Efficient Preparation of Pyridinyl-1,2,4-Triazines via Telescoped Condensation with Diversely Functionalized 1,2-Dicarbonyls

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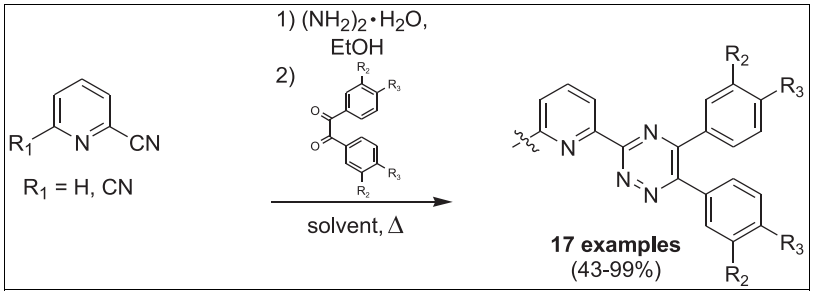
Additional Supporting Information may be found in the online version of this article.

Received August 29, 2014

DOI 10.1002/jhet.2374

Published online 00 Month 2015 in Wiley Online Library (wileyonlinelibrary.com).



The development of materials for efficient chemoselective extraction of minor actinides remains at the forefront of research efforts in the area of separation science. Lewis basic complexants derived from nitrogen-donor scaffolds are often employed in this area due to favorable complexation with the transuranic element americium. In the present work an efficient procedure for the preparation of eight useful 3-pyridin-2-yl-1,2,4-triazines (2 novel) is demonstrated via telescoped condensation with the requisite 1,2-dicarbonyl in two-pots without additives, differentially extractive work-up procedures, or recrystallization. Additional efforts in this area have demonstrated the utility of polar aprotic solvents for the preparation of nine functionalized pyridinyl-2,6-*bis*-1,2,4-triazines (4 novel) directly from the requisite 2,6-pyridine dicarbonitrile in 49–99% yield over four total steps. The streamlined preparation of these important materials and detailed synthetic procedures is reported herein.

J. Heterocyclic Chem., **00,** 00 (2015).

INTRODUCTION

The 1,2,4-triazine heterocyclic moiety is prevalent in a variety of research areas including pharmaceuticals [1], luminescent materials [2], and ligands for separation science [3]. As part of ongoing research in this laboratory to synthesize soft-*N*-donors soluble in polar solvent systems for study as chemoselective trivalent minor actinide extractants from trivalent lanthanides inherent within spent nuclear fuel a series of pyridinyl-1,2,4-triazines was prepared. Common ligand scaffolds including mono-triazinylpyridine (MTP) **1**, *bis*-triazinylpyridine (BTP) **2**, *bis*-triazinyl-bipyridine (BTBP) **3**, and *bis*-triazinylphenanthroline (BT-Phen) **4** are presented below in Figure 1. Traditional ligand scaffolds afford polydentate coordination opportunities with the central **N** atom typically possessing strong electron-donating properties, while the triazinyl **N** atom frequently must accept electron density [4].

Separation of transuranic minor actinides, specifically Am (III), from lanthanides drastically reduces the heat load, storage time, and toxicity of radioactive waste allowing for actinide recycling opportunities or the performance of further partitioning and transmutation processes [5]. Chemoselective minor actinide separation of Am^{3+} and Cm^{3+} from the lanthanides is challenging given equivalent oxidation states, as well as similar: "hard" acid properties, cationic radii, and coordination spheres [6]. Radiolytic and hydrolytic stability of synthesized ligand species in higher concentrations of nitric acid under process relevant conditions also present unique challenges for ligand development [7]. Previous work by Kolarik [8] led to the synthesis of 2,6-*bis*-(5,6-dialkyl-1,2,4-triazin-3-yl) pyridines (BTPs) as effective complexants for An(III) and Ln(III) demonstrating high distribution values. Recent reports have also illuminated the possible origins of differential selectivity of soft-*N*-donors for minor actinides over lanthanides may reside in the enhanced covalency of the ligand metal interaction [9].

Although preparations of symmetrically substituted pyridinyl-1,2,4-triazines have been documented in the literature since the 1960s [10], preparation of these materials has been largely focused on condensation of an obligatory hydrazonamide derived from the corresponding carbonitrile followed by condensation with various 1,2-dicarbonyls. Typical procedures employ hydrazonamide formation from anhydrous hydrazine or hydrazine hydrate followed by purification via recrystallization. Subsequent volume inefficient condensation with 1,2-dicarbonyls in polar protic solvents often affords incomplete conversion of the starting hydrazonamide and frequently necessitates multiple recrystallizations [11] to obtain end-products with high-levels of chemical purity. Dissemination of ligand performance in separation studies often does not include detailed synthetic procedures for the synthesis of the compounds screened [12].

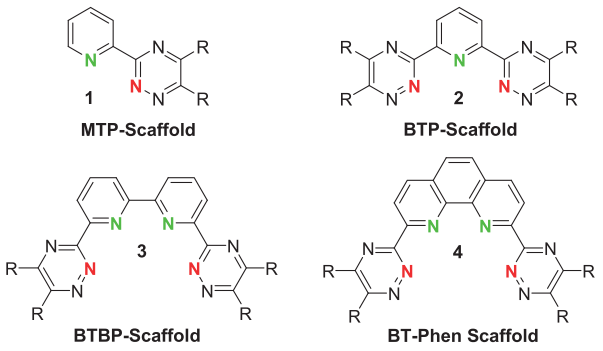


Figure 1. Common Soft-*N*-donor 1,2,4-triazinyl scaffolds. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

During a previous investigation in the area of *bis*-1,2,4-triazine synthesis on the preparation of soft-*N*-donors derived from a [1,10]-phenanthroline-2,9-dicarbonitrile scaffold it was observed that direct telescoping of the hydrazonamide through the condensation process with aromatic 1,2-dicarbonyls in a polar aprotic solvent followed by treatment of the homogeneous reaction mixture with an antisolvent, the desired *bis*-1,2,4-triazines could be afforded in moderate to good yield over four synthetic steps. As part of a larger study on the effect of ligand conformational mobility on chemoselective minor actinide extraction in polar solvents, a series of MTPs and BTPs were required. It was hypothesized that a similar procedure could be employed.

RESULTS AND DISCUSSION

In order to explore the potential of a telescoped method, complete conversion of the requisite nitrile to the desired hydrazonamide was critical. Thus, treatment of pyridine-2-carbonitrile with hydrazine hydrate at slightly elevated temperature afforded the desired hydrazonamide **6** with complete conversion after 16 h. The isolated material was judged clean by ^{1}H-NMR and telescoped directly to the condensation step (Scheme 1).

