Facile synthesis of 3-amino-5-aryl-1,2,4-oxadiazoles via PIDA-mediated intramolecular oxidative cyclization

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I. General Information

All reagents and solvents were obtained from commercial sources and used without further purification. All solvents were dried with 4Å molecular sieve before use. Reactions were monitored by thin-layer chromatography (TLC) on silica plates (F-254) and visualized under UV light. Melting points were obtained on a Büchi Melting Point B-540 apparatus and were uncorrected. All 1H NMR and 13C NMR spectra were recorded on Bruker ARX-400, 400 MHz spectrometers with TMS as an internal standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, J, are reported in hertz (Hz). HRMS analysis was performed on a Q-TOF mass analyzer using the ESI ionization method.

II. Synthesis of Substrates

Substrates (1a-u, 1x) were synthesized according to the literature methods with minor modifications.1 A representative procedure (synthesis of N-carbamimidoylbenzamide (1a)) is shown below.

![Chemical Structure](image)

Benzoic acid (8 mmol) was dissolved in 10 mL of dichloromethane and two drops of DMF were added. Then, oxalyl chloride (21.6 mmol) were pipetted to this mixture. This mixture was stirred for 2h at room temperature and then refluxed for 3h. After cooling, the solution was concentrated to dryness in vacuum and the residue was taken up in 10 mL of tetrahydrofuran. The solution obtained was slowly added dropwise to a solution of guanidine hydrochloride (36.0 mmol) in 25 mL of sodium hydroxide solution (c = 2 mol/L). The mixture was stirred for 1h at room temperature, the organic phase was separated and the aqueous phase was extracted three times with 30 mL ethyl acetate. The combined organic phases were washed with 50 mL of NaOH (c = 1 mol/L) and subsequently with 100 mL of water. Thereafter, the combined extracts were dried over Na2SO4, filtered and concentrated to give a crude residue. This was purified by flash column chromatography by using a system of dichloromethane/methanol and the desired product 1a was obtained.

Substrate N,N’-(iminomethylene)dibenzamide (1v) was synthesized according to the literature method with minor modifications.2

A solution of guanidine hydrochloride 0.2g (2 mmol) in DMF: dioxane (1:1; 10mL) was added Potassium tert-butoxide 0.45g (4 mmol) and the reaction mixture was heated at 50-55°C for 30 min. The mixture was cooled to room temperature, the solid sodium chloride was filtered and the filtrate was added to the 1-h stirred solution of benzoic acid 0.5g (4.1 mmol) and N,N’-Carbonyldiimidazole 1.3g (8.2 mmol) in DMF (10mL) at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, water (10mL) was added, the solid was collected by filtration and washed with cold water to obtain the product 1v, which was further purified by flash chromatography (silica gel, methanol/dichloromethane 1:10, v/v) Yield:73% (0.4g) white solid, m.p. 160-161°C.1H NMR (400 MHz, DM SO-d6) δH: 12.67 (1 H, s), 9.37 (2 H, s), 8.10 (4 H, d, J = 7.5 Hz), 7.63 (2 H, t, J = 7.2 Hz), 7.54 (4 H, t, J = 7.5 Hz).13C NMR (100 MHz, DM SO-d6) δC: 174.35, 165.23, 164.24, 133.71, 132.99, 132.91, 129.95, 128.88, 128.58, 128.03, 123.68. HRMS (ESI-Q-TOF, m/z) calcld for C13H13N2O2 [M + H]+: 268.1008, found [M + H]+: 268.1010.

Substrates (1y, 1z) were synthesized according to the reference 3

III. General Procedure and Product Characterization

1 General procedure for the preparation of 2a-2y

To a stirring solution of 1a (0.6 mmol) in DMF (3 mL), PIDA (0.9 mmol) was added at 0°C. The resulting reaction mixture was stirred at room temperature for 5-6 h. After completion of the reaction (monitored by TLC), the residue was diluted with ethyl acetate (5 mL). The organic layer was washed with saturated sodium bicarbonate (2 × 3 mL), water (2 × 3 mL) and brine (2 × 3 mL) and dried over anhydrous Na2SO4, filtered and concentrated to yield the crude product, which was further purified by flash chromatography (silica gel, ethyl acetate/petroleum ether triethylamine 1:5:0.1, v/v), affording the desired product 2a.
2. Product Characterization

**5-Phenyl-1,2,4-oxadiazol-3-amine (2a):**

Yield: 69% (68 mg), white solid, m.p.: 164-165°C. 1H NMR (400 MHz, DMSO-d6) δH 8.02–7.97 (2 H, m), 7.67 (1 H, t, J = 7.4 Hz), 7.60 (2 H, t, J = 7.4 Hz), 6.43 (2 H, s). 13C NMR (100 MHz, DMSO-d6) δC 176.0746, 128.74, 128.13, 126.85, 126.82. HRMS (ESI-Q-TOF, m/z) calcd for C8H5N2O [M + H]+: 169.08, found [M + H]+: 169.08.

