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

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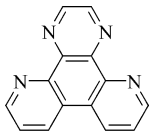
Abstract: Condensation of 5,6-diamino-4,7-phenanthroline with glyoxal provides 1,4,5,12-tetraazatriphenylene in quantitative yield. This procedure avoids the 50% loss of product inherent in previous methods. Derivatives were also prepared by using α-dicarbonyl compounds other than glyoxal. Additional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

The compound 1,4,5,12-tetraazatriphenylene, also known as 4′,7′-phenanthrolino-5,6:5′6′-pyrazine **1** (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);[1−3] others are synthetic materials.[4]



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Our earlier work described the use of ppz as a bridging ligand in the fabrication of the first 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;[7] 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.[8] 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]

The route to ppz in all previous work has been the condensation of 4,7-phenanthroline-5,6-dione **2** with ethylenediamine. However, the diimine **3** resulting from this reaction undergoes a spontaneous disproportionation reaction, producing ppz along with the nonaromatic substance 1,4,4a,12b-tetrahydro-1,4,5,12-tetraazatriphenylene **4** in equal amounts. Thus, the maximum yield of ppz is limited to 50% and no methods have been found for oxidizing **4** to ppz (Scheme 1).

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-phenanthrolines. Here, we report a more efficient synthesis of ppz and the synthesis of several new ppz derivatives.

As noted earlier, dione **2** 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]

(1) (a) Eilatin is a heptacyclic alkaloid from the purple red sea tunicate *Eudistoma* sp. Its metal complexes intercalate DNA. (b) Kuanoniamine A has been isolated from the purple marine *Cystodytes* sp. It inhibits HCT replication: Ding, Q.; Chichak, K.; Lown, J. W. *Curr. Med. Chem.* **1999**, *6*, 1.

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(21) We used molecular orbital calculations at the Gauss view 3.0/6-31G level help to clarify the difference in behavior of the two isomers. While the HOMO of 1,10-phenanthroline has its highest coefficients at the C_5 and C_6 positions, the C_5 and C_6 coefficients are actually lower than on any other carbon atoms in the HOMO of 4,7-isomer.

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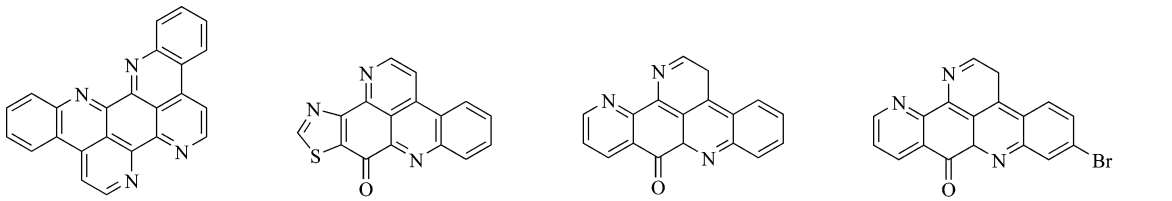
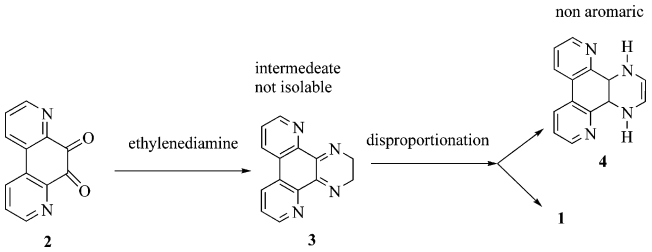


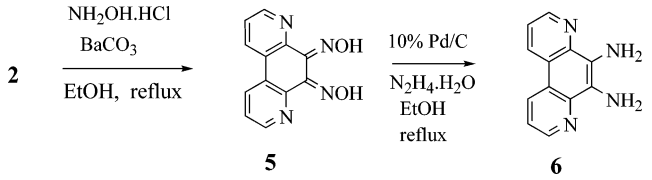
eilatin[1a] | kuanoniamine A / 6-thia-3,4,8-triazabenzo[*de*] cyclopenta [*b*]anthracen-7-one[1b] | ascididemin / 3,8a-dihydro-1,8,13-triazabenzo [*fg*]naphthacen-9-one[2] | 2-bromoleptoclinidinone / 6-bromo-3,8a-dihydro-1,8,13-triazabenzo[*fg*]naphthacen-9-one[3]

