Pyrrole as a Dienophile in Intramolecular Inverse Electron-Demand Diels–Alder Reactions with 1,2,4-Triazines

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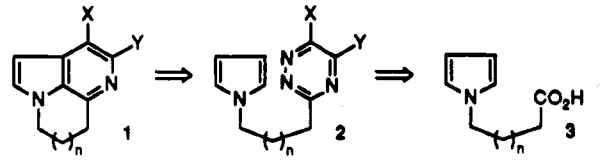
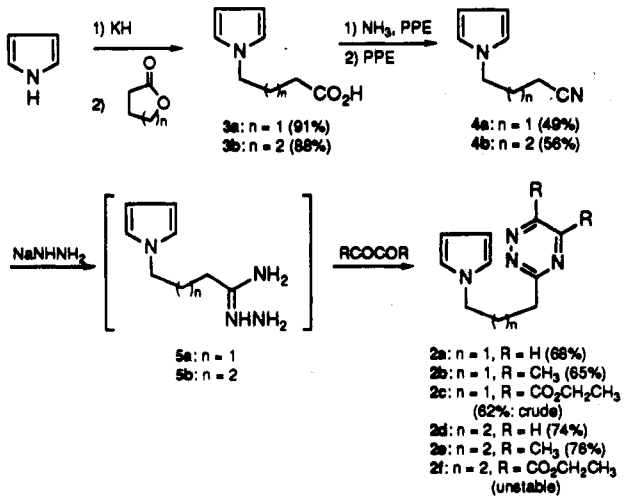
Synthetic approaches to azaindoles have become the focus of several research efforts in order to prepare analogues in novel drug design.[1] We recently reported the successful intramolecular inverse electron-demand Diels–Alder reaction of indole with 1,2,4-triazines tethered between the indole N1 position and the triazinyl C3.[2] This reaction allowed an extremely facile entry into the β-carbolines bearing the canthine alkaloidal skeleton. Given the very routine, high-yield route to the tethered triazines, we were interested in adapting this approach to other intramolecular cycloadditions. In particular, an analogous reaction with pyrroles utilizing a trimethylene tether (**2**, $n = 1$) would yield cycloadducts **1** ($n = 1$) with the intriguing 6-azaindole skeleton (Scheme I).

Balanced against this strategy was the dearth of reports of the ability of pyrrole to participate as a dienophile in inverse electron-demand Diels–Alder reactions. Indeed, the chemical history of pyrrole in electrocyclic reactions points to its well-established ability to function as the diene component in normal electron-demand cycloadditions.[3] The sole exceptions are apparently only reports by Seitz of a cycloaddition between *N*-methylpyrrole and dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate,[4] by Heine of cycloadditions of several N-substituted pyrroles with *o*-quinone monoimides,[5] and a very low yield of a biscycloadduct from the reaction of *N*-methylpyrrole with 1,3-butadiene-2,3-dicarbonitrile.[6] A few reports have appeared using pyrroles as [1,3]-dipolarophiles in both intermolecular[7] and intramolecular[8] fashion. In the former cases using nitrileimines as the [1,3]-dipole only bisadducts could be isolated in modest to poor yields, while in the latter, which employed tri- and tetramethylene tethers linking a nitrile oxide to the pyrrole at N1 analogous to our strategy in Scheme I, only the N1,C2-annulated product could be isolated due to rapid opening of the isoxazole ring. Cyclocondensative preparations of 2,3-annulated pyrroles by distinctly stepwise mechanisms are also relatively rare.[9] Against this background, the 1,2,4-triazinyl-tethered pyrroles were prepared and their intramolecular cycloaddition chemistry was examined.

Scheme I



Scheme II



The reaction of the pyrrole potassium salt with γ-butyrolactone, and with δ-valerolactone, proceeded through an S_N2-type opening of the lactone ring to produce the desired ω-(1-pyrrolyl)alkanoic acids **3a** and **3b** in excellent yields (Scheme II). Subsequent conversion of **3a** and **3b** to the nitriles **4a** and **4b** using PPE[10] by the Imamoto procedure[11] was accomplished in modest yields (49 and 56% yields, respectively).[12] The unstable amidrazones **5a** and **5b** formed from the nitriles by reaction with sodium hydrazide[13] were immediately used without purification in condensations with 1,2-dicarbonyl compounds to produce the desired triazines **2**. Triazines **2c** and **2f** proved to be very unstable and could not be purified.

