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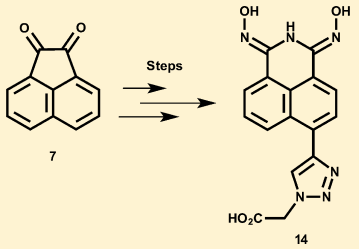
Synthesis of a Hydrophilic Naphthalimidedioxime

Christopher D. Grant, Sung Ok Kang, and Benjamin P. Hay*

Chemical Sciences Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37831, United States

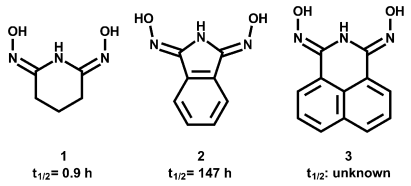
Supporting Information

ABSTRACT: Imidedioximes are formed in hydroxylamine-treated polyacrylonitrile adsorbents used in the extraction of uranium from seawater. Although known to be a good uranophile, the glutarimidedioxime model compound **1** is rapidly hydrolyzed under acidic conditions used to elute metals from the adsorbent. This work reports the synthesis of a hydrophilic naphthalimidedioxime derivative **14**, which is stable under acidic elution conditions. The synthesis starts from simple acenaphthenequinone **7** and converts it to a functional group dense imidedioxime **14** in 7 steps.



The uncommon imidedioxime functional group has found use in the synthesis of pharmaceutically active compounds[1] and as metal ion chelates.[2] Such structures are known to form in polyacrylonitrile polymers upon treatment with hydroxylamine, yielding a class of adsorbents that have been extensively studied for sequestering uranium from seawater.[2−4] It has been estimated that the world's oceans contain 4.5 billion tons of dissolved uranium, representing a sustainable resource that could be exploited for nuclear power production.[3] Japanese Atomic Energy Agency researchers demonstrated the feasibility of mining this resource, using this class of polymeric adsorbents to successfully extract a kilogram of uranium from the ocean.[4] Structures analogous to glutarimidedioxime **1** (Scheme 1) have been suggested to act as the primary metal binding site in these adsorbents.[5] However, **1** is protolytically unstable[6] and degradation of adsorbent performance after metal elution with 1 M HCl has been attributed to imidedioxime decomposition.[5a] Such degradation, which would limit the ability to recycle the material, could be eliminated by replacing **1** with an acid stable analogue.

Scheme 1. Reported Half-Lives for Imidedioximes in 1 M DCl at Room Temperature[6]



Recently, an alternative chelate, phthalimidedioxime **2**, was demonstrated to exhibit increased acid stability, attributable to aromatic resonance stabilization.[6] We anticipated that a fused aromatic system, as seen in naphthalimidedioxime **3**,[7a] would further attenuate the electrophilicity of the imide-carbon centers and thereby yield increased acid stability. Aqueous solubility is important in order to test this hypothesis as well as to allow future evaluation of uranium binding affinity. Thus, we endeavored to synthesize a hydrophilic naphthalimidedioxime **4** (Scheme 2), where the glycine residue could impart the desired hydrophilic character.

Retrosynthetically, we imagined forming the imidedioxime from the hydroxylamine condensation onto the dicyano groups in **5**.[7a] The glycine substituent could arise from the reduction of azide **6** and alkylation of the resulting amine with a 2-bromoacetate derivative. Arene **6** is known from acenaphthenequinone **7**; however, no experimental details were provided.[8]

The bromination of **7** (Scheme 3) in refluxing bromine provided our first intermediate, **8**, in 75% yield after recrystallization. The condensation of **5** and sulfamide was initially problematic. Literature conditions indicate that anhydrous HCl bubbled into a slurry of quinone **8** in alcoholic solvent would induce condensation upon reflux.[9a] Notwithstanding, this protocol produced low yields of product in our hands when saturating methanol with HCl (g) generated from 12 M HCl/$CaCl_2$.[9b] We posited that saturated methanolic HCl could be reproducibly generated in situ upon addition of acetyl chloride to a refluxing mixture of sulfamide and **8** in methanol. Once we applied these new conditions, we finally observed the formation of the desired thiadiazole dioxide **9** in 70% yield on >10 g scale. Thermolysis of **9** in refluxing ethyl diglyme furnished dinitrile **10** upon extrusion of sulfur dioxide. Azidation of aryl bromide **10** with NaN_3 in hot DMSO gave aryl azide **6** and subsequent azide reduction with $NaBH_4$ in refluxing THF to naphthylamine **11** was facile.[8]

Naphthylamine **11** proved to be a rather recalcitrant nucleophile. Methyl bromoacetate failed to yield the desired product after following a number of analogous procedures.[10] Consequently, we went back two steps to examine the feasibility of direct Ullmann-type and Buchwald-Hartwig couplings[11] on bromide **10** with different alanine and glycine derivatives but we observed no product. We thought that reductive amination would be a better alternative. We surmised