FIGURE 1. Natural products that are planar heterocycles consisting of four or more condensed rings and three or more N atoms.[1−3]

SCHEME 1. Synthesis of ppz from 4,7-Phenanthroline-5,6-dione

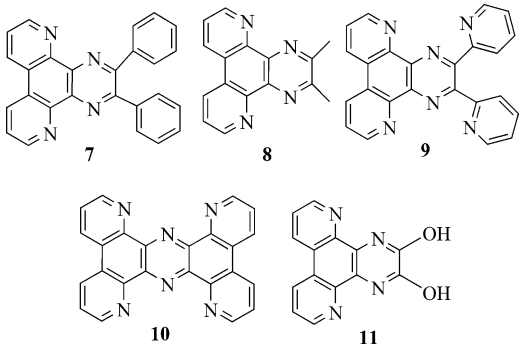


SCHEME 2. Synthesis of Diamine 6



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 **6** as a key intermediate and its condensation with dicarbonyl compounds. This condensation leads directly to ppz or ppz derivatives. The needed diamine **6** had previously been reported by Case[15] and by Meier and co-workers.[23] 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 **6** from **2** via 4,7-phenanthroline-5,6-dioxime **5** (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 **6** 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[14] 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[14] 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[15] 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%).[16] 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.[24−26] 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]phenanthrolin-5-yl)oxalamide.[27] 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 ^{1}H NMR measurements.

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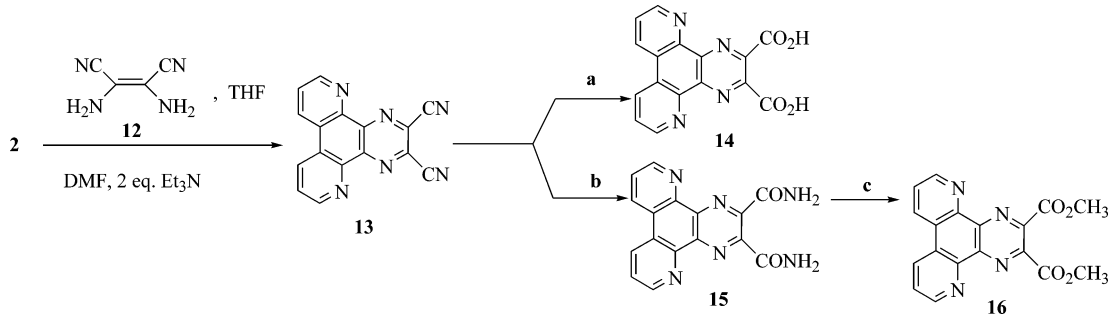
SCHEME 3. Synthesis of 13 and Other ppz Derivatives[a]



[a] Reagents and conditions: (a) 50% H_2SO_4; (b) concd H_2SO_4, rt, 3 d; (c) concd H_2SO_4, MeOH, reflux 12 h.

Another route to substituted derivatives of ppz is reaction of diaminomaleonitrile **12** with **2** (Scheme 3). Condensation leads directly to the aromatic dicyano derivative of ppz, 1,4,5,12-tetraazatriphenylene-2,3-dicarbonitrile **13** (disproportionation not possible), and it was subsequently converted to **14**, **15**, and **16** via functional group transformations. The synthesis of **13** had previously been reported[18] with 70% yield via acetic acid catalyzed condensation of **2** with excess **12**. In our study, we first attempted the synthesis by employing a simple condensation of **2** with **12** in ethanol. Although a related dicyano compound was recovered from a corresponding condensation of 1,10-phenanthroline-5,6-dione by this method, it seems that in the case of **2** reaction stopped at the hemiaminal stage.[28] Nevertheless, more forcing conditions (treatment with DMF and triethylamine) did completely convert the hemiaminal to the Schiff base (80%).

In the conversion of the dicyano compound **13** to several other new ppz derivatives, traditional standard functional group transformation methods sometimes resulted in difficulties and some modifications were necessary. Compound **13** was converted to dicarboxylic acid **14** by acidic 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 H_2SO_4, 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.