Direct telescoping of **6** with the carbonyls listed in Table 1 provided access to a diverse array of previously reported MTPs and two novel examples (**22**, **27**) in 43–87% isolated yield over two steps from **6**. It should be noted that isolated yields under this protocol were comparable [13], and in some cases, superior to previously reported procedures [14] that required substantively more complex experimental protocols. Initial solvent screening experiments in the case of entry 1 revealed that ethereal solvents, such as THF, performed superiorly overall to polar protic (EtOH or IPA) or polar aprotic solvents (DMF, DMA, DMSO, or NMP). In the case of polar aprotic solvents, treatment with water as an anti-solvent afforded inconsistent performance across the substrate scope screened, primarily due to the morphology of end products. While complete consumption of **6** was easily observed by ^{1}H-NMR by comparing pyridinyl resonances of **6** with the listed product, in all cases residual impurities during the condensation event were noted necessitating the development of an efficient purification protocol applicable to all structures screened. Initial reaction optimization focused on a decrease in the equivalents of the 1,2-dicarbonyl to promote complete formation of the desired 1,2,4-triazine without affording high levels of residual 1,2-dicarbonyl for removal. Screening experiments in the case of entry 1 with 1.20, 1.10, and 1.00 equivalents of the 1,2-dicarbonyl, as well as inverse stoichiometry with respect to **6** being in 10 mol% excess, did not provide measurable performance advantages. While successive recrystallization has been typically employed for purification of end products, such endeavors often afford the desired 1,2,4-triazine in low yield. The diverse array of compounds prepared would necessitate individual solvents or solvent systems for recrystallization and subsequent isolation of pure material. The compounds synthesized were all quite polar as expected from thin-layer chromatographic analysis using normal stationary phase silica gel. A strategic opportunity did exist, however, given the relative ease of separation between the 1,2-dicarbonyl and the desired product. As such, concentration of the crude reaction mixtures under reduced pressure, followed by a short plug filtration with silica gel, afforded the desired ligand species in moderate to good yields over two steps (Table 1).

Results from this initial investigation revealed wide functional group tolerance of the 1,2-dicarbonyl. Entry 2 with the weakly donating 4,4′-methyl substituent was obtained in 70% yield. Deactivating halogen substituents (entries 3–5) performed excellent under the listed conditions. Incorporation of strongly resonance donating substituents on the 4,4′-benzil moiety such as the *N,N′*-dimethyl or 4,4′-hydroxyl group did not afford any desired 1,2,4-triazine. It is hypothesized that diminished electrophilicity of the reacting carbonyl through resonance donation via the substituents on the aromatic group is responsible for this observation; an observation commensurate with our earlier work on the [1,10]-phenanthroline-2,9-dicarbonitrile scaffold. It should be highlighted that the described work was successful for some lesser electron-donating substituents on the benzil including 3,3′-OMe (entry 7) in addition to 4,4′-OMe (entry 8). Aliphatic dicarbonyls were also investigated using the listed procedure (entries 10–12). Preparation of **29** was successful, but the attempted synthesis of **30** was not. Formation of **28** was confirmed by ^{1}H-NMR of the crude

Scheme 1. Synthesis of 2-pyridinyl hydrazonamide.

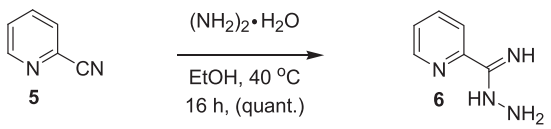
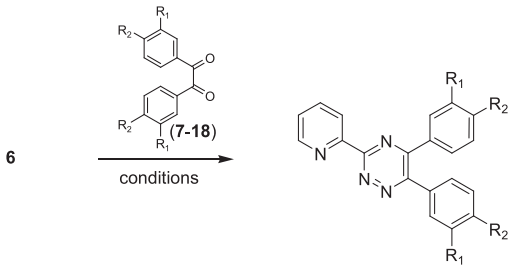
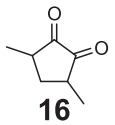
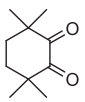


Table 1

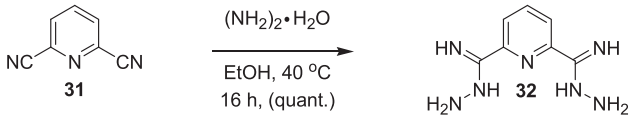
Synthesis of telescoped 2-pyridinyl-1,2,4-triazinyl pyridines.



Entry	Dicarbonyl (1.00 equiv)	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	Product
1	**7** $R_1 = H$ $R_2 = H$	THF	66	16	56	**19**
2	**8** $R_1 = H$ $R_2 = CH_3$	THF	66	16	52	**20**
3	**9** $R_1 = H$ $R_2 = F$	THF	66	16	79	**21**
4	**10** $R_1 = H$ $R_2 = Cl$	THF	66	16	43	**22**
5	**11** $R_1 = H$ $R_2 = Br$	THF	66	16	70	**23**
6	**12** $R_1 = H$ $R_2 = NMe_2$	THF	66	16	0[c]	**24**
7	**13** $R_1 = H$ $R_2 = OH$	THF	66	16	0[c]	**25**
8	**14** $R_1 = H$ $R_2 = OMe$	THF	66	16	45	**26**
9	**15** $R_1 = OMe$ $R_2 = H$	THF	66	16	58	**27**
10	 **16**	THF	66	16	63[c]	**28**
11	 **17**	THF	66	16	87	**29**
12	 **18**	THF	66	16	0[d]	**30**

[a]Unoptimized isolated yield over two telescoped steps from **6**.
[b]Starting material recovered.
[c]Conversion of **6** observed by ^{1}H-NMR, product confirmed by HRMS, purification unsuccessful.
[d]Numerous materials observed by ^{1}H-NMR. Typical experimental procedure: Telescoped 6 (0.73 mmol, 1.00 equiv) and the requisite dicarbonyl (0.73 mmol, 1.00 equiv) were dissolved in anhydrous THF (1.5 mL, 0.5 M) in an 8-mL reaction vial equipped with a magnetic stir bar and heated to 66°C for the time indicated. Afterwards, the homogeneous mixtures were concentrated under reduced pressure and adsorbed on a minimal amount of SiO_2. Elution with 40% EtOAc:hexanes (40 mL) removed the residual 1,2-dicarbonyl and observed impurities. Subsequent elution with 10% MeOH:DCM (30 mL) followed by concentration under reduced pressure afforded the desired ligands in the yield indicated.

