Reaction of *N*-Monosubstituted Hydrazones with Nitro-Olefins: A Novel Regioselective Pyrazole Synthesis

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Supporting information

- 1) General Experimental Methods
- 2) Experimental procedures
- 3) Proton and carbon NMR spectra of compound 2-14, 17 and 18. NOE spectra of compound 2, 12 and 17.

General experimental methods:

Proton and carbon NMR spectra were recorded at Bruker 500 or 400 NMR spectrometers (^1H , 500 MHz; ^{13}C , 125 MHz). One-dimension NOE experiments were performed at Bruker 500 NMR spectrometer by the method of Stott, et al. with a mixing time of 0.8 sec.¹ Infrared spectroscopy was performed on a Nicolet Avatar 360 FT-IR. Flash column chromatography was performed using Merck silica gel 60. HPLC analysis was performed on a Hewlett Packard 1100 (Agilent ZORBAX® Eclipse XDB-C8, 5 μm , 4.6x150 mm, Flow rate 1 mL/min, Gradient (acetonitrile/water with 0.05% trifluoroacetic acid): 1% acetonitrile/99% water to 99% acetonitrile/1% water ramp over 8 min, then hold at 99% acetonitrile/1% water). HRMS (ESI) was performed on Bruker μTof .

Isopropylhydrazine hydrochloride was purchased from Peakdale Molecular. All the other hydrazines, aldehydes, and nitroolefins were purchased from Aldrich and used without further purification.

General procedure for pyrazole synthesis: **5-Benzo[1,3]dioxol-5-yl-3-(4-chloro-phenyl)-1-methyl-1H-pyrazole (2):** 4-

Chlorobenzaldehyde (140 mg, 1.0 mmol, 1.0 equiv.) was dissolved in MeOH (5 mL) and then methylhydrazine (46 mg, 1.0 mmol, 1.0 equiv.) was added. After stirring at room temperature for 1 h, the methyl hydrazone was formed based on HPLC analysis. 3,4-Methylenedioxy- β -nitrostyrene (174 mg, 0.90 mmol, 0.90 equiv.) was added as solid and

¹ Stott, K.; Keeler, J.; Van, Q. N.; Shaka, A. J. *J. Magn. Reson.*, **1997**, 125, 302-324.

the reaction solution was stirred open to air at room temperature for 24 h. A lot of solid precipitated out, which was the desired pyrazole product. MeOH was evaporated and the residue was re-dissolved in EtOAc (20 mL). After washing with saturated NaHCO₃ aqueous solution and brine, the crude product was purified with flash column chromatography with EtOAc/hexanes as eluent to afford the title compound as a light yellow solid (234 mg, 0.75 mmol, 83%). ¹H NMR (500 MHz, CDCl₃, δ): 7.73 (dt, *J* = 8.9, 2.2 Hz, 2H), 7.36 (dt, *J* = 8.9, 2.2 Hz, 2H), 6.93-6.87 (m, 3H), 6.50 (s, 1H), 6.03 (s, 2H), 3.88 (s, 3H). ¹³C NMR (125.7 MHz, CDCl₃, δ): 149.3, 148.0, 147.9, 144.9, 133.3, 132.0, 128.8, 126.7, 124.1, 122.7, 109.2, 108.6, 103.0, 101.5, 37.5. IR (dry film, cm⁻¹): 2897 (w), 1501 (m), 1477 (s), 1245 (s). HRMS-ESI (*m/z*): [M+H]⁺ calcd for C₁₇H₁₄ClN₂O₂ 313.0744; found, 313.0741.

N-(1-Benzo[1,3]dioxol-5-yl-2-nitro-ethyl)-N'-(4-chloro-benzylidene)-N-methyl-

hydrazine (3): Similar to the general method described above, in this case, the solvent used was CH₃CN instead of MeOH, the title compound was isolated in 90% yield. ¹H NMR (400 MHz, CDCl₃, δ): 7.46 (dt, *J* = 8.9, 2.2 Hz, 2H), 7.30 (dt, *J* = 8.9, 2.2 Hz, 2H), 7.18 (s, 1H), 6.76 (s, 3H), 5.94 (s, 2H), 5.41 (dd, *J* = 13.2, 9.5 Hz, 1H), 4.98 (dd, *J* = 9.5, 4.8 Hz, 1H), 4.60 (dd, *J* = 13.2, 4.8 Hz, 1H), 2.77 (s, 3H). ¹³C NMR (100.0 MHz, CDCl₃, δ): 148.1, 147.9, 135.1, 133.2, 131.7, 129.7, 128.7, 127.0, 121.2, 108.5, 107.4, 101.3, 77.5, 67.6, 37.0. IR (dry film, cm⁻¹): 2891 (w), 1553 (s), 1487 (s), 1244 (s). HRMS-ESI (*m/z*): [M+H]⁺ calcd for C₁₇H₁₇ClN₃O₄ 362.0900; found, 362.0887.

