A Practical, Metal-Free Synthesis of 1*H*-Indazoles

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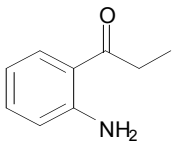
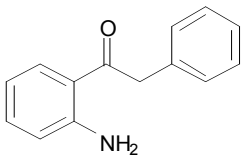
Materials and Methods. Unless stated otherwise, reactions were conducted in oven-dried glassware under an atmosphere of nitrogen using anhydrous solvents. Triethylamine was freshly distilled over CaH_2, and dichloromethane and tetrahydrofuran were passed through activated alumina columns. All other commercially obtained reagents and solvents were used as received. *o*-Aminobenzaldehyde[1] and *N*-(2-acetylphenyl)-4-methylbenzensulfonamide[2] were prepared according to known literature procedures. Thin-layer chromatography (TLC) was conducted with Sorbent Technologies silica gel UV254 pre-coated plates (0.25mm), and visualized using UV lamps. Sorbent Technologies (particle size 40-63 μm) silica gel was used for flash chromatography. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker spectrometers and are reported relative to deuterated solvent signals. IR spectra were recorded on a Perkin Elmer 1600 FT-IR spectrometer. High resolution mass spectra were obtained from the mass spectrometry facility at The Ohio State University. Elemental analyses were carried out at Robertson Microlit Laboratories, Madison, NJ.

Experimental Procedures

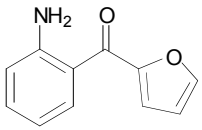


1-(2-aminophenyl)propan-1-one (1). The ketone was prepared by slight modification of a literature procedure.[2] Ethylmagnesium chloride (23.6 mL, 47.3 mmol) was added to a solution of 2-aminobenzonitrile (2.003 g, 16.94 mmol) in THF (7.0 mL) at 0 ˚C over 30 min. The reaction was warmed to ambient temperature and allowed to stir at this temperature for 6 h. The reaction was quenched at 0 °C by slow addition of 10% HCl. The reaction was cooled to 0 °C and made basic by the addition of NaOH. The organic layer was separated and the remaining aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified via flash chromatography (10% EtOAc/hexanes) to give 51.8% of the ketone (1.308 g, 8.767 mmol) as a yellow solid. Spectroscopic data for this compound matched the previously reported literature values.[3]



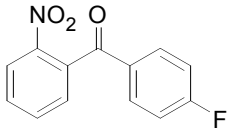
1-(2-aminophenyl)-2-phenylethanone (2). The ketone was prepared by slight modification of a literature procedure.[2] To a stirring suspension of Mg (1.222 g, 50.25 mmol) in THF (33 mL) at 0 ˚C, was added a solution of benzyl bromide (5.7 mL, 47 mmol) in THF (32 mL). The reaction was warmed to ambient temperature and allowed to stir for 1 h. After this time, the Grignard reagent was cooled to 0 ˚C and 2-aminobenzonitrile (2.005 g, 17.35 mmol) in THF (33 mL) was

added dropwise. After this time, the reaction was allowed to stir at ambient temperature for 4 h. The reaction was quenched at 0 ˚C by slow addition of NaOH. The organic layer was separated and the remaining aqueous layer was extracted with Et_2O (3 X 150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified via flash chromatography (10% EtOAc/hexanes) to give 31.2% of the ketone (1.120 g, 5.302 mmol) as a yellow solid. Spectroscopic data for this compound matched the previously reported literature values.[4]



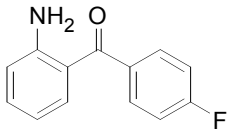
(2-aminophenyl)(furan-2-yl)methanone (3). The ketone was prepared according to a modified literature procedure.[5] Furan (8.5 mL, 0.12 mol) was dissolved in THF (46 mL) and the reaction was cooled to -78 ˚C. n-BuLi (80 mL, 0.13 mol) was added and the reaction was warmed to 0 ˚C and allowed to stir for 2 h at this temperature. During this time, anthranilic acid (4.001 g, 29.17 mmol), LiH (350 mg, 44.0 mmol), and THF (20 mL) were combined in the glovebox. The reaction was removed from the glovebox and refluxed for 30 min. After this time, the reaction was cooled to ambient temperature and the furyl lithium reagent was added via canula. The reaction was allowed to stand (unstirred) for 20 h. The reaction was then poured onto ice-water with the aid of Et_2O, saturated with ammonium chloride, and the phases were separated. The organic phase was dried over $MgSO_4$, concentrated, and purified via flash chromatography (20% EtOAc/hexanes) to give 72.1% of the ketone (3.935 g, 21.02 mmol) as a yellow-orange oil. ^{1}H NMR (500 MHz, $CDCl_3$): 5.88 (bs, 2H), 6.54-6.55 (m, 1H), 6.67-6.71 (m, 2H), 7.13 (d, J = 5.0 Hz, 1H), 7.26-7.30 (m, 1H), 7.64-7.65 (m, 1H), 7.90 (dd, J = 1.5, 10 Hz, 1H); ^{13}C NMR (125

MHz, $CDCl_3$): 111.9, 116.0, 117.0, 118.3, 119.4, 132.2, 134.0, 146.3, 150.5, 152.7, 183.8; IR (DCM): 3463, 3557, 1619; HRMS (ESI): calcd for $C_{11}H_9NO_2$ $[M+Na]^+$: 210.0531, found 210.0513.