The intramolecular cycloadditions were easily accomplished with the trimethylene-tethered triazines **2a–2c** to produce the 6-azaindoles **1a–1c** (Table I), typically by refluxing in triisopropylbenzene (TIPB). With the more reactive triazine **2c** bearing two electron-withdrawing substituents, cycloadditions could be achieved in identical

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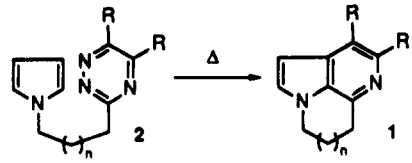
Table I. Intramolecular Cycloadditions of Pyrrolyl-Tethered 1,2,4-Triazines (2 → 1)



item	2	1	n	R	temp[a] (°C)/ time (h)	cat.	yield[b] (%)
1	**2a**	**1a**	1	H	232/5	none	80
2	**2b**	**1b**	1	CH_3	232/8	none	75
3	**2c**	**1c**	1	CO_2Et	232/0.5	none	83
4	**2c**	**1c**	1	CO_2Et	162/8	none	83
5	**2c**	**1c**	1	CO_2Et	100/72	none	85
6	**2c**	**1c**	1	CO_2Et	162/3	$Eu(fod)_3$[c]	80
7	**2c**	**1c**	1	CO_2Et	100/9	$Eu(fod)_3$[c]	84
8	**2d**	**1d**	2	H	232/48[d]	none	0
9	**2e**	**1e**	2	CH_3	232/48[d]	none	0
10	**2f**	**1f**	2	CO_2Et	232/48[d]	none	0

[a] The tethered triazines **2** (0.5 mmol) were refluxed in anhyd triisopropylbenzene (bp 232 °C), diglyme (bp 162 °C), or dioxane (bp 100 °C). [b] Isolated yields after flash chromatography. [c] Reaction employed 1 equiv of catalyst. [d] Conditions are the most extreme temperature attempted.

yields at lower temperatures (refluxing dioxane or diglyme), though with longer reaction times (0.5 h in refluxing TIPB compared to 8 h in refluxing diglyme, 72 h in refluxing dioxane). In contrast, refluxing the less reactive **2b** in diglyme for 12 h gave only minor conversion to cycloadduct **1b** with longer reaction times leading to loss of product due to decomposition. The cycloaddition of **2c** was mildly catalyzed by $Eu(fod)_3$,[14] thereby enabling the reaction to proceed at a lower temperature in shorter time (compare Table I, items 5–7).[15] Stronger Lewis acids, $AlCl_3$, Me_2AlCl, $TiCl_4$, and $Ti(O^iPr)_4$, led only to decomposition of the tethered triazine.

Attempts to promote the intramolecular cycloaddition between the pyrrole and 1,2,4-triazine linked by a tetramethylene tether met with failure. No reaction occurred under any conditions, including the use of Lewis acid catalysts such as $Eu(fod)_3$ with **2f** and $(Et_2O)BF_3$ with **2e**,[16] and extended reaction times at elevated temperatures (refluxing **2d**, **2e**, and **2f** in TIPB, 48 h) led only to decomposition of the tethered triazine. The reduced reactivity of intramolecular cycloadditions with increasing tether length in reactions involving triazines has been previously recorded,[17] with a particularly notable decrease in yield of seven-membered ring annulations occurring by cycloadditions.[8,17k]

In summary, by use of an intramolecular constraint, an electron-deficient diene system, a 1,2,4-triazine, was positioned in such a manner as to only allow pyrrole to function as a dienophile. In this fashion, successful cycloadditions were achieved in excellent yield, providing facile access to the 6-azaindole skeleton. All efforts to achieve an intermolecular cycloaddition (or perhaps more accurately, a cyclocondensation) between either pyrrole, *N*-methylpyrrole, or pyrrole potassium salt[18] and triethyl 1,2,4-triazine-3,5,6-tricarboxylate failed. Thus, the most reactive triazine in intermolecular cycloadditions with indole[19] (due to the presence of the three electron-withdrawing carbethoxy substituents) was not sufficiently reactive to undergo a cycloaddition with pyrrole in an intermolecular mode. Use of the intramolecular strategy, however, enabled even relatively unreactive 3,5,6-trialkylated 1,2,4-triazines such as **2b** to participate smoothly in cycloadditions with pyrrole.[20]