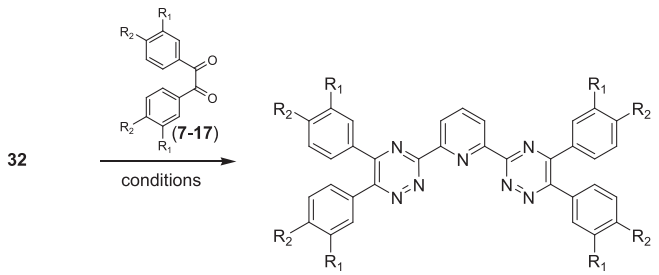
Scheme 2. Synthesis of 2,6-pyridinyl-*bis*-hydrazonamide.

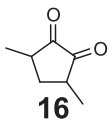
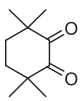


reaction mixture, but consistently afforded impure material upon isolation. Extensive optimization towards the acquisition of **30**, outside of the conditions listed, was not fruitful, although further effort continues. With the preparation of MTP analogues efficiently streamlined and applied to three

Table 2

Synthesis of telescoped 2,6-pyridinyl-*bis*-1,2,4-triazinyl pyridines.



Entry	Dicarbonyl (2.00 equiv)	Solvent	Antisolvent	Temp (°C)	Time (h)	Yield[b] (%)	Product
1	**7** $R_1 = H$ $R_2 = H$	THF	-----	66	16	96	**33**
2	**8** $R_1 = H$ $R_2 = CH_3$	NMP	H_2O	80	16	88	**34**
3	**9** $R_1 = H$ $R_2 = F$	DMF	H_2O	80	16	98	**35**
4	**10** $R_1 = H$ $R_2 = Cl$	DMF	H_2O	80	16	80	**36**
5	**11** $R_1 = H$ $R_2 = Br$	DMF	-----	80	16	99	**37**
6	**12** $R_1 = H$ $R_2 = NMe_2$	DMF	-----	80	16	0[c]	**38**
7	**13** $R_1 = H$ $R_2 = OH$	DMF	-----	80	16	49	**39**
8	**14** $R_1 = H$ $R_2 = OMe$	DMF	-----	80	16	54	**40**
9	**15** $R_1 = OMe$ $R_2 = H$	DMF	-----	80	16	85[c]	**41**
10	 **16**	DMF	-----	80	16	0[c]	**42**
11	 **17**	DMF	H_2O	80	16	91	**43**

[a]Unoptimized, isolated yield over two telescoped steps from **32**.
[b]Starting material recovered.
[c]Product co-crystalized with residual 1,2-dicarbonyl (**14**) and was recrystallized from toluene (15 vol) to afford **40** in the listed yield. Typical experimental procedure: Telescoped **32** (0.52 mmol, 1.00 equiv) and the requisite dicarbonyl (1.09 mmol, 2.10 equiv) were dissolved in the anhydrous solvent listed (1.5 mL, 0.35 M) in an 8-mL reaction vial equipped with a magnetic stir bar and heated to the listed temperature for the time indicated. Afterwards, the desired end-product was isolated by vacuum filtration and dried to constant mass.

novel heterocycles (**22**, **27**), our attention turned towards the production of BTP analogues. Relying on our previous work in this area it was postulated that the utility of polar aprotic solvents with high dielectric constants could be an initial starting point for method development.

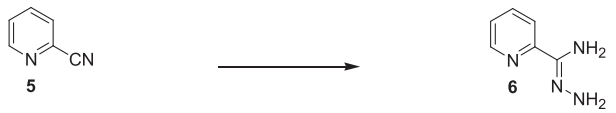
Formation of the requisite *bis*-hydrazonamide (**32**) was accomplished pursuant to the previously described protocol (Scheme 2). Thus, treatment of pyridine 2,6-dicarbonitrile with hydrazine hydrate at elevated temperature afforded **32** in quantitative conversion by ^{1}H-NMR. The isolated material was telescoped directly to the corresponding *bis*-1,2,4-triazine synthesis with various 1,2-dicarbonyls without additional purification (Table 2).

As described in Table 2, selection of an appropriate polar aprotic solvent was critical to reaction success. Pleasingly, direct telescoping of **32** with the appropriate 1,2-dicarbonyl (**7-17**) in the solvent listed afforded isolable solids that precipitated as a function of time; necessarily increasing product formation by suppression of retro-cyclization events. Attempts to further optimize stoichiometry as previously described for the examples in Table 1 did not lead to any substantive improvement in reaction performance. The scope of the method was broad and enabled access to aromatic *bis*-1,2,4-triazines with electron donating (**34**, **40–41**) and withdrawing functionality (**35–37**) in good to excellent yield over four synthetic steps without any additional purification [15] or manipulation. *Bis*-1,2,4-Triazines derived from dicarbonyls with aliphatic character (**16–17**) were also easily obtainable under the conditions listed. Similar to scaffold **6**, strong resonance donating substituents on benzil **12** failed to afford any product, thereby reinforcing the previously stated hypothesis regarding the deleterious effect on suppression of carbonyl electrophilicity by strong activating substituents in the 4,4′-positions of the aromatic benzil required for condensation. Contradictory evidence to the previously stated hypothesis was observed in the context of 4, 4′-hydroxy benzil **13** which was unsuccessful in the condensation with **6** or the [1,10]-phenanthroline scaffold, but was successful with hydrazonamide **32** in 49% yield. Interestingly, in the case of the [1,10]-phenanthroline scaffold previously reported, the weakly activating methyl substituent on benzil **8**, as well as the strongly activating methoxy substituent on benzil **15**, did not afford clean conversion/isolation, whereas on scaffold **32** good conversion and isolated yield were observed. During the course of our investigation three new 2,6-pyridinyl-*bis*-1,2,4-triazinyl pyridines (**35**, **39**, **41**) were prepared using the method described. Forthcoming results from this laboratory are focused on site-selective manipulation of resident functionality towards the preparation of more efficient ligand species via modular approaches.

CONCLUSIONS

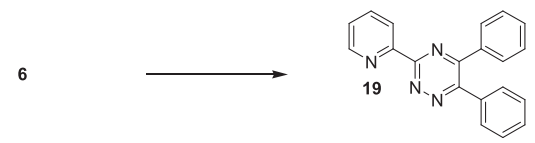
In summary, we have demonstrated two efficient methods for the construction 3-pyridin-2-yl-1,2,4-triazines and 2,6-pyridinyl-*bis*-1,2,4-triazines utilizing a focused approach which leverages the necessary telescoped hydrazonamides and the appropriate choice of solvent. While no one set of reaction conditions will ever be amenable to all possible structural variations, the methods described represent, to the best of our current knowledge, the first streamlined procedure for direct access to a broad representation of MTPs and BTPs in good to excellent yields over two and four synthetic steps, respectively. Use of this method enables rapid acquisition of the listed heterocycles without prolonged reaction times, aqueous workups, or successive recrystallization in two days instead of several days under existing protocols in comparable, and in some cases superior yields to previously reported procedures.

