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Intramolecular Inverse-Electron-Demand Diels−Alder Reactions of Imidazoles with 1,2,4-Triazines: A New Route to 1,2,3,4-Tetrahydro-1,5-naphthyridines and Related Heterocycles

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The intramolecular inverse-electron-demand Diels−Alder reaction between imidazoles and 1,2,4-triazines linked by a trimethylene tether from the imidazole N1 position to the triazine C3 proceed in excellent yields to produce 1,2,3,4-tetrahydro-1,5-naphthyridines. The reaction proceeds by a cycloaddition with subsequent loss of nitrogen, followed by a presumed stepwise loss of a nitrile. The analogous intramolecular cycloadditions employing a tetramethylene tether also proceeded to give 2,3,4,5-tetrahydro-1*H*-pyrido[3,2-*b*]azepines in acceptable yields. The reaction to produce the tetrahydro-1,5-naphthyridines can also be promoted with microwave irradiation.

Introduction

Inverse-electron-demand Diels−Alder cycloadditions using electron-deficient heteroaromatic azadienes is well-established chemistry for the synthesis of heterocyclic compounds.[1] We have been interested in the use of electron-rich heteroaromatic compounds with latent enamine functionalities, such as indoles,[2] pyrroles,[2i,3] and imidazoles,[4] as dienophiles in this chemistry for some time. Included in this work has been investigations into intramolecular cycloadditions with tethered 1,2,4-triazines.[1c,2m,5] While these reactions of indoles and pyrroles proceeded smoothly to give the anticipated pyridoannulation products following release of nitrogen and aromatization (Scheme 1, eq 1), the intramolecular cycloadditions of tethered triazine/imidazole pairs quite unexpectedly resulted in nitrile release from the intermediate cycloadduct **A** leading to an efficient synthesis of 1,2,3,4-tetrahydro-1,5-naphthyridines **1** rather than forming annulated deazapurines **2** as originally targeted (eq 2).[4b]

While unintended, this facile route to 1,5-naphthyridines was rather intriguing. Past syntheses of fully aromatized 1,5-naphthyridines have relied predominantly upon annulations beginning with 3-aminopyr-

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(2) For a review, see: (a) Lee, L.; Snyder, J. K. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press: Stamford, CT, 1999; Vol. 6, pp 119−171. For some examples of indole in cycloadditions since then, see: (b) Pelkey, E. T.; Barden, T. C.; Gribble, G. W. *Tetrahedron Lett.* **1999**, *40*, 7615−7619. (c) Benson, S. C.; Lee, L.; Yang, L.; Snyder, J. K. *Tetrahedron* **2000**, *56*, 1165−1180. (d) Gribble, G. W.; Pelkey, E. T.; Simon, W. M.; Trujillo, H. A. *Tetrahedron* **2001**, *56*, 10133−10140. (e) Muthusamy, S.; Gunanathan, C.; Babu, S. A. *Tetrahedron Lett.* **2001**, *42*, 523−526. (f) de la Mora, M. A.; Cuevas, E.; Muchowski, J. M.; Cruz-Almanza, R. *Tetrahedron Lett.* **2001**, *42*, 5351−5353. (g) Chataigner, I.; Hess, E.; Toupet, L.; Piettre, S. R. *Org. Lett.* **2001**, *3*, 515−518. (h) Wilkie, G. D.; Elliott, G. I.; Blagg, B. S. J.; Wolkenberg, S. E.; Soenen, D. R.; Miller, M. M.; Pollack, S.; Boger, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 11292−11294. (i) Giomi, D.; Cecchi, M. *Tetrahedron* **2002**, *58*, 8067−8071. (j) Lynch, S. M.; Bur, S. K.; Padwa, A. *Org. Lett* **2002**, *4*, 4643−4645. (k) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2003**, *5*, 3169−3171. (l) Chretien, A.; Chataigner, I.; L′Helias, N.; Piettre, S. R. *J. Org. Chem.* **2003**, *68*, 7990−8002. (m) Lindsley, C. W.; Wisnoski, D. D.; Wang, Y.; Leister, W. H.; Zhao, Z. *Tetrahedron Lett.* **2003**, *44*, 4495−4498.

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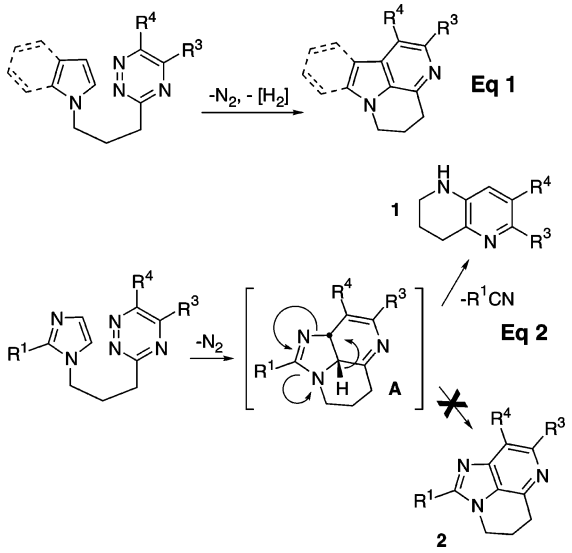
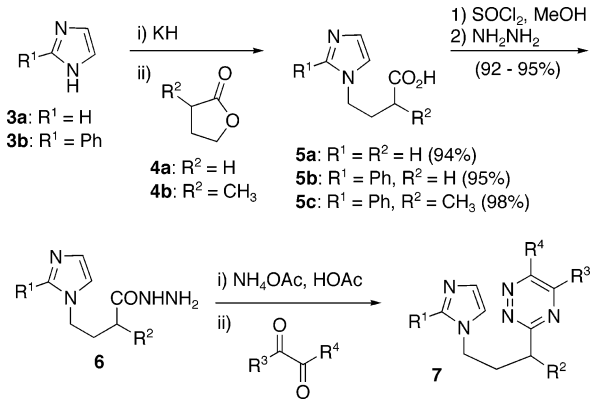
SCHEME 1



idines[6] or 3-nitropyridines.[7] These pathways have limitations in developing a variety of substitution sites on the naphthyridine core. Moreover, syntheses of 1,2,3,4-tetrahydro-1,5-naphthyridines are quite rare,[6e,k,l,8] often relying upon reduction of one of the rings of the parent naphthyridine.[6e,9] Those that do not begin with the fully aromatized 1,5-naphthyridine typically still begin with a 3-amino or 3-nitropyridine[6e,k,l,8] and thereby suffer the same limitations in diversity development as preparation of the fully aromatized naphthyridines.

As small, nitrogen-containing heterocycles, 1,5-naphthyridines are interesting structures since they feature several favorable characteristics for drug development.[10] The concept of fully aromatized 1,5-naphthyridines as drug candidates is reinforced by numerous reports of their biological activity.[11] In fact, as azaquinolines, these naphthyridines were recognized very early in the history of small-molecule drug discovery as potential antimalarial candidates,[6b,12] ultimately evolving into large antimalarial programs as exemplified by the work of Barlin and co-workers.[13] Furthermore, several tetrahydronaphthyridines **1** prepared in our preliminary studies showed good activity against a drug-resistant tuberculosis strain of *Mycobacterium avium*.[4b] We therefore sought to further develop this rather serendipitously discovered route to 1,2,3,4-tetrahydro-1,5-naphthyridines to probe its scope and limitations, with the ultimate goal of using these heterocycles as scaffolds in library development. We now report full results of this work.

SCHEME 2



Results and Discussion

Synthesis of Trimethylene-Tethered Triazines. Analogous to the indole[14] and pyrrole[3a] studies, the tethered triazines **7** were prepared by one of two basic routes; the first route proceeded through an acyl hydrazide **6** (Scheme 2, Table 1). Nucleophilic opening of γ-butyrolactone (**4a**) and 4-methyl γ−butyrolactone (**4b**) with the imidazole anions generated with KH proceeded in good yields (94−98%) to form carboxylic acids **5a**−**c**. Following esterification ($SOCl_2$/MeOH, 92−95%), the acyl hydrazides **6**, which were stable to storage under ambient conditions but could not be chromatographed on silica gel, were formed in nearly pure form (99%) by treatment with anhydrous hydrazine. Adapting the procedure of Laasko[15] as used previously in the preparation of teth-

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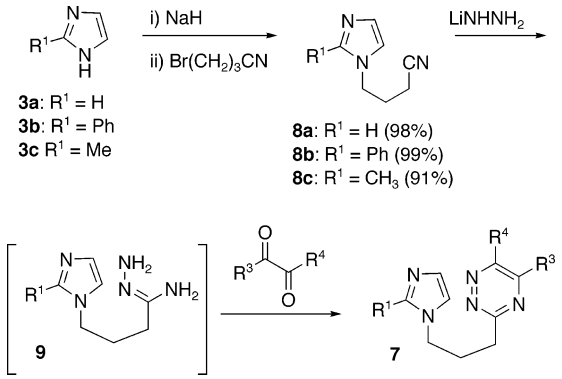
TABLE 1. Preparation of Imidazole/Triazine Tethered Pairs 7 by Acyl Hydrazide Route (Scheme 2)

item	triazine	R^1	R^2	R^3	R^4	yield[a] (%)
1	**7a**	H	H	Ph	Ph	76
2	**7b**	Ph	H	Ph	Ph	91
3	**7c**	Ph	Me	Ph	Ph	80
4	**7d**	Ph	H	Me	Me	80
5	**7e**	H	H	Me	Me	30
6	**7f**	Ph	H	Ph	H	53

[a] Isolated yields from the Laasko condensation step.

SCHEME 3



ered 1,2,4-triazines for intramolecular cycloadditions with indoles[14] and pyrroles,[3a] the crude acylhydrazides were condensed with benzil or 2,3-butanedione to give the tethered triazines **7a**–**d** in good yields (76–91%, Table 1, items 1–4).