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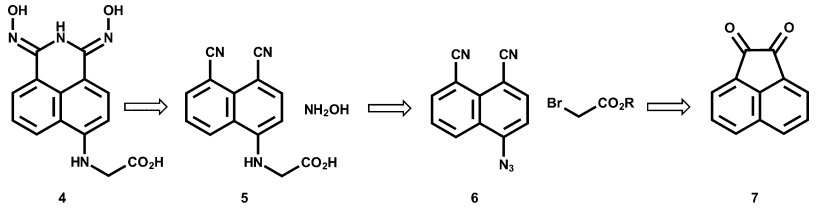
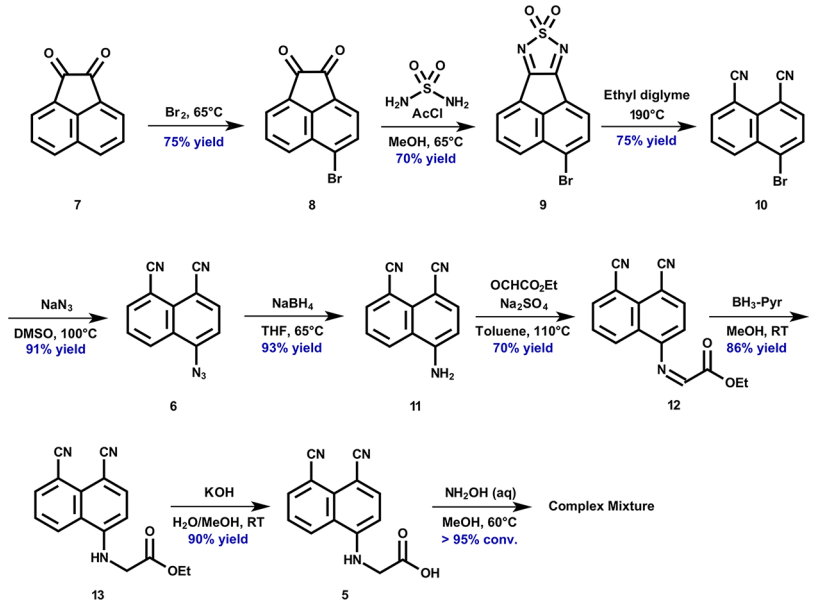
Scheme 2. Retrosynthesis of 4



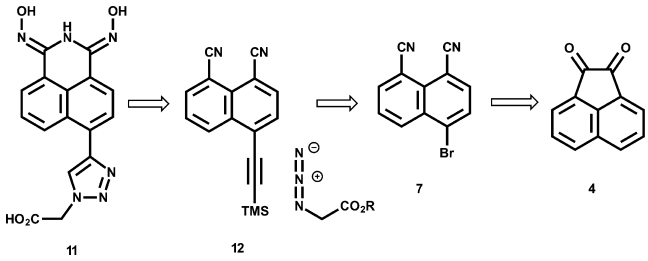
Scheme 3. Forward Synthesis from Quinone 7



that ethyl glyoxylate would be a more forgiving electrophile than bromoacetate toward nucleophilic attack by naphthylamine **11** because the dicarbonyls are potent electron-withdrawing groups. One-pot reductive amination[12] conditions failed to afford the desired product presumably because the rate of condensation is slower than the rate of glyoxylate reduction. We treated naphthylamine **11** with ethyl glyoxylate in the presence of Na_2SO_4 in refluxing toluene we obtained 70% yield of the desired Schiff base **12** after one recycle of starting material.[13] We then added an excess of borane-pyridine complex to the imine **12** in methanol to furnish the desired glycine after protolytic workup.[14] The most common reduction conditions with $NaBH_4$ produced exhaustive reduction of the iminoacetate. Other reductants such as $NaB(OAc)_3H$[12a]/$NaB(CN)H_3$[15] gave only returned starting material. Metal-mediated reductions employing Pd/C with triethylsilane,[16] Shvo's catalyst,[17] and Zn[18] produced incomplete reactions. We saponified *N*-naphthylglycine ethyl ester **13** with KOH in aqueous methanol to give amino acid **5**. When bisnitrile **5** was subjected to aqueous hydroxylamine in methanol we observed a complex mixture of products.

After a number of other procedures failed to afford any product[7] in addition to poor step economy, we decided to adjust our strategy. We would not depend upon a lengthy reductive amination sequence to install the hydrophilic carboxylic acid in our new target **14**. We anticipated that we could form **14** via Copper-Catalyzed-Azide–Alkyne Cycloaddition (CuAAC) chemistry with 2-azidoacetate (Scheme 4) and reduce our step count. We can also access the necessary alkyne **15** from previous intermediates **10** and **7**.