**5-(2-Bromophenyl)-1,2,4-oxadiazol-3-amine (2b):**

Yield: 74% (73 mg), white solid, m.p. 168-169°C. 1H NMR (400 MHz, DMSO-d6) δH 7.91 (1 H, dd, J = 7.4, 2.1 Hz), 7.87 (1 H, dd, J = 7.6, 1.5 Hz), 7.61–7.54 (2 H, m), 6.51 (2 H, s). 13C NMR (100 MHz, DMSO-d6) δC 170.31, 169.38, 148.81, 134.12, 133.93, 131.35, 125.03, 118.37. HRMS (ESI-Q-TOF, m/z) calcd for C9H4BrN2O [M + H]+: 239.9694, found [M + H]+: 239.9687.

**5-(2-Nitrophenyl)-1,2,4-oxadiazol-3-amine (2c):**

Yield: 77% (76 mg), pale yellow solid, m.p. 199-201°C. 1H NMR (400 MHz, DMSO-d6) δH 8.14 (1 H, dd, J = 5.9, 3.3Hz), 8.04 (1 H, dd, J = 5.5, 3.6 Hz), 7.95–7.89 (2 H, m), 6.59 (2 H, s). 13C NMR (100 MHz, DMSO-d6): δC 161.96, 158.39, 149.32, 132.37, 130.60, 127.69, 117.51, 106.35, 55.53. HRMS (ESI-Q-TOF, m/z) calcd for C9H4N3O3 [M + H]+: 207.0440, found [M + H]+: 207.0451.

**5-(3-Chlorophenyl)-1,2,4-oxadiazol-3-amine (2d):**

Yield: 75% (74 mg), pale yellow solid, m.p. 159-162°C. 1H NMR (400 MHz, DMSO-d6) δH 8.00–7.93 (2 H, m), 7.75 (1 H, d, J = 8.3Hz), 7.64 (1 H, t, J = 7.9 Hz), 6.50 (2 H, s). 13C NMR (100 MHz, DMSO-d6): δC 171.80, 169.08, 134.03, 132.52, 131.51, 126.89, 126.11, 125.98. HRMS (ESI-Q-TOF, m/z) calcd for C9H4ClN3O [M + H]+: 196.0199, found [M + H]+: 196.0194.

**5-(M-tolyl)-1,2,4-oxadiazol-3-amine (2e):**

Yield: 67% (66 mg), white solid, m.p. 146-148°C. 1H NMR (400 MHz, DMSO-d6): δH 7.81 (1 H, s), 7.80 – 7.76 (1 H, m), 7.48 (2 H, d, J = 5.0 Hz), 6.40 (2 H, s), 2.40 (3 H, s). 13C NMR (100 MHz, DMSO-d6): δC 173.55, 169.44, 139.32, 133.75, 129.75, 128.15, 124.99, 124.49, 21.28. HRMS (ESI-Q-TOF, m/z) calcd for C9H8N2O [M + H]+: 176.0746, found [M + H]+: 176.0757.

**5-(4-(Trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-amine (2f):**

Yield: 78% (77 mg), pale yellow solid, m.p. 186-188°C. 1H NMR (400 MHz, DMSO-d6): δH 8.20 (2 H, d, J = 8.2 Hz), 7.98 (2 H, d, J = 8.2 Hz), 6.55 (2 H, s). 13C NMR (100MHz, DMSO-d6): δC 172.24, 169.59, 132.40, 128.74, 128.13, 126.85, 126.82. HRMS (ESI-Q-TOF, m/z) calcd for C9H6F3N3O [M + H]+: 230.0463, found [M + H]+: 230.0458.
5-(4-Chlorophenyl)-1,2,4-oxadiazol-3-amine (2g):
Yield: 72% (71 mg), pale yellow solid, m.p. 224-226°C. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta_H 8.00\) (2 H, d, \(J=8.6\) Hz), 7.67 (2 H, d, \(J=8.6\) Hz), 6.46 (2 H, s). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta_C 172.36, 169.26, 137.69, 129.81, 129.41, 123.14\). HRMS (ESI-Q-TOF, m/z) calcd for C\(_9\)H\(_8\)ClN\(_3\)O [M + H]+: 196.0199, found [M + H]+: 196.0187.