As previously observed with indole- and pyrrole-tethered triazines, this acyl hydrazide route did not work with all 1,2-dicarbonyl compounds, for example, glyoxal, nor were the yields of **7e** (30%) and **7f** (53%) acceptable (Table 1, items 5 and 6). Thus, the alternative route through the amidrazone was probed and ultimately became the method of choice for preparing most tethered triazines due to its generality (Scheme 3). Imidazole-tethered nitriles **8** were readily prepared by simple bromide displacements on 4-bromobutyronitrile. Addition of lithium hydrazide (NH_2NH_2/*n*-BuLi) to **8** produced amidrazones **9**, which were immediately condensed with the α-dicarbonyl compounds to produce the tethered triazines **7** in good to excellent overall yields (61–98%, Table 2). The yields of **7e** (81%) and **7f** (98%) under these conditions increased significantly in comparison to those obtained via the acyl hydrazide route (30% and 53%, respectively, Table 1). In general, derivatives from 2-phenylimidazole were easier to monitor by TLC with simple UV lamps as the imidazole and 2-methylimidazole derivatives are nonquenchers.

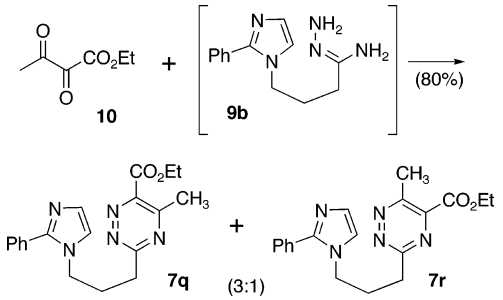
The preparation of a few other tethered triazines not listed in Tables 1 and 2 deserves special note. As observed in earlier work, the regioselectivity in the condensation of the amidrazones **9** with unsymmetric 1,2-dicarbonyl compounds was quite variable.[2m,16] With phenylglyoxal, only a single isomer was observed (**7f**, **7g**, and **7n**, Table 2, items 5, 6, and 13), with the more nucleophilic hydrazinyl amino group condensing with the more electrophilic aldehyde carbonyl.[16b–e,17] Similar exclusive regioselective was also observed in the condensation of *p*-bromo-[18] and *p*-methoxyphenyl glyoxals[19] with amidrazone **9b** to produce triazines **7o** and **7p** (Table 2, items 14 and 15). In

TABLE 2. Preparation of Tethered Imidazole/Triazine Pairs 5 by Amidrazone Route (Scheme 3)

item	triazine	R^1	R^3	R^4	yield[a] (%)
1	**7a**	H	Ph	Ph	95
2	**7b**	Ph	Ph	Ph	95
3	**7d**	Ph	Me	Me	87
4	**7e**	H	Me	Me	81
5	**7f**	Ph	Ph	H	98
6	**7g**	H	Ph	H	81
7	**7h**	Ph	H	H	96
8	**7i**	Ph	$-(CH_2)_4-$		62
9	**7j**	H	$-(CH_2)_4-$		61
10	**7k**	Ph	CO_2Et	CO_2Et	83
11	**7l**	Me	Me	Me	80
12	**7m**	Me	Ph	Ph	91
13	**7n**	Me	Ph	H	82
14	**7o**	Ph	*p*-BrPh	H	89
15	**7p**	Ph	*p*-MeOPh	H	91

[a] Isolated yields after condensation step.

SCHEME 4



contrast, an analogous reaction with ethyl 2,3-dioxobutanoate[20] (**10**) with **9b** led only to a 3:1 mixture of regioisomers **7q** and **7r** (80% combined, Scheme 4). This ratio proved to be insensitive to the solvent employed, though the yield of the **7q**/**7r** mixture was considerably lower in benzene or THF in comparison to ethanol. The assignment of the major regioisomer as **7q** was initially based on electronic considerations, with the more nucleophilic hydrazinyl amino group assumed to add preferentially to the more electophilic central carbonyl of **10**. This conclusion was confirmed following the microwave-promoted cycloaddition as described below.

To circumvent this regioselectivity issue, a new route to the monoester tethered triazine **7s** was adapted from a procedure we reported earlier (Scheme 5).[4d] Conversion

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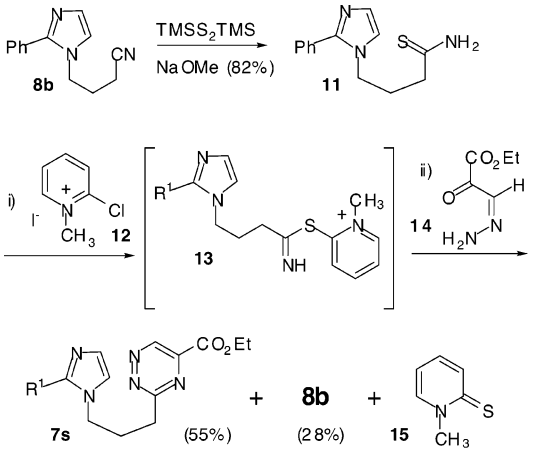
(17) Taylor, E. C.; Martin, S. F. *J. Org. Chem.* **1972**, *37*, 3958–3960.

(18) Preparation of *p*-bromophenylglyoxal: Kornblum, N.; Frazier, H. W. *J. Am. Chem. Soc.* **1966**, *88*, 865–866.

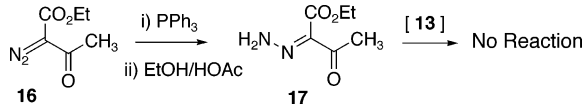
(19) *p*-Methoxyphenylglyoxal was prepared by adapting the procedure in ref 18 (see the Supporting Information). For previous preparation: (a) Sisido, K.; Nozaki, H. *J. Am. Chem. Soc.* **1948**, *70*, 3326–3329. (b) Fodor, G.; Kovacs, O. *J. Am. Chem. Soc.* **1949**, *71*, 1045–1048.

(20) Preparation of **10**: Hoffman, R. V.; Wilson, A. L.; Kim, H.-O. *J. Org. Chem.* **1990**, *55*, 1267–1270.

SCHEME 5



SCHEME 6

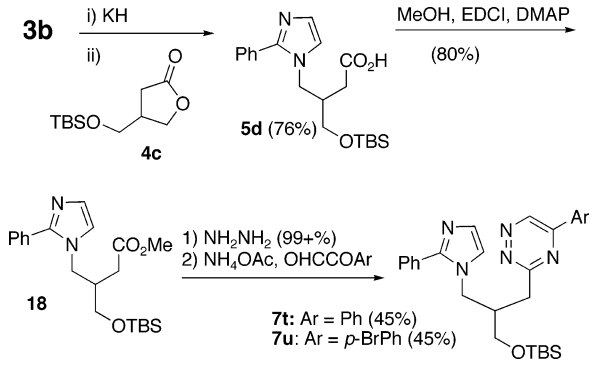


of nitrile **8b** to thioamide **11** with hexamethyldisilathiane[21] followed by condensation with hydrazone **14** (which was difficult to make)[16c] mediated by the Mukaiyama reagent 2-chloro-1-methylpyridinium iodide (**12**) produced **7s** (55%), accompanied by significant amounts (28%) of reconstituted nitrile **8b** (Scheme 5). The regeneration of nitrile **8b** presumably results from elimination of *N*-methylthiopyridone (**15**) from intermediate **13**. Addition of HOAc to the reaction mixture failed to suppress the formation of **8b**, though it did not effect the production of **7s**. Due to the difficulty in separating **8b** from **7s**, the reaction mixture was used directly in the subsequent cycloaddition as described below, after purifying small amounts of **7s** for characterization purposes.

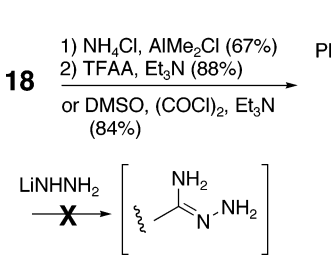
Attempts to apply this regioselective triazine preparation to the synthesis of **7q**, however, were unsuccessful. α-Diazo-*β*-keto ester **16** was readily prepared following the procedure of Baum and Davies[22] and then subsequently reduced[16c,23] to hydrazone **17**[16c] (Scheme 6). The condensation of **17** with thioamide **11** mediated by Mukaiyama reagent **12**, or the corresponding bromopyridinium reagent, failed to produce **7q**, returning only unreacted **17** (the thioamide **11** and Mukaiyama reagent were consumed). Presumably, the reduced nucleophilicity of the hydrazone **17**, a consequence of the two adjacent carbonyl groups, prevents the addition to the activated thioamide **13**.

Tethered triazines with a substituted central methylene were also of interest in order to examine the potential of generating stereochemistry in the tetrahydronaphthyridine ring at C3 with a substituent capable of further diversification of the naphthyridine scaffold, such as a hydroxymethyl group. While the amidrazone route proved to be the preferred pathway for most tethered triazine preparations, central methylene-substituted triazines **7t**

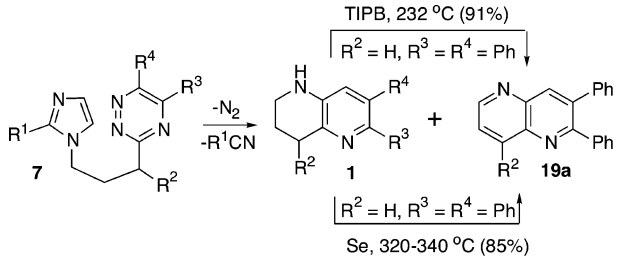
SCHEME 7



SCHEME 8



SCHEME 9



and **7u** could only be prepared via the acyl hydrazide route beginning with lactone **4c**[24] (Scheme 7). The condensations of phenyl and *p*-bromophenyl glyoxals with the acyl hydrazide formed from **18** were completely regioselective, producing only tethered triazines **7t** and **7u** in modest yields (45% each). Attempted preparation of **7t** via the amidrazone route failed. Addition of lithium hydrazide to nitrile **8d** (Scheme 8) resulted in considerable deprotection of the primary alcohol with no further reaction of the nitrile group, leading to recovery of the primary alcohol in low yield.

