Observations on the reaction of hydrazones with iodine: interception of the diazo intermediates

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Supporting Information

General Information.

All products were purified by flash column chromatography using silica gel SDS 60 C.C. 40-63 or neutral alumina SDS C.C. 50-200. NMR spectra were recorded in CDCl₃ with TMS as an internal standard at ambient temperature on a Bruker Avance 400 operating at 400 MHz for ¹H and 100 MHz for ¹³C. Infrared Absorption spectra were recorded with a Perkin-Elmer 1600 Fourier Transform Spectrophotometer. Mass spectra were recorded with a HP 5989B mass spectrometer and JEOL GC mate spectrometer for HMRS. Melting points were determined by Reichert microscope apparatus and were uncorrected.

General procedure for the preparation of diazo compounds Method A

To a solution of the hydrazone (1 mmol) and DBU (4 mmol) in toluene (8-10 mL) was added dropwise, under nitrogen, a solution of iodine (1.5 mmol) in toluene (8-10 mL) until the iodine coloration persisted. After complete consumption of the starting material (monitored by TLC) the reaction mixture was extracted with ethyl acetate, washed with an aqueous solution of HCl (1N), Na₂S₂O₃ and brine. The combined organic layers were dried (Na₂SO₄), filtered and evaporated under reduced pressure to give the diazo compound, which was purified by chromatography on a silica gel column or by recrystallisation.

Method B

To a solution of the hydrazone (1 mmol) and triethylamine (4 mmol) in toluene (10 mL) was added dropwise, under nitrogen, a solution of iodine (1.5 mmol) in toluene (5 mL) until the coloration persisted. After complete consumption of the starting material (monitored by TLC) the reaction mixture was extracted with ethyl acetate, washed with $Na_2S_2O_3$ and brine. The combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give the diazo compound, which was purified by chromatography on a silica gel column or by recrystallisation.

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6a-Phenyl-5-(toluene-4-sulfonyl)-3,3a,4,5,6,6a-hexahydro-pyrrolo[3,4-c]pyrazole **12a** *:* This compound was obtained using the general procedure (method A) in 85% yield after purification by chromatography on silica gel (petroleum ether/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.67 (d, 2H, J=8.2Hz, CHAr), 7.33 (m, 5H, CHAr), 7.23 (d, 2H, J=8.0Hz, CHAr), 4.70 (m, 2H, CH₂N=N), 4.25 (d, 1H, J=10.6Hz), 3.22 (m, 2H), 3.14 (dd, 1H, J=7.3Hz, J=9.7Hz), 2.72 (m, 1H, CH), 2.43 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ ppm 144.3, 137.8, 131.5 (*C*q), 129.9, 129.1, 128.4, 128.1 125.7 (CHAr), 104.5 (*C*q), 85.1 (CH₂N=N), 57.6, 55.5 (CH₂N), 40.0 (CH), 21.6 (CH₃). MS (CI, NH₃, m/z) 342 (MH)⁺. Mp 148-149°C (dichloromethane/petroleum ether). Anal. Calcd for C₁₈H₁₉N₃O₂S: C, 63.32; H, 5.61. Found: C, 63.39; H, 5.69.



2*a*-Phenyl-4-(toluene-4-sulfonyl)-3,4,4a,5,6,7,7a,7b-octahydro-2aH-1,2,4-triazacyclopenta[cd]indene 12b : This compound was obtained using the general procedure (method A) in 67% yield after purification by chromatography on silica gel (petroleum ether/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δppm 7.65 (d, 2H, J=8.2Hz, CHAr), 7.32 (m, 5H, CHAr), 7.23 (dd, 2H, J=1.6Hz, J=7.9Hz, CHAr), 4.71 (d, 1H, J=10.4Hz, CH₂N), 4.41 (t, 1H, J=6.7Hz), 3.18 (d, 1H, J=10.4Hz, CH₂N), 3.05 (m, 2H), 2.65 (d, 1H, J=10.6Hz), 2.60 (t, 1H, J=8.0Hz) 2.43 (s, 3H, CH₃), 1.88 (m, 1H), 1.38 (m, 3H). ¹³C NMR (100 MHz, CDCl₃) δppm 144.2, 136.4, 131.6 (Cq), 129.8, 129.0, 128.5, 128.1, 125.8 (CH), 102.0 (Cq), 86.7 (CH), 58.9 (CH₂), 58.4, 42.3 (CH), 26.0, 25.9 (CH₂), 21.6 (CH₃), 14.8 (CH₂). MS (CI, NH₃, m/z) 399 (MH+NH₃)⁺, 382 (MH)⁺. Mp 145-146°C (ethyl acetate/petroleum ether). Anal.





