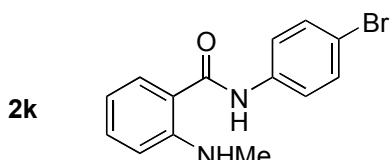
⁵ Katritzky, A. R.; Fan, W.-Q.; Akutagawa, K. *Tetrahedron* **1986**, *42*, 4027-4034.

methylanthranilate (**1a**) and 4-ethylaniline in 89% yield after purification by crystallization from Et₂O.



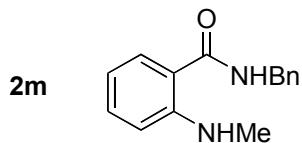
Mp 120-121 °C (Et₂O); ¹H-NMR (CDCl₃) – 1.25 (t, *J*=7.5, 3H), 2.65 (q, *J*= 7.5, 2H), 2.85 (s, 3H), 6.59-6.72 (m, 2H), 7.19 (d, *J*=7.9, 2H), 7.18-7.50 (m, 5H), 7.82 (bs, 1H); ¹³C-NMR (CDCl₃) – 15.6, 28.2, 29.5, 111.1, 114.5, 115.2, 120.8, 127.2, 128.2, 133.1, 135.3, 140.4, 150.6, 168.1; IR (KBr) 3354, 1637 cm⁻¹; MS (EI) *m/z* (%) 254 (M⁺, 27), 134 (100), 121 (48), 106 (25), 77 (21); HRMS calc. for C₁₆H₁₈N₂O 254.1419, found 254.1423.

***N*-(4-bromophenyl)-2-methylaminobenzamide (2k).** According to the general procedure 1 benzamide **2k** was obtained as a white solid from commercially available methyl *N*-methylanthranilate (**1a**) and 4-bromoaniline in 22% yield after purification by crystallization from Et₂O.



Mp 130-132 °C (Et₂O); ¹H-NMR (CDCl₃) – 2.84 (s, 3H), 6.57-6.70 (m, 2H), 7.33-7.49 (m, 7H), 7.89 (bs, 1H); ¹³C-NMR (CDCl₃) – 29.6, 111.3, 114.6, 116.9, 122.0, 127.2, 131.8, 133.4, 136.9, 150.7, 168.1; IR (KBr) 3350, 1637 cm⁻¹; MS (EI) *m/z* (%) 306 (M+2, 12), 304 (M⁺, 11), 134 (100), 91 (14), 79 (13), 77 (27); HRMS calc. for C₁₂H₁₃BrN₂O 304.0211, found 304.0217.

***N*-benzyl-2-methylaminobenzamide (2m).** According to the general procedure 1 benzamide **2m** was obtained as a white solid from commercially available methyl *N*-methylanthranilate (**1a**) and benzylamine in 88% yield after purification by crystallization from Et₂O.



Mp 93-95 °C (Et₂O); ¹H-NMR (CDCl₃) – 2.86 (s, 3H), 4.58 (d, *J*=5.5, 2H), 6.39 (bs, 1H), 6.53-6.70 (m, 2H), 7.30-7.35 (m, 7H), 7.60 (bs, 1H); ¹³C-NMR (CDCl₃) – 29.3, 43.1, 110.7, 114.2, 114.5, 127.0, 127.2, 127.3, 128.3, 132.6, 138.2, 150.3, 169.6; IR (KBr) 3354, 1631 cm⁻¹; MS (EI) *m/z* (%) 240 (M⁺, 61), 134 (34), 132 (32), 106 (100), 91 (39), 77 (25); HRMS calc. for C₁₅H₁₆N₂O 240.1263, found 240.1264.

N-allyl-2-(methylamino)benzamide (2n)⁶. According to the general procedure 1 benzamide **2n** was obtained as a white solid from commercially available methyl *N*-methylantranilate (**1a**) and allylamine in 65% yield after purification by crystallization from Et₂O.



Mp 75-76 °C (Et₂O) (lit.⁶ 70-73 °C); ¹H-NMR (CDCl₃) – 2.85 (s, 3H), 4.01-4.02 (m, 2H), 5.25-5.28 (m, 2H), 5.84-5.99 (m, 1H), 6.16 (bs, 1H), 6.55-6.69 (m, 2H), 7.29-7.36 (m, 2H), 7.53 (bs, 1H); ¹³C-NMR (CDCl₃) – 29.4, 41.7, 110.8, 114.2, 114.7, 115.8, 127.1, 132.5, 134.1, 150.2, 169.6; IR (KBr) 3354, 1631 cm⁻¹; MS (EI) *m/z* (%) 190 (M⁺, 83), 134 (100), 132 (38), 106 (25), 105 (69), 104 (53), 78 (22), 77 (52); HRMS calc. for C₁₁H₁₄N₂O 190.1106, found 190.1109.