EXPERIMENTAL

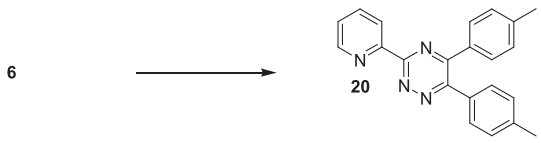


Hydrazonamide (6). Pyridine-2-carbonitrile (0.500 g, 4.80 mmol, 1.00 equiv) was dissolved in absolute ethanol (0.50 mL, 9.60 M) and treated dropwise with hydrazine monohydrate (60–65% hydrazine) (1.50 mL, 19.21 mmol, 4.00 equiv) at 0°C and continued for an additional hour. Afterwards, the homogeneous mixture was allowed to gradually warm to ambient temperature and heated to 40°C for 12 h. Afterwards, the volume of the reaction was reduced by half under reduced pressure, and the heterogeneous mixture was filtered under vacuum at ambient temperature to afford a yellow filter cake that was conditioned with 10 mL of 0°C hexanes. The resulting solids were analyzed by ^{1}H-NMR confirming consumption of all starting material and were telescoped directly to the condensation step with the appropriate 1,2-dicarbonyl. IR (solid) cm^{-1} 3436 (vs), 3285 (vs), 3173 (vs), 3060 (s), 1634 (s), 1588 (s), 1561 (s), 1380 (m), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 6.00 Hz, 1H), 8.00 (d, J = 6.00 Hz, 1H), 7.71–7.65 (m, 1H), 7.28–7.23 (m, 1H), 5.27 (br-s, 2H), 4.49 (br-s, 2H), ^{13}C-NMR (75 MHz, $CDCl_3$) δ 150.64, 148.34, 147.70, 136.17, 123.54, 119.51, HRMS (EI) m/z = 136.0753 (136.0749) calculated for $C_6H_8N_4$.

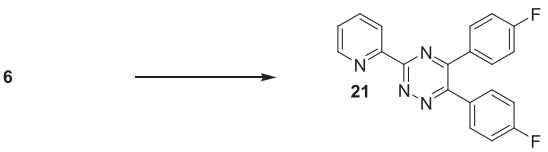
General procedure for the preparation of 2,6-pyridinyl-bis-1,2,4-triazines. To an 8-mL reaction vial equipped with a magnetic stir bar at ambient temperature was added **6** (0.100 g, 0.73 mmol, 1.00 equiv) and the required dicarbonyls (0.73 mmol, 1.00 equiv). The mixture was dissolved in the solvent listed and heated to the temperature described over the period of time indicated. Afterwards, the mixture was cooled to ambient temperature and adsorbed onto 5 g of normal phase SiO_2. The adsorbed solids were placed on a 1.5-cm column (3 g of SiO_2 slurried in 40% EtOAc: hexanes) and treated with a 40% EtOAc:hexanes mobile phase (40 mL) to remove the residual 1,2-dicarbonyl and lower polarity impurities. Afterwards, the column was flushed with a 10% MeOH: DCM mobile phase (30 mL) to elute the desired heterocycle. The eluent was concentrated under reduced pressure at ambient temperature to afford the desired compound in the morphology described in the listed yield.



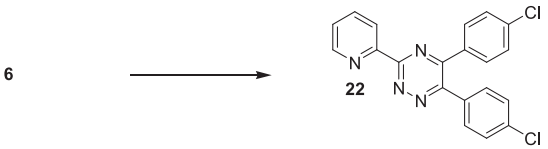
5,6-Diphenyl-3-Pyridin-2-yl-[1,2,4]triazine (19). $R_F = 0.71$ in 100% EtOAc, IR (solid) cm^{-1} 3058 (w), 1501 (m), 1493 (m), 1391 (m), 1368 (m), 697 (vs), ^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.02 (d, $J = 5.00$ Hz, 1H), 8.80 (d, $J = 10.00$ Hz, 1H), 8.06 (dt, $J = 5.00$, 1.00 Hz, 1H), 7.78 (d, $J = 10.00$ Hz, 2H), 7.66-7.64 (m, 2H), 7.61-7.59 (m, 1H), 7.48-7.35 (m, 6H), ^{13}C-NMR (125 MHz, $CDCl_3$) δ 159.47, 156.78, 156.45, 151.58, 149.30, 138.72, 135.22, 135.14, 130.97, 130.20, 129.99, 129.56, 128.68, 128.56, 125.88, 124.42, HRMS (EI) $m/z = 310.1219$ (310.1218) calculated for $C_{20}H_{14}N_4$.



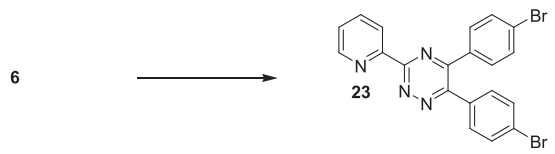
3-Pyridin-2-yl-5,6-di-p-tolyl-[1,2,4]triazine (20). $R_F = 0.30$ in 10% MeOH: DCM, IR (solid) cm^{-1} 3058 (vw), 2920 (vw), 2867 (w), 1609 (w), 1572 (w), 1492 (s), 1389 (vs), 821 (s), 726 (s), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.91 (d, $J = 6.00$ Hz, 1H), 8.70 (dd, $J = 6.00$, 3.00 Hz, 1H), 7.95-7.90 (m, 1H), 7.61 (d, $J = 6.00$ Hz, 2H), 7.54 (d, $J = 6.00$ Hz, 2H), 7.49-7.45 (m, 1H), 7.20-7.15 (m, 4H), 2.39 (s, 3H), 2.37 (s, 3H) ^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.23, 156.37, 156.12, 152.82, 150.23, 141.21, 139.92, 137.27, 132.79, 132.56, 129.93, 129.40, 129.35, 129.27, 125.33, 124.07, 21.51, 21.43, HRMS (EI) $m/z = 338.1530$ (338.1531) calculated for $C_{22}H_{18}N_4$.



