Benzimidazole- and benzothiazole-quinones: excellent substrates for NAD(P)H:quinone oxidoreductase 1

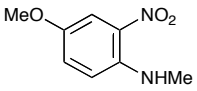
ELECTRONIC SUPPLEMENTARY INFORMATION

Chemistry

Commercially available reagents were used throughout without purification unless otherwise stated. Light petroleum refers to the fraction with bp 40 – 60 °C and was distilled before use. Ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen or argon atmosphere. Analytical thin layer chromatography was carried out on aluminium-backed plates coated with Merck Kieselgel 60 GF_{254}, and visualized under UV light at 254 and/or 360 nm. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Fully characterized compounds were chromatographically homogeneous.

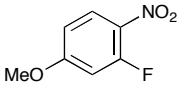
Infrared spectra were recorded in the range 4000 – 600 cm^{-1} using a Nicolet Magna FT-550 or Perkin Elmer FT-1600 spectrometers. NMR spectra were carried out on Bruker 300 and 400 MHz instruments (^1H frequencies, corresponding ^{13}C frequencies are 75 and 100 MHz). Chemical shifts are quoted in ppm with TMS as internal standard. *J* values are recorded in Hz. In the ^{13}C spectra, signals corresponding to CH, CH_2 or CH_3 groups, as assigned from DEPT, are noted; all others are C. High and low resolution mass spectra were recorded on a Micromass GCT TDF High Resolution mass spectrometer, or at the EPSRC Mass Spectrometry Service (Swansea).

4-Methoxy-*N*-methyl-2-nitroaniline 8



Trifluoroacetic anhydride (1 ml) was added to a solution of 4-methoxy-2-nitroaniline **7** (1.00 g, 5.9 mmol) in trifluoroacetic acid (6.4 ml). The reaction mixture was stirred at room temperature for 1 h and then poured over cracked ice. The resulting precipitate was collected by filtration, washed with water to give the trifluoroacetamide derivative as a bright yellow solid. The trifluoroacetamide was added to a mixture consisting of iodomethane (1.08 ml, 17.4 mmol), potassium hydroxide (0.98 g, 17.4 mmol) and acetone (32 ml). The reaction mixture was heated under reflux for 8 h. The resulting mixture was filtered and the filtrate evaporated under reduced pressure. The residue obtained purified by chromatography, eluting with ethyl acetate/light petroleum (1:3), to give the *title compound* (1.08 g, 100%) as a red solid; mp 105-106 °C (lit.,[1] mp 98-99 °C); δ_H (300 MHz; $CDCl_3$) 7.95 (1 H, bs, NH), 7.60 (1 H, d, *J* 2.9, H-3), 7.16 (1 H, dd, *J* 9.3, 2.9, H-5), 6.82 (1 H, d, *J* 9.3, H-6), 3.78 (3 H, s, OMe), 3.01 (3 H, s, NMe); δ_C (75 MHz; $CDCl_3$) 149.5 (C), 142.4 (C), 130.7 (C), 127.5 (CH), 114.8 (CH), 106.9 (CH), 55.8 (Me), 29.9 (Me).

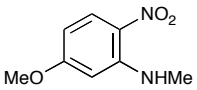
3-Fluoro-4-nitroanisole



3-Fluoro-4-nitrophenol (15.0 g, 95 mmol) was dissolved in butan-2-one (90 ml) and treated with potassium carbonate (24.7 g, 179 mmol) at 40 °C for 10 min. The resulting suspension was cooled to 0 °C, treated with iodomethane (17.8 ml, 290 mmol) and heated to 40 °C for 18 h. The resulting lemon yellow suspension was concentrated *in vacuo* to 20 ml and dichloromethane (50 ml) was added. The resulting suspension was filtered and the filtrate dried ($MgSO_4$) and concentrated *in vacuo* to give the *title compound* (16.0 g, 97%) as a

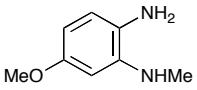
colourless crystalline solid; mp 56-58 °C (from ethanol) (lit.,[2] mp 56.5 °C); δ_H (300 MHz; $CDCl_3$) 8.07-8.13 (1 H, m, ArH), 6.72-6.80 (2 H, m, ArH), 3.91 (3 H, s, OMe); δ_C (75 MHz; $CDCl_3$) 165.3 (d, *J* 11.0, C), 157.5 (d, *J* 263.4, C), 127.93 (C), 127.91 (CH), 110.4 (d, *J* 3.0, CH), 103.2 (d, *J* 24.1, CH), 56.3 (Me).

5-Methoxy-*N*-methyl-2-nitroaniline 12



Methylamine (40% in water; 94 ml, 1.2 mol) was carefully added to a suspension of 3-fluoro-4-nitroanisole (15.98 g, 93.4 mmol) and potassium carbonate (25.83 g, 186.9 mmol) in dichloromethane (94 ml) and the resulting biphasic solution stirred at room temperature for 48 h. The reaction mixture was diluted with water (100 ml), extracted into dichloromethane (3 × 100 ml), dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* to give the *title compound* (17.0 g, 100%) as a bright yellow crystalline solid; mp 118.5-119.5 °C (from ethanol) (lit.,[3] mp 116 °C); δ_H (300 MHz; $CDCl_3$) 8.30 (1 H, bs, NH), 8.14 (1 H, d, *J* 9.5, 3-H), 6.25 (1 H, dd, *J* 9.6, 2.5, 4-H), 6.13 (1 H, d, *J* 2.5, 6-H), 3.89 (3 H, s, OMe), 3.01 (3 H, d, *J* 4.7, NMe); δ_C (75 MHz; $CDCl_3$) 166.5 (C), 149.1 (C), 129.6 (C + CH), 105.0 (CH), 95.1 (CH), 56.1 (Me), 30.1 (Me).

2-Amino-5-methoxy-*N*-methylaniline



To a solution of 5-methoxy-*N*-methyl-2-nitroaniline **12** (3.00 g, 16.6 mmol) in ethanol (180 ml) was added palladium 10% on carbon (300 mg). The mixture was stirred under a hydrogen atmosphere for 20 h. The reaction mixture was filtered through Celite and the solvent

removed *in vacuo* to give the *title compound* (2.44 g, 97%) as a purple oil; (Found: MH^+, 153.1034. $C_8H_{12}N_2O$ + H requires 153.1028); ν_{max} (KBr)/cm^{-1} 3368, 2937, 2833, 2804, 2360, 1733, 1699, 1683, 1607, 1558, 1520, 1457, 1425, 1210, 1170; δ_H (300 MHz; $CDCl_3$) 6.65 (1 H, d, *J* 8.2, 3-H), 6.25 (1 H, d, *J* 2.7, 6-H), 6.18 (1 H, dd, *J* 8.2, 2.7, 4-H), 3.77 (3 H, s, OMe), 3.20 (3 H, vbs, NH_2 + NH), 2.84 (3 H, s, NMe); δ_C (75 MHz; $CDCl_3$) 155.7 (C), 141.8 (C), 127.0 (C), 118.0 (CH), 101.1 (CH), 98.8 (CH), 55.9 (Me), 31.2 (Me); *m/z* (CI) 153 (MH^+, 100%), 152 (95), 122 (36), 138 (64), 122 (36), 150 (25).

References

1. W. N. White and J. R. Klink, *J. Org. Chem.*, 1970, **35**, 965.

2. T. O. Bamkole, J. Hirst and E. I. Udoessien, *J. Chem. Soc., Perkin Trans. 2*, 1973, 110.

3. W. Friedrich and K. Bernhauer, *Chem. Ber.*, 1956, **89**, 2030.