Scheme 4. Retrosynthesis of Imidioxime 14



Sonogashira alkynylation[19] (Scheme 5) of aryl bromide **10** with TMS-acetylene proceeded smoothly to afford TMS acetylide **15** in warm THF/NEt_3 in 85% yield. The condensation of hydroxylamine with bisnitrile **15** in refluxing methanol formed the imidedioxime **16** with concomitant desilation in >95% yield. 2-Azidoacetate methyl ester underwent CuAAC reaction[20] with alkyne **16** at 75 °C in wet DMSO.[21,22] Finally, treatment of methyl ester **17** with aqueous Na_2CO_3 in THF gave the saponification product in good yield. With naphthalimidedioxime **14** in hand we subjected it to 1 M DCl in heavy water to determine its protolytic stability, analogous to the experiments performed with imidedioximes **1** and **2**,[6] and we observed no degradation after a week in contact with acid at room temperature.

We have developed a chromatography-free and potentially scalable synthesis of imidedioxime **14** in 7 steps in with an average yield of 80% in 22% overall yield.

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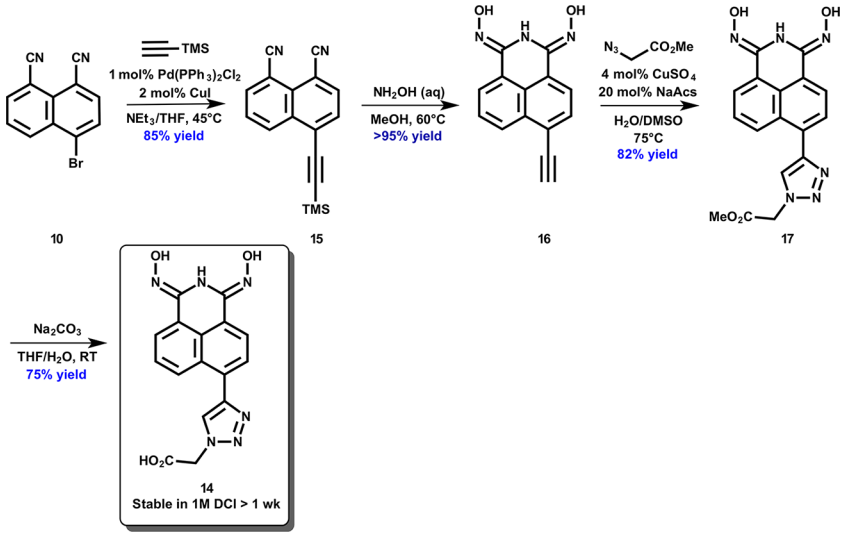
Scheme 5. Forward Synthesis to Imidedioxime 14 from Aryl Halide 10



EXPERIMENTAL SECTION

General Methods. All reagents and solvents were used as received unless otherwise specified. No solvents or glassware were dried. All reactions were performed under inert atmosphere maintained by a balloon of argon and sealed with a rubber septum unless stated otherwise. All reactions were stirred magnetically. Melting points were determined after crystallization from the reported solvent(s). FT-IR data was recorded using ATR with a diamond crystal.

*5-Bromo-1,2-dihydroacenaphthylene-1,2-dione (**8**).* Compound **8** was prepared according to literature precedence; however, no experimental details were provided.[8] Acenaphthenequinone **7** (10 g, 54.9 mmol, 1 equiv) and bromine (20 mL, 388 mmol, 7 equiv) were charged to a 250 mL flask containing a magnetic stir bar. It was fitted with a reflux condenser and a glass T-adapter under a positive flow of nitrogen. The outlet was fitted with a Teflon tube which was bubbled into a 1 M NaOH (200 mL) to neutralize evolved HBr. The reaction vessel was placed into a 75 °C oil bath and aged for 2.5 h. The reaction mixture was cooled to room temperature, diluted with water (40 mL), and cooled to 0 °C. The biphasic mixture was stirred vigorously, and a saturated solution of $NaHSO_3$ (~75 mL) was added, at which point the reaction mixture became yellow orange. The solid material was filtered by vacuum and washed thoroughly with water. The filtrand was split into approximately four equal portions, dissolved in hot toluene (1 L total), dried on $MgSO_4$, vacuum filtered again, and concentrated to saturation in hot toluene (~70% of solvent removed). It was then allowed to come to room temperature and placed in the −25 °C freezer overnight. The orange-yellow needles were isolated by vacuum filtration and washed with hexanes to give the bromide **8** (first crop: 9 g, second crop: 1.7 g, total: 10.7 g, 75% yield). R_f = 0.43 (100% DCM). Mp: 230−232 °C (toluene). ^{1}H NMR (400 MHz, DMSO): δ 8.42 (dd, J = 8.4 and 0.6 Hz, 1H), 8.25 (d, J = 7.5 Hz, 1H), 8.18 (dd, J = 7.0 and 0.6 Hz, 1H), 8.08 (dd, J = 8.4 and 7.0 Hz, 1H), 7.99 (d, J = 7.5 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 187.8, 187.6, 145.3, 132.9, 131.5, 131.1, 130.6, 130.5, 129.8, 127.4, 123.1, 123.0 ppm. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{12}H_5BrO_2$ 259.9473, found 259.9471. FT-IR: 2407, 2283, 1901, 1723, 1573, 1605, 1476, 1423, 1263, 1203, 1164, 1082, 1018, 943, 896, 847, 818, 765, 719, 620, 548 cm^{-1}.