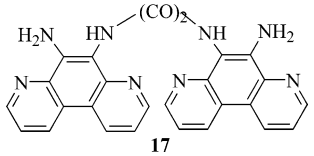
In summary, efficient procedures have been developed for the synthesis of ppz and several of its substituted derivatives. Several new ppz derivatives have been prepared (2,3-diphenyl-1,4,5,12-tetraazatriphenylene-7,2,3-dimethyl-1,4,5,12-tetraazatriphenylene **8**, 1,4,5,12-tetraazatriphenylene-2,3-diol **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-6,2,3-dipyridin-2-yl-1,4,5,12-tetraazatriphenylene **9**, 1,8,9,10,17,18-hexaazaphenanthro[9,10-*b*]-triphenylene **10**, and 1,4,5,12-tetraazatriphenylene-2,3-dicaronitrile **13**).

Experimental Section:

4,7-Phenanthroline-5,6-diamine (6).[29] An argon-flushed mixture of **2** (1.0 g, 4.76 mmol), $NH_2OH{\cdot}HCl$ (1.16 g, 16.6 mmol), and (1.41 g, 7.14 mmol) of $BaCO_3$ 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 Et_2O 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 $C_{12}H_8N_4O_2$ *m*/*z* 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 argon and refluxed. A solution of 7.0 mL of $N_2H_4{\cdot}H_2O$ 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 Et_2O, 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) δ 5.52 (s, NH_2, 4H), δ 7.47 (dd, 2H, J = 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); ^{13}C NMR (DMSO) δ 118.1, 118.2, 125.7, 131.2, 140.0, 148.7; HRMS (MH^+) calcd for $C_{12}H_{10}N_4$ *m*/*z* 211.0984, found 211.0976. Anal. Calcd for $C_{12}H_{10}N_4$: C, 68.56; H, 4.79; N, 26.65. Found: C, 68.10; H, 4.65; N, 26.36.

4′,7′-Phenanthrolino-5,6:5′6′-pyrazine (ppz) (1). To a stirred solution of diamine **6** (200 mg, 0.952 mmol) in 10 mL of anhyd EtOH under an argon atmosphere at 0 °C was added aqueous glyoxal (40%, 125.6 mg, 0.866 mmol) in absolute EtOH (6 mL) dropwise over 30 min. The solution was refluxed for 3.5 h and cooled in a refrigerator overnight. The red mixture obtained was concentrated under vacuum and dissolved in few drops of MeOH,

(27) In the absence of pyridine, the dimer *N*,*N*-bis(6-amino[4,7]-phenanthrolin-5-yl)oxalamide **17** was obtained: IR (Nujol) 1590, 1617, 1690, 3166, 3283.5, 3424.6 cm^{-1}; ^1H NMR (DMSO) δ 7.74 (br, 2H), 8.03 (dd, 2H, J = 8.4, 4.0 Hz), 8.88 (d, 2H, J = 4.0 Hz), 9.17 (d, 2H, J = 4.6 Hz), 9.40 (d, 2H, J = 8.4 Hz), 9.58 (br, 2H), 10.66 (s, 2H); ^1H NMR spectrum available in the Supporting Information; HRMS (MH^+) calcd for $C_{26}H_{18}N_8O_2$ *m*/*z* 475.1604, found 475.1617.



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(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 Et_2O (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; ^{1}H NMR ($CDCl_3$) δ 7.78 (dd, 2H, J = 8.2, 4.4 Hz), 8.89 (dd, 2H, J = 1.6, 8.2 Hz), 9.21 (s, 2H), 9.23 (dd, 2H, J = 1.6, 4.4 Hz); ^{13}C NMR ($CDCl_3$) δ 124.3, 125.8, 131.1, 142.9, 145.2, 146.0, 151.3; HRMS (MH^+) calcd for m/z $C_{14}H_8N_4$ 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 injected and refluxed for 3 h under argon. After being cooled to room temperature, the product was filtered and washed with anhyd EtOH and Et_2O to afford 333 mg (73%) of **7** as a beige solid: mp 300−301 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.37 (m, 6H), 7.73 (dd, 4H, J = 6.6, 2.0 Hz), 7.79 (dd, 2H, J = 8.4, 4.4 Hz), 8.95 (dd, 2H, J = 8.4, 1.4 Hz), 9.27 (dd, 2H, J = 4.4, 1.4 Hz); ^{13}C NMR ($CDCl_3$) δ 123.8, 125.9, 128.3, 128.9, 130.3, 131.0, 138.8, 140.5, 145.4, 151.4, 154.4; HRMS (MH^+) calcd for $C_{26}H_{16}N_4$ m/z 385.1453, found 385.1456. Anal. Calcd for $C_{26}H_{16}N_4$: C, 81.23; H, 4.20; N, 14.57. Found: C, 81.45; H, 3.98; N, 14.5. Compounds **8**−**10** were synthesized following the procedures described above.

