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Efficient Synthesis of 1,4,5,12-Tetrazatriphenylene and Derivatives

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Abstract: Condensation of 5,6-diamino-4,7-phenanthroline with glyoxal provides 1,4,5,12-tetrazatriphenylene in quantitative yield. This procedure avoids the 50% loss of product inherent in previous methods. Derivatives were also prepared by using α,β-dicarbonyl compounds other than glyoxal. Additional derivatives were prepared from 1,4,5,12-tetrazatriphenylene, 2,3-dicarbonitrile, produced by condensation of diaminomaleonitrile with 4,7-phenanthroline-5,6-dione.

The compound 1,4,5,12-tetrazatriphenylene, also known as 4,7-phenanthroline-5,6:5′,6′-pyrazine (ppz) is a member of a small family of documented planar heterocyclic molecules containing three or more nitrogen atoms and four or more condensed rings. Like ppz, many of these are biologically active and also act as bis-bidentate or polydentate ligands toward a variety of metal ions. Some of these are natural products (Figure 1); others are synthetic materials.6

Our earlier work described the use of ppz as a bridging ligand in the fabrication of the one of the most luminescent complexes containing two ruthenium atoms.5 The degree of electronic communication between metal centers connected by such bridging ligands is an area of interest that has been explored by experimental and computational methods.6 Also of interest is the use of ppz and analogues in the fabrication of dendrimers and microporous network structures;6 e.g., the bridging ability of ppz makes it an attractive building block for constructing polynuclear systems where lattice interpenetration is diminished due to the rigidity of the ligand.6 Grove and co-workers have also reported the X-ray structure of ppz, drawing attention to the importance of π stacking.7

Another attribute of ppz and analogues related to their planar structures is an ability to intercalate DNA,9,11 Applications as sensitive diagnostic tools and novel chemotherapeutic agents have been examined by our group and others.2,3,12,13

We have sought improved synthetic routes to ppz and to ppz derivatives potentially useful in fine-tuning the photochemical and redox properties of metal complexes, DNA-intercalating properties, and also for the construction of more elaborate structures in which the substituents can serve as a site for structural architecture. Only a few ppz derivatives have been reported in the past,14–18 reflecting the observation that the known chemistry of 4,7-phenanthroline and its derivatives is sparse compared to that of 1,10-phenanthroline. Here, we report a more efficient synthesis of ppz and the synthesis of several new ppz derivatives.

As noted earlier, dione has been used as a precursor to 1. Direct oxidation of 4,7-phenanthroline to 2 is unsuccessful,19 even though the corresponding 1,10-phenanthroline is easily oxidized to isomeric 1,10-phenanthroline-5,6-dione.20,21 However, electron-rich 4,7-phenanthrolines such as 5-methoxy-4,7-phenanthroline can be oxidized to the dione.22

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Nevertheless, condensation of 2 with ethylenediamine results in an isolated yield of only 20–30% of ppz, and substituents are not easily introduced via modifications of this procedure. Therefore, we have developed alternative and more versatile routes to ppz and derivatives that avoid the disproportionation problem mentioned earlier.

One approach has centered on the formation of 4,7-phenanthroline-5,6-diamine as a key intermediate and its condensation with dicarbonyl compounds. This condensation leads directly to ppz or ppz derivatives. The needed diamine had previously been reported by Case and by Meier and co-workers. Only Case described a preparative procedure involved tosylation of 5-amino-4,7-phenanthroline (which itself required synthesis) followed by nitration, hydrolysis, and reduction. Because of the difficulties of this multistep sequence and the relatively poor overall yield (15%), we explored a simpler new route to diamine from 2 via 4,7-phenanthroline-5,6-dioxime (Scheme 2). The dioxime was not purified; TLC showed it to be a mixture, as expected because of the possibility of syn and anti isomers. This mixture was subjected to Pd/C catalytic reduction with hydrazine hydrate, giving diamine in 84% yield. Condensation of 6 with glyoxal afforded ppz in 100% yield. This procedure is clean and practicable. Furthermore, dicarbonyl compounds other than glyoxal can be used to prepare a family of ppz derivatives. In this manner, 7–11 were prepared.