Cycloadditions of Trimethylene-Tethered Triazine/Imidazole Pairs. Inverse-electron-demand Diels–Alder reactions of the tethered imidazole/triazine pairs **7** were initially accomplished by refluxing in triisopropylbenzene (TIPB, bp 232 °C) under argon (Scheme 9) optimizing with diphenyl triazines **7a** and **7b**. Rather than the anticipated annulated deazapurines **2** (see Scheme 1), 1,2,3,4-tetrahydro-1,5-naphthyridines **1** were obtained along with lesser amounts of the fully aromatized 1,5-naphthyridines **19** (Table 3). Apparently, the [4 + 2] cycloaddition with immediate loss of N_2 is followed by rapid nitrile elimination rather than dehydrogenation.

(21) Lin, P.-Y.; Ku, W.-S.; Shiao, M.-J. *Synthesis* **1992**, 1219–1220.
(22) Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17*, 1709–1716.
(23) (a) Ohsumi, T.; Neunhoeffer, H. *Heterocycles* **1992**, *33*, 893–903. (b) Ohsumi, T.; Neunhoeffer, H. *Tetrahedron* **1992**, *48*, 5227–5234.

(24) Lactone **4c** was prepared by the hydrogenation of the corresponding butenolide (see the Supporting Information). For the preparation of the butenolide: Takabe, K.; Tanaka, M.; Sugimoto, M.; Yamada, T.; Yoda, H. *Tetrahedron Asymm.* **1992**, *3*, 1385–1386.

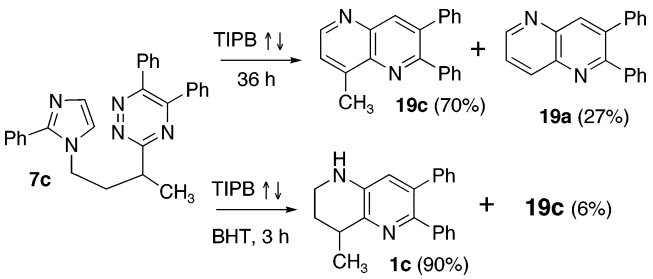
TABLE 3. Cycloadditions of Trimethylene Tethered Imidazole/Triazine Pairs 7

	triazine						cycloadduct[b]	
item	no.	R^1	R^2	R^3	R^4	conditions[a]	**1**	**19**
1	**7a**	H	H	Ph	Ph	7.5 h	**a**: 65	**a**: 10
2	**7a**	H	H	Ph	Ph	3 h, BHT (1 equiv)	**a**: 92	trace
3	**7b**	Ph	H	Ph	Ph	9 h	**a**: 57	**a**: 38
4	**7b**	Ph	H	Ph	Ph	3 h, BHT (1 equiv)	**a**: 92	trace
5	**7c**	Ph	Me	Ph	Ph	36 h	0	**c**: 70[c]
6	**7c**	Ph	Me	Ph	Ph	3 h, BHT (1 equiv)	**c**: 70	**c**: 19
7	**7c**	Ph	Me	Ph	Ph	3.2 h, BHT (2 equiv)	**c**: 90	**c**: 6
8	**7d**	Ph	H	Me	Me	7 h	**d**: 60	**d**: 25
9	**7d**	Ph	H	Me	Me	3 h, BHT (1 equiv)	**d**: 90	trace
10	**7e**	H	H	Me	Me	24 h	**d**: 52	**d**: 25
11[d]	**7e**	H	H	Me	Me	12 h, BHT (1.2 equiv)	**d**: 48	**d**: 18
12	**7f**	Ph	H	Ph	H	4 h,[e] Ph_2O	f: 75	**f**: 0
13	**7g**	H	H	Ph	H	7 h, BHT (1.2 equiv)	**f**: 81	trace
14	**7h**	Ph	H	H	H	42 h	**h**: 34	**h**: 23
15	**7h**	Ph	H	H	H	3 h, BHT (1 equiv)	**h**: 87	trace
16	**7i**	Ph	H	$-(CH_2)_4-$		6 h, BHT (1 equiv)	**i**: 89	trace
17	**7j**	H	H	$-(CH_2)_4-$		13 h, BHT (1.2 equiv)[f]	**i**: 54	trace
18	**7k**	Ph	H	CO_2Et	CO_2Et	1.5 h,[g] C_6H_5Br	0[h]	0
19	**7k**	Ph	H	CO_2Et	CO_2Et	5 h, BHT (1.2 equiv)	**k**: 91	0
20	**7l**	Me	H	Me	Me	6 h, BHT (1.2 equiv)	**d**: 77	**d**: 2
21	**7m**	Me	H	Ph	Ph	1.5 h	**a**: 82	**a**: 8
22	**7m**	Me	H	Ph	Ph	1 h, BHT (1.2 equiv)	**a**: 91	trace
23	**7n**	Me	H	Ph	H	3 h, BHT (1.2 equiv)	**f**: 83	trace
24	**7o**	Ph	H	*p*-BrPh	H	Ph_2O, 1.3 h[e]	**o**: 89	0
25	**7p**	Ph	H	*p*-MeOPh	H	Ph_2O, 5 h[e]	**p**: 85	0

[a] All reactions performed in refluxing TIPB (232 °C) unless otherwise noted. [b] Isolated yields. [c] In addition, **19a** (27%) was also isolated. [d] Starting material (**7e**) also isolated (24%). [e] Reflux: bp = 259 °C. Reaction in TIPB was very messy, even with BHT added. [f] Starting material (**7j**) also isolated (24%). [g] Reflux: bp = 156 °C. [h] Gave only **20k** (99%); see text and Scheme 11.

Adventitious oxygen presumably accounts for the aromatization of **1** to produce the varying quantities of **19**. In support of this, resubjecting purified **1a** to the cycloaddition conditions (refluxing TIPB) under ambient atmosphere resulted in a clean conversion to **19a** (91%). Conversion of the tetrahydronaphthyridines to the fully aromatized naphthyridines could also be accomplished by heating with selenium (e.g., **1a** → **19a**, 320–340 °C, 8 h, 85%). Aromatization following the cycloaddition could be greatly reduced or eliminated by the addition of BHT (1.0–2 equiv) to the reaction mixture, leading to the optimal yields of the tetrahydronaphthyridines **1**. Furthermore, the presence of BHT also accelerated the cycloadditions to a degree in all cases (compare items 1 vs 2, 3 vs 4, 5 vs 6, 8 vs 9, 10 vs 11, and 14 vs 15). For example, the cycloadditions of triazines **7a** and **7b** required 7.5 and 9 h, respectively (items 1 and 3), for completion without BHT, while only 3 h was necessary in the presence of BHT in both cases (items 2 and 4). Control experiments showed large amounts of **7a** remaining after only 3 h without BHT present. Thus, BHT could also be functioning as a general acid catalyst in promoting the reaction by protonating or hydrogen bonding to a triazinyl nitrogen and thereby lowering the diene LUMO. Indeed, the reduced reaction times in the presence of BHT undoubtedly also helps to minimize the aromatization. Nitrile elimination has been reported from other cycloadducts in inverse-electron-demand Diels–Alder reactions,[1b,4h] though to the best of our knowledge, always from a bridged system such as in the cycloadditions of pyrimidines[25] and 1,3,5-triazines,[26] or of 1,2,4-triazines with ynamines,[1b,27] not a fused system as observed here.

SCHEME 10



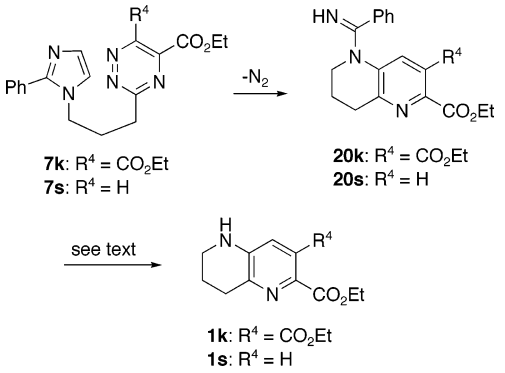
Several of the cycloadditions deserve special note. The cycloaddition of **7c** without BHT resulted in the production of significant amounts (27%) of demethylated, aromatized 1,5-naphthyridine **19a** (R^2 = H, R^3 = R^4 = Ph) in addition to the major product naphthyridine **19c** (70%, Table 3, item 5, Scheme 10). No tetrahydronaphthyridine **1c** could be detected under these conditions. In the presence of BHT, however, only the 4-methyl products **1c** and **19c** were produced, though considerably more BHT (2 equiv) was required to suppress the aromatization (items 6 and 7).

(25) For examples since the review (ref 1h), see: (a) Frissen, A. E.; Marcelis, A. T. M.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 803–812. (b) Frissen, A. E.; Marcelis, A. T. M.; Buurman, D. G.; Pollman, C. A. M.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 5611–5620.

(26) For examples since the review (ref 1h), see ref 4h and also: (a) Boger, D. L.; Dang, O. *J. Org. Chem.* **1992**, *57*, 1631–1633. (b) Boger, D. L.; Menezes, R. F.; Dang, Q. *J. Org. Chem.* **1992**, *57*, 4333–4336. (c) Boger, D. L.; Menezes, R. F.; Honda, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 273–275. (d) Boger. D. L.; Honda, T.; Menezes, R. F.; Colletti, S. L.; Dang, Q.; Yang, W. *J. Am. Chem. Soc.* **1994**, *116*, 82–92. (e) Boger, D. L.; Kochanny, M. J. *J. Org. Chem.* **1994**, *59*, 4950–4955. (f) Boger, D. L.; Honda, T.; Dang, Q. *J. Am. Chem. Soc.* **1994**, *116*, 5619–5630.

(27) Another example: Tahri, A.; Buysens, K. J.; van der Eycken, E. V.; Vandenberghe, D. M.; Hoornaert, G. J. *Tetrahedron* **1998**, *54*, 13211–13226.