N-methoxy-2-methylaminobenzamide (2o) According to the general procedure 1 benzamide **2o** was obtained as a white solid from commercially available methyl *N*-methylantranilate (**1a**) and NH₂OMe·HCl in 18% yield after purification by crystallization from Et₂O.

⁶ Coppola, G. M.; Mansukhani, R. I. *J. Heterocycl. Chem.* **1978**, 15, 1169-1173.



Mp 90-91 °C (Et₂O); ¹H-NMR (CDCl₃) – 2.81 (s, 3H), 3.78 (s, 3H), 6.47-6.86 (m, 2H), 7.29-7.39 (m, 2H), 9.35 (bs, 1H); ¹³C-NMR (CDCl₃) – 29.5, 64.2, 110.9, 111.7, 114.4, 127.3, 133.2, 150.4, 169.0; IR (KBr) 3367, 1637 cm⁻¹; MS (EI) *m/z* (%) 180 (M⁺, 25), 150 (93), 148 (38), 134 (100), 133 (78), 105 (98), 77 (68); HRMS calc. for C₉H₁₂N₂O₂ 180.0899, found 180.0894.

Typical procedure 2 for the synthesis of benzamides 2f-g. Synthesis of 2-ethoxycarbonylamino-N-(4-methoxyphenyl)benzamide (2f). LiOH·H₂O (658 mg, 15.7 mmol) was added to a solution of methyl N-ethoxycarbonylantranilate⁷ (**1f**) (700 mg, 3.14 mmol) in THF/H₂O (50 mL, 4/1). The mixture was stirred at rt until conversion was complete. Then, the solution was treated with HCl (5% aq.) and extracted with Et₂O (3x15 mL). The organic extracts were dried over sodium sulfate and the solvent was evaporated under reduced pressure. The resulting residue, *p*-anisidine (423 mg, 3.44 mmol), and Et₃N (0.6 mL, 4.31 mmol) were dissolved in CH₂Cl₂ (11 mL). Then, the obtained suspension was treated with a solution of EDC·HCl (826 mg, 4.31 mmol) and HOBT (543 mg, 4.02 mmol) in the same solvent (5 mL). The mixture was cooled (0 °C) and Et₃N (0.48 mL, 3.44 mmol) was added dropwise. After stirring for 2 h, temperature was raised to rt and stirring was continued until the conversion was complete. Then, the solution was washed with water, extracted with CH₂Cl₂ (3x15 mL), dried over sodium sulfate, and the solvent was evaporated at reduced pressure. The resulting residue was crystallized from Et₂O to afford benzamide **2f** as a white solid in 85% yield.



Mp 62-63 °C (Et₂O); ¹H-NMR (CDCl₃) – 1.29 (t, *J*= 7.1, 3H), 3.81 (s, 3H), 4.19 (t, *J*= 7.1, 2H), 6.81-7.00 (m, 4H), 7.36-7.55 (m, 4H), 8.25-8.28 (m, 1H), 8.37 (bs, 1H), 10.09

⁷ Schmidt, R. R.; Wagner, A. *Synthesis* **1982**, 958-962.

(bs, 1H); ^{13}C -NMR (CDCl_3) – 14.4, 55.4, 61.1, 114.1, 119.9, 120.7, 121.7, 122.6, 127.0, 130.6, 132.3, 139.4, 154.0, 167.2; IR (KBr) 3308, 1737, 1630 cm^{-1} ; MS (EI) m/z (%) 314 (M^+ , 2), 269 (11), 268 (98), 149 (15), 146 (100), 123 (45), 119 (76), 92 (38), 64 (13); HRMS calc. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_4$ 314.1267, found 314.1276.

N-(4-methoxyphenyl)-2-(methylphenylsulfonyl)benzamide (2g). According to the general procedure 2 benzamide **2g** was obtained as a white solid from methyl *N*-tosylantranilate⁸ (**1g**) in 86% yield after purification by crystallization from Et_2O .



Mp 150-151 °C (Et_2O); ^1H -NMR (CDCl_3) – 2.33 (s, 3H), 3.82 (s, 3H), 6.68-6.93 (m, 3H), 7.09-7.88 (m, 9H), 9.14 (bs, 1H), 10.3 (bs, 1H); ^{13}C -NMR (CD_3COCD_3) – 20.0, 54.3, 113.3, 120.8, 122.3, 123.5, 126.4, 127.6, 128.9, 129.1, 130.7, 131.9, 135.9, 138.2, 143.4, 156.3, 166.3; IR (KBr) 3343, 1643 cm^{-1} ; MS (EI) m/z (%) 396 (M^+ , 16), 123 (100), 92 (20), 91 (30), 65 (12); HRMS calc. for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$ 396.1144, found 396.1148.

⁸ Tsunoda, T.; Tanaka, A.; Mase, T.; Sakamoto, S. *Heterocycles* **2004**, 1113-1122.