Case and co-workers described the synthesis of 9 from 1,4-phenylenediamine. The procedure involved Skraup reactions with an overall yield of 22%. In contrast, the preparation of 9 described here via condensation of 6 with 2,2′-pyridil occurred smoothly with 70% yield.

Case and co-workers first described the synthesis of 10 with an overall yield of 58% by double-Skraup reaction of 10,13-diacetamidodipyrido(2,3-a:3′,2′-c)phenazine obtained by condensation of 2 with N,N′-diacetyl-2,3-diamino-1,4-phenylenediamine, followed by catalytic reduction. Later, Case did report a procedure similar to the one we describe here but used extra steps which we have found unnecessary. Compound 10 has also been synthesized by Bonhote et al. via coupling of 2 with ammonia under reductive conditions (65%). In the present work, reaction of 2 with 6 forms 10 in 81% yield.

The outcome of the condensation of 6 with oxalyl chloride is of interest because the spectroscopic data suggest that tautomers of 11 are also present. In addition, when the condensation is performed in the absence of pyridine, the major product is the dimeric N,N-bis(6-amino[4,7]phenanthroin-5-yl)oxalamide. It seems that the HCl produced after the reaction of one of the amine groups in 6 with oxalyl chloride protonates the second amine group and renders it unavailable for further reaction. Therefore, in the synthesis of 11, we used pyridine to capture the liberated HCl. This strategy was successful as indicated by mass spectrometry and 1H NMR measurements.

\[(22) \text{Imor, S.; Morgan, R. J.; Wang, S.; Morgan, O.; Baker, A. D.} \]
\[\text{Synth. Commun.} \text{1996, 26, 2197.}\]
\[(23) \text{Meier, R.; Schuler, W.; Krueger, R. Arch. Exp. Path. U. Pharmakol.} \text{1955, 224, 206.}\]
Another route to substituted derivatives of ppz is reaction of dianmonaleonitrile 12 with 2 (Scheme 3). Condensation leads directly to the aromatic dicyano derivative of ppz, 1,4,5,12-tetraazatriphenylene-2,3-dicarboxylic acid 14 by acid-catalyzed hydrolysis. It was purified by conversion to its disodium salt followed by acidification with concd HCl, causing 14 to precipitate. Diamide 15 was prepared by stirring 13 with concd H2SO4, followed by neutralization. Diester 16 was obtained from 15 via acid-catalyzed methanolysis. Although 15 was sparingly soluble in hot MeOH, the transformation was complete within 15 h.

In summary, efficient procedures have been developed for the synthesis of ppz and several of its substituted derivatives. Several new ppz derivatives have been prepared (2,3-diphenyl-1,4,5,12-tetraazatriphenylene-7,2,3-dimethyl-1,4,5,12-tetraazatriphenylene 13, 1,4,5,12-tetraazatriphenylene-2,3-diol 11, 1,4,5,12-tetraazatriphenylene-2,3-dicarboxylic acid 14, 1,4,5,12-tetraazatriphenylene-2,3-dicarboxylic acid diamide 15, and 1,4,5,12-tetraazatriphenylene-2,3-dicarboxylic acid dimethyl ester 16), and improved procedures have been described for several known ppz derivatives (4,7-phenanthroline-5,6-diamine 1, 4,5,12-tetraazatriphenylene-8, 1,4,5,12-tetraazatriphenylene-2,3-diol 11, 1,4,5,12-tetraazatriphenylene-2,3-dicarboxylic acid 14, and 1,4,5,12-tetraazatriphenylene-2,3-dicarboxylic acid dimethyl ester 16).

