Facile Synthesis of Tetrapyrido[2,3-*a*:3',2'-*c*:2'',3''-*h*:3''',2'''-*j*]phenazine

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Abstract: The title compound, a potential ligand for transition metals, was prepared by coupling of two 4,7-phenanthroline-5,6-dione molecules in presence of ammonia under reductive conditions. A straightforward synthesis of 4,7-phenanthroline-5,6-dione is also presented.

Tetrapyrido[2,3-*a*:3',2'-*c*:2'',3''-*h*:3''',2'''-*j*]phenazine (TPP, **1**) is a potential bis-tridentate bridging ligand for d^6 ions of transition metals like ruthenium (II) or iron (II). It was first synthesized by Case in 1966[2] by coupling of 2,3-diamino-1,4-phenylenedi-*N*,*N*'-acetamide with 4,7-phenanthroline-5,6-dione, followed by a double Skraup cyclisation. Except that it was shown to form an insoluble precipitate with iron (II),[3] TPP otherwise has never been used to build polynuclear metallic complexes. For the purpose of preparing mono- and oligonuclear ruthenium complexes, we have developed a straightforward synthesis of TPP, *via* coupling of two 4,7-phenanthroline-5,6-dione (**7**) molecules with ammonia under reductive conditions. The starting quinone **7** was synthesized by oxidation of 5-methoxy-4,7-phenanthroline (**6**),[4] a compound that was prepared from 2-methoxy-1,4-phenylenediamine (**2**) according to a new, straightforward procedure.

The complete synthesis of TPP is depicted in Scheme 1. Commercial 2-methoxy-1,4-phenylenediamine dihydrogensulfate was deprotonated and isolated under argon owing to the oxygen-sensitivity of the free base **2**. The subsequent acetylation was designed to reduce the electronic density on the aromatic ring and to avoid undesired oxidations in the next reaction. The diacetylated compound **3** was oxygen stable. The pyrido cycles were formed by a modified double Skraup cyclisation, in presence of 2-nitrobenzenesulfonate and iron(II).[5-7] The reaction mechanism involves a Michael addition to acrolein, this intermediate being formed *in situ* by dehydration-oxidation of the glycerol. Iron (II) sulfate serves as oxidation moderator. Under the conditions described in the experimental part, the reaction proceeded smoothly and was never observed to go out of control as is sometimes the case in Skraup syntheses. The main compound obtained was the 4,7-phenanthroline derivative **4** with the diazaanthracene **5** as a byproduct. These two isomers can be selectively extracted by dichloromethane and ethyl acetate respectively. The 5-methoxy-4,7-phenanthroline dihydrogensulfate (**6**) was oxidized to the diquinone **7** in a refluxing mixture of sulfuric and nitric acid, following the procedure of Druey and Schmidt,[4] except that ammonium bicarbonate was used instead of sodium hydroxide for the final neutralization. The diquinone **7** is in fact highly base sensitive and even under strong stirring and keeping the measured pH below 7, the use of sodium hydroxide led to considerable decarbonylation to the diazafluorenone **8**.[4, 8] Finally, the formation of the pyrazine ring of TPP did not require the coupling of the diquinone with the corresponding diamine. A simple dimerization under reductive conditions afforded TPP in good yield. It is known that α-keto alcohols dimerize to pyrazines in presence of ammonium acetate.[9] As expected, the diquinone **7** underwent the same reaction under reductive conditions. However, due to its sensitivity to base, it is subject to self decomposition in solution except when protonated. Therefore, **7** must be added to the solution containing ammonium acetate and sodium borohydride. Different procedures gave poor yields. As noticed by Case, TPP is soluble in alcohols only when they contain a few percents of water. By reaction of **1** with an equimolar amount of iron (II) sulfate