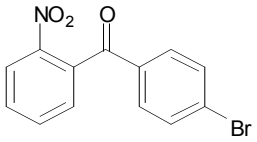


((4-fluorophenyl)(2-nitrophenyl)methanone (4). The ketone was prepared by slight modification of a literature procedure.[6] Under nitrogen, a suspension of *o*-nitrobenzoic acid (5.004 g, 29.94 mmol) in DCM (105 mL) and anhydrous DMF (0.1 mL) were cooled to 0 ºC and oxalyl chloride (5.2 mL, 60 mmol) was added slowly. The mixture was stirred at 0 °C for 30 min, then ambient temperature for 30 min until the reaction became clear. The reaction was then concentrated to leave the crude acid chloride as a light yellow oil, which was directly used in the next step without further purification. This oil was dissolved in 1,2-dichloroethane (11.6 mL) and fluorobenzene (4.5 mL, 48 mmol) and cooled to 0 ºC. Iron (III) chloride (5.35 g, 33.0 mmol) was added to this solution in 3 portions over 30 min, and the reaction was stirred at 0 ºC for 1 h, then poured onto ice-water (60 mL). The solution was heated at 95 ºC to remove 1,2-dichloroethane, then allowed to reach 75 ºC. Isobutanol (20 mL) was added and the hot solution was washed with water (3 x 50 mL). The product precipitated upon cooling to ambient temperature. The precipitate was collected and washed with water to give 85.7% of the ketone (6.294 g, 25.67 mmol) as a light brown solid that was judged to be >90% pure by ^{1}H NMR spectroscopy. An analytically pure sample of this compound as a white solid was obtained by filtering through a plug of silica. ^{1}H NMR (500 MHz, $CDCl_3$): 7.08-7.12 (m, 2H), 7.46 (dd, J = 1.5, 7.5 Hz, 1H), 7.65-7.69 (m, 1H), 7.74-7.79 (m, 3H), 8.21 (dd, J = 1.0, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 116.1 (d, $J_{C\text{-}F}$ = 22 Hz), 124.6, 128.8, 130.8, 131.9 (d, $J_{C\text{-}F}$ = 9.6 Hz), 132.5

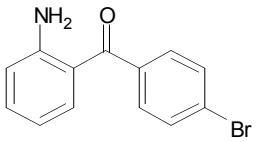
(d, $J_{C\text{-}F}$ = 2.8 Hz), 134.3, 135.8, 146.6, 166.1 (d, $J_{C\text{-}F}$ = 255 Hz), 192.0; ^{19}F NMR(376 MHz, $CDCl_3$): -104.5; IR (DCM): 1674, 1531, 1347; HRMS (ESI): calcd for $C_{13}H_8FNO_3$ $[M+Na]^+$: 268.0386, found 268.0376.



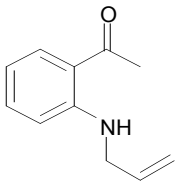
(2-aminophenyl)(4-fluorophenyl)methanone (5). The ketone was prepared by slight modification of a literature procedure.[7] Iron powder (13.758 g, 2.4634 mol), (4-fluorophenyl)(2-nitrophenyl) methanone (6.038 g, 24.62 mmol), AcOH (48 mL), water (68.5 mL), and EtOAc (14 mL) were refluxed for 1.5 h. After this time, 100 mL ethyl acetate was added and the aqueous layer was separated. The organic layer was washed with water, 10% aqueous $NaHCO_3$ solution, and an additional amount of water. The organic layer was dried over Na_2SO_4, and concentrated to give a yellow residue, which was purified via filtration through a plug of silica to give 88.7% of the ketone (4.700 g, 21.84 mmol) as a light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): 6.01 (bs, 2H), 6.60-6.63 (m, 1H), 6.74 (d, J = 8.0 Hz, 1H), 7.11-7.16 (m, 2H), 7.28-7.32 (m, 1H), 7.41 (dd, J = 1.5, 8.0 Hz, 1H), 7.66-7.69 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 115.3 (d, $J_{C\text{-}F}$ = 22 Hz), 115.8, 117.2, 118.3, 131.8 (d, $J_{C\text{-}F}$ = 8.9 Hz), 134.3, 134.4, 136.3 (d, $J_{C\text{-}F}$ = 2.8 Hz), 151.0, 164.7 (d, $J_{C\text{-}F}$ = 251 Hz), 197.7; ^{19}F NMR (376 MHz, $CDCl_3$): -108.2; IR (DCM): 3440, 3326, 1633; HRMS (ESI): calcd for $C_{13}H_{10}FNO$ $[M+Na]^+$: 238.0644, found 238.0643.



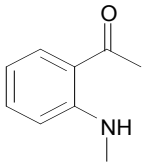
(2-nitrophenyl)(4-bromophenyl)methanone (6). This reaction was performed according to the procedure for (2-nitrophenyl)(4-fluorophenyl)methanone with 10.041 g (60.083 mmol) of *o*-nitrobenzoic acid. During the addition of isobutanol and water, the product precipitated and was collected and washed with water to give 34.2% of the ketone (6.288 g, 20.54 mmol) as a dark brown solid that was judged to be >90% pure by ^{1}H NMR spectroscopy. An analytically pure sample of this compound as a white solid was obtained via filtration through a plug of silica. ^{1}H NMR (500 MHz, $CDCl_3$): 7.48 (dd, J = 1.5, 7.5 Hz, 1H), 7.58-7.63 (m, 4H), 7.68-7.71 (m, 1H), 7.80 (ddd, J = 1.0, 7.5, 7.5 Hz, 1H), 8.24 (dd, J = 1, 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 124.7, 128.9, 129.3, 130.7, 130.9, 132.3, 134.4, 134.9, 135.8, 146.8, 192.5; IR (DCM): 1674, 1529, 1348, HRMS (ESI): calcd for $C_{13}H_8BrNO_3$ $[M+Na]^+$: 327.9585, found 327.9576.