3-(4-Chloro-phenyl)-1,4-dimethyl-5-phenyl-1H-pyrazole (4): Using the general method described above, the title compound was isolated in 92% yield. ^1H NMR (500 MHz, CDCl_3 , δ): 7.68 (dt, $J = 8.5, 1.9$ Hz, 2H), 7.55-7.49 (m, 2H), 7.49-7.43 (m, 1H), 7.42 (dt, $J = 8.5, 1.9$ Hz, 2H), 7.39-7.34 (m, 2H) 3.82 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (125.7 MHz, CDCl_3 , δ): 148.2, 142.7, 133.1, 132.8, 130.4, 129.9, 128.8, 128.7, 128.6, 128.6, 112.1, 37.3, 10.1. IR (dry film, cm^{-1}): 2946 (w), 1604 (w), 1437 (s). HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{16}\text{ClN}_2$ 283.0998; found, 283.0999.

3-(4-Chloro-phenyl)-1-methyl-4,5,6,7-tetrahydro-1H-indazole (5): Using the general method described above, the title compound was isolated in 81% yield. ^1H NMR (500 MHz, CDCl_3 , δ): 7.64 (dt, $J = 8.5, 1.9$ Hz, 2H), 7.33 (dt, $J = 8.5, 1.9$ Hz, 2H), 3.75 (s, 3H), 2.66 (t, $J = 6.0$ Hz, 2H), 2.58 (t, $J = 6.0$ Hz, 2H), 1.88-1.80 (m, 2H), 1.80-1.73 (m, 2H). ^{13}C NMR (125.7 MHz, CDCl_3 , δ): 145.9, 139.9, 132.9, 132.6, 128.5, 127.7, 113.6, 35.5, 23.2, 22.3, 22.3, 21.6. IR (dry film, cm^{-1}): 2924 (s), 2854 (m), 1697 (m), 1441 (m), 1252 (s). HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{16}\text{ClN}_2$ 247.1002; found, 247.1009.

5-Benzo[1,3]dioxol-5-yl-3-benzyl-1-methyl-1H-pyrazole (6): Using the general method described above, the title compound was isolated in 82% yield. ^1H NMR (500 MHz, CDCl_3 , δ): 7.32-7.25 (m, 4H), 7.25-7.20 (m, 2H), 6.85-6.81 (m, 3H), 5.976 (s, 2H), 5.974 (s, 1H), 3.98 (s, 2H), 3.81 (s, 3H). ^{13}C NMR (125.7 MHz, CDCl_3 , δ): 150.9, 147.7, 147.7, 144.1, 140.0, 128.7, 128.3, 126.0, 124.5, 122.5, 109.0, 108.3, 105.0, 101.3, 37.1, 34.7. IR (dry film, cm^{-1}): 2900 (w), 1604 (w), 1487 (s), 1242 (s). HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_2$ 293.1290; found, 293.1299.

5-Benzo[1,3]dioxol-5-yl-3-tert-butyl-1-methyl-1H-pyrazole (7): Using the general method described above, the title compound was isolated in 56% yield. ^1H NMR (500 MHz, CDCl_3 , δ): 6.85 (s, 3H), 6.07 (s, 1H), 6.00 (s, 2H), 3.79 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (125.7 MHz, CDCl_3 , δ): 161.0, 147.7, 147.6, 143.5, 124.9, 122.5, 109.1, 108.4, 102.2, 101.3, 37.1, 31.9, 20.6. IR (dry film, cm^{-1}): 2958 (m), 1493 (s), 1476 (s), 1228 (s). HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_2$ 259.1446; found, 259.1447.

3-(4-Methoxy-phenyl)-1-methyl-5-p-tolyl-1H-pyrazole (8): Using the general method described above, the title compound was isolated in 72% yield along with the Michael addition product **18** in 10% yield. ^1H NMR (500 MHz, CDCl_3 , δ): 7.77-7.72 (m, 2H), 7.36-7.32 (m, 2H), 7.28-7.24 (m, 2H), 6.96-6.91 (m, 2H), 6.50 (s, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (125.7 MHz, CDCl_3 , δ): 159.2, 150.3, 145.0, 138.4,

129.3, 128.6, 127.9, 126.7, 126.4, 114.0, 102.5, 55.3, 37.4, 21.2. IR (dry film, cm^{-1}): 2922 (w), 1612 (w), 1493 (m), 1246 (s). HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}$ 279.1497; found, 279.1507.

