Synthesis of Bis-1,2,4-triazines via Telescoped Condensation of [1,10]-Phenanthroline-2,9-dicarbonitrile with Aromatic 1,2-Dicarbonyls Serene Tai,^a Neil J. Williams,^b and Jesse D. Carrick^a*

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Efficient separation of minor actinides from spent nuclear fuel remains a formidable challenge. As part of ongoing efforts to identify effective ligands for separation of toxic radionuclides, a series of bis-1,2,4-triazines, three novel, have been prepared from [1,10]-phenanthroline-2,9-dicarbonitrile in two-telescoped steps without additives, complicated workups, prolonged reaction times, or additional purification.

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INTRODUCTION

Efficient chemoselective extraction of minor actinides present within spent nuclear fuel in an environmentally responsible way continues to be an area of significant interest for the scientific community. Spent nuclear fuel is composed of a variety of radionuclides derived from the lanthanides and actinides. Minor actinides, Am3+ and Cm³⁺ specifically, compose just a fraction of the waste generated from spent nuclear fuel with percentage compositions less than 0.1 wt% [1]. Although low in composition, these materials display extremely long half-lives and high levels of radio toxicity, rendering their effective separation from lanthanides contained in nuclear waste streams of paramount importance [2]. Ongoing research at Oak Ridge National Laboratory (ORNL), in addition to other efforts [3], has focused on the evaluation of soft Lewis basic donor ligands for the effective separation of Am³⁺ and Cm^{3+} from spent nuclear fuel (Fig. 1).

Previous work by Kolarik [4] led to the synthesis of 2,6bis-(5,6-dialkyl-1,2,4-trizazin-3-yl) pyridines as effective heterocyclic complexants for An(III) and Ln(III). These materials also displayed high distribution values in biphasic extraction media. Lanthanides and actinides display similar electronic properties, rendering chemoselective separation challenging [5]. In order for any potential ligand to have utility on scale, current engineering processes seek a chemoselective moiety, which is stable at low pH, does not inhibit facile phase separation, possesses one or fewer *pseudo*-benzylic hydrogens [6], and is effective in a continuous flow extraction process.

Given the renewed interest in the phenanthroline scaffold (3) for the development of efficient ligands and solubility challenges frequently experienced in synthetic preparations, a direct telescoping procedure of 6 to the corresponding bis-1,2,4-triazines without additives, extended reaction times, or additional purification seemed prudent. Often, construction of bis-1,2,4-triazines employs the use of the extremely flammable and hazardous anhydrous hydrazine [7]. Herein is described an efficient two-pot (four-step) protocol using hydrazine hydrate at elevated temperature



Figure 1. Common soft Lewis basic ligand scaffolds.





followed by homogeneous condensation with functionalized aromatic 1,2-dicarbonyls in polar aprotic solvent. The desired ligands are obtained directly after treatment with an anti-solvent in good chemical purity thereby avoiding further purification via recrystallization or chromatography. Starting dicarbonitrile **6** was prepared at ORNL according to the three-step protocol described by Lewis (Scheme 1) [8].

Oxidation of commercially sourced 2,9-dimethyl-[1,10]phenanthroline with SeO₂ afforded the requisite dialdehyde **5**. One-pot hydroxamic acid formation followed by

Scheme 2. Bis-hydrazonamide formation.



 Table 1

 Synthesis of bis-1,2,4-triazines via telescoped condensation.



Entry	Dicarbonyl (2.20 equiv)	Solvent	Anti-solvent	Temp (°C)	Time (h)	Yield ^a (%)	Product
1	8 $R_1 = H$	NMP	H ₂ O	78	16	75	16
	$R_2 = H$						
2	9 $R_1 = H$	NMP	H_2O	78	16	29	17
	$R_2 = CH_3$						
3	10 $R_1 = H$	NMP	H_2O	78	16	50	18 ^b
	$R_2 = CHCH_2$						
4	11 $R_1 = H$	NMP	H_2O	78	16	55	19
	$R_2 = F$						
5	12 $R_1 = H$	NMP	H_2O	78	16	75	20
	$R_2 = Cl$						
6	13 $R_1 = H$	NMP	—	78	16	85	21
	$R_2 = Br$						
7	14 $R_1 = OMe$	NMP	H_2O	78	16	40	22
	$R_2 = H$						
8	15 $R_1 = H$	NMP	H ₂ O	78	16	0	23
	$R_2 = NMe_2$						

^aOver four steps.