in methanol-water 5:1, a light green precipitate was obtained for which the elemental analysis is in agreement with a stoichiometry Fe / TPP 1:1 suggesting a polymeric complex of high-spin Fe(II). Dissolution of this compound in acidic methanol followed by oxidation with H_2O_2 and precipitation of iron oxides by a base allows quantitative recovery of the TPP. TPP was observed to form mono and binuclear complexes with ruthenium (II). Investigations on these compounds are in progress and will be reported elsewhere.
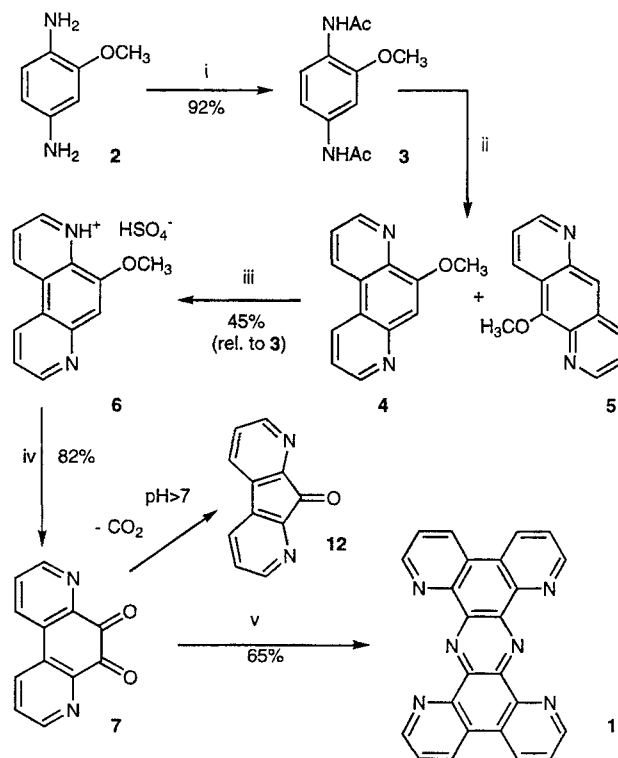
Reagents: i. Ac_2O, pyridine; ii. Skraup reaction: glycerol, sodium 2-nitrobenzenesulfonate, H_2SO_4, $FeSO_4$ 140°C; iii. MeOH, H_2SO_4; iv. H_2SO_4, HNO_3 120°C; v. NH_4CH_3COO, $NaBH_4$, CH_3OH.

Scheme 1

Experimental section

General procedures. UV-visible spectra were recorded using an HP 8451A diode array spectrophotometer. The extinction coefficients were calculated with at least 3 different dilutions. NMR spectra were recorded using a Bruker AC-250 spectrometer (250 MHz). Chemical shifts are given in ppm relative to Me_4Si or sodium 3-trimethylsilyl-1-propanesulfonate (in D_2O). Mass spectra were recorded on a Finnigan MAT 8200 spectrometer (intensities in parentheses). Elemental analyses were carried out by the Galbraith Laboratories in Knoxville, TN. Chemicals and solvents (Omnisolve, Baker) were used as purchased, unless specified otherwise.

2-Methoxy-1,4-phenylenediamine (2). In a 3-L 3-neck flask under Ar, 2-methoxy-1,4-phenylenediamine sulfate hydrate (261 g, 1.10 mol, *Aldrich*) was added under strong stirring to a solution of NaOH (100 g, 2.5 mol) in 1 L H_2O. After 30 min, 1 L ethyl acetate was added, the flask was equipped as a continuous extractor and continuous extraction

by ethyl acetate under Ar was carried out over 17 h. The extract was concentrated to 300 mL and cooled to 0°C. The precipitate was filtered off, washed rapidly with 100 mL ethyl acetate at 0°C and dried *in vacuo* 1.5 h at 80°C to give 143 g (1.04 mol, 95%) of a pale yellow solid, highly air-sensitive until dry: ^{1}H-NMR (CD$_3$OD) 3.79 (*s*, H$_3$C-O), 6.23 (*d*, *J* = 7.6, H-C(5)), 6.41 (*s*, H-C(3)), 6.61 (*d*, *J* = 7.6, H-C(6)); MS, *m/e* 139 (8, $M^{+\cdot}$ +1), 138 (100, $M^{+\cdot}$), 123 (53), 95 (95).