(2-aminophenyl)(4-bromophenyl)methanone (7). This reaction was performed according to the procedure for (2-aminophenyl)(4-fluorophenyl)methanone with 6.122 g (20.00 mmol) of (2-nitrophenyl)(4-bromophenyl)methanone. The crude product was filtered through a plug of silica to give 77.9% of the ketone (4.302 g, 15.58 mmol) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): 6.08 (bs, 2H), 6.59-6.62 (m, 1H), 6.74 (d, J = 8.0 Hz, 1H), 7.28-7.32 (m, 1H), 7.39 (dd, J = 1.5, 8.5 Hz, 1H), 7.50-7.53 (m, 2H), 7.60-7.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 115.8, 117.3, 117.9, 125.9, 130.9, 131.5, 134.4, 134.6, 139.0, 151.1, 197.9; IR (DCM): 3480, 3354, 1615; HRMS (ESI): calcd for $C_{13}H_{10}BrNO$ $[M+Na]^+$: 297.9843, found 297.9816.



1-(2-(allylamino)phenyl)ethanone (8). The ketone was prepared by slight modification of a literature procedure.[8] Potassium carbonate (4.910 g, 35.53 mmol) was added to a solution of 2'-aminoacetophenone (2.0 mL, 14.8 mmol) in DMF (37 mL). The reaction was stirred at ambient temperature for 30 min. Allyl bromide (1.28 mL, 14.8 mmol) was added dropwise to this solution and the reaction was heated at 80 °C for 18 h. The reaction was quenched with water and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified via flash chromatography (10% EtOAc/hexanes) to give 28.7% of the ketone (744 mg, 4.25 mmol) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): 2.58 (s, 3H), 3.86-3.89 (m, 2H), 5.16-5.19 (m, 1H), 5.26-5.30 (m, 1H), 5.90-5.97 (m, 1H), 6.57-6.61 (m, 1H), 6.67 (d, *J* = 8.8, 1H), 7.31-7.35 (m, 1H), 7.74 (dd, *J* = 1.2, 6.8, 1H), 9.02 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 28.0, 45.0, 112.0, 114.2, 116.1, 117.7, 132.7, 134.4, 134.9, 150.9, 200.9; IR (DCM): 3308, 1637.

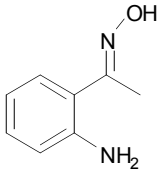


1-(2-(methylamino)phenyl)ethanone (9). The reaction was performed according to the procedure for 1-(2-(allylamino)phenyl)ethanone with 1.5 mL (24 mmol) of iodomethane. The crude product was purified via flash chromatography (10% EtOAc/hexanes) to give 31.7% of the ketone (1.152 g, 7.722 mmol) as a yellow solid. Spectroscopic data for this compound matched the previously reported literature values.[9]

General Procedures for the Synthesis of Oximes.

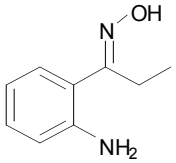
Method A. The oxime was prepared according to a modified literature procedure.[10] The corresponding ketone (1 equiv), 4 equiv of hydroxylamine hydrochloride, and 11 equiv of pyridine were added to methanol (0.3 M). The reaction was heated at reflux until complete consumption of the starting material was observed by TLC. After this time, the reaction was concentrated in vacuo, water was added, and the mixture was re-concentrated. The crude product was dissolved in EtOAc, washed twice with water, dried over Na_2SO_4, and concentrated. The crude oxime was purified via crystallization or flash chromatography.

Method B. The oxime was prepared according to a modified literature procedure.[11] The ketone (1 equiv) was dissolved in a 15% (v/v) solution of H_2O/EtOH (0.69 M). Hydroxylamine hydrochloride (3 equiv) was added followed by the addition of NaOH (8 equiv). The reaction was allowed to stir at 60 ˚C until complete consumption of the starting material was observed by TLC. The bulk of the ethanol was removed in vacuo and water was added. The crude product was extracted with EtOAc (3 X 75 mL), dried over Na_2SO_4, and concentrated. The crude oxime was purified via crystallization or flash chromatography.

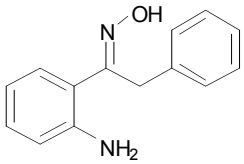


2'-aminoacetophenone oxime (10). The reaction was performed according to Method B with 0.50 mL (4.1 mmol) of 2'-aminoacetophenone to give the 80.2% of the oxime (495 mg, 3.30 mmol) as a white solid. ^{1}H NMR (400 MHz, DMSO): 2.17 (s, 3H), 6.36 (s, 2H), 6.54 (t, J = 7.6 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 7.01 (t, J = 7.2 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 10.97 (s, 1H);

^{13}C NMR (100 MHz, DMSO): 12.6, 115.5, 116.1, 118.2, 128.9, 129.2, 147.2, 156.4; IR (DCM): 3404, 3248, 1615; HRMS (ESI): calcd for $C_8H_{10}N_2O$ $[M+Na]^+$: 173.0691, found 173.0674.