^bDecomposes at ambient temperature.

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Figure 2. Spectral data for structure 7. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

sulfonation and elimination at elevated temperature afforded dinitrile **6** in 36% isolated yield over three steps. Lewis described the preparation of bis-hydrazonamide **7** using hydrazine hydrate at ambient temperature and a reaction time of 14 days. A modest increase of the reaction temperature to 40°C afforded **7** in quantitative conversion (¹H-NMR) and isolated yield after 16 h (Scheme 2).

Condensation of **7** with a series of aromatic dicarbonyls (**8–15**) with varying functionality and substitution was explored leading to the formation of **16**, **17**, and **21** described elsewhere [9] and four novel heterocycles **18–20**, and **22** (Table 1).

Dissolution of **7** (Fig. 2) in NMP followed by addition of the desired 1,2-dicarbonyl afforded a homogeneous mixture that produced the listed heterocycle after heating overnight at 78°C. Treatment of the crude mixtures with water as an anti-solvent afforded ligands (**16–22**) (Figs. 3–7) in 29–85% yield over two reaction pots (four steps) from **7**.

RESULTS AND DISCUSSION

After optimization of the reaction conditions listed in Table 1, a general trend emerged paralleling ease of



Figure 3. Spectral data for structure 16. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

condensation with the electronic nature of the substituent on the aromatic 1,2-dicarbonyl. Inductive electronwithdrawing substituents (entries 4-6) resulted in favorable condensation and yield. Inductively electron-donating substituents such as entry 2 did not afford the desired ligand in good yield. Aromatic 1,2-dicarbonyl 10 was not commercially available and was prepared via Suzuki-Miyaura coupling of the corresponding Br-derivative 13 with potassium vinyltrifluoroborate according to the Molander procedures [10]. While the divinylbenzil 10 was stable, the resulting condensation product rapidly decomposed at ambient temperature. In entry 8, possessing the strongresonance donating N,N-dimethylamino substituent no conversion to the desired bis-1,2,4-triazine was afforded [11]. 4,4'-Dimethoxybenzil was also screened under this protocol and afforded a complex mixture of products.

CONCLUSIONS

In summary, an operationally simple and efficient synthesis of useful bis-1,2,4-triazines derived from [1,10]-phenanthroline-2,9-dicarbonitrile has been achieved. Highlights of this work include quantitative conversion of

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Figure 4. Spectral data for structure 19. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

6 to **7** without additives or prolonged reaction times, efficient homogeneous condensation with aromatic 1,2-dicarbonyls containing electron-withdrawing substituents under mild conditions, and effective isolation of the desired ligands in reasonable yields over four steps from **7** without purification. Distribution studies on ligands synthesized are ongoing at ORNL. Solubility of ligands in process relevant solvents remains at the forefront of synthetic efforts, and additional ligand syntheses are ongoing in this laboratory.

EXPERIMENTAL

All reagents were purchased from U.S. chemical suppliers, stored according to published protocols, and used as received unless indicated otherwise. All experiments were performed in oven-dried glassware under an inert atmosphere of Ar except where indicated. All reported yields are listed for pure compounds as judged from ¹H-NMR spectroscopy over four total steps from the corresponding bis-1,2,4-hydrazonamide unless otherwise indicated. Infrared spectral data were obtained on a Varian (Palo Alto, CA) Excalibur 3100 FT-IR spectrometer. All ¹H-and ¹³C-NMR data were acquired on a Bruker (Billerica, MA) Avance 500 MHz or Varian Mercury 300 MHz NMR spectrometer. All chemical shifts are reported using the δ scale and are



Figure 5. Spectral data for structure 20. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

referenced to the residual solvent signal: chloroform (δ 7.26), DMSO- d_6 (δ 2.50) for ¹H and chloroform (δ 77.0) and DMSO- d_6 (δ 39.5) for ¹³C. Physical property data for **5**, **6**, and **17** have been previously reported.