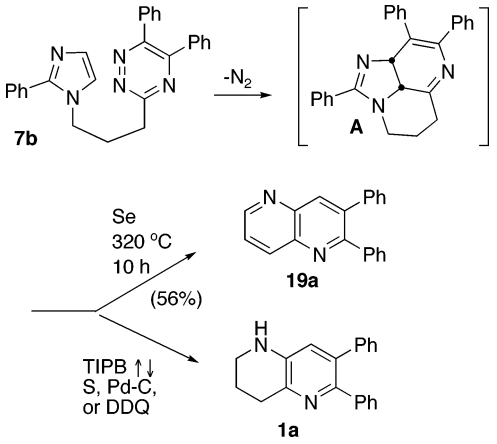
SCHEME 11



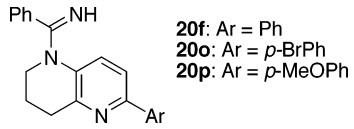
The cycloaddition of tethered triazines **7d**, **7e**, **7i**, **7j**, and **7l** (Table 3, items 8−11, 16, 17, and 20, respectively) are also noteworthy inasmuch as these cases represent relatively electron-rich (high LUMO) trialkyl triazines reacting with an imidazole, thereby illustrating the entropic advantage of intramolecular reactions.[28] In intermolecular studies,[4d] it was found that only more electron-deficient 1,2,4-triazines underwent cycloadditions with imidazoles, and then only with highly electron-rich imidazoles such as 2-aminoimidazole and, to a lesser extent, the 2-(methylthio)imidazole. Typically, these reactions required the presence of at least two electron-withdrawing substituents (esters) on the triazine ring. Less reactive imidazoles such as imidazole and 2-phenyl- and 2-methylimidazole failed to react intermolecularly even with the highly electron-deficient triethyl 1,2,4-triazine-3,5,6-tricarboxylate.

The diester triazines **7k**, and **7s** with the correspondingly lower triazinyl LUMO's due to the presence of the electron-withdrawing ester substituents underwent cycloadditions at considerably lower temperatures. The cycloaddition of **7k** proceeded at 110 °C (20 h) in refluxing toluene to give a quantitative yield of amidine **20k** (Scheme 11). Indeed, **7k** slowly underwent the cycloaddition upon storage under ambient conditions leading to complete conversion to **20k** over the course of several days. Increasing the temperature to 156 °C (refluxing bromobenzene) accelerated the reaction, giving a quantitative yield of **20k** in only 1.5 h (Table 3, item 18), while refluxing in TIPB with BHT (1 h) produced **20k** (46%) along with tetrahydronaphthyridine **1k** (47%). No deazapurine analogue **2** (see Scheme 1) was detected at any of the lower temperatures as initially desired. Increasing the reaction time in TIPB to 5 h led to the sole production of **1k** (91%, Table 3, item 19). The isolation of **20k** suggests that the nitrile elimination proceeds through a stepwise pathway. Indeed, refluxing **20k** in TIPB in the presence of BHT for 2 h gave **1k** in 66% yield along with 21% recovered **20k** and a trace amount of the fully aromatized naphthyridine. Similar results were observed for **7s** (as the major component of the 2:1 mixture with nitrile **8b** as described previously, Scheme 5), producing a mixture of amidine **20s** and tetrahydronaphthyridine **1s** upon refluxing in bromobenzene. Treatment of this mixture with KOBu^t in THF (0 C, 30 min) completely converted the amidine to the desired naphthyridine **1s**, producing an 86% overall yield of **1s** from **7s**.

SCHEME 12



The cycloadditions of monoaryl-substituted triazines **7f**, **7o**, and **7p** with the 2-phenylimidazole dienophilic subunit (Table 3, items 12, 24, and 25) were successful in refluxing diphenyl ether without added BHT. In this solvent (bp = 259 °C), no fully aromatized naphthyridines were detected, so the addition of BHT was not necessary. Indeed, under the standard conditions (refluxing TIPB with BHT), these triazines produced profound mixtures of products that were extremely difficult to purify and in which only small amounts of the desired tetrahydronaphthyridines could be observed in the NMR spectra. Furthermore, when BHT was added to the reaction in diphenyl ether, varying amounts of amidines (**20f**, **20o**, **20p**) could be isolated.



Several conditions were examined in an effort to promote the dehydrogenation of the intermediate cycloadduct **A** to form the annulated deazapurines **2**. Thus, **7b** was treated to the classic selenium melt procedure[29] (Se, 320 °C, 10 h), but only naphthyridine **19a** was produced (56%, Scheme 12). Other attempts included the addition of elemental sulfur, Pd−C, and DDQ to the reaction of **7b** (refluxing TIPB), but in these cases only tetrahydronaphthyridine **1a** was generated.

The facile loss of nitrile from the cycloadduct intermediate **A** to form the tetrahydronaphthyridines **1** led to a reexamination of the intramolecular cycloaddition of tethered pyrrole/triazine pairs, which in principle can also form 1,5-naphthyridines by loss of acetylene from the intermediate cycloadduct. As previously reported,[3a] the cycloaddition of tethered triazine **21** in refluxing TIPB produced pyrrolonaphthyridine **22** in 80% yield. Examination of the remaining material also revealed the presence of tetrahydronaphthyridine **1h** (12%) which presumably results from the loss of acetylene from the intermediate cycloadduct **B** (Scheme 13), which is more difficult than loss of the nitrile.

(28) (a) Ciganek, E. In *Organic Reactions*; Dauben, W. G., Ed.-in-Chief; Wiley: New York, 1984; Vol. 32, Chapter 1. (b) Taylor, E. C. *Bull. Soc. Chim. Belg.* **1988**, *97*, 599−613.

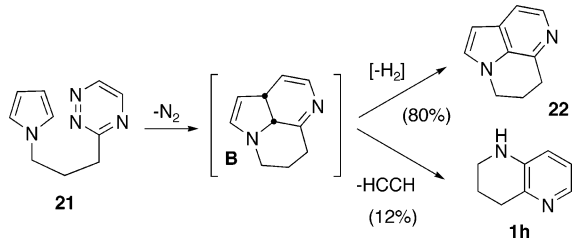
(29) Procedure adapted from: Bartlett, M. F.; Taylor, W. I. *J. Am. Chem. Soc.* **1960**, *82*, 5941−5946.

TABLE 4. Microwave-Promoted Cycloadditions of Trimethylene-Tethered Imidazole/Triazine Pairs 7

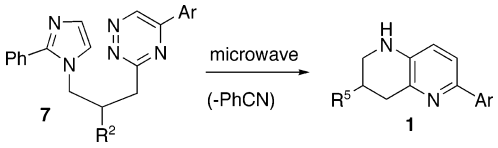
	triazine					cycloadduct **1**[b]
item	no.	R^5	R^3	R^4	conditions[a]	yield (%)
1	**7o**	H	*p*-BrPh	H	210 °C, 20 min	85 (**1o**)
2	**7p**	H	*p*-MeOPh	H	210 °C, 30 min	70 (**1p**)
3	**7f**	H	Ph	H	210 °C, 25 min	80 (**1f**)
4	**7q/7r**	H	CO_2Et/Me	Me/CO_2Et	225 °C, 20 min	56 (**1q**)/15 (**1r**)
5	**7t**	CH_2OTBS	Ph	H	210 °C, 20 min	70 (**1t**)
6	**7u**	CH_2OTBS	*p*-BrPh	H	210 °C, 20 min	73 (**1u**)

[a] All reactions performed in *o*-dichlorobenzene with NH_4OAc as energy transfer agent. [b] Isolated yields.

SCHEME 13

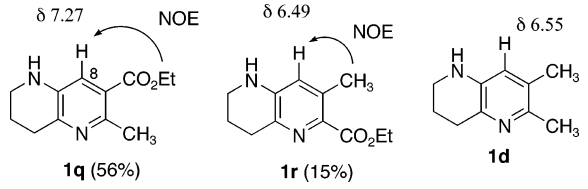


SCHEME 14



Microwave-Promoted Cycloadditions. Recently, Lindsley reported that microwave irradiation significantly accelerated the intramolecular cycloaddition of indole/1,2,4-triazine-tethered pairs,[2m] chemistry we had earlier established under relatively harsh thermal conditions.[14] We therefore also briefly examined the cycloaddition of select imidazole/triazine-tethered partners under microwave irradiation (Scheme 14).[30,31] The conditions were optimized using tethered triazine **7o** to produce naphthyridine **1o**. The best conditions for the cycloaddition were found to be microwave irradiation (210 °C, 20 min, 85%, Table 4, item 1) in *o*-dichlorobenzene in the presence of NH_4OAc (15 equiv), which proved comparable to refluxing in diphenyl ether in yield (89%, 1.3 h, Table 3, item 24), but in considerably less time. In the absence of NH_4OAc, only trace amounts of product **1o** were detected. Presumably, the NH_4OAc serves as an energy transfer agent. The use of other salts such as $(n\text{-Bu})_4NPF_6$ or 1-alkyl-3-methylimidazolium ionic solvents[32] were considerably less effective. Microwave irradiation also worked well in promoting the cycloadditions of other triazines (Table 4, items 2–6). The advantage of the microwave-promoted chemistry was particularly noteworthy in the reduced reaction times (from 3.5 h or more under reflux to 20–30 min with microwave irradiation) giving yields comparable to those observed under thermal conditions. Microwave irradiation was not effective, however, with triazine/imidazole pairs **7d** and **7h**.

The cycloaddition of the mixture of regioisomeric triazines **7q** and **7r** was also successful under microwave irradiation (Table 4, item 4). The structural distinction of **7q** and **7r** originally suggested by electronic considerations in the condensation of the amidrazone **9b** with the α,β-diketone **10** (Scheme 4 above) was confirmed by NOE studies on the separable cycloadducts **1q** and **1r**, which identified the substituent adjacent to H8 as illustrated. Also as anticipated, the naphthyridines could also be distinguished by the chemical shifts of their respective pyridine ring protons (H8). In **1q**, this proton was considerably deshielded (δ 7.27) in comparison to that in **1r** (δ 6.49) due to the influence of the adjacent ester substituent in comparison to the methyl group of **1r**. The H8 chemical shift in **1r** was comparable to that observed with the 6,7-dimethytetrahydronaphthyridine **1d** (δ 6.55).