3a-Phenyl-2-(toluene-4-sulfonyl)-1,2,3,3a,5a,6,7,8,9,10-decahydro-2,4,5-triaza-cyclopenta [c] azulene **12c** *:* This compound was obtained using the general procedure (method A) in quantitative yield. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.71 (d, 2H, J=8.3Hz, CHAr), 7.38 (d, 2H, J=8.0Hz, CHAr), 7.33 (m, 3H, CHAr), 6.95 (dd, 2H, J=1.7Hz, J=7.8Hz, CHAr), 4.62 (dd, 1H, J=2.7Hz, J=12.3Hz, CHN=N), 3.80 (d, 1H, J=10.9Hz, CH₂N), 3.61 (d, 1H, J=10.9Hz, CH₂N), 3.26 (d, 1H, J=9.4Hz, CH₂N), 2.98 (d, 1H, J=9.4Hz, CH₂N), 2.64 (m, 1H), 2.48 (s, 3H, CH₃), 1.95 (m, 1H), 1.71 (m, 1H), 1.59 (m, 1H), 1.35 (m, 1H), 1.25-0.97 (m, 4H), 0.59 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ ppm 144.4, 135.8, 131.5 (Cq), 129.9, 128.6, 128.3, Supplementary Material (ESI) for Chemical Communications This journal is (c) The Royal Society of Chemistry 2006

128.2, 126.4, (CHAr), 104.8 (Cq), 101.3 (CHN=N), 62.7, 56.4 (CH₂N), 53.1 (Cq), 32.9, 30.6, 29.6, 27.8, 25.7 (CH₂), 21.7 (CH₃). Mp 158-159°C (Ethyl acetate, petroleum ether). Anal. Calcd for $C_{23}H_{27}N_3O_2S$: C, 67.45; H, 6.65. Found : C, 67.49; H, 6.61.



9b-Methyl-3,3a,4,9b-tetrahydro-chromeno[4,3-c]pyrazole 12d : This compound was obtained using the general procedure (method A) in 76% yield as a yellowish oil after purification by chromatography on silica gel (petroleum ether/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.84 (dd, 1H, J=1.7Hz, J=7.8Hz, CHAr), 7.18 (ddd, 1H, J=1.7Hz, J=7.3Hz, J=8.1Hz, CHAr), 7.07 (m, 1H, CHAr), 6.86 (dd, 1H, J=1.3Hz, J=8.1Hz, CHAr), 4.66 (dd, 1H, J=8.0Hz, J=17.6Hz, CH₂), 4.39 (dd, 1H, J=4.8Hz, J=17.6Hz, CH₂), 4.08 (dd, 1H, J=4.7Hz, J=11.3Hz, CH₂), 3.43 (dd, 1H, J=8.6Hz, J=11.3Hz, CH₂), 2.26 (tt, 1H, J=4.7Hz, J=8.4Hz, CH), 1.60 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ ppm 154.6 (Cq), 129.0, 128.6, (CHAr), 123.6 (Cq), 122.1, 117.4 (CHAr), 87.6 (Cq), 77.7 (CH₂N=N), 65.0 (CH₂O), 37.8 (CH), 25.9 (CH₃). Anal. Calcd for C₁₁H₁₂N₂O : C, (70.19), H, (6.43), Found : C, (69.88), H, (6.26).



9b-Methyl-4,9b-dihydro-chromeno[4,3-c]pyrazole **12e** *:* This compound was obtained using the general procedure (method A) in 60% yield as a yellow oil after purification by chromatography on silica gel (petroleum ether/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δppm 7.87 (dd, 1H, J=1.7Hz, J=7.7Hz, CHAr), 7.56 (d, 1H, J=1.1Hz, C=CH), 7.18 (ddd, 1H, J=1.7Hz, J=7.3Hz, J=9.0Hz, CHAr), 6.99 (ddd, 1H, J=1.1Hz, J=2.2Hz, J=8.5Hz, CHAr), 6.90 (dd, 1H, J=0.7Hz, J=8.3Hz, CHAr), 5.19 (d, 1H, J=13.6Hz, CHHO), 5.12 (dd, 1H, J=1.8Hz, J=13.6Hz, CHHO), 1.63 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ ppm 153.3, 152.1 (Cq), 137.8 (NCH=C, 129.2, 128.1 (CHAr), 123.0 (Cq), 121.6, 116.7 (CHAr), 91.7 (Cq), 61.5 (CH₂O), 24.0 (CH₃).MS (CI, NH₃, m/z) 187 (MH)⁺. Anal. Calcd for C₁₁H₁₀N₂O : C, 70.95; H, 5.41. Found : C, 70.35; H, 5.42.