General experimental conditions. [1,10]-Phenanthroline-2,9-dicarbonitrile (100 mg, 0.434 mmol, 1.00 equiv) was slurried in hydrazine hydrate-65% max (0.30 mL, 8.00 equiv) and anhydrous ethanol (2 mL) at 0°C. The mixture was heated to 40°C for 16 h. The bis-hydrazonamide was isolated via vacuum filtration as a white-crystalline solid. ¹H-NMR conversion of 6 to 7 was quantitative in DMSO- d_6 . The bis-hydrazonamide was telescoped to the condensation step without additional purification. Thus, 7 was dissolved in the polar aprotic solvent listed, and the required 1,2-dicarbonyl (2.20 equiv) was charged in one portion followed by heating to 78°C for 16h. After cooling to ambient temperature, the homogenous mixture was treated with 1 mL of water, and the resulting crystalline material was isolated by vacuum filtration and dried under reduced pressure to constant mass at 100°C.

Bis-hydrazonamide (7). [1,10]-Phenanthroline-2,9-dicarbonitrile (100 mg, 0.434 mmol, 1.00 equiv) was slurried in hydrazine hydrate-65% max (0.30 mL, 8.00 equiv) and anhydrous ethanol (2 mL) at 0°C. The mixture was heated to 40°C for 16 h. The bis-hydrazonamide was isolated via vacuum filtration as a yellow-crystalline solid. ¹H-NMR conversion of **6** to **7** was quantitative

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Figure 6. Spectral data for structure 21. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

in DMSO-*d*₆. The bis-hydrazonamide was telescoped to the condensation without additional purification. IR (solution; CHCl₃) cm⁻¹, ¹H-NMR (300 MHz, DMSO-*d*₆) δ 8.38 (d, *J*=8.60 Hz, 2H), 8.28 (d, *J*=8.50 Hz, 2H), 7.95 (s, 2H), 6.15 (br-s, 4H), 5.65 (br-s, 4H), ¹³C-NMR (75 MHz, DMSO-*d*₆) δ 151.7, 143.9, 143.6, 136.5, 128.6, 126.5, 119.4, HRMS (EI) *m*/*z*=294.1346 (294.1341) calculated for C₁₄H₁₄N₈.

2,9-Bis-(5,6-diphenyl-[1,2,4]triazin-3-yl)-[1,10]-phenanthroline (*16*). IR (solution; CHCl₃) cm⁻¹ 3633, 3392, 3055, 1618, 1486, 1443, 1379, 1221, 1135, ¹H-NMR (300 MHz, CDCl₃) δ 9.05 (dd, J = 8.40, 4.00 Hz, 2H), 8.61 (d, J = 8.40 Hz, 2H), 8.05 (s, 2H), 7.93 (d, J = 7.50 Hz, 4H), 7.73 (d, J = 7.50 Hz, 4H), 7.55–7.44 (m, 12H), ¹³C-NMR (75 MHz, solvent) δ 160.8, 156.6, 156.3, 146.6, 137.6, 135.4, 130.9, 130.4, 130.1, 130.0, 129.7, 128.7, 128.7, 127.9, 123.4, HRMS (EI) m/z = 642.2271 (642.2280 calculated for C₄₂H₂₆N₈).

2,9-Bis-[5,6-bis-(4-fluoro-phenyl)-[1,2,4]triazin-3-yl]-[1,10] phenanthroline (19). IR (solution, CHCl₃) cm⁻¹ 3070, 1602, 1487, 1381, 1227, 1160, 841, ¹H-NMR (500 MHz, DMSO- d_6 -373 K) δ 8.87 (d, J = 10.0 Hz, 2H), 8.83 (d, J = 5.0 Hz, 2H), 8.25 (s, 2H), 7.79 (br-t, J = 5.0 Hz, 4H), 7.71 (br-t, J = 5.0 Hz, 4H), 7.34 (t, J = 10.0 Hz, 4H), 7.26 (t, J = 10.0 Hz, 4H), ¹³C-NMR (125 MHz, DMSO- d_6 -373 K) δ 164.6 (d, J = 150 Hz (¹J C-F)), 162.6 (d, J = 150 Hz (¹J C-F)), 161.2, 155.8, 155.1, 152.9, 146.2, 138.0, 132.8, 132.7, 132.1, 132.0, 129.9, 128.2, 123.5, 116.1, 116.0, 115.8, 115.7, HRMS (EI) m/z = 714.1916 (714.1904 calculated for C₄₂H₂₂F₄N₈).