N,N'-Diacetyl-2-methoxy-1,4-phenylenediamine (3). In a 2-L 3-neck flask under Ar, **2** (142 g, 1.03 mol) was dissolved in 800 mL Ar-purged dry pyridine (*Mallinckrodt*). The mixture was cooled to 0°C in an ice-salt bath. Acetic anhydride (235 mL, 2.5 mol, *Aldrich*) was added dropwise over 1 h under stirring, at 0°C. Stirring was continued for 1 h, the precipitate formed was filtered, twice suspended in 500 mL diethyl ether and refiltered, and finally dried 3 h *in vacuo* at 80°C. Yield: 211 g (0.95 mmol, 92%). The product requires no further purification: ^{1}H-NMR (CD$_3$OD) 2.11 (*s*, H$_3$C-O), 2.14 (*s*, H$_3$C-O), 6.94 (*dd*, *J* = 2.2, 8.7, H-C(5)), 7.45 (*d*, *J* = 2.2, H-C(3)), 7.79 (*d*, *J* = 8.6, H-C(6)); MS *m/e* 223 (13, $M^{+\cdot}$ +1), 222 (100, $M^{+\cdot}$), 180 (59), 138 (80), 137 (35), 95 (21), 43 (53).

5-Methoxy-4,7-phenanthroline hydrogensulfate (6). Modified Skraup reaction according to the literature.[5-7] In a 3-necked, 2-L flask equipped with a reflux condenser and a powerful mechanical stirrer, **3** (120 g, 0.54 mol) together with sodium 2-nitrobenzenesulfonate (122 g, 0.54 mol, *Aldrich*), iron (II) sulfate heptahydrate (50 g, 0.18 mol, *Baker*) and glycerol (600 mL, *Aldrich*, 99 %) were mixed. With ice-bath cooling, 96% H$_2$SO$_4$ (88 mL, *Mallinckrodt*) was slowly added to the stirred paste, keeping the temperature below 40°C. The mixture was heated up to 98°C on a water bath over 1 h and then to 140°C on an air bath. After 1 h at this temperature, it was cooled down to 70°C and a second potion of H$_2$SO$_4$ (88 mL) was carefully added, keeping the temperature below 90°C. The mixture was heated up to 145°C. As water was formed, a reflux started and the temperature decreased. After 4 h, it stabilized at 133°C. The solution was cooled to r.t., poured onto ice (1 kg) and neutralized by 30% aqueous ammonia (500 mL). The mixture, containing almost unfiltrable iron oxide, was extracted continuously 36 h with dichloromethane. The extract was dried over MgSO$_4$ and the solvent distilled, leaving 76.8 g of black resin. It was dissolved in 500 mL CH$_3$OH and, with ice-bath cooling and stirring, acidified by dropwise addition of 96% H$_2$SO$_4$ (20 mL, 0.37 mol). The precipitate was filtered, washed with ethanol (200 mL), diethyl ether (200 mL), and dried *in vacuo* 1 h at 80°C. Yield: 74.6 g (0.242 mol, 45%). The product requires no further purification: ^{1}H-NMR (D$_2$O) 4.19 (*s*, H$_3$C-O), 7.26 (*s*, H-C(6)), 8.03, 8.06 (2 overlapping *dd*, *J* = 5.3, 8.5, H-C(2), H-C(9)), 8.96 (*dd*, *J* = 1.2, 4.9, H-C(3)), 9.02 (*dd*, *J* = 1.2, 5.6, H-C(8)), 9.17 (*dd*, *J* = 1.2, 8.5, H-C(1)), 9.38 (*d*, *J* = 8.4, H-C(10)).

By addition of an excess of H$_2$SO$_4$ to the methanolic solution, the dihydrogensulfate was obtained. ^{1}H-NMR (D$_2$O) 4.26 (*s*, H$_3$C-O), 7.55 (*s*, H-C(6)), 8.11 (*dd*, *J* = 5.4, 8.5, H-C(9)), 8.18 (*dd*, *J* = 5.0, 8.6, H-C(2)), 9.08 (*m*, H-C(3), H-C(8)), 9.43 (*dd*, *J* = 1.3, 8.6, H-C(1)), 9.56 (*d*, *J* = 8.3, H-C(10)).

By continuous extraction of the reaction mixture with ethyl acetate followed by the procedure described above, the isomer 9-methoxy-1,5-diazaanthracene hydrogensulfate (hydrogensulfate of **5**) was obtained in a 30% yield. ^{1}H-NMR (D$_2$O) 4.42 (*s*, H$_3$C-O), 7.91 (*s*, H-C(10)), 8.29 (*dd*, *J* = 5.3, 8.5, H-C(2)), 8.49 (*dd*, *J* = 5.5, 8.5, H-C(6)), 9.24 (*d*, *J* = 5.5, H-C(5)), 9.32 (*d*, *J* = 5.3, H-C(1)), 9.83 (*d*, *J* = 8.5, H-C(7)), 9.89 (*d*, *J* = 8.5, H-C(3)).