6a-Phenyl-5-(toluene-4-sulfonyl)-4,5,6,6a-tetrahydro-pyrrolo[3,4-c]pyrazole 12f: This compound was obtained using the general procedure (method B) isolated as crystals in 60% yield after purification by chromatography on silica gel (petroleum ether/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δppm 7.55 (d, 2H, J=8.2Hz, CHAr), 7.30 (m, 5H, CHAr), 7.22 (s, 1H, CH=C), 7.19 (d, 2H, J=8.1Hz, CHAr), 4.47 (d, 1H, J=9.6Hz, CH₂N), 4.31 (dd, 1H, J=1.8Hz, J=13.6Hz, CH₂N), 4.16 (d, 1H, J=13.6Hz, CH₂N), 2.83 (d, 1H, J=9.6Hz, CH₂N), 2.39 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ ppm 158.3, 144.2 (Cq), 140.8 (CH=C), 133.3, 131.6, (Cq), 130.0, 129.3, 129.0, 127.2, 126.7 (CHAr), 106.0 (Cq), 53.8 (CH₂N), 43.2

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(*C*H₂N), 21.6 (*C*H₃). Mp 148-150°C (dichloromethane/petroleum ether). Anal. Calcd for $C_{18}H_{17}N_3O_2SC(63.70)$, H(5.05), N(12.38), found C(63.05), H(5.09), N(12.21).). HMRS (EI) (M-N₂)⁺ $C_{18}H_{17}NO_2S$: calcd 311.0980; found 311.0977.



5-(4-Chloro-phenyl)-3a,4,5,5a,6,7,8,9-octahydro-3H-1,2,5-triaza-cyclopenta[c]indene 12g : This compound was obtained using the general procedure (method B) in 79% yield as crystals after purification by chromatography on silica gel (petroleum ether/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.11 (d, 2H, J=9.0Hz, CHAr), 6.48 (d, 2H, J=9.0Hz, CHAr), 4.79 (d, 1H, J=17.6Hz, CHHN=N), 4.63 (dd, 1H, J=6.1Hz, J=11.3Hz, CHN), 4.45 (dd, 1H, J=7.1Hz, J=17.7Hz, CHHN=N), 3.31 (t, 1H, J=9.5Hz, CH₂N), 2.89 (dd, 1H, J=2.8Hz, J=10.2Hz, CH₂N), 2.46 (m, 1H), 2.23 (m, 1H), 2.01 (td, 1H, J=4.2Hz, J=13.8Hz), 1.88 (m, 1H),), 1.79 (m, 1H),), 1.41 (m, 1H), 1.35-1.21 (m, 2H), 0.92 (ddt, 1H, J=3.7Hz, J=11.3Hz, J=13.5Hz). ¹³C NMR (100 MHz, CDCl₃) δ ppm 144.8 (Cq), 129.0 (CHAr), 121.8 (Cq), 114.9 (CHAr), 101.8 (Cq), 83.9 (CH₂N=N), 59.2 (CHN), 53.4 (CH₂N), 35.7 (CH), 27.5, 24.1, 23.2, 22.8 (CH₂). MS (CI, NH₃, m/z) 276, 278 (MH)⁺. Mp 133-134 °C (diethyl ether/petroleum ether). HMRS (EI) (M-N₂)^{+.} C₁₅H₁₈N₃CI : calcd 275.1189 ; found 275.1189.