Figure 7. Spectral data for structure 22. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

2,9-Bis-[5,6-bis-(4-chloro-phenyl)-[1,2,4]triazin-3-yl]-[1,10] phenanthroline (20). IR (solution, CHCl₃) cm⁻¹ 3057, 1593, 1479, 1377, 1089, 1004, 831, ¹H-NMR (300 MHz, CDCl₃) δ 9.00 (d, *J*=9.0 Hz, 2H), 8.54 (d, *J*=6.0 Hz, 2H), 8.00 (s, 2H), 7.92 (d, *J*=9.0 Hz, 4H), 7.70 (d, *J*=9.0 Hz, 4H), 7.70 (d, *J*=9.0 Hz, 4H), 7.45 (d, *J*=6.0 Hz, 4H), 7.43 (d, *J*=6.0 Hz, 4H), ¹³C-NMR (75 MHz, CDCl₃) δ 160.6, 155.7, 155.6, 152.3, 146.4, 137.5, 137.4, 136.5, 133.5, 131.7, 130.8, 129.9, 129.2, 129.1, 127.8, 123.1, HRMS 778.0738 (EI) *m*/*z*=(778.0721 calculated for C₄₂H₂₂Cl₄N₈).

2,9-Bis-[5,6-bis-(4-bromo-phenyl)-[1,2,4]triazin-3-yl]-[1,10]phenanthroline (21). IR (solution, CHCl₃) cm⁻¹ 3037, 1586, 1477, 1362, 1147, 1069, 831, ¹H-NMR (300 MHz, CDCl₃) δ 9.03 (d, *J*=9.0 Hz, 2H), 8.65 (d, *J*=9.0 Hz, 2H), 8.07 (s, 2H), 7.88–7.81 (m, 4H), 7.69–7.58 (m, 12H), ¹³C-NMR (75 MHz, CDCl₃) δ 160.4, 155.2, 154.6, 152.2, 145.9, 137.8, 133.4, 132.5, 132.3, 131.3, 129.9, 127.8, 126.2, 124.9, 123.0, HRMS (ESI) *m*/*z*=954.8793 (954.8779 calculated for C₄₂H₂₃Br₄N₈ [M + H]).

2,9-Bis-[5,6-bis-(3-methoxy-phenyl)-[1,2,4]triazin-3-yl]-[1,10] phenanthroline (22). IR (solution, CHCl₃) cm⁻¹ 2935, 2832, 1580, 1482, 1379, 1038, 861, 785, ¹H-NMR (500 MHz, DMSO- d_6 -373 K) δ 8.88 (d, J = 10.0 Hz, 2H), 8.83 (d, J = 10.0 Hz, 2H), 8.25 (s, 2H), 7.39 (t, J = 10.0 Hz, 2H), 7.35–7.17 (br-m, 10H), 7.10–7.05 (m, 4H), 3.74 (s, 6H), 3.68 (s, 6H), ¹³C-NMR (125 MHz, DMSO- d_6 -373 K) δ 161.0, 159.2, 159.0, 156.2, 155.6, 152.8, 145.9, 137.7, 136.7, 129.6, 129.6, 129.5, 128.0, 123.3, 121.7, 121.7, 116.6, 115.4, 115.0, 55.2, 55.2, HRMS (EI) m/z = 762.2768 (762.2703 calculated for C₄₆H₃₄N₈O₄).

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[10] **10** was synthesized from **5** under modified Suzuki–Miyaura conditions with PdCl₂, PPh₃, CH₂CHBF₃⁻ K⁺, Cs₂CO₃, THF/H₂O, 90°C, 14 h, in 70% isolated yield as a green solid. Molander, G. A.; Brown, A. R. J Org Chem 2006, 71, 9681.

[11] A subsequent experiment in DMF also did not afford the desired ligand after treatment with 1,2-bis-(4-dimethylamino-phenyl)-ethane-1,2-dione. In both cases, the hydrazonamide **2** was observed in the crude reaction mixture. Further optimization was not investigated.