*4-Bromo-12λ^6-thia-11,13-diazatetracyclo[7.5.1.0^{5,15}.0^{10,14}]-pentadeca-1,3,5(15),6,8,10,13-heptaene-12,12-dione (**9**).* Compound **9** was prepared according to literature precedence; however, no experimental details were provided.[8] Quinone **8** (10.52 g, 40.3 mmol, 1 equiv), sulfamide (7.75 g, 80 mmol, 2 equiv), and methanol (40 mL) and a large magnetic stir bar were charged to a 250 mL 3-neck round-bottom flask fitted with two septa and a reflux condenser. Atop the reflux condenser was a glass vacuum adapter, and the system was placed under nitrogen atmosphere and into a 75 °C oil bath with vigorous stirring. Acetyl chloride (28 mL, 400 mmol, 10 equiv) was added to the reaction mixture via syringe over 10−15 min maintaining a vigorous reflux. (Care must be taken to avoid extended contact of metal needles with the reaction mixture and atmosphere. Metal will leach into the reaction causing the formation of decomposition products.) The dull orange yellow colloidal reaction mixture became a bright yellow suspension after 10 min, and the reaction was aged further for 4 h. The reaction was then cooled to room temperature, diluted with ether (~80 mL) and the precipitant was filtered via vacuum filtration. The solid was split in three batches then dissolved in hot DCM (~350 mL/ea), filtered to remove unreacted starting material then concentrated to saturation (~50% solvent removed) and a layer of hexanes placed atop and allowed to diffuse into the DCM layer at −25 °C overnight inducing crystallization. The product was isolated by filtration to give the thiadiazole dioxide **9**, as a yellow powder (9.1 g, 70% yield). R_f = 0.53 (100% DCM). Mp: 177 °C dec (DCM/hexanes). ^{1}H NMR (400 MHz, DMSO): δ 8.58 (d, J = 6.2 Hz, 1H), 8.48 (d, J = 7.6 Hz, 1H), 8.37 (m, 2H), 8.17 (dd, J = 7.4 and 7.3 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 167.2, 166.7, 149.6, 134.3, 132.7, 132.3, 129.2, 128.6, 128.2, 125.1, 124.4, 123.1 ppm. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{12}H_5BrN_2O_2S$ 321.9248, found 321.9249. FT-IR: 1632, 1559, 1473, 1410, 1350, 1102, 1066, 1028, 967, 945, 849, 822, 761, 754, 702, 599, 555, 518 cm^{-1}.

*4-Bromonaphthalene-1,8-dicarbonitrile (**10**).* Compound **10** was prepared according to literature precedence; however, no experimental details were provided.[8] Thiadiazole dioxide **9** (8.7 g, 27.1 mmol, 1 equiv), diethyl glyme (130 mL), and a magnetic stir bar were charged into a 500 mL flask and then sparged with argon for 10−15 min via balloon. It was placed into a 200 °C oil bath and stirred. After ~3 min, the reaction mixture began to reflux, and then it was aged for 10 min; within 8 min the reaction became homogeneous and the color changed from yellow to brown. Evolution of SO_2 rapidly increased. The reaction vessel was then cooled to room temperature using an ice bath. The product was triturated with hexanes (~200 mL), cooled to 0 °C with an ice bath, and then filtered cold. The resulting brown solid was dissolved in warm DCM (150 mL), treated with decolorizing carbon (three scoops), and aged from 10 min. It was then filtered through a pad of diatomaceous earth and washed with EtOAc until no more UV active material eluted (~500 mL). The yellow solution was concentrated to dryness to afford and off-white solid. The solid was then dissolved in hot toluene, and the solvent was removed in vacuo until saturation and then placed in the −25 °C freezer after cooling to room temperature to afford cream colored needles (5.4 g, 76% yield). R_f = 0.37 (100% DCM). Mp: 210−212 °C (toluene). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (dd, J = 8.6 and 0.9 Hz, 1H), 8.20 (dd, J = 7.3 and 0.9 Hz, 1H), 8.02 (d, J = 7.9 Hz, 1H), 7.95 (d, J = 7.9 Hz, 1H)

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7.80 (dd, J = 8.6 and 7.3 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 140.3, 139.3, 134.4, 132.5, 132.1, 130.8, 130.0, 129.8, 117.2, 117.1, 109.0, 108.3 ppm. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{12}H_5BrN_2$ 255.9616, found 255.9647. FT-IR: 3021, 2223, 1565, 1504, 1369, 1044, 986, 840, 814, 760, 615, 558 cm^{-1}.