Given the success of the microwave-promoted cycloaddition, the possibility of accomplishing the tethered triazine preparation with subsequent cycloaddition in a single step via the acyl hydrazide route was also examined (Scheme 15). Lindsley had reported such a strategy in the microwave-promoted synthesis of canthines after noting the formation of cycloadducts in the microwave-promoted triazine formation from the condensation of acyl hydrazides with α,β-diketones.[2m] In the preparation of tethered triazines **7**, no cycloadducts had been detected under these conditions (refluxing acetic acid, see Table 1) presumably due to the higher temperature required to effect the cycloaddition. In most cases, the one-pot

(30) For reviews of microwave promoted organic chemistry, see: (a) Abramovitch, R. A. *Org. Prep. Proc. Int.* **1991**, *23*, 683–711. (b) Caddick, S. *Tetrahedron* **1995**, *51*, 10403–10432. (c) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665–1692. (d) Majetich, G.; Wheless, K. *Microwave-Enhanced Chemistry*; American Chemical Society: Washington, D.C., 1997; pp 455–505. (e) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213–1234. (f) Strauss, C. R. *Aust. J. Chem.* **1999**, *52*, 83–96. (g) Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J. L.; Petit, A. *Tetrahedron* **1999**, *55*, 10851–10870. (h) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223. (i) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283. (j) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95–105. (k) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717–727. (l) Bose, A. K.; Manhas, M. S.; Ganguly, S. N.; Sharma, A. H.; Banik, B. K. *Synthesis* **2002**, 1578–1591.

(31) The first example of microwave-promoted cycloaddition: (a) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945–4948. Also, see reviews (ref 30a,d,e,i). For examples since these reviews, see: (b) Hong, B.-C.; Shr, Y.-J.; Liao, J.-H. *Org. Lett.* **2002**, *4*, 663–666. (c) Van der Ecken, E.; Appukkuttan, P.; De Borggraeve, W.; Dehaen, W.; Dallinger, D.; Kappe, C. O. *J. Org. Chem.* **2002**, *67*, 7904–7907. Also, ref 2m.

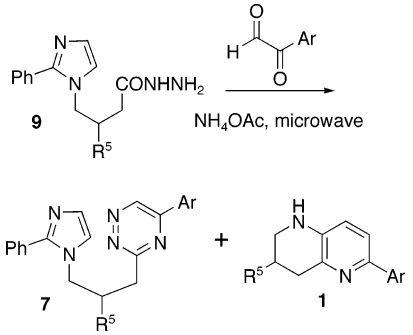
(32) (a) Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999**, *40*, 793–796. (b) Leadbeater, N. E.; Torenius, H. M. *J. Org. Chem.* **2002**, *67*, 3145–3148.

TABLE 5. One-Pot Microwave-Promoted Synthesis of 1,2,3,4-Tetrahydro-1,5-naphthyridines 1 from Acylhydrazides 9 (Scheme 15)[a]

item	R^2	Ar	time (min)	**7** (%)	**1** (%)
1	H	Ph	10	**f**: 40	**f**: 14
2	H	*p*-BrPh	6	**o**: 54	**o**: 9
3	H	*p*-MeOPh	6	**p**: 68	**p**: 0
4	CH_2OTBS	Ph	6	**t**: 31	**t**: 30
5	CH_2OTBS	*p*-BrPh	6	**u**: 28	**u**: 32
6	CH_2OTBS	*p*-MeOPh	6	**v**: 45	**v**: 10

[a] All reactions run in *o*-dichlorobenzene with NH_4OAc (15 equiv), 190 °C.

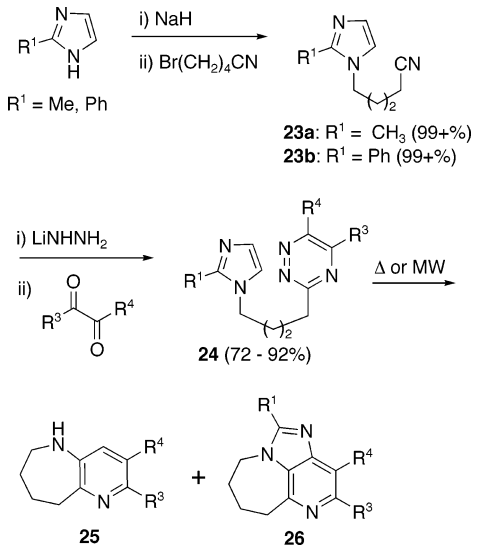
SCHEME 15



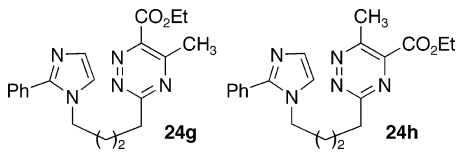
approach to the naphthyridines beginning with the acylhydrazide **9b** or **9d** resulted in the production of some naphthyridine **1** (Table 5), though invariably in considerably lower yield than resulted from the two-step preparation wherein the tethered triazine was isolated and then subjected to microwave irradiation to promote the cycloaddition. The main product in most cases was the tethered triazine **7**. With *p*-methoxyphenylglyoxal and acyl hydrazide **9b**, no naphthyridine at all was detected, only the tethered triazine **7p**.

Increasing the Tether Length; Preparation of 2,3,4,5-Tetrahydro-1*H*-pyrido[3,2-*b*]azepines. In prior studies of the intramolecular cycloadditions of indole and pyrrole with 1,2,4-triazines, the tether length was observed to have a significant effect. Trimethylene tethers giving rise to six-membered annulations were optimal, tetramethylene tethers were considerably more sluggish with indole, and failed completely with pyrrole, while dimethylene tethers with indole allowed for the reaction but produced unstable products.[3a,14] We therefore investigated an increase in the tether length to four methylene units in the intramolecular reactions of imidazoles in order to generate 2,3,4,5-tetrahydro-1*H*-pyrido[3,2-*b*]-azepines and thereby use ring expansion of the A-ring as a possible diversity element for these heterocyclic scaffolds. Earlier reports of pyrido[3,2-*b*]azepine preparations have relied upon nitrogen insertion chemistry with the Schmidt reaction[33] or the Beckman rearrangement[34] acting upon a tetrahydroquinolone precursor. This pyridoazepine system also lies within the alkaloid maxonine, which was prepared by Kelly closing the azepine ring by an intramolecular Heck coupling.[35]

SCHEME 16



Tetramethylene tethered imidazole/triazine pairs **24** were prepared analogously to those with trimethylene tethers beginning with the imidazole and 5-bromovaleronitrile via the amidrazone route (Scheme 16, Table 6). Interestingly, the condensation of ethyl 2,3-dioxobutanoate (**10**) with the amidrazone derived from nitrile **23b** gave a 6:1 ratio of regioisomers (**24g**/**24h**, 88% combined yield) in favor of **24g**. Thus, a slight improvement was observed in the regioselectivity in comparison to that obtained with the trimethylene-tethered amidrazone **9b** (see Scheme 4). Cycloadditions of **24** (Table 6) were noticeably more sluggish than their trimethylene-tethered counterparts (Table 3), and refluxing in diphenyl ether could be used to decrease the reaction time and eliminate the need for added BHT (compare items 3−5). In the few cases where a direct comparison could be made, the cycloadditions employing 2-methylimidazole as the dienophile where noticeably faster than those using the less electron rich 2-phenylimidazole (compare items 1 and 2 with 3 and 4, also item 6 with 7). In the case of the trimethylene-tethered imidazole/triazine pairs, there was little distinction between the 2-methyl- and 2-phenylimidazole dienophilic subunits in reactivity.



Surprisingly, while the nitrile elimination products **25** were dominant, small yet reproducible amounts of the aromatized deazapurine **26a** were also obtained when diphenyl triazines (**24a** and **24b**) were employed. Microwave irradiation was disappointingly unsuccessful in promoting the reaction, returning only unreacted starting materials, with the exception of the diester triazine **24f** (Item 11).

As observed with the trimethylene-tethered imidazole/triazine pair **7k** with the diester substitution on the

(33) (a) Klar, H. *Arch. Pharm. (Weinheim)* **1976**, *309*, 550−557. (b) Gatta, F.; Del Giudice, M. R.; Pomponi, M.; Marta, M. *Heterocycles* **1992**, *34*, 991−1004.

(34) (a) Jossang-Yanagida, A.; Gansser, C. *J. Heterocycl. Chem.* **1978**, *15*, 249−251. (b) Maquestiau, van Haverbeke, Y.; Vanden Eynde, J.-J.; de Pauw, N. *Bull. Soc. Chim. Belg.* **1980**, *89*, 45−50. (c) Albright, J. D.; Du, X. *J. Heterocycl. Chem.* **2000**, *37*, 41−46.

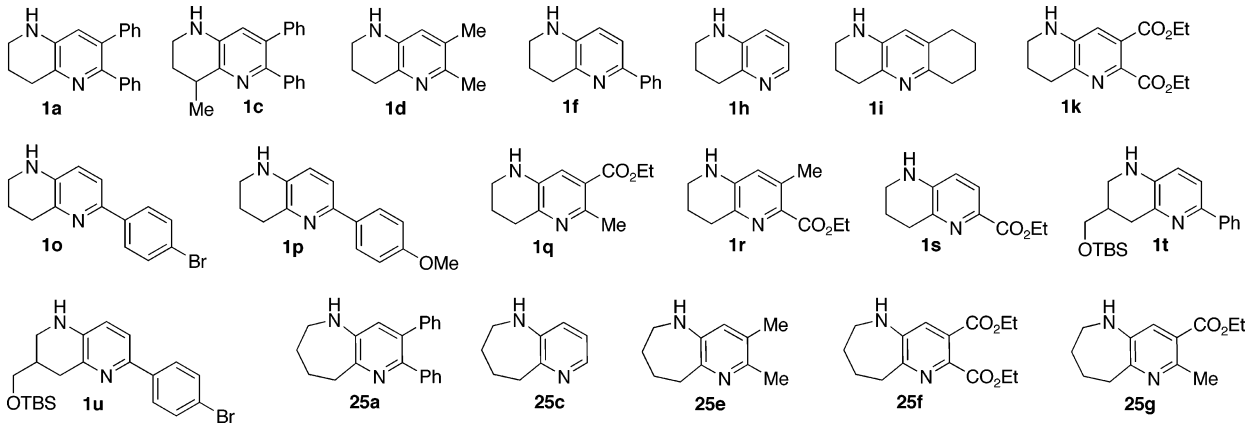
(35) Kelly, T. R.; Xu, W.; Sundaresan, J. *Tetrahedron Lett.* **1993**, *34*, 6173−6176.