2,3-Dimethyl-1,4,5,12-tetraazatriphenylene (8). This compound was purified by flash chromatography (2 M ammonia in MeOH/CH_2Cl_2 4.8: 0.4, R_f 0.45) to afford 83% of **8** as a white solid: mp 241−243 °C; ^{1}H NMR ($CDCl_3$) δ 2.99 (s, 6H), 7.76 (dd, 2H, J = 8.3, 4.4 Hz), 8.93 (dd, 2H, J = 8.3, 1.6 Hz), 9.26 (dd, 2H, J = 4.4, 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 123.5, 125.2, 131.0, 140.3, 145.4, 151.2, 155.2; HRMS (MH^+) calcd for $C_{16}H_{12}N_4$ m/z 261.1140, found 261.1131. Anal. Calcd for $C_{16}H_{12}N_4$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.63; H, 4.50; N, 21.06.

2,3-Dipyridin-2-yl-1,4,5,12-tetraazatriphenylene (9). This compound was purified by flash chromatography (2 M ammonia in MeOH/CH_2Cl_2 4.8: 0.4, R_f 0.67) to afford 70% of **9** as a white solid: mp > 360 °C; ^{1}H NMR ($CDCl_3$) δ 7.26 (dd, 2H, J = 7.6, 4.8 Hz), 7.81 (dd, 2H, J = 8.4, 4.4 Hz), 7.88 (dd, 2H, J = 7.6, 7.6 Hz), 8.27 (d, 2H, J = 7.6 Hz), 8.38 (d, 2H, J = 4.8 Hz), 8.96 (dd, 2H, J = 8.4, 1.6 Hz), 9.29 (dd, 2H, J = 4.4, 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 123.1, 124.0, 125.2, 126.1, 131.1, 136.8, 140.9, 145.2, 148.4, 151.5, 153.6, 157.2; HRMS (MH^+) calcd for $C_{24}H_{14}N_6$ m/z 387.1358, found 387.1360. Anal. Calcd for $C_{24}H_{14}N_6 \cdot 0.4H_2O$: C, 73.06; H, 3.65; N, 21.10. Found: C, 73.28; H, 3.71; N, 21.37.

1,8,9,10,17,18-Hexaazaphenanthro[9,10-*b*]triphenylene (10). The isolated yield was 81%: mp > 360 °C; ^{1}H NMR (CD_3OD/D_2O 10:1) δ 7.62 (dd, 4H, J = 8.0, 4.4 Hz), 8.32 (br, 4H), 8.77 (d, 4H, J = 8.0); HRMS (MH^+) calcd for $C_{24}H_{12}N_6$ m/z 385.1202, found 385.1190.

1,4,5,12-Tetraazatriphenylene-2,3-diol (11). To a vigorously stirred mixture of diamine **6** (100 mg, 0.476 mmol) in 100 mL of THF and **5** equiv of anhyd pyridine[27] (0.2 mL, 2.3 mmol) under an argon atmosphere at −78 °C was added oxalyl chloride (66.48 mg, 0.524 mmol) dropwise. After the red mixture was stirred at −78 °C for 4 h under argon, the temperature was gradually raised to room temperature, stirred for 3 h, and refluxed for 2 h. The orange mixture was filtered and the filtrate concentrated, after which 5 mL of H_2O and 0.5 mL of saturated Na_2CO_3 were added and the residue filtered and recrystallized from CH_2Cl_2 to afford 69.1 mg (55%) of **11** as a light brown solid: mp 331−332 °C dec; IR (Nujol) 1695, 3236−3612 (br) cm^{-1}; ^{1}H NMR (DMSO) δ 7.83 (dd, 2H, J = 8.0, 4.0 Hz), 9.07 (br, 2H), 9.37 (dd, 2H, J = 8.0, 1.0 Hz), 11.86 (s, 2H); HRMS (MH^+) calcd for $C_{14}H_8N_4O_2$ m/z 265.0712, found 265.0717.