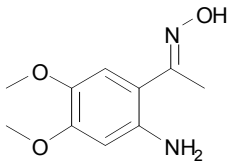


1-(2-aminophenyl)propan-1-one oxime (11). The reaction was performed according to Method B with 4.489 g (30.09 mmol) of 1-(2-aminophenyl)propan-1-one. The reaction was purified via flash chromatography (10% EtOAc/hexanes, 1% Et_3N) to give 47.7% of the oxime (2.356 g, 14.35 mmol) as an off-white solid. ^{1}H NMR (400 MHz, DMSO): 1.05 (t, *J*= 7.5 Hz, 3H), 2.72 (q, *J*= 7.6 Hz, 2 H), 6.32 (s, 2H), 6.53-6.57 (m, 1H), 6.68 (dd, *J*= 0.8, 9.2 Hz, 1H), 6.99-7.03 (m, 1H), 7.27 (dd, *J*= 1.6, 6.4 Hz, 1H), 10.88 (s, 1H); ^{13}C NMR (100 MHz, DMSO): 11.8, 19.2, 115.6, 116.2, 116.8, 128.6, 129.2, 147.7, 161.2; IR (KBr): 3358, 3250, 1622; HRMS (ESI): calcd for $C_9H_{12}N_2ONa$ $[M+Na]^+$: 187.8047, found 187.0862.

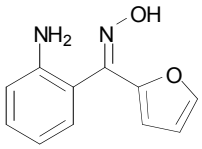


1-(2-aminophenyl)-2-phenylethanone oxime (12). The reaction was performed according to Method B with 720 mg (3.41 mmol) of 1-(2-aminophenyl)-2-phenylethanone. The crude oxime was purified via flash chromatography (10% EtOAc/hexanes, 1% Et_3N) to give 55.5% of the oxime (429 mg, 1.90 mmol) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO): 4.17 (s, 2H), 6.43-6.47 (m, 3H), 6.67 (d, *J*= 8.1 Hz, 1H), 6.96 (t, *J*= 9.2 Hz, 1H), 7.16 (t, *J*= 7.2 Hz, 1H), 7.20-7.27 (m, 5H), 11.18(s, 1H); ^{13}C NMR (100 MHz, DMSO): 31.4, 115.4, 116.2, 116.7, 126.4,

128.7, 128.9, 129.1, 129.2, 138.2, 147.8, 158.2; IR (KBr): 3396, 3233, 1600; HRMS (ESI): calcd for $C_{14}H_{14}N_2ONa$ $[M+Na]^+$ 249.1004, found 249.0986.

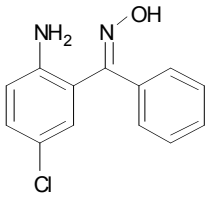


1-(2-amino-4,5-dimethoxyphenyl)ethanone oxime (13). The reaction was performed according to Method B with 1.003 g (5.138 mmol) of 2-amino-4,5-dimethoxyacetophenone to give 68.3% of the oxime (738 mg, 3.51 mmol) as a tan solid. ^{1}H NMR (500 MHz, DMSO): 2.14 (s, 3H), 3.64 (s, 3H), 3.69 (s, 3H), 6.10 (s, 2H), 6.32 (s, 1H), 6.82 (s, 1H), 10.70 (s, 1H); ^{13}C NMR (125 MHz, DMSO): 12.7, 55.6, 57.4, 100.4, 109.8, 114.6, 139.8, 142.9, 150.7, 156.0; IR (KBr): 3474, 3442, 3314, 1603, 1560, 1518, 1459; HRMS (ESI): calcd for $C_{10}H_{14}N_2O_3Na$ $[M+Na]^+$: 233.0902, found 233.0894.

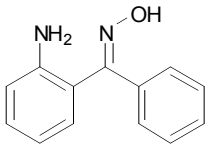


(2-aminophenyl)(furan-2-yl)methanone oxime (14). The reaction was performed according to Method A with 3.300 g (17.63 mmol) of (2-aminophenyl)(furan-2-yl)methanone. The reaction produced 51.1% of the oxime (1.817 g, 8.986 mmol) as a mixture of isomers. The oxime was purified via flash chromatography (2:1 EtOAc/hexanes, 1% Et_3N) to give the anti isomer as a tan solid. ^{1}H NMR (500 MHz, DMSO): 5.05 (s, 2H), 6.57 (t, J = 7.5 Hz, 1H), 6.63-6.64 (m, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 3.5 Hz, 1H), 7.68 (s, 1H), 11.76 (s, 1H); ^{13}C NMR (125 MHz, DMSO): 112.2, 115.8, 116.1, 117.7,

119.1, 129.6, 131.0, 143.4, 145.4, 145.7, 147.2; IR (DCM): 3272, 1608; HRMS (ESI): calcd for $C_{10}H_{10}N_2O_2Na$ $[M+Na]^+$: 225.0640, found 225.0634.