5-(4-Chloro-phenyl)-3-phenyl-3a,4,5,5a,6,7,8,9-octahydro-3H-1,2,5-triaza-

cyclopenta[c]indene 12h : This compound was obtained as crystals using the general procedure (method B) in quantitative yield. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.38 (t, 2H, J=7.3Hz), 7.31 (t, 1H, J=7.3Hz), 7.15 (d, 4H, J=8.8Hz), 6.56 (d, 2H, J=8.9Hz), 5.90 (d, 1H, J=1.4Hz, CHN=N), 4.57 (dd, 1H, J=6.2Hz, J=11.1Hz, CHN), 3.45 (dd, 1H, J=8.1Hz, J=10.1Hz, CH₂N), 3.26 (dd, 1H, J=1.4Hz, J=10.2Hz, CH₂N), 2.41 (d, 1H, J=8.0Hz, CHCH₂N), 2.23 (dd, 1H, J=4.5Hz, J=13.7Hz), 2.16 (dd, 1H, J=5.2Hz, J=14.7Hz), 1.79 (m, 2H), 1.42 (m, 2H), 1.19 (m, 1H), 0.96 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ ppm 145.1, 138.7 (Cq Ar), 129.1, 128.9, 127.8, 126.5 (CHAr), 122.4 (Cq), 115.7 (CH), 103.1 (Cq), 102.1 (CH), 58.9 (CHN), 53.9 (CH₂N), 43.8 (CH), 29.9, 23.2, 22.6, 22.4 (CH₂). MS (CI, NH₃, m/z) 352, 354 (MH)⁺. Mp 167-169°C (ethyl acetate/petroleum ether). HMRS (EI) C₂₁H₂₂N₃Cl : calcd 351.1502; found 351.1503.



5-Methyl-5-(4-trifluoromethyl-phenyl)-4,5-dihydro-3H-pyrazole-3,4-dicarboxylic acid dimethyl ester

A mixture of hydrazone **1i** (0.202g, 1 mmol), dimethylfumarate (0.72g, 5 mmol) and triethylamine (0.55 mL, 4 mmol) in toluene (1.5 mL) was heated under nitrogen at 60°C until complete dissolution. To this solution maintained at 60°C was added dropwise over a period of 5.5 hrs a solution of iodine (0.3g, 1.2 mmol) in toluene (2.5 mL). The reaction mixture was extracted with ethyl acetate. The organic layer was washed with a saturated solution of Na₂S₂O₃, brine and dried over Na₂SO₄. After filtration and evaporation of the solvent under reduced pressure, the residue was purified by chromatography on silica gel to afford the diazo derivative **12i** as an orange foam and as a 1:1 mixture of diastereomers (0.227g, 66%).

¹H NMR (400 MHz, CDCl₃) of the 4,5-*cis* diastereomer (more polar isomer): δ ppm 7.57 (m, 4H, CHAr), 6.62 (s, 1H, CH-N=N), 3.97 (s, 1H, CHCO₂CH₃), 3.79 (s, 3H, CO₂CH₃), 3.11 (s, 3H, CO₂CH₃), 1.74 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ ppm 168.0, 162.4 (CO), 143.8, 137.6 (Cq), 130.2 (q, J=32.5Hz, CqAr), 127.0 (CH), 125.2 (q, J=3.7Hz, CHAr), 123.9 (q, J=270Hz, CF₃), 73.2 (Cq), 61.8, 52.4, 51.9 (CH, CO₂CH₃), 28.2 (CH₃). IR (CCl₄, v_{max}) 1747, 1713 (CO); 1326, 1133 (CF₃) cm-¹. MS (CI, NH₃, m/z) 362 (MH+NH₃)⁺, 345 (MH)⁺. HMRS (EI) C₁₅H₁₅F₃N₂O₄ : calcd 344.0984; found 344.0974.

¹H NMR (400 MHz, CDCl₃) of the 4,5-*trans* diastereomer (less polar isomer; the values were deduced from the mixture of isomers, since this isomer could not be obtained completely pure): δ ppm 7.61 (d, 2H, J=8.6Hz, CHAr), 7.54 (d, 2H, J=8.4Hz, CHAr), 6.73 (s, 1H, CH-N=N), 4.04 (s, 1H, CHCO₂CH₃), 3.80 (d, 3H, J=1.0Hz, CO₂CH₃), 3.77 (d, 3H, J=1.0Hz, CO₂CH₃), 1.59 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃) δ ppm 168.5, 162.3 (CO), 149.3, 137.6 (Cq), 130.1 (q, J=32.6Hz, CqAr), 126.0 (q, J=3.7Hz, CHAr), 125.4 (CH), 123.9 (q, J=270Hz, CF₃), 72.4 (Cq), 60.9, 52.7, 52.3 (CH, CO₂CH₃), 24.1 (CH₃).