TABLE 6. Cycloadditions of Tetramethylene-Tethered Imidazole/Triazine Pairs 24

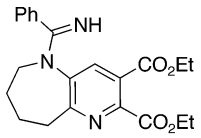
	triazine					cycloadduct[a]	
item	no.	R^1	R^3	R^4	conditions	**25**	**26**
1	**24a**	Me	Ph	Ph	TIPB, 232 °C, 7.5 h	**a**: 72	**a**: 3
2	**24a**	Me	Ph	Ph	TIPB, 232 °C, 3 h, BHT (1.2 eq)	**a**: 41	**a**: 9
3	**24b**	Ph	Ph	Ph	TIPB, 232 °C, 48 h	**a**: 38	**b**: 4
4	**24b**	Ph	Ph	Ph	TIPB, 232 °C, 22 h, BHT (1 eq)	**a**: 11	**b**: 7
5	**24b**	Ph	Ph	Ph	Ph_2O, 258 °C, 18 h	**a**: 72	**b**; 7
6	**24c**	Ph	H	H	Ph_2O, 258 °C, 29 h	**c**: 59	**c**: 5
7	**24d**	Me	H	H	Ph_2O, 258 °C, 7 h	**c**: 54	0
8	**24e**	Me	Me	Me	Ph_2O, 258 °C, 20 h	**e**: 56	0
9	**24f**	Ph	CO_2Et	CO_2Et	PhBr, 156 °C, 30 h	trace[b]	0
10	**24f**	Ph	CO_2Et	CO_2Et	Ph_2O, 258 °C, 45 min	**f**: 70	0
11	**24f**	Ph	CO_2Et	CO_2Et	microwave, 225 °C, 25 min[c]	**f**: 63	0
12	**24g/h**	Ph	Me	CO_2Et	Ph_2O, 258 °C, 9 h	**g**: 39	0

[a] Isolated yields. [b] Gave amidine **27f** as the sole product (99+%). [c] Reaction run in *o*-dichlorobenzene with NH_4OAc (15 equiv).

CHART 1



triazine, **24f** produced unstable amidine **27f** in quantitative yield upon refluxing in bromobenzene. Brief refluxing in diphenyl ether (Table 6, item 10) or microwave-promoted cycloaddition yielded the pyridoazepine **25f** without any amidine precursor (Table 6, item 11). In contrast, the monoester substituted triazine regioisomeric pair **24g**/**24h** underwent the cycloaddition in refluxing diphenyl ether to produce the separable pyridoazepines **25g** and **25h** in low yield (39%, item 12) without any detected amidine. Microwave promotion of this reaction was also unsuccessful.



27f

Conclusions

The intramolecular inverse-electron-demand Diels–Alder reaction of imidazoles tethered with 1,2,4-triazines between the imidazole N1 and triazinyl C-3 positions via tri- and tetramethylene tethers has been explored. These linked diene/dienohile pairs are easily prepared, and the cycloadditions with three-carbon linkers occur readily under either thermal or microwave promotion to produce 1,2,3,4-tetrahydro-1,5-naphthyridines in good to excellent yields. The cycloaddition is followed by immediate release of nitrogen and then presumably a stepwise loss of a nitrile from the original imidazole C2/N3 position. The intramolecular reactions with four carbon tethers were also successful, though somewhat more sluggish than those utilizing a three carbon tether, to give modest to good yields of 2,3,4,5-tetrahydro-1*H*-pyrido[3,2-*b*]azepines. This chemistry thus provides a very efficient route to both the tetrahydronaphthyridines and the pyridoazepines, and enables diverse substitution to be incorporated on these heterocyclic cores. Current work is exploring the chemistry of these heterocyclic cores for development as scaffolds in diversity oriented library synthesis.[36] The 19 scaffolds now available from this work for library synthesis are shown in Chart 1 (**1c**, **1t**, and **1u** were prepared in racemic form).

Experimental Section

General Procedure A: Preparation of 4-Imidazol-1-ylbutanoic Acids 5a–d. Into a predried, thick-walled test tube was added KH (35% suspension in mineral oil, 1.17 g). The mineral oil was removed by washing three times with hexanes and then adjusting the amount of KH to 0.41 g (10.2 mmol). Excess KH was quenched by transferring to hexanes and adding acetone. (The reaction works equally well without removing the mineral oil in most cases, with the exception being the preparation of **5d**.) Imidazole (~10 mmol, **3a** or **3b**) was added and the mixture was mechanically mixed under argon with careful warming with a heat gun. (CAUTION: Once the deprotonation is initiated, it is very exothermic and warming must cease immediately!) After the imidazole potassium salt was formed, the γ-butyrolactone (11 mmol, **4a**, **4b**,

(36) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46–58.

or **4c**) was added dropwise. The mixture was then heated to 160−170 °C in a sand bath with stirring for 3 h. After the mixture was cooled to rt, water (5 mL) was added, and the mixture was then neutralized to pH paper with 5% HCl solution. The mixture was then extracted with ethyl acetate, the organic layer discarded, and the solvent removed from the aqueous layer under reduced pressure to provide the crude product, which was purified as indicated. Due to the need to stir this reaction in the absence of a solvent other than the γ-butyrolactone, this reaction works best at this or larger scale.

General Procedure B: Preparation of Methyl 4-Imidazol-1-ylbutanoate Esters. To anhydrous MeOH (30 mL) cooled to −78 °C was added $SOCl_2$ (1.9−2.4 mL, 20−25 mmol) dropwise, with stirring continued for 30 min following completion of the addition. To this solution was then added dropwise the 4-imidazol-1-ylbutanoic acid (**5a**−**d**, 10 mmol) dissolved in a minimum amount of anhydrous methanol. After completion of the addition, the cooling bath was removed, the temperature was allowed to rise to rt, and stirring was continued for 3 h. The reaction was then quenched by the addition of saturated aq $NaHCO_3$ (30 mL) and the reaction mixture extracted with methylene chloride. The organic layer was dried over Na_2SO_4 and then the solvent removed in vacuo. The crude product was purified by flash chromatography as indicated. This procedure could be scaled.

General Procedure C: Preparation of 4-Imidazol-1-ylbutanoyl Hydrazides (6a−c). To a solution of the methyl 4-imidazol-1-ylbutanoate ester in anhydrous ethanol was added anhydrous hydrazine (2.0 equiv) at rt. The resultant clear solution was refluxed overnight, and then the solvent and excess hydrazine were removed in vacuo to afford acylhydrazides as nearly pure white solids, which were used in the next step without further purification.

General Procedure D: Preparation of 3-(3-(Imidazol-1-yl)propyl)-1,2,4-triazines 7 via the Acylhydrazide Route (Table 1). The crude acylhydrazide (typically 1 mmol), dicarbonyl compound (1−1.2 equiv), and NH_4OAc (15 equiv) in glacial acetic acid (3−5 mL) or bromobenzene (3−5 mL) were refluxed for 6 h. After removal of most of the HOAc in vacuo, saturated aq $NaHCO_3$ (10 mL) was added to the cooled reaction mixture. The aqueous layer was thoroughly extracted with EtOAc, the combined organic layers were dried over Na_2SO_4, and then the solvent was removed in vacuo to provide the crude product. Purification by flash chromatography gave the tethered triazines **7**.

General Procedure E: Preparation of 4-(Imidazol-1-yl)butyro- and 5-(Imidazol-1-yl)valeronitriles 8 and 23. To a solution of the imidazole (10 mmol) in dry DMF (20 mL) at 0 °C was added NaH (60% in mineral oil, 800 mg, 20 mmol, mineral oil not removed), and the mixture was stirred for 15 min. To this mixture was added 4-bromobutyronitrile or 5-bromovaleronitrile (12 mmol, 1.2 equiv), and stirring was continued overnight at rt. The reaction was quenched with ice−water (50 mL) and then extracted with EtOAc. The combined organic layers were washed with brine and then dried over Na_2SO_4. After removal of the solvent in vacuo, the crude product was purified by flash chromatography.

General Procedure F: Preparation of 3-(3-Imidazol-1-ylpropyl)-1,2,4-triazines 7 (Table 2) and 3-(4-Imidazol-1-ylbutyl)-1,2,4-triazines 24 via the Amidrazone Route. To a solution of anhydrous hydrazine (typically 4−6 mmol) in anhydrous THF (10 mL) at 0 °C was added dropwise *n*-BuLi (1.6 M in hexanes, 4−6 mmol, 1 equiv). After the suspension was stirred at 0 °C for 20 min, a solution of the 4-imidazol-1-ylbutyronitrile or 5-imidazol-1-ylvaleronitrile (1 mmol) in anhydrous THF (2−4 mL) was added dropwise at 0 °C. The resultant solution was stirred at rt for 2 h and then quenched by adding ice−water until the mixture became translucent. After removal of the solvent in vacuo, the oily residue was triturated with dry EtOH. The solvent from the combined EtOH washings was then removed in vacuo to provide the crude amidrazone as light yellow oil, which was used immediately in the next step. To a solution of the dicarbonyl compound (1−1.2 mmol) in anhydrous EtOH (2 mL) was added the freshly prepared amidrazone (∼1 mmol) as a solution in EtOH (3−5 mL) dropwise at 0 °C under Ar. The ice bath was removed, and the reaction mixture was stirred at rt overnight and then refluxed for 1 h. After removal of the solvent in vacuo, the residue was purified by flash chromatography to provide the desired triazine.