In contrast to the analogous intramolecular reactions between indole and the tetramethylene-tethered triazines which proceeded in modest yields (38–51%),[2a] the inability of triazines **2d–2f** which also employed the tetramethylene rather to produce cycloadducts and the failure of pyrrole or *N*-methylpyrrole to participate in intermolecular cycloadditions with the more reactive 1,2,4-triazine-3,5,6-tricarboxylate esters suggest that pyrrole may be a less reactive dienophile in these inverse electron-demand Diels–Alder reactions than indole. The cycloadditions of **2a–2b** nevertheless proceeded in excellent yields under conditions comparable to those employed in the intramolecular cycloadditions of indole with 1,2,4-triazines also linked by trimethylene tethers.

Experimental Section

General. The NMR spectra were recorded at 93.94 kG (400 MHz for ^1H, 100 MHz for ^{13}C) in $CDCl_3$. Residual $CHCl_3$ (δ 7.24 ppm) and the center line of the $^{13}CDCl_3$ triplet (δ 77.0 ppm) were used as internal references for ^1H and ^{13}C, respectively. All O*H* proton assignments were confirmed by D_2O exchange. All compounds were shown to be >98% pure by ^1H NMR with the exception of **2c** and **2f** which could not be purified due to rapid decomposition. All solvents were purified and dried prior to use.[21] "Pet ether" refers to petroleum ether, bp 35–60 °C. All flash chromatography was run using standard flash silica gal 60

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(15) A similar result was also observed in the indole chemistry with the 3-tethered diethyl 1,2,4-triazine-5,6-dicarboxylate. Li, J.-H.; Snyder, J. K., Boston University, unpublished results.
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as adsorbent. A "silica gel plug" refers to either a disposable Pasteur pipet or a 10-mm i.d. flash column filled with approximately 5 cm of flash silica gel. Only fragment peaks in the LRMS spectra with intensities 25% of the base peak are listed unless fragment represents a well-known fragmentation pathway.

Starting Materials. Pyrrole, anhyd hydrazine, 2,3-butanedione, γ-butyrolactone, δ-valerolactone, and trimeric glyoxal dihydrate were commercially available from Aldrich and were used without further purification. Ethyl polyphosphate (PPE) was prepared from phosphorus pentoxide and anhyd diethyl ether immediately before use.[10a] Diethyl 2,3-dioxosuccinate was prepared from dihydroxytartaric acid (Sigma) and could be stored at 4 °C for up to 1 month.[22]

4-(1-Pyrrolyl)butanoic Acid (3a).[23] In an AtmosBag (Aldrich) thoroughly purged with nitrogen and maintained under positive nitrogen pressure were thoroughly mixed pyrrole (0.67 g, 10 mmol) and potassium hydride (0.408 g, 10.2 mmol) in a predried 50-mL thick-walled test tube. (CAUTION: Once initiated, this reaction is exothermic!) The bottom of the test tube could be gently heated with a heat gun in order to initiate the reaction. At this point, the heat source was immediately extinguished!) The liquid mixture was stirred with a glass rod until the solid pyrrole potassium salt formed. To this salt was slowly (dropwise) added γ-butyrolactone (1.119 g, 13.0 mmol) with stirring, the tube was sealed with a septum secured with copper wire and removed from the AtmosBag, and a balloon filled with nitrogen was fitted through the septum. The reaction mixture was heated in a sand bath to 160 °C for 3 h. After being cooled to rt, the mixture was partitioned between water (100 mL) and EtOAc (200 mL). The aqueous layer was collected, neutralized (pH 7 by pH paper) by the addition of aqueous HCl (1 N), and then extracted with EtOAc (3 × 100 mL). The combined EtOAc extract was washed with water (200 mL) and saturated brine (200 mL) and then dried over Na_2SO_4. The EtOAc solution was decanted and passed directly through a plug of silica gel, eluting with additional CH_2Cl_2 (100 mL), and the solvent removed in vacuo to provide **3a** as a colorless oil (1.392 g, 91% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.65 (m, 2 H), 6.15 (m, 2 H), 3.96 (t, J = 6.8 Hz, 2 H), 2.32 (t, J = 7.2 Hz, 2 H), 2.09 (tt, J = 7.2, 6.8 Hz, 2 H), COO*H* was not observed; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.3, 120.5 (2 C), 108.3 (2 C), 48.3, 30.7, 26.4; IR (NaCl) 3105 (% transmittance 35), 2935 (29), 1709 (1), 1500 (22), 1282 (18), 729 (14) cm^{-1}; LRMS (EI, 70 eV) m/z ([M + 1]$^+$, rel int 10), 153 (M$^+$, 100), 81 (84), 80 (79); HRMS (EI, 70 eV) m/z 153.0798 (M$^+$, calcd for $C_8H_{11}NO_2$ 153.0790).