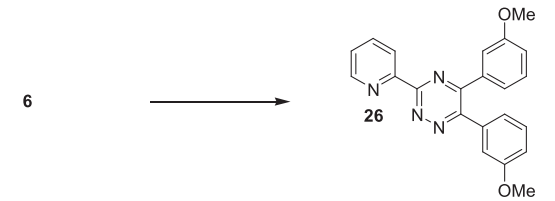
5,6-Bis-(4-fluoro-phenyl)-3-pyridin-2-yl-[1,2,4]triazine (21). IR (solid) cm^{-1} 3050 (vw), 1582 (w), 1485 (w), 1389 (m), 1366 (s), 773 (s), 696 (vs), ^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.00 (d, $J = 5.00$ Hz, 1H), 8.79 (d, $J = 5.00$ Hz, 1H), 8.07-8.04 (m, 1H), 7.77 (d, $J = 10.00$ Hz, 2H), 7.64 (d, $J = 10.00$ Hz, 2H), 7.60-7.58 (m, 1H), 7.46-7.34 (m, 4H), ^{13}C-NMR (125 MHz, $CDCl_3$) δ 159.53, 156.74, 156.42, 151.63, 149.34, 138.62, 135.22, 135.13, 131.07, 130.16, 129.90, 129.54, 128.64, 128.57, 125.83, 124.39, HRMS (EI) $m/z = 346.1043$ (346.1030) calculated for $C_{20}H_{12}F_2N_4$.



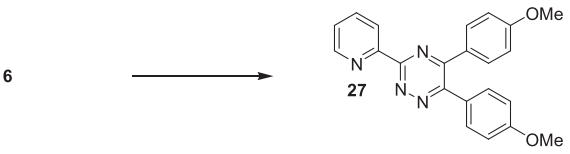
5,6-Bis-(4-chloro-phenyl)-3-pyridin-2-yl-[1,2,4]triazine (22). $R_F = 0.52$ in 40% EtOAc:hexanes, IR (solid) cm^{-1} 3060 (vw), 1595 (m), 1571 (vw), 1488 (m), 1388 (m), 1093 (m), 833 (w), 729 (vs), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.93 (d, $J = 5.00$ Hz, 1H), 8.71 (d, $J = 5.00$ Hz, 1H), 7.95-7.93 (m, 1H), 7.65 (d, $J = 15.00$ Hz, 2H), 7.59 (d, $J = 15.00$ Hz, 2H), 7.54-7.52 (m, 1H), 7.42-7.36 (m, 4H), ^{13}C-NMR (125 MHz, $CDCl_3$) δ 160.61, 155.29, 155.06, 155.24, 150.36, 137.46, 137.38, 136.41, 133.62, 133.34, 131.27, 130.78, 129.14, 129.09, 125.68, 124.25, HRMS (EI) $m/z = 378.0440$ (378.0439) calculated for $C_{20}H_{12}Cl_2N_4$.



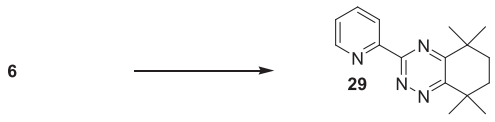
5,6-Bis-(4-bromo-phenyl)-3-pyridin-2-yl-[1,2,4]triazine (23). $R_F = 0.65$ in 10% MeOH: DCM, IR (solid) cm^{-1} 3062 (w), 1587 (m), 1569 (w), 1480 (s), 1383 (vs), 1069 (vs), 818 (s), 788 (m), ^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.04 (d, $J = 5.00$ Hz, 1H), 8.83 (d, $J = 10.00$ Hz, 1H), 8.13 (dt, $J = 10.00$, 5.00 Hz, 1H), 7.72 (d, $J = 10.00$ Hz, 2H), 7.68-7.65 (m, 1H), 7.59-7.52 (m, 6H), ^{13}C-NMR (125 MHz, $CDCl_3$) δ 159.07, 155.68, 155.24, 150.65, 148.89, 139.50, 133.65, 133.59, 132.40, 132.22, 131.77, 131.00, 126.45, 126.34, 125.13, 124.64, HRMS (EI) $m/z = 465.9441$ (465.9429) calculated for $C_{20}H_{12}Br_2N_4$.



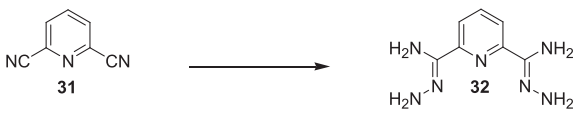
5,6-Bis-(3-methoxy-phenyl)-3-pyridin-2-yl-[1,2,4]triazine (26). $R_F = 0.32$ in 10% MeOH:DCM, IR (solid) cm^{-1}, 3062 (vw), 2962 (vw), 2941 (vw), 2836 (vw), 1698 (w), 1599 (m), 1582 (s), 1388 (vs), 1366 (s), 1243 (s), 784 (m), 701 (m), ^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.06 (d, $J = 5.00$ Hz, 1H), 8.84 (d, $J = 5.00$ Hz, 1H), 8.13 (t, $J = 5.00$ Hz, 1H), 7.68-7.66 (m, 1H), 7.46 (br-s, 1H), 7.32-7.24 (m, 4H), 7.18 (d, $J = 5.00$ Hz, 1H), 7.02-6.99 (m, 2H), 3.79 (s, 3H), 3.77 (s, 3H), ^{13}C-NMR (125 MHz, $CDCl_3$) δ 159.75, 158.97, 156.75, 156.42, 150.99, 148.76, 139.41, 139.41, 136.29, 129.70, 129.55, 126.10, 124.55, 122.65, 122.07, 117.75, 116.35, 114.96, 114.79, 114.35, 55.60, 55.34, HRMS (EI) $m/z = 370.1434$ (370.1430) calculated for $C_{22}H_{18}N_4O_2$.



5,6-Bis-(4-methoxy-phenyl)-3-pyridin-2-yl-[1,2,4]triazine (27). $R_F = 0.31$ in 10% MeOH:DCM, IR (solid) cm^{-1} 3061 (vw), 2964 (vw), 2937 (vw), 2840 (vw), 1607 (m), 1491 (m), 1372 (m), 1255 (vs), 730 (vs), ^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.05-9.01 (m, 1H), 8.80-8.78 (m, 1H), 8.08 (dt, $J = 7.50$, 5.00 Hz, 1H), 7.87-7.84 (m, 2H), 7.65-7.59 (m, 3H), 6.94-6.92 (m, 2H), 6.89-6.87 (m, 2H), ^{13}C-NMR (125 MHz, $CDCl_3$) δ 162.09, 161.07, 158.45, 155.98, 155.43, 151.45, 148.81, 139.12, 132.05, 130.88, 127.71, 127.42, 125.77, 124.30, 114.21, 114.09, 55.37, 55.33, HRMS (EI) $m/z = 370.1438$ (370.1430) calculated for $C_{22}H_{18}N_4O_2$.