N'-(4-Methoxy-benzylidene)-N-methyl-N-(2-nitro-1-p-tolyl-ethyl)-hydrazine (18):

The title compound was isolated as a side product in 10% yield. ^1H NMR (500 MHz, CDCl_3 , δ): 7.52 (dt, $J = 8.5, 1.9$ Hz, 2H), 7.24 (s, 1H), 7.21 (d, $J = 8.1$ Hz, 2H), 7.14 (d, $J = 8.1$ Hz, 2H), 6.92 (dt, $J = 8.5, 1.9$ Hz, 2H), 5.50 (dd, $J = 13.1, 9.4$ Hz, 1H), 5.00 (dd, $J = 9.4, 4.9$ Hz, 1H), 4.64 (dd, $J = 13.1, 4.9$ Hz, 1H), 3.83 (s, 3H), 2.73 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (125.7 MHz, CDCl_3 , δ): 159.4, 138.3, 133.4, 129.4, 127.5, 127.1, 114.0, 77.6, 67.6, 55.2, 37.1, 21.0. IR (dry film, cm^{-1}): 2938 (w), 1606 (m), 1551 (s), 1511 (s), 1249 (s). HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{22}\text{N}_3\text{O}_3$ 328.1661; found, 328.1653.

N-(1-Benzo[1,3]dioxol-5-yl-2-nitro-ethyl)-N-methyl-N'-(4-nitro-benzylidene)-

hydrazine (9): Using the general method described above, the title compound was isolated in 90% yield. ^1H NMR (500 MHz, CDCl_3 , δ): 8.20 (dt, $J = 8.9, 2.2$ Hz, 2H), 7.63 (dt, $J = 8.9, 2.2$ Hz, 2H), 7.21 (s, 1H), 6.80-6.72 (m, 3H), 5.95 (s, 2H), 5.41 (dd, $J = 13.5, 9.9$ Hz, 1H), 5.10 (dd, $J = 9.9, 4.5$ Hz, 1H), 4.51 (dd, $J = 13.5, 4.5$ Hz, 1H), 2.88 (s, 3H).

^{13}C NMR (125.7 MHz, CDCl_3 , δ): 148.4, 148.2, 146.6, 143.0, 129.4, 128.9, 125.8, 124.2, 121.0, 108.7, 107.2, 101.4, 67.7, 37.0. IR (dry film, cm^{-1}): 1563 (s), 1549 (m), 1504 (s), 1484 (s), 1339 (s), 1245 (s). HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{17}\text{N}_4\text{O}_6$ 373.1148; found, 373.1150.

1-Benzyl-3-(4-chloro-phenyl)-5-p-tolyl-1H-pyrazole (10): Similar to the general method described above, in this case, the solvent used was 10:1 MeOH/ H_2O mixture instead of pure MeOH, the title compound was isolated in 90% yield. ^1H NMR (500 MHz, CDCl_3 , δ): 7.79 (dt, $J = 8.9, 2.2$ Hz, 2H), 7.42 (dt, $J = 8.9, 2.2$ Hz, 2H), 7.32-7.15 (m, 7H), 7.10 (d, $J = 7.0$ Hz, 2H), 6.60 (s, 1H), 5.36 (s, 2H), 1.46 (s, 3H). ^{13}C NMR (125.7 MHz, CDCl_3 , δ): 149.8, 145.7, 138.7, 137.6, 133.3, 132.1, 129.7, 129.4, 128.7, 128.6, 127.5, 127.4, 126.9, 126.7, 103.4, 53.2, 21.3. IR (dry film, cm^{-1}): 2927 (w), 1606 (w), 1554 (m), 1490 (s). HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{20}\text{ClN}_2$ 359.1315; found, 359.1304.

3-(4-Chloro-phenyl)-1-isopropyl-5-p-tolyl-1H-pyrazole (11): Similar to the general method described above, in this case, the solvent used was 10:1 MeOH/ H_2O mixture instead of pure MeOH, the title compound was isolated in 26% yield after 7 days at room

temperature. ^1H NMR (500 MHz, CDCl_3 , δ): 7.78 (td, $J = 8.6, 1.9$ Hz, 2H), 7.35 (td, $J = 8.6, 1.9$ Hz, 2H), 7.31-7.24 (m, 4H), 6.45 (s, 1H), 4.53 (sept, $J = 6.6$ Hz, 1H), 2.42 (s, 3H), 1.49 (d, $J = 6.6$ Hz, 6H). ^{13}C NMR (125.7 MHz, CDCl_3 , δ): 149.1, 144.2, 138.5, 132.9, 132.6, 129.4, 128.9, 128.7, 128.1, 126.8, 102.8, 50.2, 23.0, 21.3. IR (dry film, cm^{-1}): 2976 (w), 2927 (w), 1489 (s), 1436 (s). HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{20}\text{ClN}_2$ 311.1315; found, 311.1304.