5-(1-Pyrrolyl)pentanoic Acid (3b). Prepared from pyrrole (6.70 g, 100 mmol) and δ-valerolactone (13.00 g, 130 mmol) according to the same, scaled procedure as described above for **3a**, with the sole modification of maintaining the reaction in the sand bath to 200 °C for 3 h, to provide **3b** as colorless crystals (14.70 g, 88% yield): mp 54–56 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.64 (m, 2 H), 6.13 (m, 2 H), 3.89 (t, J = 7.0 Hz, 2 H), 2.35 (t, J = 7.3 Hz, 2 H), 1.82 (tt, J = 7.3, 7.0 Hz, 2 H), 1.62 (tt, J = 7.3, 7.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.8, 120.4 (2 C), 108.0 (2 C), 49.1, 33.4, 30.8 21.7; IR (NaCl) 3102 (% transmittance 63), 2934 (52), 1708 (14), 1500 (51), 1282 (42), 726 (30) cm^{-1}; LRMS (EI, 70 eV) m/z 168 ([M + 1], rel int 9), 167 (M$^+$, 92), 108 (14), 94 (14), 81 (100), 80 (90), 67 (19); HRMS (EI, 70 eV) m/z 167.0951 (M$^+$, calcd for $C_9H_{13}NO_2$ 167.0946).

4-(1-Pyrrolyl)butanenitrile (4a). Carboxylic acid **3a** (1.224 g, 8.0 mmol) and freshly prepared PPE[10a] (3.2 g) in anhyd CH_2Cl_2 (1.0 mL) were mechanically stirred for 10 min at 0 °C, and then the reaction mixture was saturated with ammonia by maintaining an ammonia atmosphere above the mixture and the stirring was continued for 3 h at 0 °C. To this viscous mixture was added another portion of PPE (8.0 g) and anhyd CH_2Cl_2 (2.0 mL) and the stirring continued at rt for 12 h. The reaction was then quenched after cooling to 0 °C by the addition of aqueous K_2CO_3 solution (30% w/v, 60 mL) with subsequent stirring for 0.5 h. The mixture was extracted with EtOAc (2 × 80 mL) and the organic layer washed with water (80 mL) and saturated brine (80 mL) and dried over $MgSO_4$. After decanting, the solvent was removed in vacuo to give a dark oil which was purified by flash chromatography (pet ether:EtOAc = 20:1) to give **4a** (0.525, 49%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.66 (m, 2 H), 6.18 (m, 2 H), 4.03 (t, J = 6.5 Hz, 2 H), 2.22 (t, J = 7.0 Hz, 2 H), 2.08 (tt, J = 7.0, 6.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 120.3 (2 C), 118.6, 108.6 (2 C), 47.2, 27.1, 14.1; IR (NaCl) 3100 (% transmittance 64), 2937 (48), 2881 (61), 2247 (58), 1678 (23), 1500 (19), 1393 (27), 1280 (22), 1091 (23), 732 (5) cm^{-1}; LRMS (EI, 70 eV) m/z 135 ([M + 1]$^+$, rel int 13), 134 (M$^+$, 100), 81 (89), 80 (68): HRMS (EI, 70 eV) m/z 134.0843 (M$^+$, calcd for $C_8H_{10}N_2$ 134.0843).