5-(4-Methoxyphenyl)-1,2,4-oxadiazol-3-amine (2l):
Yield: 62% (61 mg), pale yellow solid, m.p. 155-158°C. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta_H 7.93\) (2 H, d, \(J=8.9\) Hz), 7.13 (2 H, d, \(J=8.9\) Hz), 6.33 (2 H, s), 3.85 (3 H, s). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta_C 173.00, 169.05, 162.68, 129.44, 116.66, 114.93, 55.75\). HRMS (ESI-Q-TOF, m/z) calcd for C\(_9\)H\(_8\)NO\(_2\) [M + H]+: 192.0695, found [M + H]+: 192.0691.

5-(3,4-Dimethoxyphenyl)-1,2,4-oxadiazol-3-amine (2j):
Yield: 57% (56 mg), yellow solid, m.p. 163-165°C. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta_H 7.56\) (1 H, d, \(J=8.4\) Hz), 7.43 (1 H, s), 7.12 (1 H, d, \(J=8.4\) Hz), 6.31 (2 H, s), 3.81 (6 H, s). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta_C 173.44, 169.36, 152.80, 149.37, 121.50, 116.85, 112.36, 110.32, 56.21, 56.02\). HRMS (ESI-Q-TOF, m/z) calcd for C\(_{10}\)H\(_{11}\)N\(_3\)O\(_3\) [M + H]+: 222.0800, found [M + H]+: 222.0809.

5-(3-Methoxy-4-methyl phenyl)-1,2,4-oxadiazol-3-amine (2k):
Yield: 66% (65 mg), pale yellow solid, m.p. 133-136°C. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta_H 7.50\) (1 H, d, \(J=7.8\) Hz), 7.45 (1 H, s), 7.36 (1 H, d, \(J=7.8\) Hz), 6.40 (2 H, s), 3.88 (3 H, s), 2.23 (3 H, s). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta_C 173.50, 169.35, 157.99, 131.60, 131.57, 123.30, 119.90, 108.83, 55.84, 16.62\). HRMS (ESI-Q-TOF, m/z) calcd for C\(_{10}\)H\(_{11}\)N\(_3\)O\(_2\) [M + H]+: 206.0851, found [M + H]+: 206.0846.

5-(5-Methoxy-2-nitrophenyl)-1,2,4-oxadiazol-3-amine (2l):
Yield: 73% (72 mg), yellow solid, m.p. 140-143°C. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta_H 8.20\) (1 H, d, \(J=9.1\) Hz), 7.44 (1 H, d, \(J=2.8\) Hz), 7.39 (1 H, dd, \(J=9.1, 2.8\) Hz), 6.55 (2 H, s), 3.95 (3 H, s). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta_C 170.90, 169.24, 163.21, 141.32, 128.00, 122.16, 118.16, 116.79, 57.12\). HRMS (ESI-Q-TOF, m/z) calcd for C\(_9\)H\(_8\)NO\(_4\) [M + H]+: 237.0546, found [M + H]+: 237.0538.
5-(3-Methyl-2-nitrophenyl)-1,2,4-oxadiazol-3-amine (2m):
Yield: 75% (74 mg), white solid, m.p. 172-175°C. 1H NMR (400 MHz, DMSO-d6): δH 7.98 (1 H, d, J= 7.5 Hz), 7.80 (1 H, d, J= 7.4 Hz), 7.73 (1 H, t, J= 7.7 Hz), 6.58 (1 H, s), 4.14 (1 H, s), 2.34 (3 H, s). 13C NMR (100MHz, DMSO-d6): δC 169.41, 148.95, 136.33, 131.75, 131.10, 128.21, 116.27, 16.92. HRMS (ESI-Q-TOF, m/z) calcld for C10H9N2O3 [M +H]+: 221.0596, found [M +H]+: 221.0606.

5-(2,4-Difluorophenyl)-1,2,4-oxadiazol-3-amine (2n):
Yield: 77% (76 mg), pale yellow solid, m.p. 163-165°C. 1H NMR (400 MHz, DMSO-d6): δH 8.09 (1 H, dd, J= 15.1, 8.6 Hz), 7.62 - 7.54 (1 H, m), 7.34 (1 H, dd, J= 10.5, 8.6 Hz), 6.52 (2 H, s). 13C NMR (100MHz, DMSO-d6): δC 169.45, 169.02, 164.99, 160.74, 132.42, 113.23, 109.62, 106.06. HRMS (ESI-Q-TOF, m/z) calcld for C14H8F2N3O [M +H]+: 198.0401, found [M +H]+: 198.0400.