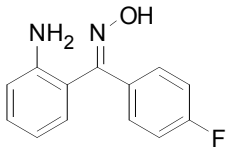


(2-amino-5-chlorophenyl)(phenyl)methanone oxime (15). The reaction was performed according to Method A with 5.013 g (21.64 mmol) of (2-amino-5-chlorophenyl)(phenyl)methanone. The reaction produced 72.9% of the oxime (3.890, 15.77 mmol) as a mixture of isomers. The oxime was crystallized with Et_2O/hexanes to remove the syn isomer followed by flash chromatography (30% EtOAc/hexanes) to give the anti isomer as a light yellow solid. ^1H NMR (500 MHz, DMSO): 6.48 (d, J = 2 Hz, 1H), 6.65 (bs, 2H), 6.78 (d, J = 8.5 Hz, 1H), 7.04 (dd, J = 2, 8.5 Hz, 1H), 7.22 (d, J = 8 Hz, 2H), 7.41-7.49 (m, 3H), 11.18 (s, 1H); ^{13}C NMR (125 MHz, DMSO): 117.2, 117.7, 118.3, 128.3, 128.3, 128.4, 128.6, 129.4, 133.7, 146.3, 157.5; IR (DCM): 3394, 1614; HRMS (ESI): calcd for $C_{13}H_{11}ClN_2O$ $[M+Na]^+$: 269.0458, found 269.0437.

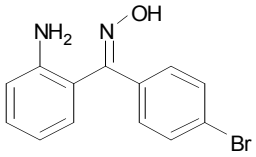


2-aminobenzophenone oxime (16). The reaction was performed according to Method A with 5.016 g (25.43 mmol) of 2-aminobenzophenone. The reaction produced 63.1% of the oxime (3.405 g, 16.04 mmol) as a mixture of isomers. The oxime was purified via flash chromatography (30% EtOAc/hexanes, 1% Et_3N) to give the anti isomer a light yellow solid.

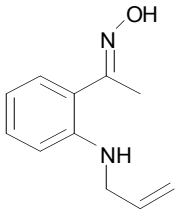
^{1}H NMR (500 MHz, DMSO): 6.35-6.38 (m, 1H), 6.48 (bs, 2H), 6.54 (dd, J = 1, 8 Hz, 1H), 6.74 (d, J = 8 Hz, 1H), 6.98-7.01 (m, 1H), 7.19 (dd, J = 1, 8 Hz, 2H), 7.37-7.45 (m, 3H), 10.94 (s, 1H); ^{13}C NMR (125 MHz, DMSO): 115.1, 116.0, 117.6, 128.4, 128.6, 129.0, 129.4, 131.2, 135.0, 147.9, 159.1; IR (KBr): 3474, 3378, 1603, 1555, 1486, 1443, 1374; HRMS (ESI): calcd for $C_{13}H_{12}N_2ONa$ $[M+Na]^+$: 235.0847, found 235.0841.



(2-aminophenyl)(4-fluorophenyl)methanone oxime (17). The reaction was performed according to Method A with 4.610 g (21.42 mmol) of (2-aminophenyl)(4-fluorophenyl)methanone. During the concentration of the excess pyridine, the product precipitated out of solution. The water was decanted off and crude solid was extracted with Et_2O, washed with water, dried with $MgSO_4$, and concentrated. The reaction produced 69.1% of the oxime (3.407 g, 14.80 mmol) as a mixture of isomers. The oxime was purified via flash chromatography (30% EtOAc/hexane, 1% Et_3N) to give the anti isomer as a white solid. ^{1}H NMR (500 MHz, DMSO): 6.40 (ddd, J = 1, 7, 8 Hz, 1H), 6.43 (bs, 2H), 6.51 (dd, J = 1.5, 8 Hz, 1H), 6.75 (dd, J = 1, 8 Hz, 1H), 6.99-7.03 (m, 1H), 7.26-7.29 (m, 4H), 11.04 (s, 1H); ^{13}C NMR (125 MHz, DMSO): 114.7, 115.0 (d, $J_{C\text{-}F}$ = 21 Hz), 115.6, 117.1, 129.0, 130.5, 130.6, 130.8 (d, $J_{C\text{-}F}$ = 8.1 Hz), 147.4, 157.6, 161.6 (d, $J_{C\text{-}F}$ = 244 Hz); ^{19}F NMR (376 MHz, DMSO): -113.6; IR (DCM): 3406, 1609; HRMS (ESI): calcd for $C_{13}H_{11}FN_2O$ $[M+Na]^+$: 253.0753, found 253.0744.

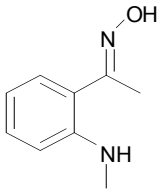


(2-aminophenyl)(4-bromophenyl)methanone oxime (18). The reaction was performed according to Method A with 4.198 g (15.20 mmol) of (2-aminophenyl)(4-bromophenyl)methanone. During the concentration to remove excess pyridine, the product precipitated out of solution. The water was decanted off and crude solid extracted with Et_2O, washed with water, dried with $MgSO_4$ and concentrated. The reaction produced 64.6% of the oxime (2.860 g, 9.823 mmol) as a mixture of isomers. The oxime was purified via flash chromatography (30% EtOAc/hexane, 1% Et_3N) to give the anti isomer as a white solid. ^{1}H NMR (500 MHz, DMSO): 6.38-6.42 (m, 1H), 6.45 (bs, 2H), 6.54 (dd, *J* = 1.5, 8.0 Hz, 1H), 6.75 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.00-7.03 (m, 1H), 7.16-7.19 (m, 2H), 7.63-7.66 (m, 2H), 11.09 (s, 1H); ^{13}C NMR (125 MHz, DMSO): 114.7, 115.6, 116.7, 121.3, 129.1, 130.5, 130.8, 131.1, 133.5, 147.4, 157.5; IR (DCM): 3393, 1610; HRMS (ESI): calcd for $C_{13}H_{11}BrN_2O$ $[M+Na]^+$: 312.9952, found 312.9931.