5-(1-Pyrrolyl)pentanenitrile (4b). Prepared from **3b** (3.34 g, 2.0 mmol) according to the same procedure as described above for **4a** to provide **4b** after flash chromatography (pet ether:CH_2Cl_2 = 1:1) as a colorless, light-sensitive oil (1.646 g, 56% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.62 (m, 2 H), 6.14 (m, 2 H), 3.92 (t, J = 6.7 Hz, 2 H), 2.28 (t, J = 7.1 Hz, 2 H), 1.91 (tt, J = 7.8, 6.7 Hz, 2 H), 1.61 (tt, J = 7.8, 7.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 120.4 (2 C), 119.2, 108.4 (2 C), 48.6, 30.4, 22.7, 16.9; IR (NaCl) 3100 (% transmittance 35), 2958 (25), 2874 (27), 2246 (30), 1729 (0), 1626 (7), 1598 (2), 1578 (0), 1518 (28), 726 (31) cm^{-1}; LRMS (EI, 70 eV) m/z 149 ([M + 1]$^+$, rel int 10), 148 (M$^+$, 65), 81 (61), 80 (100), 53 (36); HRMS (EI, 70 eV) m/z 148.0991 (M$^+$, calcd for $C_9H_{12}N_2$ 148.1000).

General Procedure A: Preparation of 3-[ω-(1-Pyrrolyl)-alkyl]-1,2,4-triazines 2a–2f from ω-(1-Pyrrolyl)alkanenitriles 4 via Amidrazones 5.[24] To a suspension of sodium hydride (60% dispersion in mineral oil, 0.240 g, 6.0 mmol, or scaled equivalent) in anhyd ether (5 mL) cooled to 0 °C was added anhyd hydrazine (0.192 g, 6.0 mmol) with vigorous stirring. After the mixture was stirred for 20 min, a solution of the ω-(1-pyrrolyl)-alkanenitrile (**4a** or **4b**, 2.0 mmol) in anhyd THF (10 mL) was added dropwise with stirring to the sodium hydrazide suspension over 15 min. The solution was stirred for 2 h at 0 °C, and then the reaction was quenched by the dropwise addition of ice–water (4 mL). Ether (100 mL) was added to the mixture and then the organic layer separated. The aqueous layer was extracted with another portion of ether (20 mL), and the combined ether extracts were washed with saturated brine (30 mL) and dried over $MgSO_4$. After decanting, the solvent was removed in vacuo to provide the unstable crude amidrazone (**5a** or **5b**) which was used immediately in the next step without further purification.

The crude amidrazone and anhyd $MgSO_4$ (0.6 g, 5.0 mmol) were suspended in anhyd ethanol (2.0 mL) under an argon atmosphere. To the suspension was added a solution of the α,β-dicarbonyl compound (2.0 mmol) in anhyd ethanol (2.0 mL) with stirring at rt. The stirring was continued at rt for 12 h and then the solution refluxed for 0.5 h. After cooling and filtration, the solvent was removed in vacuo and the crude tethered triazine purified by flash chromatography.

3-[3-(1-Pyrrolyl)propyl]-1,2,4-triazine (2a). Prepared from nitrile **4a** (0.268 g, 2.0 mmol) and trimeric glyoxal dihydrate (0.441 g, 2.1 mmol) according to General Procedure A. Purification by flash chromatography (CH_2Cl_2:EtOAc = 1:1) gave **2a** (0.256 g, 68% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.09 (d, J = 2.4 Hz, 1 H), 8.52 (d, J = 2.4 Hz, 1 H), 6.65 (m, 2 H), 6.10 (m, 2 H), 4.01 (t, J = 6.8 Hz, 2 H), 3.12 (t, J = 7.6 Hz, 2 H), 2.36 (tt, J = 7.6, 6.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7, 148.6, 147.7, 120.6 (2 C), 108.2 (2 C), 48.7, 34.3, 29.5; IR (NaCl) 3098 (% transmittance 55), 2932 (44), 1653 (43), 1528 (15), 1500 (19), 1412 (8), 1281 (20), 1090 (15), 1050 (22), 730 (3) cm^{-1}; LRMS (EI, 70 eV) m/z 189 ([M + 1]$^+$, rel int 79), 188 (M$^+$, 100), 122 (35), 121 (32), 81 (28), 80 (29); HRMS (EI, 70 eV) m/z 188.1069 (M$^+$, calcd for $C_{10}H_{12}N_4$ 188.1062).