Experimental Section:

4,7-Phenanthroline-5,6-diamine (6). 29 An argon-flushed mixture of 2 (1.0 g, 4.76 mmol), NH2OH·HCl (1.16 g, 16.6 mmol), and (0.952 mmol) of BaCO3 in 70 mL of anhyd EtOH was refluxed for 18 h. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was treated with 120 mL of 0.2 M HCl. The solution was stirred for 45 min and filtered. The filtered solid was washed with water, EtOH, anhyd Et2O and then dried under vacuum at 90 °C to afford 0.914 g (80%) of 4,7-phenanthroline-5,6-dioxime 5 as a yellow-brown solid: mp 240–241 °C dec; IR 1698, 3447 cm−1; HRMS (MH+) calcd for C12H10N4O2 241.0712, found 241.0717. A mixture of 5 (0.80 g, 3.33 mmol) and 10% Pd/C (0.80 g) in anhyd EtOH (200 mL) was flushed with hydrogen and refluxed. A solution of 7.0 mL of N2H4·H2O in 30 mL of anhyd EtOH was injected in the above mixture dropwise over 1 h. After the solution was refluxed overnight, the hot mixture was passed through a pad of Celite with suction, and the Celite was thoroughly washed with boiling EtOH. The filtrate was concentrated. The residue was then triturated with 60 mL of cold water and cooled in a refrigerator overnight. The tan solid obtained was filtered, washed with cold water and anhyd Et2O, and dried under vacuum to give 0.59 g (84%) of 6 as a tan solid: mp 217–218 °C; IR 1343,1630, 3425 cm−1; 1H NMR (DMSO−d6) δ 5.52 (s, NH2, 4H), δ 7.47 (dd, 2H, J = 8.3, 4.3, 8.3, 4.3 Hz), 8.85 (dd, 2H, J = 4.3, 1.4 Hz), 9.08 (dd, 2H, J = 8.3, 1.4 Hz); 13C NMR (DMSO−d6) δ 118.1, 118.2, 125.7, 131.2, 140.0, 148.7; HRMS (MH+) calcd for C12H10N4 201.0984, found 201.0976. Anal. Calcd for C12H10N4: C, 68.10; H, 4.65; N, 26.36. Found: C, 68.10; H, 4.65; N, 26.36.

4,7-Phenanthroline-5,6-dipipyridin-2-yl-1,4,5,12-tetraazatriphenylene (10), and 1,4,5,12-tetraazatriphenylene-2,3-dicarboxylic acid 13.


(29) A similar procedure has been described for the preparation of 1,10-phenanthroline-5,6-diamine; see: Bodige, S.; MacDonnell, F. M. Tetrahedron Lett. 1997, 38, 8159.
anhyd Et₂O (3 mL) was added, and then the reaction mixture was filtered. The filtrate was concentrated to afford 221 mg (100%) of ppz 1 as a beige solid: mp 284–285 °C; 1H NMR (CDCl₃) δ 0.78 (dd, 2H, J = 8.2, 4.4 Hz), 8.89 (dd, 2H, J = 1.6, 8.2 Hz), 9.23 (dd, 2H, J = 1.6, 4.4 Hz); 13C NMR (CDCl₃) δ 124.3, 125.8, 131.1, 142.9, 145.2, 146.0, 151.3; HRMS (MH⁺) calc'd for m/z C₂H₄N₄O₂ 233.0827, found 233.1818.

2,3-Diphenyl-1,4,5,12-tetraazatriphenylene (7). Diamine 6 (250 mg, 1.19 mmol) was stirred in anhyd EtOH (15 mL) at room temperature and degassed with argon for 15 min. 1,2-Diphenylethane-1,2-dione (benzil) (270 mg, 1.31 mmol) was added, and the suspension was cooled to 78 °C. Then, oxalyl chloride (5 mL) was added, after which 5 mL of H₂O and 0.5 mL of saturated Na₂CO₃ were added and the residue filtered and recrystallized from DMF (56.4 mL), and 2 equiv of Et₃O (1.26 mL) was added. The mixture was heated to 100 °C for 1 h and cooled to room temperature, and the solvent was removed under reduced pressure. The solid obtained was purified by flash chromatography in MeOH/CH₂Cl₂ 4.8:0.4, Rf (CH₂Cl₂) to give 103.1 mg (80%) of 13: mp > 360 °C; 1H NMR (DMSO) δ 8.10 (dd, 2H, J = 8.4, 4.4 Hz), 9.27 (dd, 2H, J = 4.4, 1.2 Hz), 9.42 (dd, 2H, J = 8.4, 1.2 Hz); 13C NMR (DMSO) δ 114.6, 126.5, 128.0, 132.5, 137.2, 142.7, 145.2, 151.9; HRMS (MH⁺) calc'd for C₂H₄N₆O₂ m/z 283.0732, found 283.0736. This procedure results in a significant higher yield than reported previously. 18