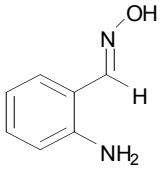


1-(2-(allylamino)phenyl)ethanone oxime (19). The reaction was performed according to Method B with 1.380 g (7.875 mmol) of 1-(2-(allylamino)phenyl)ethanone. The crude product was purified via flash chromatography (10% EtOAc/hexanes, 1% Et_3N) to give 67.0% of the oxime (1.002 g, 5.267 mmol) as a yellow oil. ^{1}H NMR (400 MHz, DMSO): 2.22 (s, 3H), 3.82 (t, *J*= 4.8 Hz, 2H), 5.14 (d, *J*= 10.4, 1H), 5.24 (d, *J*= 17.2, 1H), 5.91-5.98 (m, 1H), 6.59-6.64 (m,

2H), 7.13 (t, *J*= 7.6, 1H), 7.38 (t, *J*= 7.6, 1H), 7.88 (t, *J*= 5.2, 1H), 11.11(s, 1H); ^{13}C NMR (100 MHz, DMSO): 12.7, 45.5, 111.2, 115.3, 115.8, 118.6, 129.2, 129.7, 136.0, 146.9, 156.8; IR (DCM): 3312, 1604.

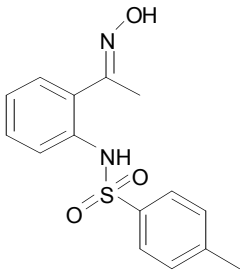


1-(2-(methylamino)phenyl)ethanone oxime (20). The reaction was performed according to Method B with 846 mg (5.67 mmol) of 1-(2-(methylamino)phenyl)ethanone. The crude product was purified via flash chromatography (10% EtOAc/hexanes, 1% Et_3N) to give 67.0% of the oxime (698 mg, 4.25 mmol) as an off-white solid. ^{1}HNMR (400 MHz, DMSO): 2.20 (s, 3H), 2.80 (d, *J*= 5.0 Hz, 3H), 6.58-6.63 (m, 2H), 7.17 (t, *J*= 7.6 Hz, 1H), 7.36 (d, *J*= 7.6 Hz, 1H), 7.59 (t, *J*= 4.7 Hz, 1H), 11.09(s, 1H); ^{13}CNMR (100 MHz, DMSO): 12.7, 30.0, 110.3, 115.0, 118.5, 129.1, 129.8, 148.1, 156.7; IR (KBr): 3316, 1609; HRMS (ESI): calcd for $C_9H_{12}N_2ONa$ $[M+Na]^+$ 187.0847, found 187.0843.



2-aminobenzaldehyde oxime (21). *o*-Aminobenzaldehyde (1.481 g, 12.23 mmol) and hydroxylamine hydrochloride (1.702 g, 24.49 mmol) were dissolved in 15 % (v/v) solution of H_2O/EtOH (18 mL), and the reaction was stirred at ambient temperature for 1 h. After this time, water (20 mL) was added and the reaction mixture was extracted with EtOAc (4 X 20 mL). The organic layers were dried over Na_2SO_4, and concentrated. The crude product was crystallized from DCM/hexanes to give 40.6% of the oxime (675 mg, 4.96 mmol) as a white solid. ^{1}H NMR

(400 MHz, DMSO): 6.34 (bs, 2H), 6.54 (t, J = 7.0 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 7.02-7.06 (m, 1H), 7.15 (dd, J = 1.2, 7.6 Hz, 1H), 8.20 (s, 1H), 10.91 (s, 1H); ^{13}C NMR (100 MHz, DMSO): 114.8, 115.3, 115.7, 130.0, 131.8, 147.3, 152.0; IR (DCM): 3392, 3284, 1609; HRMS (ESI): calcd for $C_7H_8N_2O$ $[M+H]^+$: 137.0715, found 137.0708.

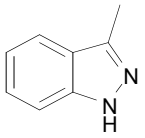


***N*-(2-(1-(hydroxyimino)ethyl)phenyl)-4-methylbenzenesulfonamide (22).** The reaction was performed according to Method A with 2.299 g (7.945 mmol) of *N*-(2-acetylphenyl)-4-methylbenzenesulfonamide. The crude product was purified via crystallization from ether to give 56.5% of the oxime (1.366 g, 4.488 mmol) as a white solid. ^{1}H NMR (400 MHz, DMSO): 2.02 (s, 3H), 2.31 (s, 3H), 7.10-7.14 (m, 1H), 7.27-7.32 (m, 3H), 7.44 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 11.09 (s, 1H), 11.76 (s, 1H); ^{13}C NMR (100 MHz, DMSO): 13.0, 21.4, 121.2, 124.8, 125.8, 127.1, 129.4, 129.7, 130.1, 135.6, 136.5, 144.1, 155.9; IR (KBr): 3413, 1615, 1327, 1149; Anal. Calcd for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20. Found. C, 59.17; H, 5.20; N, 9.16.

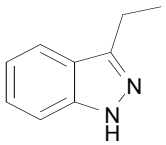
General Procedure for the Synthesis of 1*H*-Indazoles.

The oxime (1 mmol) was dissolved in DCM (15 mL) and 2 mmol of Et_3N was added. The reaction was stirred at ambient temperature for 15 min, then cooled to 0 ˚C. A solution of MsCl (1.2 mmol) in DCM (5 mL) was added slowly over 90 s and the reaction was allowed to warm to

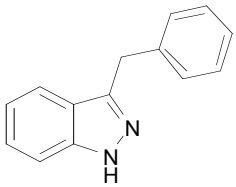
ambient temperature over 5 h unless otherwise stated. The reaction was concentrated in vacuo and purified via flash chromatography.