5,6-Dimethyl-3-[3-(1-pyrrolyl)propyl]-1,2,4-triazine (2b). Prepared from nitrile **4a** (0.268 g, 2.0 mmol) and 2,3-butanedione (0.172 g, 2.0 mmol) according to General Procedure A. Purification by flash chromatography (CH_2Cl_2:EtOAc = 1:1) gave **2b** (0.281 g, 65% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.64 (m, 2 H), 6.09 (m, 2H), 3.98 (t, J = 7.0 Hz, 2 H), 3.01 (t, J = 7.5 Hz, 2 H), 2.63 (s, 3 H), 2.48 (s, 3 H), 2.32 (tt, J = 7.5, 7.0 Hz 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.8, 158.6, 155.5, 120.6

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(23) Procedure is based upon: Reppe, W. *Liebigs Ann. Chem.* **1955**, *596*, 1 (actual procedure given on p 215).
(24) General procedures for the condensation of amidrazones with 1,2-dicarbonyl compounds: (a) Ratz, R.; Schroeder, H. *J. Org. Chem.* **1958**, *23*, 1931. (b) Neunhoffer, H.; Hennig, H.; Fruhauf, H.-W.; Mutterer, M. *Tetrahedron Lett.* **1969**, 3147.

(2 C), 108.0 (2 C), 48.8, 33.8, 29.7, 21.7, 19.3; IR (NaCl) 3098 (% transmittance 42), 2930 (28), 1768 (47), 1718 (42), 1528 (30), 1500 (30), 1402 (17), 1282 (34), 1090 (34), 728 (21) cm^{-1}; LRMS (EI, 70 eV) m/z 217 ($[M + 1]^+$, rel int 6), 216 (M^+, 22), 149 (96), 123 (100), 81 (45), 80 (28), 43 (39); HRMS (EI, 70 eV) m/z 216.1370 (M^+, calcd for $C_{12}H_{16}N_4$ 216.1375).

Diethyl 3-[3-(1-Pyrrolyl)propyl]-1,2,4-triazine-5,6-dicarboxylate (2c). Prepared from nitrile **4a** (0.268 g, 2.0 mmol) and ethyl dioxosuccinate[22] (0.404 g, 2.0 mmol) according to General Procedure A. Purification by flash chromatography (CH_2Cl_2:EtOAc = 10:1 gave **2c** (0.411 g, 62% yield) as a yellow oil, which decomposed quickly and was immediately subjected to cycloaddition (vide infra): ^1H NMR ($CDCl_3$, 400 MHz) δ 6.63 (m, 2 H), 6.08 (m, 2 H), 4.52 (q, J = 7.1 Hz, 2 H), 4.49 (q, J = 7.1 Hz, 2 H), 4.03 (t, J = 6.7 Hz, 2 H), 3.24 (t, J = 7.4 Hz, 2 H), 2.40 (tt, J = 7.4, 6.7 Hz, 2 H), 1.46 (t, J = 7.1 Hz, 3 H), 1.42 (t, J = 7.1 Hz, 3 H); ^{13}C NMR spectrum could not be obtained due to instability; IR (NaCl) 2982 (% transmittance 60), 1750 (39), 1734 (38), 1274 (22), 1192 (30), 728 (48) cm^{-1}; LRMS (EI, 70 eV) m/z 332 (M^+, rel int 13), 304 (12), 239 (12), 231 (30), 167 (47), 81 (100), 80 (67), HRMS (EI, 70 eV) m/z 332.1479 (M^+, calcd for $C_{16}H_{20}N_4O_4$ 332.1484).