5-(3-Fluoro-4-methylphenyl)-1,2,4-oxadiazol-3-amine (2o):
Yield: 75% (74 mg), pale grey solid, m.p. 170-173°C. 1H NMR (400 MHz, DMSO-d6): δH 7.71 (1 H, d, J= 7.9 Hz), 7.66 (1 H, d, J= 10.0 Hz), 7.51 (1 H, t, J= 7.8 Hz), 6.43 (2 H, s), 2.31 (3 H, s). 13C NMR (100 MHz, DMSO-d6): δC 172.50, 169.45, 162.25, 159.82, 133.25, 130.22, 123.84, 114.20, 14.86. HRMS (ESI-Q-TOF, m/z) calcld for C12H9FN2O [M +H]+: 194.0651, found [M +H]+: 194.0646.

5-(5-Bromo-2-chlorophenyl)-1,2,4-oxadiazol-3-amine (2p):
Yield: 72% (71 mg), white solid, m.p., 174-177°C. 1H NMR (400 MHz, DMSO-d6): δH 8.13 (1 H, d, J= 2.4 Hz), 7.86 (1 H, d, J= 8.6, 2.4 Hz), 7.66 (1 H, d, J= 8.6 Hz), 6.57 (2 H, s). 13C NMR (100 MHz, DMSO-d6): δC 170.79, 169.20, 136.64, 134.13, 133.60, 131.82, 125.70, 120.75. HRMS (ESI-Q-TOF, m/z) calcld for C13H9BrClN2O [M +H]+: 273.9305, found [M +H]+: 273.9314.

5-(2,4,5-Trifluorophenyl)-1,2,4-oxadiazol-3-amine (2q):
Yield: 79% (78 mg), pale yellow solid, m.p. 165-167°C. 1H NMR (400 MHz, DMSO-d6): δH 8.08 (1 H, d, J= 15.5, 10.4 Hz), 7.90 (1 H, d, J= 17.2, 10.6 Hz), 6.56 (2 H, s). 13C NMR (100 MHz, DMSO-d6): δC 169.32, 168.78, 118.57, 118.47, 108.85, 108.63, 108.57, 108.35. HRMS (ESI-Q-TOF, m/z) calcld for C10H7F3N2O [M +H]+: 216.0306, found [M +H]+: 216.0308.

5-(3,4,5-Trimethoxyphenyl)-1,2,4-oxadiazol-3-amine (2r):
Yield: 52% (51 mg), pale yellow solid, m.p. 201-203°C. 1H NMR (400 MHz, DMSO-d6): δH 2.25 (2 H, s), 6.40 (2 H, s), 3.86 (6 H, s), 3.74 (3 H, s). 13C NMR (100 MHz, DMSO-d6): δC 173.29, 169.43, 153.76, 141.67, 119.66, 105.09, 60.68, 56.53. HRMS (ESI-Q-TOF, m/z) calcld for C15H12N2O4 [M +H]+ 252.0906, found [M +H]+: 252.0914.
5-(6-Bromonaphthalen-2-yl)-1,2,4-oxadiazol-3-amine (2s):

Yield: 55% (54 mg), white solid, m.p. 235-238°C. 1H NMR (400 MHz, DMSO-d6): δH 8.69 (1 H, s), 8.36 (1 H, s), 8.14 (1 H, d, J = 8.9 Hz), 8.12 – 8.05 (2 H, m), 7.79 (1 H, dd, J = 8.7, 2.0 Hz), 6.48 (2 H, s). 13C NMR (100 MHz, DMSO-d6): δC 173.45, 169.73, 136.18, 131.90, 131.55, 130.97, 130.48, 129.02, 128.81, 125.18, 122.56, 122.49. HRMS (ESI-Q-TOF, m/z) calcd for C15H13BrN3O [M + H]+: 289.9851, found [M + H]+: 289.9856.

5-(Furan-2-yl)-1,2,4-oxadiazol-3-amine (2t):

Yield: 59% (58 mg), white solid, m.p. 147-150°C. 1H NMR (400 MHz, DMSO-d6): δH 8.07 (1 H, d, J = 1.8 Hz), 7.38 (1 H, d, J = 3.5 Hz), 6.79 (1 H, dd, J = 3.5, 1.8 Hz), 6.44 (2 H, s). 13C NMR (100 MHz, DMSO-d6): δC 169.32, 165.77, 148.12, 140.22, 116.69, 113.34. HRMS (ESI-Q-TOF, m/z) calcd for C14H7N2O [M + H]+: 212.0382, found [M + H]+: 212.0378.