4,7-Phenanthroline-5,6-dione (7). Modified procedure according to the literature.[4] **10** (46.0 g, 0.15 mol) was dissolved in 96% H$_2$SO$_4$ (170 mL). With ice-bath cooling, 90% HNO$_3$ (100 mL, *Aldrich*) was added dropwise under stirring. The mixture was refluxed on an oil bath. The

initial temperature was 92°C, reaching 96°C after 2 h. The reflux was continued for 8 h, the solution then cooled to r. t., poured onto ice (1 kg) and neutralized by stepwise addition ammonium bicarbonate (560 g). The final pH was 6.8 to 7.2. After 2 h, the pale yellow precipitate was filtered off, washed twice with H$_2$O (100 mL), twice with acetone (200 mL), twice with ether (200 mL), and dried *in vacuo* 2 h at 60°C. Yield: 25.8 g (82%). No recrystallization must be attempted as the product decomposes when warmed up in solution. The crude product appeared pure by NMR: ^{1}H-NMR (D$_2$O/D$_2$SO$_4$) 8.33 (*dd*, *J* = 5.5, 8.0, H-C(2), H-C(9)), 8.91 (*d*, *J* = 5.5, H-C(3)), H-C(8)), 9.25 (*d*, *J* = 8.0, H-C(1), H-C(10)). MS, *m/e* 212 (9, $M^{+\cdot}$ +2), 211 (4.5, $M^{+\cdot}$ +1), 210 (26, $M^{+\cdot}$), 182 (100), 154 (82), 128 (40), 127 (36).

Tetrapyrido[2,3-a:3',2'-c:2'',3''-h:3''',2'''-j]phenazine (TPP) (1). Under Ar, ammonium acetate (27 g, 0.35 mol) was dissolved in deaerated CH$_3$OH (400 mL). To the refluxing solution, **7** (7.35 g, 35 mmol) and sodium borohydride (7 g, 185 mmol, *Johnson Matthey*) were added simultaneously by small portions at intervals of a few minutes, starting with the borohydride. The mixture was refluxed for another 15 min and the solvent then evaporated to dryness. The residue was dissolved in H$_2$O (200 mL) and the solution basified to pH 12 by 5M NaOH. The precipitate was filtered off, three times suspended in H$_2$O (200 mL) and refiltered. The purification was carried out as follows. The product was dissolved in 0.3M HCl (450 mL) and the solution filtered off. Under stirring, 2M HCl (200 mL) was added to the filtrate, causing the precipitation the tetrahydrochloride of **1**. The precipitate was washed with 1M HCl (50 mL) and then dissolved in hot H$_2$O (300 mL). The solution was made basic to pH 12 by dropwise addition of 2M NaOH under stirring. The precipitate was filtered off, suspended in 200 mL H$_2$O, re-filtered, and dried *in vacuo* 1 h at 70 °C. Yield: 5.0 g (11.4 mmol, 65%): UV λ_{max} (ε) in CHCl$_3$: 274 nm (53600), 320 (32800), 346 (13600), 353 (12700), 364 (13600), 384 (13500); in CH$_3$OH: 272 (48900), 318 (31000), 362 (12900), 382 (13300); ^{1}H-NMR (CD$_3$OD/D$_2$O 9:1) 7.63 (*dd*, *J* = 4.0, 8.2, H-C(2), H-C(5), H-C(11), H-C(14)), 8.32 (*d*, *J* = 4.0, H-C(1), H-C(6), H-C(10), H-C(15)), 8.81 (*d*, *J* = 8.2, H-C(3), H-C(4), H-C(12), H-C(13)); MS, *m/e* 386 (46, $M^{+\cdot}$ +2), 385 (41, $M^{+\cdot}$ +1), 384 (100, $M^{+\cdot}$), 393 (22), 347 (39), 346 (26). Elem. anal. Calcd for C$_{24}$H$_{12}$N$_6$·3H$_2$O: C, 65.75; H, 4.11; N, 19.16. Found: C, 66.17; H, 4.49; N, 18.71.

References and Notes

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