3-[4-(1-Pyrrolyl)butyl]-1,2,4-triazine (2d). Prepared from nitrile **4b** (0.296 g, 2.0 mmol) and trimeric glyoxal dihydrate (0.420 g, 2.0 mmol) according to General Procedure A. Purification by flash chromatography (CH_2Cl_2:EtOAc = 1:1) gave **2d** (0.299 g, 74% yield) as a yellow oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 9.06 (d, J = 2.4 Hz, 1 H), 8.50 (d, J = 2.4 Hz, 1 H), 6.61 (m, 2 H), 6.09 (m, 2 H), 3.90 (t, J = 6.6 Hz, 2 H), 3.12 (t, J = 7.2 Hz, 2 H), 1.85 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 148.5, 147.4, 120.2 (2 C), 107.7 (2 C), 48.9, 36.4, 30.7, 24.9; IR (NaCl) 3098 (% transmittance 33), 2932 (7), 2868 (15), 1718 (23), 1550 (9), 1526 (4), 1500 (5), 1412 (2), 1366 (3), 1280 (1), 1090 (2), 1052 (5), 728 (0) cm^{-1}; LRMS (EI, 70 eV) m/z 203 ($[M + 1]^+$, rel int 25), 202 (M^+, 93), 136 (69), 135 (100), 120 (67), 108 (72), 107 (33), 106 (83), 96 (36), 95 (28), 91 (32), 81 (98), 80 (98), 67 (40), 53 (62), 41 (44), 39 (47), 28 (27), 27 (33), 26 (34); HRMS (EI, 70 eV) m/z 202.1218 (M^+, calcd for $C_{11}H_{14}N_4$ 202.1218).

5,6-Dimethyl-3-[4-(1-pyrrolyl)butyl]-1,2,4-triazine (2e). Prepared from nitrile **4b** (0.335 g, 2.26 mmol) and 2,3-butanedione (0.195 g, 2.26 mmol) according to General Procedure A. Purification by flash chromatography (CH_2Cl_2:EtOAc = 1:1) gave **2e** (0.395 g, 76% yield) as a yellow oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.61 (m, 2 H), 6.08 (m, 2 H), 3.89 (t, J = 6.6 Hz, 2 H), 3.01 (t, J = 7.0 Hz, 2 H), 2.62 (s, 3 H), 2.47 (s, 3 H), 1.83 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.2, 158.6, 155.4, 120.4, (2 C), 107.0 (2 C), 49.2, 36.1, 31.0, 25.4, 21.7, 19.3; IR (NaCl) 3098 (% transmittance 63), 2932 (18), 1528 (5), 1502 (9), 1472 (7), 1378 (0), 1343 (0), 1280 (0), 1090 (3), 726 (10) cm^{-1}; LRMS (EI, 70 eV) m/z 230 (M^+, rel int 12%), 202 (57), 163 (100), 135 (76), 120 (34), 108 (32), 106 (54), 81 (98), 80 (92), 67 (26), 54 (33), 53 (51), 41 (36), 39 (45), 28 (28), 27 (28); HRMS (EI, 70 eV) m/z 230.1534 (M^+, calcd for $C_{13}N_{18}N_4$ 230.1531).

General Procedure B: Intramolecular Cycloaddition of the Tethered Triazines 2a–2c. The 3-[3-(1-pyrrolyl)propyl]-1,2,4-triazine (**2a–2c**, 0.7–0.9 mmol) was dissolved/suspended in the appropriate solvent (9 mL, see Table I) by sonication in an ultrasound cleaning bath for 5 min and then purged with argon. The reaction mixture was then refluxed as specified in Table I. After cooling, the reaction mixture was placed on a flash chromatography column, eluting first with pet ether–CH_2Cl_2 (1:1, 100 mL) to remove reaction solvent and then with the final purification solvent mixture (vide infra) to provide the cycloadduct. All cycloadducts showed a characteristic blue fluorescent spot on TLC under short wavelength UV (254 nm). No cycloadducts were obtained from the reactions of **2d**, **2e**, or crude **2f**.