1,4,5,12-Tetraazatriphenylene-2,3-dicarboxylic Acid (14). A solution of dicarboxonitrile 13 (200 mg, 0.79 mmol) in concd H₂SO₄ (5 mL) was stirred at room temperature for 3 d and diluted by dropwise addition to vigorously stirred ice–H₂O (20 mL). The mixture was neutralized with solid NaHCO₃ until no more precipitation occurred. The suspension was filtered, washed with cold H₂O, cold acetone, and Et₂O, and dried in a vacuum at 100 °C to afford 197.5 mg (87%) of 14 as a light yellow solid: mp > 360 °C; IR (Nujol) 349.0937, found 349.0934.

1,4,5,12-Tetraazatriphenylene-2,3-dicarboxylic Acid Dimide (15). A solution of dicarboxonitrile 13 (200 mg, 0.79 mmol) in concd H₂SO₄ (5 mL) was stirred at room temperature for 3 d and diluted by dropwise addition to vigorously stirred ice–H₂O (20 mL). The mixture was neutralized with solid NaHCO₃ until no more precipitation occurred. The suspension was filtered, washed with cold H₂O, cold acetone, and Et₂O, and dried in a vacuum at 100 °C to afford 178.2 mg (79%) of 15 as a beige solid: mp 260–261 °C dec; IR (Nujol) 1684, 3275 cm⁻¹; 1H NMR (DMSO) δ 7.9 (s, 2H), 8.0 (dd, 2H, J = 8.1, 4.4 Hz), 8.22 (s, 2H), 9.22 (dd, 2H, J = 4.4, 1.4 Hz), 9.39 (dd, 2H, J = 8.4, 1.4 Hz); 13C NMR (DMSO) δ 125.3, 126.9, 134.1, 143.6, 143.5, 151.2, 166.2; Anal. Calc’d for C₂H₄N₆O₂.7H₂O: C, 57.73; H, 2.85; N, 16.83, found C, 57.62; H, 2.77, N, 17.19; HRMS (MH⁺) calc’d for C₂H₄N₆O₂.7H₂O m/z 319.0943, found 319.0939.

1,4,5,12-Tetraazatriphenylene-2,3-dicarboxylic Acid Dimethyl Ester (16). To an argon-flushed solution of diamine 15 (200 mg, 0.629 mmol) in concd H₂SO₄ (4 mL) was added anhyd MeOH (15 mL) at room temperature. The reaction mixture was refluxed for 12 h until the full consumption of the diamine 15 was observed (TLC, 2 M ammonia in MeOH/CH₂Cl₂ 2.8:1.2, Rf 0.65). The brown mixture was cooled, water was added (25 mL), and then the solution was filtered. The filtrate was neutralized with solid NaHCO₃. The product was extracted with CHCl₃, and the combined organic layers were washed with brine, dried (MgSO₄), and concentrated. The residue was dissolved in CHCl₃ (5 mL) and filtered and the filtrate concentrated to afford 151 mg (69%) of ester 16: IR 1737 cm⁻¹; 1H NMR (DMSO) δ 4.14 (s, 6H), 7.86 (dd, 2H, J = 8.4, 4.4 Hz), 8.96 (dd, 2H, J = 8.4, 1.2 Hz), 9.31 (dd, 2H, J = 4.4, 1.2 Hz); 13C NMR (DMSO) δ 52.6, 124.1, 126.0, 130.2, 141.4, 143.0, 144.0, 150.9, 163.9; HRMS (MH⁺) calc’d for C₉H₄N₄O₂ m/z 349.0937, found 349.0934.

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Supporting Information Available: NMR spectra for compounds 1, 6–11, and 13–17. This material is available free of charge via the Internet at http://pubs.acs.org.

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