3-methyl-1*H*-indazole (23). The reaction was performed according to the general procedure with 5.011 g (33.37 mmol) of 2'-aminoacetophenone oxime. The reaction was allowed to stir for 3 h then concentrated in vacuo. The crude product was purified via flash chromatography (30% EtOAc/hexanes) to give 70.0% of the indazole (3.082 g, 23.32 mmol) as a tan solid. Spectroscopic data for this compound matched previously reported literature values.[12]

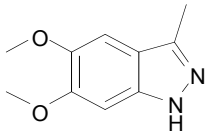


3-ethyl-1*H*-indazole (24). The reaction was performed according to the general procedure with 164 mg (1.00 mmol) of 1-(2-aminophenyl)propan-1-one oxime. The crude was purified via flash chromatography (20% EtOAc/hexanes) to give 80.8% of the indazole (118 mg, 0.807 mmol) as a pale yellow solid. Spectroscopic data for this compound matched the previously reported literature values.[13]

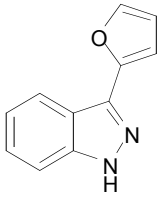


3-benzyl-1*H*-indazole (25). The reaction was performed according to the general procedure with 228 mg (1.00 mmol) of 1-(2-aminophenyl)-2-phenylethanone oxime. The crude product was

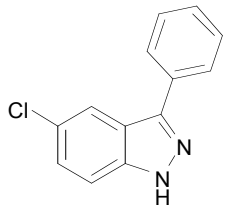
purified via flash chromatography (20% EtOAc/hexanes) to give 86.4% of the indazole (180 mg, 0.864 mmol) as a white solid. Spectroscopic data for this compound matched the previously reported literature values.[14]



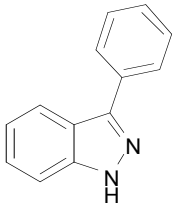
5,6-dimethoxy-3-methyl-1*H*-indazole (26). The reaction was performed according to the general procedure with 211 mg (1.00 mmol) of 1-(2-amino-4,5-dimethoxyphenyl)ethanone oxime. The crude product was purified via flash chromatography (80% EtOAc/hexanes) to give 75.0% of the indazole (144 mg, 0.749 mmol) as a tan solid. Spectroscopic data for this compound matched the previously reported literature values.[15]



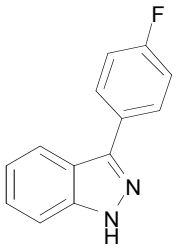
3-(furan-2-yl)-1*H*-indazole (27). The reaction was performed according to the general procedure with 203 mg (1.00 mmol) of (2-aminophenyl)(furan-2-yl)methanone oxime. The crude product was purified via flash chromatography (50% EtOAc/hexanes) to give 85.9% of the indazole (158 mg, 0.858 mmol) as a tan solid. ^{1}H NMR (500 MHz, $CDCl_3$): 6.58-6.59 (m, 1H), 6.97 (d, *J* = Hz, 1H), 7.24-7.27 (m, 1H), 7.41-7.44 (m, 1H), 7.48-7.50 (m, 1H), 7.60-7.61 (m, 1H), 8.12-8.14 (m, 1H), 10.85 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 107.3, 110.1, 111.5, 120.2, 121.4, 121.6, 127.2, 137.9, 141.2, 142.4, 148.9; IR (DCM): 3144, 2931, 1619; HRMS (ESI): calcd for $C_{11}H_8N_2O$ $[M+Na]^+$: 207.0534, found 207.0515.



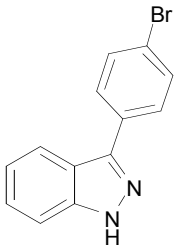
5-chloro-3-phenyl-1*H*-indazole (28). The reaction was performed according to the general procedure with 237 mg (0.960 mmol) of (2-amino-5-chlorophenyl)(phenyl)methanone oxime. The crude product was purified via flash chromatography (25% EtOAc/hexane) to give 81.9% of the indazole (180 mg, 0.786 mmol) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): 7.14 (d, J = 9.0 Hz, 1H), 7.31 (dd, J = 2.0, 9.0 Hz, 1H), 7.46-7.50 (m, 1H), 7.54-7.57 (m, 2H), 7.94-7.98 (m, 3H), 11.52 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 111.6, 120.5, 122.0, 127.3, 127.7, 127.8, 128.7, 129.3, 133.0, 140.2, 145.5; IR (DCM): 3170, 1605; HRMS (ESI): calcd for $C_{13}H_9ClN_2$ $[M+H]^+$: 229.0533, found 229.0525.



3-phenyl-1*H*-indazole (29). The reaction was performed according to the general procedure with 213 mg (1.00 mmol) of 2-aminobenzophenone oxime. The reaction was purified via flash chromatography (20% EtOAc/hexanes) to give 82.0% of the product (159 mg, 0.819 mmol) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): 7.17 (d, J = 8.4, 1H), 7.21-7.24 (m, 1H), 7.33-7.36 (m, 1H), 7.48-7.50 (m, 1H), 7.55-7.59 (m, 2H), 8.03-8.07 (m, 3H), 12.05 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 110.5, 121.1, 121.2, 121.5, 126.9, 128.0, 128.4, 129.2, 133.7, 141.9, 145.8; IR (DCM): 3165, 2931, 1624, 1474, 1342; HRMS (ESI): calcd for $C_{13}H_1N_2Na$ $[M+Na]^+$: 217.0742, found 217.0727.