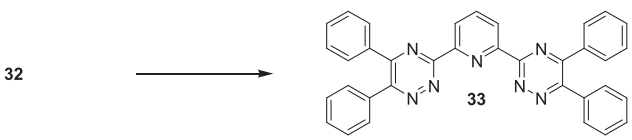


5,5,8,8-Tetramethyl-3-pyridin-2-yl-5,6,7,8-tetrahydro-benzo [1,2,4]triazine (29). $R_F = 0.15$ in 10% MeOH:DCM, IR (solid) cm^{-1} 2962 (m), 2935 (m), 1517 (m), 1472 (m), 1394 (vs), 1361 (w), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.88 (d, $J = 6.00$ Hz, 1H), 8.54 (d, $J = 9.00$ Hz, 1H), 7.91-7.86 (m, 1H), 7.45-7.41 (m, 1H), 1.86 (s, 4H), 1.50 (s, 6H), 1.45 (s, 6H), ^{13}C-NMR (75 MHz, $CDCl_3$) δ 164.12, 162.66, 160.29, 153.00, 149.74, 136.60, 124.57, 123.39, 36.83, 36.03, 33.33, 32.89, 29.29, 28.76, HRMS (EI) $m/z = 268.1680$ (268.1688) calculated for $C_{16}H_{20}N_4$.

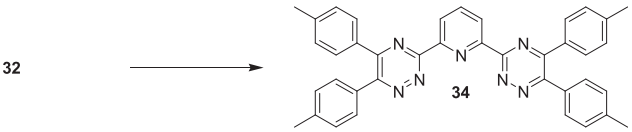


Bis-Hydrazonamide (32). Pyridine-2,6-dicarbonitrile (1.00 g, 7.75 mmol, 1.00 equiv) was dissolved in absolute ethanol (4.00 mL, 1.90 M) and treated dropwise with hydrazine monohydrate (60-65% hydrazine) (4.80 mL, 61.96 mmol, 8.00 equiv) at 0°C and continued for an additional hour. Afterwards, the slurry was allowed to gradually warm to ambient temperature and heated to 40°C for 12 h. Afterwards, the heterogeneous mixture was filtered under reduced pressure at ambient temperature, and the filter cake was conditioned with (5 mL) of 0°C ethanol. The resulting solids were analyzed by ^{1}H-NMR confirming consumption of all starting material and were telescoped directly to the condensation step with the appropriate 1,2-dicarbonyl. IR (solid) cm^{-1} 3448 (w), 3289 (w), 1660 (w), 1585 (w), 1568 (w), 1381 (w), ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.80-7.77 (m, 2H), 7.65-7.60 (m, 1H), 6.04 (br-s, 4H), 5.12 (br-s, 4H), ^{13}C-NMR (75 MHz, DMSO-d_6) δ 150.74, 144.06, 136.44, 118.42, HRMS (EI) $m/z = 193.1080$ (193.1076) calculated for $C_7H_{11}N_7$.

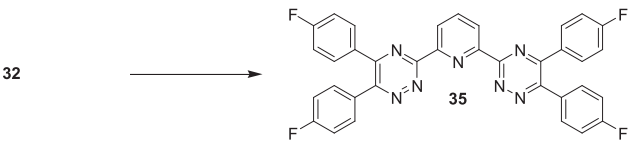
General procedure for the preparation of 2,6-pyridinyl-bis-1,2,4-triazines. To an 8-mL reaction vial equipped with a magnetic stir bar at ambient temperature was added **32** (0.100 g, 0.52 mmol, 1.00 equiv) and the required 1,2-dicarbonyl (1.09 mmol, 2.10 equiv). The mixture was dissolved in the solvent listed and heated to the temperature described over the period of time indicated. Afterwards, the mixture was cooled to ambient temperature and the solids were isolated via filtration under reduced pressure at ambient temperature to afford the desired compound in the indicated yield.



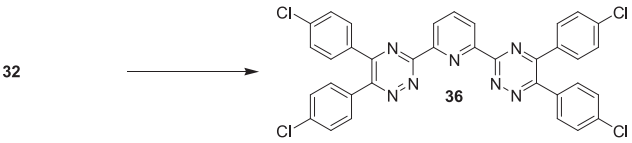
BTP-phenyl (33). IR (solid) cm^{-1} 3062 (vw), 1503 (w), 1487 (w), 1436 (w), 1374 (s), 762 (s), 701 (vs), 537 (m), ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.91 (d, $J = 5.00$ Hz, 2H), 8.26 (t, $J = 5.00$ Hz, 1H), 7.82-7.80 (m, 4H), 7.68-7.66 (m, 4H), 7.50-7.45 (m, 4H), 7.42-7.38 (m, 8H), ^{13}C-NMR (125 MHz, $CDCl_3$), 159.75, 156.72, 156.69, 152.73, 138.97, 135.32, 134.99, 131.11, 130.17, 130.01, 129.59, 128.71, 128.58, 125.88, HRMS (EI) $m/z = 541.2008$ (541.2015) calculated for $C_{35}H_{23}N_7$.



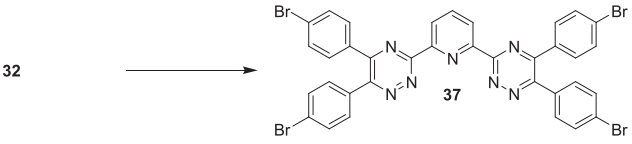
BTP-4,4′-dimethylphenyl (34). IR (solid) cm^{-1} 3029 (vw), 2947 (vw), 2919 (vw), 2863 (vw), 1607 (w), 1581 (w), 1488 (m), 1442 (vw), 1371 (vs), 824 (s), 800 (s), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.88 (d, $J = 9.00$ Hz, 1H), 8.17 (t, $J = 9.00$ Hz, 2H), 7.73 (d, $J = 6.00$ Hz, 2H), 7.59 (d, $J = 9.00$ Hz, 2H), 7.23-7.18 (m, 4 H), 2.40 (s, 6H), ^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.17, 156.28, 155.98, 153.58, 141.29, 139.97, 138.24, 132.84, 132.62, 130.07, 129.41, 129.38, 129.25, 125.39, 21.58, 21.46, HRMS (EI) $m/z = 597.2655$ (597.2641) calculated for $C_{39}H_{31}N_7$.



BTP-4,4′-difluorophenyl (35). IR (solid) cm^{-1} 3062 (vw), 1599 (s), 1581 (w), 1489 (s), 1354 (s), 1226 (vs), 840 (vs), 817 (s), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.90 (d, $J = 9.00$ Hz, 2H), 8.22 (t, $J = 9.00$ Hz, 1H), 7.82-7.77 (m, 4H), 7.69-7.66 (m, 4H), 7.16-7.07 (m, 8H), ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.18, 165.55, 162.80, 162.22, 160.31, 155.46, 155.09, 153.22, 138.57, 132.34 (d, $J = 36.60$ Hz), 131.58 (d, $J = 36.60$ Hz), 131.33 (d, $J = 13.80$ Hz), 131.12 (d, $J = 13.80$ Hz), 125.83, HRMS (EI) $m/z = 613.1635$ (613.1638) calculated for $C_{35}H_{19}F_4N_7$.