1-tert-Butyl-3-(4-chloro-phenyl)-4-p-tolyl-1H-pyrazole (12): Similar to the general method described above, in this case, the solvent used was 10:1 MeOH/ H_2O mixture instead of pure MeOH, the title compound was isolated in 15% yield after refluxing for 4 days. ^1H NMR (500 MHz, CDCl_3 , δ): 7.57 (s, 1H), 7.50 (td, $J = 8.5, 1.9$ Hz, 2H), 7.27 (td, $J = 8.5, 1.9$ Hz, 2H), 7.18 (td, $J = 8.1, 1.9$ Hz, 2H), 7.13 (td, $J = 8.1, 1.9$ Hz, 2H), 2.37 (s, 3H), 1.67 (s, 9H). ^{13}C NMR (125.7 MHz, CDCl_3 , δ): 146.5, 136.1, 133.0, 132.8, 130.6, 129.6, 129.2, 128.5, 128.3, 126.0, 119.9, 58.6, 29.9, 21.1. IR (dry film, cm^{-1}): 2956 (w), 2924 (m), 2855 (w), 1552 (w), 1501 (w), 1212 (s). HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{22}\text{ClN}_2$ 325.1468; found, 325.1464.

5-Benzo[1,3]dioxol-5-yl-3-(4-chloro-phenyl)-1-phenyl-1H-pyrazole (13): Using the general method described above, the title compound was isolated in 42% yield after heating at refluxing temperature for 4 days. ^1H NMR (500 MHz, CDCl_3 , δ): 7.86 (td, $J = 8.6, 1.9$ Hz, 2H), 7.42-7.30 (m, 7H), 6.78 (d, $J = 0.8$ Hz, 2H), 6.73 (s, 1H), 6.73-6.71 (m, 1H), 6.00 (s, 2H). ^{13}C NMR (125.7 MHz, CDCl_3 , δ): 150.7, 147.8, 147.7, 144.3, 140.0, 133.7, 131.6, 129.0, 128.8, 127.6, 127.0, 125.2, 124.2, 122.8, 109.1, 108.4, 104.9, 101.3. IR (dry film, cm^{-1}): 2923 (w), 1596 (w), 1499 (m), 1479 (s), 1454 (m), 1235 (s). HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{16}\text{ClN}_2\text{O}_2$ 375.0897; found, 375.0892.

3-Ethyl-1,5-diphenyl-1H-pyrazole (14): Using the general method described above, the title compound was isolated in 76% yield. ^1H NMR (500 MHz, CDCl_3 , δ): 7.34-7.20 (m, 10H), 6.36 (s, 1H), 2.79 (q, $J = 7.6$ Hz, 2H), 1.36 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (125.7 MHz, CDCl_3 , δ): 155.5, 143.5, 140.3, 130.9, 128.8, 128.6, 128.4, 128.0, 127.0, 125.2, 106.2, 21.5, 13.8. IR (dry film, cm^{-1}): 3059 (w), 2968 (w), 1597 (w), 1550 (w), 1503 (s). HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{17}\text{N}_2$ 249.1388; found, 249.1381.

3-(4-Methoxy-phenyl)-1-methyl-4-nitro-5-p-tolyl-pyrazolidine (17): In a NMR tube, 4-methoxybenzaldehyde (18.9 mg, 1.0 equiv) was dissolved in EtOH-d₆ (0.75 mL) and then methylhydrazine (6.4 mg, 1.0 equiv.) was added. After shaking at room temperature for 1 h, the methylhydrazone was formed based on NMR analysis. 4-Methyl- ω -nitrostyrene (22.6 mg, 1.0 equiv.) was added as solid. In several minutes, the title compound was formed, based on NMR analysis. ¹H NMR (400 MHz, EtOH-d₆, δ): 7.34 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.42 (dd, J = 7.3, 5.3 Hz, 1H), 4.97 (d, J = 7.3 Hz, 1H), 4.18 (d, J = 5.3 Hz, 1H), 3.75 (s, 3H), 2.63 (s, 3H), 2.36 (s, 3H). ¹³C NMR (100 MHz, EtOH-d₆, δ): 161.7, 140.3, 136.8, 131.5, 130.0, 129.6, 129.1, 115.7, 101.7, 81.3, 67.9, 56.6, 42.4, 22.4. IR (dry film, cm⁻¹): 2956 (w), 2837 (w), 1682 (w), 1602 (w), 1547 (s), 1512 (s), 1250 (s). HRMS-ESI (m/z): [M+H]⁺ calcd for C₁₈H₂₂N₃O₃ 328.1657; found, 328.1649.