*4-Azidonaphthalene-1,8-dicarbonitrile (**6**).* Compound **6** was prepared according to literature precedence; however, no experimental details were provided.[8] Caution: explosion hazard when heating azides. Aryl bromide **10** (5.2 g, 20 mmol, 1 equiv), NaN_3 (1.56 g, 24 mmol, 1.2 equiv) and DMSO (80 mL) were charged to a 500 mL flask containing a stir bar under argon atmosphere. The flask was placed in a 100 °C oil bath and stirred for 30 min. The reaction was cooled to room temperature and diluted with water (250 mL) the suspended solid was then filtered. The solid was dissolved in DCM and dried on $MgSO_4$. It was concentrated to saturation then crystallized with hexanes (layer method) to give aryl azide **6** as brown fluffy needles (3.74 g, 85% yield). R_f = 0.33 (100% DCM). Mp: 168−170 °C (DCM/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (dd, J = 8.6 and 1.3 Hz, 1H), 8.17 (dd, J = 7.3 and 1.3 Hz, 1H), 8.11 (d, J = 8 Hz, 1H), 7.69 (dd, J = 8.6 and 7.3 Hz, 1H), 7.42 (d, J = 8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 139.0, 138.1, 130.1, 129.1, 126.9, 126.5, 116.9, 116.7, 114.7, 109.1, 104.6 ppm. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_5N_5Na$ 242.0443, found 242.0444. FT-IR: 3023, 2221, 2109, 1573, 1511, 1409, 1373, 1278, 1444, 1020, 955, 843, 818, 760, 658, 549 cm^{-1}.

*4-Aminonaphthalene-1,8-dicarbonitrile (**11**).* Compound **11** was prepared according to literature precedence; however, no experimental details were provided.[8] Azide **6** (3.67 g, 16.7 mmol, 1 equiv), $NaBH_4$ (1.9 g, 50 mmol, 3 equiv), and THF (50 mL) were charged to a 250 mL round-bottom flask with a stir bar under argon atmosphere fitted with a reflux condenser. The reaction mixture immediately began to evolve nitrogen; once the gas evolution slowed, the reaction vessel was placed in a 65 °C oil bath and stirred for 1 h. The reaction mixture was cooled to room temperature and concentrated to dryness. It was then diluted with water (80 mL) and the pH was adjusted to pH 5−6 with citric acid with hydrogen evolution. The solid was filtered and washed into a round-bottom with toluene, and the solvent was removed in vacuo. The residual water was removed by azeotroping with toluene (3×, 20 mL) and then dried in vacuo overnight to give naphthylamine **11** as a tan powder (3.2 g, > 95% yield). R_f = 0.46 (30% EtOAc/DCM). Mp: 220 °C dec (THF). ^{1}H NMR (400 MHz, DMSO): δ 8.86 (dd, J = 8.6 and 1.2 Hz, 1H), 8.25 (dd, J = 7.3 and 1.2 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.65 (dd, J = 8.6 and 7.3 Hz, 1H), 7.38 (broad, s, 2H), 6.85 (d, J = 8.4 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 152.4, 140.6, 139.3, 131.3, 130.1, 125.0, 122.2, 119.7, 118.2, 109.0, 107.6, 91.2 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_8N_3$ 194.0718, found 194.0719. FT-IR: 3226, 2214, 1649, 1577, 1521, 1356, 754, 566 cm^{-1}.

*Ethyl (2E)-2-[(4,5-Dicyanonaphthalen-1-yl)imino]acetate (**12**).* Compound **12** was synthesized by analogy from Zhu et al.[13] Naphthylamine **11** (868 mg, 4.54 mmol, 1 equiv), Na_2SO_4 (3.22 g, 22.7 mmol, 5 equiv), and toluene (45 mL,) were charged to a 250 mL flask containing a stir bar. Ethyl glyoxylate (50%) in toluene (4.75 M, 1.9 mL, 9 mmol, 2 equiv) was next added, and the flask was fitted with a reflux condenser and placed under argon atmosphere. The reaction vessel was then placed in a 120 °C oil bath and stirred vigorously for 18 h. The reaction mixture was cooled to room temperature, vacuum filtered to remove unreacted starting material and Na_2SO_4, and then washed with toluene. The filtrate can be collected and resubmitted to identical reaction conditions for the recycle. The toluene was removed in vacuo to afford a tan powder. The solid was then washed with ether (30 mL) to remove excess ethyl glyoxylate and vacuum filtered and dried in vacuo to give pure anil **12** (550 mg, recycle: 367 mg, 73% yield). R_f = 0.54 (20% EtOAc/DCM, partial decomposition to **11**). Mp: 205−207 °C (toluene). ^{1}H NMR (400 MHz, DMSO): δ 8.54 (d, J = 8.5 Hz, 1H), 8.48 (d, J = 7.2 Hz, 1H), 8.45 (d, J = 7.8 Hz, 1H), 8.14 (s, 1H), 7.92 (dd, J = 8.2 and 7.6 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 4.41 (qt, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 171.5, 152.4, 140.7, 139.4, 131.4, 130.2, 125.1, 122.2, 119.7, 118.2, 109.0, 107.7, 91.2, 87.8, 61.1, 15.0 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}N_3O_2$ 278.0930, found 278.0936. FT-IR: 2996, 2415, 2228, 1741, 1580, 1372, 1345, 1213, 1033, 961, 865, 769, 555 cm^{-1}.