5-(Pyridin-3-yl)-1,2,4-oxadiazol-3-amine (2u):

Yield: 62% (61 mg), pale yellow solid, m.p. 176-179°C. 1H NMR (400 MHz, DMSO-d6): δH 9.13 (1 H, s), 8.81 (1 H, d, J = 4.8 Hz), 8.33 (1 H, d, J = 8.0 Hz), 7.62 (1 H, dd, J = 8.0, 4.8 Hz), 6.51 (2 H, s). 13C NMR (100 MHz, DMSO-d6): δC 171.76, 169.47, 153.53, 148.45, 135.44, 124.85, 120.99. HRMS (ESI-Q-TOF, m/z) calcd for C15H7N2O [M + H]+: 266.0851, found [M + H]+: 266.0849.

N-(5-phenyl-1,2,4-oxadiazol-3-yl)benzamide (2v):

Yield: 78% (77 mg), white solid, m.p. 205-206°C. 1H NMR (400 MHz, DMSO-d6): δH 11.69 (1 H, s), 8.15 – 8.10 (2 H, m), 8.08 – 8.03 (2 H, m), 7.75 (1 H, t, J = 7.4 Hz), 7.66 (3 H, dd, J = 15.3, 7.6 Hz), 7.55 (2 H, t, J = 7.6 Hz). 13C NMR (100 MHz, DMSO-d6): δC 173.94, 164.82, 163.84, 133.30, 132.58, 132.50, 129.55, 128.47, 128.17, 127.62, 123.28. HRMS (ESI-Q-TOF, m/z) calcd for C16H11N3O [M + H]+: 293.0849.

N-methyl-5-phenyl-1,2,4-oxadiazol-3-amine (2w):

Yield: 57% (56 mg), white solid, m.p. 111-112°C. 1H NMR (400 MHz, DMSO-d6): δH 8.00 (2 H, d, J = 7.3 Hz), 7.67 (1 H, t, J = 7.3 Hz), 7.60 (2 H, t, J = 7.3 Hz), 6.89 (1 H, q, J = 4.7 Hz), 2.76 (3 H, d, J = 1.7 Hz). 13C NMR (100 MHz, DMSO-d6): δC 173.48, 170.09, 133.12, 129.79, 127.82, 124.49, 29.54. HRMS (ESI-Q-TOF, m/z) calcd for C16H11N3O [M + H]+: 266.0746 found [M + H]+: 266.0783.

N,N-di-phenyl-1,2,4-oxadiazol-3-amine (2x):

Yield: 42% (41 mg), white solid, m.p. 129-130°C. 1H NMR (400 MHz, DMSO-d6): δH 10.06 (1 H, s), 8.08 (2 H, d, J = 8.5 Hz), 7.72 (1 H, t, J = 7.4 Hz), 7.65 (2 H, t, J = 8.0 Hz), 7.52 (2 H, d, J = 8.5 Hz), 7.34 (2 H, t, J = 8.0 Hz), 6.97 (1 H, t, J = 7.3 Hz). 13C NMR (100 MHz, DMSO-d6): δC 172.58, 165.46, 139.84, 133.03, 129.43, 128.90, 127.53, 123.51, 121.01, 116.93. HRMS (ESI-Q-TOF, m/z) calcd for C17H12N3O [M + H]+: 238.0902 found [M + H]+: 238.0945.
**N-benzyl-5-phenyl-1,2,4-oxadiazol-3-amine (2y)**

Yield: 63% (62 mg), white solid, m.p. 111-112°C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ 8.02 – 7.97 (2 H, m), 7.67 (1 H, t, $J=7.4$ Hz), 7.63 – 7.57 (3 H, m), 7.39 – 7.31 (4 H, m), 7.25 (1 H, t, $J=6.9$ Hz), 4.35 (2 H, d, $J=6.9$ Hz) $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta_C$ 173.57, 169.43, 139.69, 133.17, 129.80, 128.66, 127.83, 127.70, 127.29, 124.40, 46.48. HRMS (ESI-Q-TOF, m/z) calcd for C$_{15}$H$_{13}$N$_3$O [M + H]$^+$: 252.1059 found [M + H]$^+$ 252.1068

**IV. References**


V. Copies of $^1$H NMR and $^{13}$C NMR Spectra