1,4,5,12-Tetraazatriphenylene-2,3-dicarbonitrile (13). Dione **2** (960 mg, 4.57 mmol) was dissolved in THF (117 mL) at room temperature under argon, and with stirring **12** (544 mg, 5.03 mmol) was added and refluxed for 2 h. The solvent was evaporated, the light brown residue was redissolved in anhyd DMF (56.4 mL), and 2 equiv of Et_3N (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 (2 M ammonia in MeOH/CH_2Cl_2 4.8: 0.4, R_f 0.47) to give 103.1 mg (80%) of **13**: mp > 360 °C; ^{1}H 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); ^{13}C NMR (DMSO) δ 114.6, 126.5, 128.0, 132.5, 132.7, 142.2, 142.5, 151.9; HRMS (MH^+) calcd for $C_{16}H_6N_6$ 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 dicarbonitrile **13** (200 mg, 0.709 mmol) in 50% H_2SO_4 (14 mL) was heated under reflux for 3 h. The mixture was cooled, H_2O added (4 mL), and $NaHCO_3$ used for neutralization. Precipitation was then initiated by adding concentrated HCl (4 mL). After the mixture was stirred for 20 min, additional HCl was added until there was no more precipitation. The light yellow suspension was filtered, washed with cold H_2O, cold acetone, and Et_2O, 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 1658, 3470 cm^{-1}; ^{1}H NMR (DMSO) δ 8.01 (dd, 2H, J = 8.2, 4.4 Hz), 9.21 (dd, 2H, J = 4.4, 1.4 Hz), 9.38 (dd, 2H, J = 8.4, 1.4 Hz); ^{13}C NMR (DMSO) δ 125.3, 126.9, 132.4, 141.6, 143.6, 145.3, 151.2, 166.2; Anal. Calcd for $C_{16}H_8N_4O_4 0.7H_2O$: C, 57.73; H, 2.85; N, 16.83, found C, 57.62; H, 2.77; N, 17.19; HRMS (MH^+) calcd for $C_{16}H_8N_4O_4$ m/z 321.0624, found 321.0620.

1,4, 5,12-Tetraazatriphenylene-2,3-dicarboxylic Acid Diamide (15). A solution of dicarbonitrile **13** (200 mg, 0.709 mmol) in concd H_2SO_4 (5 mL) was stirred at room temperature for 3 d and diluted by dropwise addition to vigorously stirred ice−H_2O (20 mL). The mixture was neutralized with solid $NaHCO_3$ until no more precipitation occurred. The suspension was filtered, washed with cold H_2O, acetone, and Et_2O, 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}; ^{1}H 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 = 8.1, 1.4 Hz); HRMS (MH^+) calcd for $C_{16}H_{10}N_6O_2$ 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 diamide **15** (200 mg, 0.629 mmol) in concd H_2SO_4 (4 mL) was injected anhyd MeOH (15 mL) at room temperature. The reaction mixture was refluxed for 12 h until the full consumption of the diamide **15** was observed (TLC, 2 M ammonia in MeOH/CH_2Cl_2 2.8:1.2, R_f 0.65). The brown mixture was cooled, water was added (25 mL), and then the solution was filtered. The filtrate was neutralized with solid $NaHCO_3$. The product was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was dissolved in $CHCl_3$ (5 mL) and filtered and the filtrate concentrated to afford 151 mg (69%) of ester **16**: IR 1737 cm^{-1}; ^{1}H 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); ^{13}C NMR (DMSO) δ 52.6, 124.1, 126.0, 130.2, 141.4, 143.0, 144.0, 150.9, 163.9; HRMS (MH^+) calcd for $C_{18}H_{12}N_4O_4$ 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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