*Ethyl 2-[(4,5-Dicyanonaphthalen-1-yl)amino]acetate (**13**).* The procodure was adapted from Bomann and co-workers' conditions.[14] Iminoacetate **12** (653 mg, 2.36 mmol, 1 equiv) was charged to a 50 mL flask containing a stir bar under argon atmosphere. Methanol (10 mL) was added via syringe forming a suspension. Next, BH_3·Py (0.79 mL, 7.78 mmol, 3.3 equiv) was added via syringe, and the reaction mixture was allowed to stir for 1 h. HCl (6 M, 5 mL, 30 mmol, 12.7 equiv) was added with the evolution of H_2 over 10 min, and the reaction mixture was stirred for 30 min. It was vacuum filtered and washed with water. Once the filtrate appeared dry, it was dissolved in DCM, dried on $MgSO_4$, filtered, and concentrated to dryness to give the *N*-naphthylglycine **13** as a tan residue (549 mg, 83% yield). R_f = 0.61 (20% EtOAc/DCM). Mp: 172−173 °C (DCM/hexanes). ^{1}H NMR (400 MHz, DMSO): δ 8.67 (d, J = 8.7 Hz, 1H), 8.29 (d, J = 7.2 Hz, 1H), 8.08 (t, J = 6.1 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.74 (t, J = 7.9 Hz, 1H), 6.64 (d, J = 8.5 Hz, 1H), 4.28 (d, J = 6.1 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 170.7, 150.1, 140.9, 139.2, 130.8, 129.2, 125.8, 123.0, 119.3, 118.1, 108.0, 105.4, 92.8, 61.7, 45.3, 15.0 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{13}N_3O_2$ 280.1086, found 280.1088. FT-IR: 2995, 2209, 1743, 1580, 1345, 1218, 1116, 1021, 809, 750 cm^{-1}.

*2-[(4,5-Dicyanonaphthalen-1-yl)amino]acetic Acid (**5**).* Ethyl ester **13** (500 mg, 1.79 mmol, 1.0 equiv) and methanol (8 mL) were charged to a 50 mL flask along with a magnetic stir bar. Water (2 mL) and KOH (221 mg, 3.94 mmol, 2.2 equiv) were next added, and the reaction mixture immediately became red-orange and cloudy. The reaction was then stirred for 18 h. The reaction mixture was then concentrated to remove the methanol. The remaining residue was diluted with water (20 mL), and the pH was adjusted to 2−3 with citric acid and the suspended solid was vacuum filtered then washed with water. The solid was then dissolved in acetone, dried on $MgSO_4$ and filtered. The acetone solution was warmed near boiling and concentrated to saturation, and a layer of hexanes was placed on top and allowed to slowly diffuse. Once it cooled to room temperature, it was placed in a −25 °C freezer overnight. After vacuum filtration, we obtained free acid **5** as a canary yellow powder (450.3 mg, >95% yield). R_f = 0.43 (20% EtOAc/DCM). Mp: 210 °C dec (acetone/hexanes). ^{1}H NMR (400 MHz, DMSO): δ 12.93 (broad, s, 1H), 8.97 (d, J = 8.7 Hz, 1H), 8.29 (d, 7.2 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 6.1 Hz, 1H), 7.34 (dd, J = 8.6 and 7.4 Hz, 1H), 6.64 (d, J = 8.5 Hz, 1H), 4.18 (d, J = 6.1 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 172.1, 150.2, 140.9, 139.1, 130.8, 129.2, 125.7, 123.0, 119.4, 118.1, 107.9, 105.4, 92.5, 45.3 ppm. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{14}H_9N_3O_2$ 251.0708, found 251.0709. FT-IR: 3411, 3075, 2200, 1753 1580, 1537, 1537, 1428, 1342, 1121, 805, 658. 565 cm^{-1}.