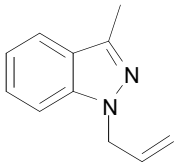


3-(4-fluorophenyl)-1*H*-indazole (30). The reaction was performed according to the general procedure with 230 mg (1.00 mmol) of (2-aminophenyl)(4-fluorophenyl)methanone oxime. The crude product was purified via flash chromatography (25% EtOAc/hexane) to give 86.1% of the indazole (183 mg, 0.861 mmol) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): 7.20-7.25 (m, 3H), 7.40-7.46 (m, 2H), 7.95-7.98 (m, 3H), 10.51 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 110.3, 116.1 (d, $J_{C\text{-}F}$ = 21 Hz), 121.0, 121.1, 121.7, 127.1, 129.5 (d, $J_{C\text{-}F}$ = 8.1 Hz), 129.8 (d, $J_{C\text{-}F}$ = 3.4 Hz), 141.8, 145.1, 163.0 (d, $J_{C\text{-}F}$ = 246 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): -114.5; IR (DCM): 3160, 1621; HRMS (ESI): calcd for $C_{13}H_9FN_2$ $[M+H]^+$: 213.0828, found 213.0810.

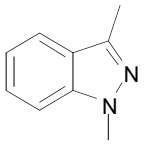


3-(4-bromophenyl)-1*H*-indazole (31). The reaction was performed according to the general procedure with 291 mg (1.00 mmol) of (2-aminophenyl)(4-bromophenyl)methanone oxime. The crude product was purified via flash chromatography (25% EtOAc/hexane) to give 80.8% of the indazole (221 mg, 0.808 mmol) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): 7.23-7.27 (m, 1H), 7.38-7.43 (m, 2H), 7.64-7.67 (m, 2H), 7.87-7.89 (m, 2H), 7.98 (d, J = 8.0 Hz, 1H), 10.95 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 110.3, 121.0, 121.0, 121.8, 122.4, 127.2, 129.2,

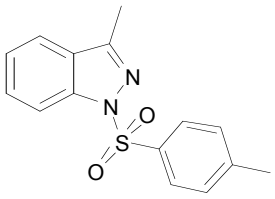
132.2, 132.7, 141.8, 144.9; IR (DCM): 3260, 1622; HRMS (ESI): calcd for $C_{13}H_9BrN_2$ $[M+Na]^+$: 294.9847, found 294.9832.



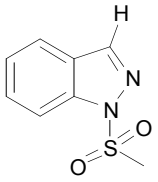
1-allyl-3-methyl-1*H*-indazole (32). The reaction was performed according to the general procedure with 191 mg (1.01 mmol) of 1-(2-(allylamino)phenyl)ethanone oxime. The crude product was purified via flash chromatography (20% EtOAc/hexanes) to give 69.5% of the indazole (121 mg, 0.703 mmol) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 2.57 (s, 3H), 4.92-4.94 (m, 2H), 5.10-5.21 (m, 2H), 5.97-6.04 (m, 1H), 7.08-7.12 (m, 1H), 7.32-7.34 (m, 2H), 7.63-7.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.9, 51.4, 109.1, 119.7, 120.4, 123.6, 126.2, 129.8, 133.1, 140.4, 141.7; IR (DCM): 1616; HRMS (ESI): calcd for $C_{11}H_{13}N_2$ $[M+H]^+$: 173.1079, found 173.1076.



1,3-dimethyl-1*H*-indazole (33). The reaction was performed according to the general procedure with 165 mg (1.00 mmol) of 1-(2-(methylamino)phenyl)ethanone oxime. The crude product was purified via flash chromatography (30% EtOAc/hexanes) to give 87.2% of the indazole (128 mg, 0.872 mmol) as a yellow oil. Spectroscopic data for this compound matched the previously reported literature values.[16]



3-methyl-1-tosyl-1*H*-indazole (34). The reaction was performed according to the general procedure with 306 mg (1.01 mmol) of N-(2-(1-(hydroxyimino)ethyl)phenyl)-4-methylbenzenesulfonamide. The crude product was purified via flash chromatography (20% EtOAc/hexanes) to give 35.3% of the indazole (102 mg, 0.356 mmol) as a white solid. Spectroscopic data for this compound matched previously reported literature values.[18]



1-(methylsulfonyl)-1*H*-indazole (35). The oxime (137 mg, 1.01 mmol) was dissolved in DCM (15 mL) and cooled to ⁻ 20 °C. Et_3N (280 μL, 2.02 mmol) was added and the reaction was stirred at ⁻ 20 °C for 15 min. A solution of MsCl (1.2 mmol) in DCM (5 mL) was added slowly over 90 s and the reaction was allowed to stir at ⁻ 20 °C for 30 min. The reaction was concentrated in vacuo and purified via flash chromatography (30% EtOAc/hexanes) to give 54.5% of the indazole (108 mg, 0.550 mmol) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): 3.23 (s, 3H), 7.34-7.38 (m, 1H), 7.53-7.56 (m, 1H), 7.75-7.77 (m, 1H), 8.05-8.07 (m, 1H), 8.27 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 41.0, 113.1, 121.6, 124.5, 125.7, 129.6, 140.3, 141.3; IR ($CDCl_3$): 3025, 2919, 1608; Anal. Calcd for $C_8H_8N_2O_2S$: C, 48.97; H, 4.11; N, 14.28. Found. C, 49.00; H, 3.96; N, 14.37.

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