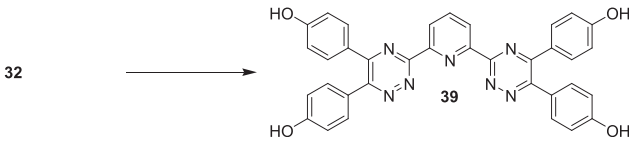


BTP-4,4′-dichlorophenyl (36). IR (solid) cm^{-1} 3067 (vw), 1594 (m), 1571 (m), 1490 (s), 1372 (vs), 1090 (vs), 822 (s), 799 (s), ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.94 (d, $J = 5.00$ Hz, 2H), 8.32 (t, $J = 5.00$ Hz, 1H), 7.92 (d, $J = 10.00$ Hz, 4H), 7.64 (d, $J = 10.00$ Hz, 4H), 7.43 (d, $J = 10.00$ Hz, 4H), 7.40 (d, $J = 10.00$ Hz, 4H), ^{13}C-NMR (125 MHz, $CDCl_3$) δ 159.16, 151.91, 139.79, 138.17, 136.94, 133.25, 132.91, 131.59, 130.88, 129.32, 129.11, 128.27, 127.91, 126.42, HRMS (EI) $m/z = 677.0434$ (677.0456) calculated for $C_{35}H_{19}Cl_4N_7$.

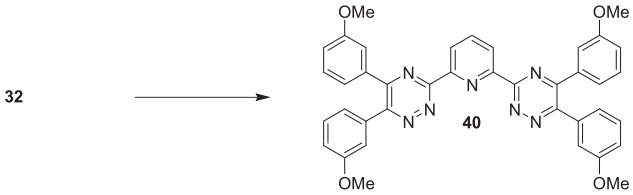


BTP-4,4′-dibromophenyl (37). IR (solid) cm^{-1} 3063 (w), 1588 (m), 1568 (w), 1496 (s), 1371 (vs), 1067 (vs), 1003 (vs), 820 (vs), 797 (s), ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.94 (d, $J = 10.00$ Hz, 2H), 8.31 (t, $J = 10.00$ Hz, 1H), 7.70 (d, $J = 10.00$ Hz, 4H), 7.63-7.56 (m, 12H), ^{13}C-NMR (125 MHz, $CDCl_3$) δ 159.42, 155.75, 155.55, 152.15, 139.58, 133.77,

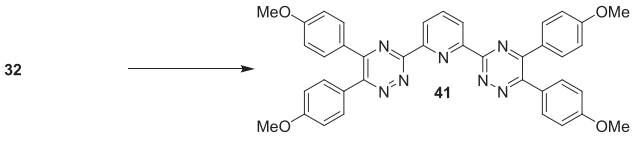
133.40, 132.29, 132.22, 131.64, 131.09, 126.59, 126.28, 125.30, HRMS (EI) $m/z = 854.8409$ (854.8415) calculated for $C_{35}H_{19}Br_4N_7$ ($3 \times {}^{79}Br$; $1 \times {}^{81}Br$)



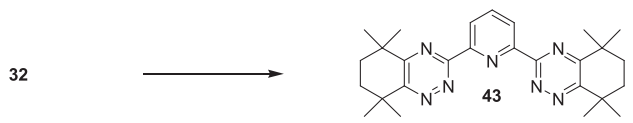
BTP-4,4′-dihydroxyphenyl (39). IR (solid) cm^{-1}, 3109 (br), 1652 (s), 1606 (vs), 1586 (vs), 1367 (vs), 1170 (s), 835 (m), 808 (m), ^{1}H-NMR (500 MHz, DMSO-d_6) δ 10.17 (s, 2H), 9.94 (s, 2H), 8.70 (d, $J = 10.00$ Hz, 2H), 8.32 (t, $J = 10.00$ Hz, 1H), 7.64-7.61 (m, 4H), 7.51-7.48 (m, 4H), 6.88-6.85 (m, 4H), 6.84-6.81 (m, 4H), ^{13}C-NMR (125 MHz, DMSO-d_6) δ 160.13, 159.54, 158.85, 155.58, 154.70, 153.39, 138.54, 131.57, 130.68, 126.20, 125.88, 125.13, 116.09, 115.45, HRMS (EI and MALDI-TOF failed due to extremely poor vaporization at maximum temp of 450 °C) $m/z = (605.1812)$ calculated for $C_{35}H_{23}N_7O_4$.



BTP-3,3′-dimethoxyphenyl (40). IR (solid) cm^{-1} 3060 (vw), 2970 (vw), 2934 (vw), 2840 (vw), 1673 (m), 1661 (m), 1462 (m), 1365 (s), 1232 (vs), 1039 (vs), 784 (vs), 703 (m), ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.92 (d, $J = 10.00$ Hz, 2H), 8.28 (t, $J = 10.00$ Hz, 1H), 7.36-7.27 (m, 10H), 7.16 (d, $J = 10.00$ Hz, 2H), 7.04-6.95 (m, 4H), 3.77 (s, 3H), 3.70 (s, 3H), ^{13}C-NMR (125 MHz, $CDCl_3$) δ 159.81, 159.60, 159.51, 156.85, 156.64, 152.39, 139.25, 136.37, 136.07, 129.71, 126.14, 122.58, 122.12, 117.51, 116.46, 114.96, 114.92, 114.37, 55.38, 55.35, HRMS (EI) $m/z = 661.2466$ (661.2438) calculated for $C_{39}H_{31}N_7O_4$.



BTP-4,4′-dimethoxyphenyl (41). IR (solid) cm^{-1} 3020 (vw), 2965 (vw), 2935 (vw), 2838 (vw), 1604 (s), 1575 (m), 1485 (s), 1372 (vs), 1253 (vs), 1170 (s), 834 (s), 812 (m), ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.84 (d, $J = 5.00$ Hz, 2H), 8.20 (t, $J = 5.00$ Hz, 1H), 7.80 (d, $J = 5.00$ Hz, 4H), 7.63 (d, $J = 5.00$ Hz, 4H), 6.92 (d, $J = 5.00$ Hz, 4H), 6.88 (d, $J = 5.00$ Hz, 4H), 3.85 (s, 3H), 3.84 (s, 3H), ^{13}C-NMR (125 MHz, $CDCl_3$) δ 162.24, 161.10, 159.98, 155.94, 155.72, 152.64, 138.68, 131.96, 130.90, 127.45, 125.65, 114.22, 114 (unresolved), 114.09, 55.40, 55.34, HRMS (EI) $m/z = 661.2462$ (661.2438) calculated for $C_{39}H_{31}N_7O_4$.