*4-[2-(Trimethylsilyl)ethynyl]naphthalene-1,8-dicarbonitrile (**15**).* A 50% solution of THF/NEt_3 (25 mL) was sparged with argon in a 50 mL round-bottom flask for 15 min, while aryl bromide **10** (2.81 g, 10.9 mmol, 1.0 equiv), $Pd(PPh_3)_2Cl_2$ (70.5 mg, 0.109 mmol, 1 mol %), and cuprous iodide (41.5 mg, 0.218 mmol, 2 mol %) were charged to a separate 100 mL round-bottom flask containing a stir bar fitted with a reflux condenser under argon atmosphere. The solvent mixture (10 mL) followed by TMS-acetylene and the last half of the solvent (10 mL) were added to the flask via syringe. The mixture was stirred vigorously, placed into the 45 °C oil bath, and aged for 18 h. The reaction could be monitored by removing small aliquots and analyzing by ^{1}H NMR since the product cospots with starting material on TLC. The reaction mixture was then allowed to cool to room temperature and vacuum filtered to remove the ammonium salts. The filtrate was washed with EtOAc (50 mL). The organics were extracted with water (20 mL) and then brine (20 mL). The organics were then dried on $MgSO_4$ and filtered. The solvent was removed in vacuo to afford an analytically pure brown solid (2.54 g, 85% yield). Mp: 150 °C dec (DCM/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (dd, J = 8.5 and 1.3 Hz, 1H), 8.18 (dd, J = 7.3 and 1.3 Hz, 1H), 8.07 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.78 (dd, J = 8.5 and 7.3 Hz, 1H), 0.38

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(s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 137.0, 133.5, 133.0, 131.0, 128.8, 127.9, 127.5, 116.7, 116.6, 109.2, 108.5, 107.2, 100.3, −0.1 ppm. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{17}H_{14}N_2Si$ 274.0926, found 274.0937. FT-IR: 4092, 3421, 2965, 2906, 2368, 1961, 1579, 1248, 837, 763, 632, 552 cm^{-1}.

*N-[(2Z,4Z)-8-Ethynyl-4-(hydroxyimino)-3-azatricyclo[7.3.1.0^{5,13}]-trideca-1(12),5,7,9(13),10-pentaen-2-ylidene]hydroxylamine (**16**).* Naphthyl TMS acetylene **15** (2.44 g, 8.89 mmol, 1.0 equiv) was charged to a 250 mL round-bottom flask fitted with a reflux condenser under argon atmosphere. Methanol (35 mL) and 35% aq hydroxylamine (2.7 mL, 16.5M, 5 equiv) were added via syringe. The reaction mixture was placed in a 65 °C oil bath to stir for 18 h. The reaction vessel was removed from the hot oil bath and concentrated to a residue. The water was azeotropically removed with toluene (3×, 25 mL) via rotary evaporator. The solid was then washed with Et_2O (50 mL) to remove residual toluene and dried in vacuo to a give analytically pure brown solid (2.2 g, > 95% yield). Mp: > 250 °C (THF). ^{1}H NMR (400 MHz, DMSO): δ 11.26 (s, 1H), 11.17 (s, 1H), 8.96 (s, 1H), 8.33 (dd, J = 8.4 and 1.1 Hz, 1H), 8.23 (dd, J = 7.5 and 1.1 Hz, 1H), 8.12 (d, J = 7.7 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.78 (dd, J = 8.4 and 7.5 Hz, 1H), 4.86 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 141.7, 141.6, 133.2, 132.1, 128.6, 127.8, 126.3, 123.8, 123.6, 122.3, 121.5, 121.0, 88.8, 81.8 ppm. HRMS (ESI-TOF) m/z: $[M - H]^-$ calcd for $C_{14}H_8N_3O_2$ 250.0635, found 250.0628. FT-IR: 3050, 2964, 2900, 2226, 1641, 1580, 1378, 1248, 1087, 1009, 955, 886, 838, 763, 703, 633, 561 cm^{-1}.