4,5-Dihydro-6*H*-pyrrolo[3,2,1-*de*][1,5]naphthyridine (1a). Prepared from triazine **2a** (0.150 g, 0.88 mmol) according to General Procedure B using the conditions of Table I (item 1). Flash chromatography (EtOAc:MeOH = 10:1) gave **1a** (0.111 g, 80% yield) as yellow crystals: mp 71–73 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, J = 6.5 Hz, 1 H), 7.70 (d, J = 2.8 Hz, 1 H), 7.65 (d, J = 6.5 Hz, 1 H), 6.73 (d, J = 2.8 Hz, 1 H), 4.35 (t, J = 5.8 Hz, 2 H), 3.64 (t, J = 6.2 Hz, 2 H), 2.46 (tt, J = 6.2, 5.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.9, 138.3, 130.8, 129.8, 129.0, 113.5, 100.3, 44.0, 27.8, 23.2; IR (KBr) 2940 (% transmittance 65), 2871 (63), 1612 (57), 1501 (37), 1337 (29), 1213 (40), 737 (48) cm^{-1}; LRMS (EI 70 eV) m/z 159 ($[M + 1]^+$, rel int 10), 158 (M^+, 100), 157 (80), 156 (26); HRMS (EI 70 eV) m/z 158.0840 (M^+, calcd for $C_{10}H_{10}N_2$ 158.0844).

4,5-Dihydro-1,2-dimethyl-6*H*-pyrrolo[3,2,1-*de*][1,5]naphthyridine (1b). Prepared from triazine **2b** (0.164 g, 0.76 mmol) according to General Procedure B using the conditions of Table I (item 2). Flash chromatography (EtOAc:MeOH = 6:1) gave **1b** (0.106 g, 75% yield) as yellow crystals: mp 67–69 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.15 (d, J = 2.9 Hz, 1 H), 6.35 (d, J = 2.9 Hz, 1 H), 4.13 (t, J = 5.7 Hz, 2 H), 3.07 (t, J = 6.2 Hz, 2 H), 2.55 (s, 3 H), 2.40 (s, 3 H), 2.31 (tt, J = 6.2, 5.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.6, 140.1, 131.6, 129.5, 128.8, 119.8, 98.7, 43.9, 27.5, 23.4, 21.4, 15.1; IR (KBr) 2948 (% transmittance 24), 1619 (3), 1501 (0), 1479 (0), 1451 (0), 1340 (0), 1229 (10), 728 (43) cm^{-1}; LRMS (EI 70 eV) m/z 187 ($[M + 1]^+$, rel int 24), 186 (M^+, 100), 185 (89), 171 (39); HRMS (EI 70 eV) m/z 186.1155 (M^+, calcd for $C_{12}H_{14}N_2$ 186.1157).

Diethyl 4,5-Dihydro-6*H*-pyrrolo[3,2,1-de][1,5]naphthyridine-1,2-dicarboxylate (1c). Prepared from triazine **2c** (0.300 g, 0.90 mmol) according to General Procedure B using the conditions of Table I (items 3–7). Flash chromatography (CH_2Cl_2:EtOAc = 1:1) gave **1c** (0.227 g, 83% yield, item 3, preferred conditions) as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, J = 2.9 Hz, 1 H), 6.77 (d, J = 2.9 Hz, 1 H), 4.44 (q, J = 7.2 Hz, 2 H), 4.42 (q, J = 7.2 Hz, 2 H), 4.20 (t, J = 5.7 Hz, 2 H), 3.17 (t, J = 6.1 Hz, 2 H), 2.35 (tt, J = 6.1, 5.7 Hz, 2 H), 1.40 (t, J = 7.2 Hz, 3 H), 1.39 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.8, 166.5, 146.1, 141.4, 132.0, 131.2, 128.7, 117.5, 102.6, 61.9, 61.4, 44.1, 27.7, 22.9, 14.2, 14.1; IR (NaCl) 2928 (% transmittance 33), 1732 (8), 1716 (8), 1610 (27), 1500 (21), 1400 (22), 1372 (18), 1346 (19), 1284 (19), 1260 (18), 1228 (17), 1200 (18), 1184 (18), 1112 (22), 1034 (26), 736 (26) cm^{-1}; LRMS (EI 70 eV) m/z 302 (M^+, rel int 24), 229 (41), 158 (100), 157 (33); HRMS (EI 70 eV) m/z 302.1271 (M^+, calcd for $C_{16}H_{18}N_2O_4$ 302.1267).

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds **1** (**1a–1c**), **2** (**2a**, **2b**, **2d**, and **2e**), **3a**, **3b**, **4a**, and **4b** and ^1H NMR spectra (no ^{13}C NMR spectra) for **2c** (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.