BTP-tetramethylcyclohexyl (43). IR (solid) cm^{-1} 3076 (vw), 2964 (m), 2933 (m), 1518 (s), 1505 (m), 1457 (s), 1387 (m), 1361 (vs), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.69 (d, $J = 6.00$ Hz, 2H), 8.10 (t, $J = 6.00$ Hz, 1H), 1.88 (s, 4H), 1.51 (s, 6H), 1.48 (s, 6H), ^{13}C-NMR (75 MHz, $CDCl_3$) δ 164.97, 163.38, 160.66, 153.77, 138.04, 125.19, 37.40, 36.58, 33.69, 33.43, 29.76, 29.12, HRMS (EI) $m/z = 457.2966$ (457.2954) calculated for $C_{27}H_{35}N_7$.

Acknowledgments. Financial support for this project was provided by a grant from the Fuel Cycle Research and Development program, Office of Nuclear Energy, U.S. Department of Energy, and the Tennessee Technological University Department of Chemistry. Support from NSF-RUI 9970016 is gratefully acknowledged for the acquisition of the department's 300-MHz NMR spectrometer. The authors would also like to thank Dr. Markus W. Voehler, Vanderbilt University for the acquisition of ^{13}C-NMR data for compounds, **19**, **21**, **26-27**, **36-37**, **39**, **42**; supported in part by a grant for NMR instrumentation NIH (S10 RR025677) and Vanderbilt University matching funds, the University of Alabama and Dr. Qiaoli Liang for acquisition of HRMS data, and Neil J. Williams of Oak Ridge National Laboratory for the preparation of dicarbonyl **17**.

REFERENCES AND NOTES

[1] (a) Downward, A. M.; Jane, R. T.; Polson, M. I. J.; Moore, E. G.; Hartshorn, R. M. Dalton Trans 2012, 41, 14425; (b) Downward, A. M.; Moore, E. G.; Hartshorn, R. M. Chem Comm 2011, 47, 7692; (c) Xian-Lan, H.; Li, H.; Peng, C.-H. J Mol Struct 2011, 990, 197.

[2] (a) Katsagounos, G.; Stathatos, E.; Arabatzis, N. B.; Keramidas, A. D.; Lianos, P. J Lumin 2011, 131, 1776; (b) Miguirditchian, M.; Guillaneux, D.; Francois, N.; Airvault, S.; Ducros, S.; Thauvin, D.; Madic, C.; Illemassene, M.; Lagarde, G.; Krupa, J.-C. Nuc Sci Eng 2006, 153, 223.

[3] (a) For a recent review see: Panak, P. J.; Geist, A. Chem Rev 2013, 113, 1199; (b) Lewis, F. W.; Harwood, L. M.; Hudson, M. J.; Distler, P.; John, J.; Stamberg, K.; Núñez, A.; Galán, H.; Espartero, A. Eur J Org Chem 2012, 2012, 1509; (c) Laventine, D. M.; Afsar, A.; Hudson, M. J.; Harwood, L. M. Heterocycles 2012, 86, 1419; (d) Lewis, F. W.; Harwood, L. M.; Hudson, M. J.; Drew, M. G. B.; Desreux, J. F.; Vidick, G.; Bouslimani, N.; Modolo, G.; Wilden, A.; Sypula, M.; Vu, T.-H.; Simonin, J.-P. J Am Chem Soc 2011, 133, 13093; (e) Afsar, A.; Laventine, D. M.; Harwood, L. M.; Hudson, M. J.; Geist, A. Chem Comm 2013, 49, 8534; (f) Hudson, M. J.; Harwood, L. M.; Laventine, D. M.; Lewis, F. W. Inorg Chem 2013, 52, 3413.

[4] Kolarik, Z.; Müllich, U.; Gassner, F. Solvent Extr Ion Exch 1999, 17, 1155.

[5] McKibben, J. M. Radiochem Acta 1984, 36, 3.

[6] (a) Dam, H. H.; Reinhoudt, D. N.; Verboom, W. Chem Soc Rev 2007, 36, 367; (b) Ekberg, C.; Fremvik, A.; Retegan, T.; Skarnemark, G.; Foreman, M. R. S.; Hudson, M. J.; Englund, S.; Nilsson, M. Radiochim Acta 2008, 96, 225; (c) Kolarik, Z. Chem Rev 2008, 108, 4208; (d) Steppert, M.; Cisařova, T.; Fanghänel, T.; Geist, A.; Lindqvist-Reis, P.; Panak, P.; Štěpnička, P.; Trumm, S.; Walther, C. Inorg Chem 2012, 51, 591; (e) Cotton, S. Comprehensive Coordination Chemistry II; Elsevier: Oxford, 2004; Vol. 3, p 93.

[7] Hill, C.; Guillaneux, D.; Berthon, L.; Madic, C. J Nucl Sci Technol 2002, 39, 309.

[8] Kolarik, Z.; Müllich, U.; Gassner, F. Solvent Extr Ion Exch 1999, 17, 23.

[9] Adam, C.; Kaden, P.; Beele, B. B.; Müllich, U.; Trumm, S.; Geist, A.; Panak, P. J.; Denecke, M. A. Dalton Trans 2013, 42, 14068.

[10] (a) Case, F. H. J Org Chem 1965, 2, 931–933; (b) Case, F. H. J Het Chem 1971, 8, 1043.

[11] Szumera, J.; Welniak, M.; Olejniczak, A.; Lukaszewicz, J. J Forensic Sci 2010, 55, 944.

[12] Drew, M. G. B.; Hudson, M. J.; Youngs, G. A. J Alloys and Cmpds 2004, 374, 408.

[13] **29**, reported yield of 100%. Recrystallization done on an analytical sample see: Hudson, M. J.; Boucher, C. E.; Brackers, D.; Desreux, J. F.; Drew, M. G. B.; Foreman, M. R. St. J.; Harwood, L. M.; Hill, C.; Madic, C.; Marken, F.; Youngs, T. G. A. New J Chem 2006, 30, 1171. **27**, 72.3%, from ref. 12.

[14] **19**, 40% yield obtained by: Hage, R.; Haasnoot, J. G.; Reedijk, J. Inorg Chim Acta 1990, 172, 19. **19**, 55.9% from ref. 12. **20**, 66.8%, from ref. 12.

[15] Often purification of these types of structures require multiple recrystallizations to afford the desired product. Strukelj, M.; Hedrick, J. C. Macromolecules 1994, 27, 7511. Reported yields for **35** =83%, **41** =48%.