*Methyl 2-[4-[(2Z,4Z)-2,4-Bis(hydroxyimino)-3-azatricyclo-[7.3.1.0^{5,13}]trideca-1(12),5,7,9(13),10-pentaen-8-yl]-1H-1,2,3-triazol-1-yl]acetate (**17**).* Caution: explosion hazard when heating low molecular weight organoazides. A solution of 10% H_2O/DMSO (7.2 mL) was sparged with argon (15 min) while cupric sulfate pentahydrate (71.9 mg, 0.29 mmol, 4 mol %), L-sodium ascorbate (285.3 mg, 1.44 mmol, 20 mol %), and terminal acetylene **16** (1.81 g, 7.2 mmol, 1.0 equiv) were charged to a 100 mL flask with a stir bar fitted with a reflux condenser under argon atmosphere. The sparged DMSO solution (7.2 mL) and methyl azidoacetate[23] (1.04 mL, 10.8 mmol, 1.5 equiv) were added via syringe. The reaction mixture was placed in a 75 °C oil bath to stir for 18 h. The reaction could be monitored removing small aliquots and analyzing by ^{1}H NMR; the product was too polar to monitor by TLC. The reaction mixture was diluted with water (200 mL), the finely divided solid was allowed to settle for 2 h, and then the mixture was vacuum filtered. The solid was washed with water and allowed to air-dry. The solid was collected and dissolved in warm THF (150 mL) at which point a black fine particulate was present. The solid material was vacuum filtered, and the filtrate was concentrated to a residue. The residual water was azeotropically removed with toluene (3×, 20 mL) in vacuo to afford triazole **17** as a tan powder (2.16 g, 82% yield). Mp: 205 °C dec (THF/toluene). ^{1}H NMR (400 MHz, DMSO): δ 11.15 (s, 1H), 11.12 (s, 1H), 9.00 (s, 1H), 8.71 (s, 1H), 8.65 (d, J = 8.5 Hz, 1H), 8.24 (d, J = 7.7 Hz, 2H), 7.92 (d, J = 7.7 Hz, 1H), 7.73 (dd, J = 8.5 and 7.7 Hz, 1H) 5.58 (s, 2H), 3.78 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 168.6, 146.0, 142.1, 141.9, 130.6, 130.1, 128.2, 128.1, 128.0, 127.1, 126.9, 123.3, 123.0, 121.9, 121.4, 53.6, 51.5 ppm. HRMS (ESI-TOF) m/z: $[M - H]^-$ calcd for $C_{17}H_{13}N_6O_4$ 365.1012, found 365.1010. FT-IR: 3401, 2957, 2839, 1746, 1640, 1640 199, 1462, 1378, 1219, 986, 953, 885, 838, 764, 697, 609, 535 cm^{-1}.

*2-[4-[(2Z,4Z)-2,4-Bis(hydroxyimino)-3-azatricyclo[7.3.1.0^{5,13}]-trideca-1(12),5,7,9(13),10-pentaen-8-yl]-1H-1,2,3-triazol-1-yl]acetic Acid (**14**).* Methyl ester **17** (796 mg, 2.17 mmol, 1 equiv) was charged to a 100 mL round-bottom flask containing a magnetic stir under argon atmosphere. Sodium carbonate (570 mg, 5.37 mmol, 3.2 equiv) dissolved in water (9 mL) was added via syringe. THF (4.5 mL) was used to wash any remaining solids from the walls of the flask. The mixture was stirred with vigor for 18 h. The THF and methanol were removed in vacuo, and the resulting residue was diluted with water (30 mL) and cooled to 0 °C. 6 M HCl was added dropwise to adjust the pH to ∼1. The gelatinous solid was vacuum filtered (use an oversized Büchner funnel, it will clog the filter paper) and washed with cold water. The solid was air-dried for 10 min and dissolved in warm THF (∼60 mL). The THF solution was then dried on $MgSO_4$, filtered, and concentrated to saturation. A layer of toluene was placed over it, and the solution was allowed to cool to room temperature. It was then allowed to crystallize in the −25 °C freezer overnight to give a yellow-orange powder (553.4 mg, 72% yield). Mp: 243 °C dec (THF/toluene). ^{1}H NMR (400 MHz, DMSO): δ 11.18 (s, 1H), 11.16 (s, 1H), 9.02 (broad, s, 1H), 8.73 (s, 1H), 8.71 (dd, J = 8.6 and 1.0 Hz, 1H), 8.26 (d, J = 7.7 Hz, 2H), 7.94 (d, J = 7.7 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.60 (dd, J = 8.6 and 7.4 Hz, 1H), 5.46 (s, 2H) ppm. ^{13}C NMR (100 MHz, DMSO): δ 169.6, 146.0, 142.1, 142.0, 130.6, 130.2, 128.2, 128.0, 127.2, 127.0, 123.3, 122.9, 121.9, 121.5, 51.7 ppm. HRMS (ESI-TOF) m/z: $[M - H]^-$ calcd for $C_{16}H_{11}N_6O_4$ 351.0842, found 351.0847. FT-IR: 3411, 1726, 1642, 1599, 1460, 1367, 1269, 1224, 1173, 1119, 1043, 987, 916, 849, 828, 766, 698 cm^{-1}.

*Acid Stability Test for **14**.* Imidedioxime **14** (35.2 mg, 0.1 mmol, 1 equiv) and 3-(trimethylsilyl)propionic acid sodium salt (17.2 mg, 0.1 mmol, 1 equiv) were a charged to a 10 mL round-bottom flask containing a magnetic stir bar. DCl (1 M) in D_2O (2 mL, 2 mmol, 20 equiv) was added, and the yellow slurry was stirred vigorously. Approximately 50 μL aliquots were removed at t = 0, 1, 17, 42, 138 (6.8 days), and 186 h (7.8 days) for ^{1}H NMR analysis (DMSO-d_6) using 3-(trimethylsilyl)propionic acid sodium salt as a reference. There was no change in the NMR spectrum though out the reaction.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for compounds **5**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: haybp@ornl.gov.

Notes

The authors declare no competing financial interest.

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