General Procedure G: Preparation of 1,2,3,4-Tetrahydro-1,5-naphthyridines 1 (Table 3) and 2,3,4,5-Tetrahydro-1*H*-pyrido[3,2-*b*]azepines 25 (Table 6) by Thermally Promoted Cycloadditions of the Imidazole/Triazine Tethered Pairs 7 and 24, Respectively. Triazine **7** or **24** (typically 0.5 mmol) and BHT (0−1.0 mmol, 0−2 equiv) were suspended in an appropriate solvent (typically 20 mL). (Reactions in Ph_2O did not use BHT.) The reaction mixture was slowly warmed until the starting material was completely dissolved, and then the mixture was heated to reflux and monitored by TLC until the starting material was gone. After cooling, the reaction mixture was passed through a short silica gel plug, eluting with hexanes and then hexanes/CH_2Cl_2 (2:1) to remove solvent (TIPB). The crude product was eluted by further washing with CH_2Cl_2/MeOH (1:1). The solvent was removed in vacuo, and the residue was purified by flash chromatography.

General Procedure H: Preparation of 1,2,3,4-Tetrahydro-1,5-naphthyridines 1 by Microwave-Promoted Cycloadditions of Imidazole/Triazine Tethered Pairs 7 (Table 4). Triazine (0.1−0.3 mmol), ammonium acetate (12−20 equiv), and 1,2-dichlorobenzene (1−3 mL) were placed in a 10 mL microwave vessel and heated (190−225 °C) for 20−40 min (power = 300 W, pressure = 250 psi). After cooling, the reaction mixture was diluted with water (5 mL) and extracted with CH_2Cl_2, and the organic layer dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by flash chromatography.

Methyl 3-(*tert*-Butyldimethylsilyloxymethyl)-4-(2-phenylimidazol-1-yl)butanoate (18). A solution of **5d** (45 mg, 0.12 mmol), DMAP (2 mg, 0.012 mmol), and anhydrous MeOH (25 μL, 0.6 mmol) in CH_2Cl_2 (2 mL) was stirred at 0 °C for 30 min under Ar. Solid EDCI (25 mg, 0.123 mmol) was quickly added to the reaction mixture, stirred for 2 h at 0 °C, and then stirred for another 3 h at rt. After removal of the solvent in vacuo, water (5 mL) was added to the residue, which was then extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo and the residue purified by flash chromatography (eluting initially with hexanes/EtOAc, 3:1, then EtOAc) to give **18** as a yellow oil (37 mg, 80%): IR (NaCl) ν_{max} 1734 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.55 (dd, J = 7.8, 1.4 Hz, 2H), 7.42−7.34 (m, 3H), 7.10 (s, 1H), 7.01 (s, 1H), 4.14 (dd, J = 14.2, 7.8 Hz, 1H), 4.03 (dd, J = 14.2, 6.8 Hz, 1H), 3.55 (s, 3H), 3.43 (dd, J = 10.4, 4.0 Hz, 1H), 3.39 (dd, J = 10.4, 3.8 Hz, 1H), 2.34 (m, 1H), 2.27 (dd, J = 16.0, 6.8 Hz, 1H), 2.08 (dd, J = 16.0, 6.0 Hz, 1H), 0.80 (s, 9H), −0.05 (s, 3H), −0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.5, 148.2, 131.0, 129.1 (2C), 128.9, 128.80, 128.75 (2C), 121.3, 62.0, 51.8, 47.2, 39.0, 33.3, 26.0 (3C), 18.3, −5.4, −5.6; EIMS (70 eV) m/z 389 ($[M + 1]^+$, 36), 331 ($[M]^+$, 100); CIHRMS (NH_3, 140 eV) m/z 389.2254 ($[M + 1]^+$, 41), calcd for $C_{21}H_{32}N_2O_3Si$ 389.2260.

3-(*tert*-Butyldimethylsilyloxymethyl)-4-(2-phenylimidazol-1-yl)butyronitrile (8d). A solution of $AlMe_2Cl$ in hexanes (1 M, 900 μL, 0.9 mmol) was added slowly to a suspension of NH_4Cl (50 mg, 0.9 mmol) in anhydrous CH_2Cl_2 (1 mL) at 0 °C with stirring. The mixture was allowed to warm to rt over a period of 1 h. To this aluminum amide complex solution was added a solution of methyl 3-*tert*-butyldimethylsilyloxymethyl-4-(2-phenylimidazol-1-yl)butanoate (**18**, 50 mg, 0.12 mmol) in CH_2Cl_2 (1 mL), and the mixture was refluxed for 24 h. After cooling, the reaction mixture was diluted to pH 8 with phosphate buffer (5 mL) and stirred at rt for 10 min. The mixture was then passed through a Celite plug, thoroughly

washing with CH_2Cl_2. The combined CH_2Cl_2 washings were extracted with water, and the organic layer was washed with brine and then dried over Na_2SO_4. The solvent was removed in vacuo and the residue purified by flash chromatographed on (CH_2Cl_2/MeOH, 10:1) to give **3-(*tert*-butyldimethylsilyloxymethyl)-4-(2-phenylimidazol-1-yl)butanamide** as a white solid (30 mg, 67%): IR (NaCl) ν_{max} 3317, 3172, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, J = 8.0 Hz, 2H), 7.43−7.37 (m, 3H), 7.11 (s, 1H), 7.05 (s, 1H), 5.33 (br s, NH), 5.20 (br s, NH), 4.17−4.06 (m, 2H), 3.48 (dd, J = 10.2, 4.2 Hz, 1H), 3.41 (dd, J = 10.6, 4.2 Hz, 1H), 2.40 (m, 1H), 2.15 (dd, J = 14.8, 7.2, 1H), 1.98 (dd, J = 14.8, 6.2 Hz, 1H), 0.81 (s, 9H), −0.04 (s, 3H), −0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3, 148.2, 130.9, 129.1 (2C), 129.0, 128.82 (2C), 128.78, 121.4, 62.0, 47.3, 39.1, 34.4, 26.0 (3C), 18.3, −5.36, −5.44; EIMS (70 eV) *m*/*z* 374 ([M + 1]$^+$, 15), 373 ([M]$^+$, 6.9), 316 (100); EIHRMS (70 eV) *m*/*z* 373.2159 ([M]$^+$, 1) calcd for $C_{20}H_{31}N_3O_2Si$ 373.2186. This amide was dehydrated to the nitrile **8d** by two different routes.

Route A to 8d.[37] Trifluoroacetic anhydride (TFAA, 5 μL, 0.03 mmol) was added to a stirred solution of the amide (10 mg, 0.026 mmol) and pyridine (5 μL, 0.053 mmol) in anhydrous THF (500 μL) at 0 °C. The reaction mixture was allowed to warm to rt over 10 min and then stirred at rt for 7 h. The reaction was quenched with water (5 mL) and then extracted with CH_2Cl_2. The combined organic extracts were washed with brine and then dried over Na_2SO_4. The solvent was removed in vacuo and the residue purified by flash chromatography (hexanes/EtOAc, 2:1, then EtOAc) to give **8d** as a yellow oil (8.4 mg, 88%): IR (NaCl) ν_{max} 2250 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.54 (dd, J = 7.6, 1.4 Hz, 2H), 7.46−7.40 (m, 3H), 7.14 (s, 1H), 6.99 (s, 1H), 4.19 (dd, J = 14.2, 7.2 Hz, 1H), 4.10 (dd, J = 14.2, 7.2 Hz, 1H), 3.54 (dd, J = 10.6, 3.8 Hz, 1H), 3.43 (dd, J = 10.6, 4.2 Hz, 1H), 2.24 (dd, J = 16.8, 8.0 Hz, 1H), 2.23−2.10 (m, 2H), 0.82 (s, 9H), −0.003 (s, 3H), −0.014 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.2, 130.7, 129.33, 129.26, 129.1 (2C), 128.9 (2C), 121.3, 117.7, 61.2, 46.9, 39.5, 26.0 (3C), 18.3, 17.2, −5.40, −5.48; EIMS (70 eV) *m*/*z* (%) 356 ([M+1]$^+$, 88), 298 (100); EIHRMS (70 eV) *m*/*z* 356.2180 ([M + 1]$^+$, 3), calcd for $C_{20}H_{30}N_3OSi$ 356.2158.

Route B to 8d.[38] A solution of freshly distilled $(COCl)_2$ (17 μL, 0.19 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added to solution of amide (57 mg, 0.16 mmol) and freshly distilled DMSO (18 μL, 0.26 mmol) in CH_2Cl_2 (1.0 mL) at −78 °C and the mixture stirred for 15 min. Triethylamine (67 μL, 4.83 mmol) was added dropwise and then stirred for another 20 min at −78 °C. The reaction was quenched at −78 °C with water (5 mL) and then allowed to warm to rt. The reaction mixture was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine and then dried over Na_2SO_4. The solvent was removed in vacuo and the residue purified by flash chromatography as above give **8d** as a yellow oil (45 mg, 84%).

Ethyl 5-Methyl-3-(3-(2-phenylimidazol-1-yl)propyl)-1,2,4-triazine-6-carboxylate (7q) and Ethyl 6-Methyl-3-(3-(2-phenylimidazol-1-yl)propyl)-1,2,4-triazine-5-carboxylate (7r). A solution of ethyl dioxobutanoate[20] (**10**) was freshly prepared from ethyl 2-(((*p*-nitrophenyl)sulfonyl)oxy)-acetoacetate (500 mg, 1.51 mmol) in anhydrous EtOH (15 mL) with Et_3N (0.5 mL, 3.6 mmol). Triazines **7q** and **7r** were then prepared from nitrile **8b** (240 mg, 1.1 mmol), NH_2NH_2 (0.175 mL, 5.5 mmol), *n*-BuLi (3.5 mL, 5.5 mmol), and this solution of freshly prepared **10** according to general procedure F with reverse addition. (The solution of **10** was cannulated into the solution of the amidrazone.) Flash chromatography (eluting initially with hexanes/EtOAc, 3:1, then EtOAc) gave **7q** and **7r** as an inseparable mixture (3:1) as a yellow oil (310 mg, 80% combined yield): IR (NaCl) ν_{max} 1726 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.52 (dd, J = 7.8, 1.8 Hz, 2H), 7.41−7.36 (m, 3H), 7.11 (d, J = 1.2 Hz, 1H), 7.05 (d, J = 1.2 Hz, 1H), 4.51 (q, J = 7.1 Hz, 2H), 4.17 (t, J = 7.2 Hz, 2H), 3.06 (t, J = 7.2 Hz, 2H), 2.70 (s, 3H), 2.33 (tt, J = 7.2, 7.2 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H); EIMS (70 eV) *m*/*z* 351 ([M]$^+$, 37), 171 (100); EIHRMS (70 eV) *m*/*z* 351.1668 ([M]$^+$, 17), calcd for $C_{19}H_{21}N_5O_2$ 351.1695.

4-(2-Phenylimidazol-1-yl)thiobutyramide (11). Hexamethyldisilathiane (1.64 mL, 7.8 mmol) was added dropwise to a solution of NaOMe (442 mg, 7.8 mmol) in anhydrous DMF (10 mL) and stirred at rt for 15 min. The dark blue solution that resulted was then added to a solution of nitrile **8b** (657 mg, 3.1 mmol) in DMF (6 mL) at rt and stirred for 80 h. The solvent was removed by directing a stream of dry air into the flask and the residue purified by flash chromatography (EtOAc, followed by CH_2Cl_2/MeOH, 30:1) to give **11** (626 mg, 82%) as an off-white solid: mp 158−158 °C; IR (NaCl) ν_{max} 1472, 1419 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 7.56 (dd, J = 7.8, 1.7 Hz, 2H), 7.52−7.46 (m, 3H), 7.27 (d, J = 1.5 Hz, 1H), 7.06 (d, J = 1.5 Hz, 1H), 4.10 (br t, J = 7.3 Hz, 2H), 2.49 (t, J = 7.3 Hz, 2H), 2.19 (tt, J = 7.3, 7.3 Hz, 2H); ^{13}C NMR (CD_3OD, 75 MHz) δ 204.0, 143.1, 125.5, 124.4, 124.3 (2C), 124.0 (2C), 122.5, 116.3, 40.8, 35.7, 25.5; EIMS (70 eV) *m*/*z* 246 ([M + 1]$^+$, 15), 245 ([M]$^+$, 52), 102 (100); EIHRMS (70 eV) *m*/*z* 245.1006 ([M]$^+$, 8), calcd for $C_{13}H_{15}N_3S$ 245.0987.

Ethyl 3-(3-(2-Phenylimidazol-1-yl)propyl)-1,2,4-triazine-5-carboxylate (7s). Thioamide **11** (144 mg, 0.58 mmol) and 2-chloro-1-methylpyridinium iodide[39] (**12**, 163 mg, 0.64 mmol) were stirred in CH_2Cl_2 (5 mL) at rt for 10 min. A solution of α-ketohydrazone **14**[16c] (169 mg, 1.17 mmol) in CH_2Cl_2 (6 mL) was added, and the reaction mixture was stirred at rt for 15 h, refluxed for 0.5 h, and then diluted with additional CH_2Cl_2 (15 mL). The yellow precipitate (**15**, identified by HNMR[40]) was removed by filtration, and the solvent removed from the filtrate in vacuo. Purification by flash chromatography (2% MeOH in CH_2Cl_2) gave **7s** (55%) and nitrile **8b** (28%) as an inseparable mixture (142 mg) which was used directly in the cycloaddition. A small amount of **7s** was purified to ∼90% purity as a yellow oil by the above conditions for characterization purposes: IR (NaCl) ν_{max} 1749, 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.63 (s, 1H), 7.51 (dd, J = 7.8, 1.5 Hz, 2H), 7.40−7.36 (m, 3H), 7.10 (d, J = 1.0 Hz, 1H), 7.05 (d, J = 1.0 Hz, 1H), 4.52 (q, J = 7.3 Hz, 2H), 4.19 (t, J = 7.1 Hz, 2H), 3.18 (t, J = 7.3 Hz, 2H), 2.39 (tt, J = 7.3, 7.1 Hz, 2H), 1.45 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.3, 162.9, 147.8, 146.3, 146.1, 130.8, 128.96 (2C), 128.88, 128.7, 128.5 (2C), 120.3, 63.4, 45.8, 33.8, 28.9, 14.1; EIMS (70 eV) *m*/*z* 337 ([M]$^+$, 81), 171 (100); EIHRMS (70 eV) *m*/*z* 337.1522 ([M]$^+$, 12), calcd for $C_{18}H_{19}N_5O_2$ 337.1539.

2,3-Diphenyl-1,5-naphthyridine (19a): From 1a. A solution of **1a** (33 mg, 0.115 mmol) was refluxed in TIPB (3 mL, 48 h) under air. Removal of the solvent in vacuo, and then purification by flash chromatography (CH_2Cl_2/EtOAc, 6:1) gave **19a** as a yellow oil (29.5 mg, 91%). Alternatively, **1a** (51 mg, 0.178 mmol) and Se (1.7 g) were heated together to 320−340 °C in a sand bath for 10 h. The cooled solid was ground carefully and then thoroughly triturated with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), the solvent removed in vacuo, and the residue purified by flash chromatography (CH_2Cl_2/EtOAc, 6:1) to give **19a** (42.5 mg, 85%). **Preparation of 19a from 7b.** A mixture of **7b** (65 mg, 0.156 mmol) and Se (1.5 g) was heated to 320−340 °C in a sand bath for 10 h. Workup and purification as described in the text gave **19a** (25 mg, 56%): ^1H NMR ($CDCl_3$, 400 MHz) δ 8.98 (dd, J = 4.0, 1.5 Hz, 1H), 8.47 (br d, J = 8.2 Hz, 1H), 8.41 (s, 1H), 7.64 (dd, J = 8.2, 4.0 Hz), 7.43 (dd, J = 7.5, 2.0 Hz, 2H), 7.25−7.31 (m, 8H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 159.2, 151.2, 143.0, 142.6, 139.8, 139.1, 138.4, 138.0, 137.1, 129.9 (2C), 129.6 (2C),

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128.3 (3C), 128.1 (2C), 127.5, 124.4; CIMS (NH_3, 140 eV) *m*/*z* 283 ([M + 1]$^+$, 100), 282 ([M]$^+$, 18); EIHRMS (70 eV) *m*/*z* 282.1136 ([M]$^+$, 72), calcd for $C_{20}H_{14}N_2$ 282.1156; **19a** was also isolated as a minor product from the cycloadditions of **7a** (10%), **7b** (38%), and **7c** (27%) in the absence of BHT (see Table 3).

Ethyl 1,2,3,4-Tetrahydro-1,5-naphthyridine-6-carboxylate (1s). Triazine **7s** (21 mg **7s**, 0.062 mmol, in a 2:1 mixture with **8b** as described above) was refluxed in bromobenzene (2 mL) for 22 h, the reaction cooled to rt, and the solvent removed by directing a stream of air into the flask. The residue was dissolved in CH_2Cl_2, dried over $MgSO_4$, and filtered, and then the solvent was removed from the filtrate in vacuo. The residue was redissolved in THF (3 mL) and cooled to 0 °C, KOBu^t (10 mg, 0.093 mmol) was added, and the solution was stirred for 30 min at 0 °C. The reaction was quenched with HCl (1 N, 0.1 mL), and then saturated aqueous $NaHCO_3$ was added (10 mL) and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and filtered, and then the solvent was removed in vacuo. Purification by flash chromatography (8% acetone in CH_2Cl_2) gave **1s** as a colorless oil (11 mg, 86%): IR (NaCl) ν_{max} 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, J = 8.3 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 4.36 (br s, NH), 3.36 (t, J = 5.6 Hz, 2H), 3.00 (t, J = 6.3 Hz, 2H), 2.00 (tt, J = 6.3, 5.6 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.8, 143.8, 142.4, 135.3, 125.1, 118.4, 61.1, 41.3, 30.6, 20.9, 14.3; EIMS (70 eV) *m*/*z* 207 ([M + 1]$^+$, 7), 206 ([M]$^+$, 52), 134 (100); EIHRMS (70 eV) *m*/*z* 206.1049 ([M]$^+$, 56), calcd for $C_{11}H_{14}N_2O_2$ 206.1055.

Ethyl 5-Methyl-4-(2-phenylimidazol-1-yl)butyl-1,2,4-triazine-6-carboxylate (24g) and Ethyl 6-Methyl-4-(2-phenylimidazol-1-yl)butyl-1,2,4-triazine-5-carboxylate (24h). A solution of ethyl dioxobutanoate (**10**) was freshly prepared from ethyl 2-(((*p*-nitrophenyl)sulfonyl)oxy)acetoacetate (260 mg, 0.79 mmol) in anhydrous EtOH (7 mL) with Et_3N (2.26 mL, 1.9 mmol).[20] Triazines **24g** and **24h** were then prepared from nitrile **23a** (225 mg, 0.75 mmol), NH_2NH_2 (120 μL, 3.7 mmol), and *n*-BuLi (2.4 mL, 3.7 mmol), and this solution of freshly prepared **10** according to general procedure F with reverse addition. (The solution of **10** was cannulated into the solution of the amidrazone.) Purification by flash chromatography (eluting initially with hexanes/EtOAc, 2:1, then EtOAc) gave **24g** and **24h** as an inseparable yellow oil mixture (240 mg, 6:1 **24g**/**24h**, 88%): IR (NaCl) ν_{max} 1728 cm^{-1}; ^{1}H NMR of **24g** ($CDCl_3$, 400 MHz) δ 7.53 (dd, J = 8.1, 1.5 Hz, 2H), 7.45−7.35 (m, 3H), 7.10 (s, 1H), 6.99 (s, 1H), 4.51 (q, J = 7.1 Hz, 2H), 4.06−4.02 (m, 2H), 3.08−3.04 (m, 2H), 2.73 (s), 1.84−1.80 (m, 4H), 1.44 (t, J = 7.1 Hz, 3H); EIMS (70 eV) *m*/*z* 365 ([M]$^+$, 13), 28 (100); EIHRMS (70 eV) *m*/*z* 365.1852 ([M]$^+$, 28), calcd for $C_{20}H_{23}N_5O_2$ 365.1852.

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Supporting Information Available: General experimental methods, experimental procedures, and characterization data for all compounds prepared following general procedures A−H and ^{1}H and ^{13}C NMR spectra for all previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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