Inverse Electron Demand Diels–Alder Reactions of Heterocyclic Azadienes: [4 + 2] Cycloaddition Reaction of Amidines with 1,3,5-Triazines

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A detailed study of the scope of the amidine Diels–Alder reaction with 1,3,5-triazines is described. The thermal reaction of amidines with symmetrical 1,3,5-triazines proceeds with in situ amidine to 1,1-diaminoethene tautomerization, [4 + 2] cycloaddition with the 1,3,5-triazine, loss of ammonia from the initial Diels–Alder adduct with imine generation, imine to enamine tautomerization, and retro Diels–Alder loss of ethyl cyanoformate to provide substituted 4-aminopyrimidines in excellent conversions. The reaction proceeds best with the amidine hydrochloride salts at intermediate reaction temperatures (90–100 °C) in polar, aprotic solvents, is rather invariant to the ratio of dienophile–diene used (1:2 ≅ 1:1 ≅ 2:1), and is subject to triazine substituent effects characteristic of an inverse electron demand Diels–Alder reaction ($R = CO_2Et > R = H \gg R = SCH_3$). Notably, the generality of the amidine [4 + 2] cycloaddition reaction with 1,3,5-triazines which has been extended to include cyclic amidines effectively addresses the limitations of the alternative ynamine or *N,O*-ketene acetal dienophiles. A comparative examination of amidines, thioimidates, and imidates revealed that amidines are uniquely suited for use in this reaction cascade.

The inverse electron demand Diels–Alder reaction of electron-deficient heteroaromatic azadienes[1] has proven to be unusually versatile and in recent years we have productively exploited its use in natural products total synthesis for agents possessing highly substituted and highly functionalized heteroaromatic ring systems.[2–13] In the course of these studies and following the initial disclosure of the [4 + 2] cycloaddition reaction of 1,3,5-triazine with ynamines and *N,O*-ketene acetals by Neunhoeffer and Bachmann,[14] the use of the Diels–Alder reactions of 1,3,5-triazines with electron-rich dienophiles for introduction of functionalized pyrimidines[15–18] has been described and we have detailed their use in the key steps of the total synthesis of (+)-P-3A,[9] bleomycin A_2,[10] and related agents.[11] Notably, the inherent limitations of their use in the preparation of 4-aminopyrimidines observed with ynamines[14,18] or *N,O*-ketene acetals[14] were addressed with our observation that amidines, stable tautomers of the nonisolatable and reactive 1,1-diaminoethenes (ketene aminals),[9–11] effectively participate in [4 + 2] cycloaddition reactions with 1,3,5-triazines and serve as effective equivalents of ynamine or *N,O*-ketene acetal dienophiles (Scheme 1).[19,20] In addition to the differences in the relative ease of preparation of amidines versus ynamines or *N,O*-ketene acetals especially where R = H, amidines may be employed without deliberate introduction of an amino protecting group, their use is readily extended to cyclic dienophiles inaccessible to ynamines, and they do not suffer from the competitive

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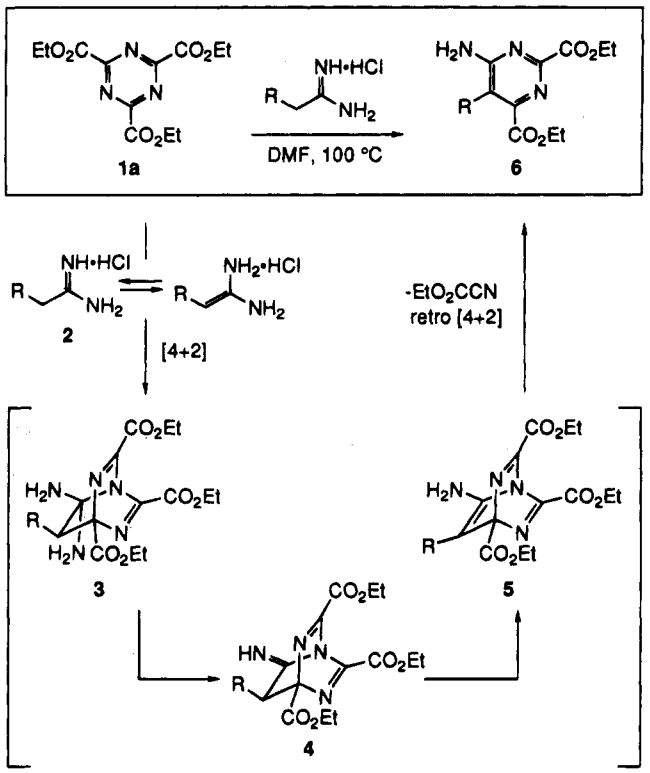
(19) For examples of amidines, imidates, thioimidates, and imines participating as 2π C=N dienophiles in [4 + 2] cycloaddition reactions with the more reactive 1,2,4,5-tetrazines: Roffey, P.; Verge, J. P. *J. Heterocycl. Chem.* **1969**, *6*, 497. Seitz, G.; Overheu, W. *Arch. Pharm.* **1979**, *312*, 452. Seitz, G.; Overheu, W. *Arch. Pharm.* **1981**, *314*, 376. Figeys, H. P.; Mathy, A. *Tetrahedron Lett.* **1981**, *22*, 1393. Seitz, G.; Dhar, R.; Huehnermann, W. *Chem.-Ztg.* **1982**, *106*, 100. Seitz, G.; Dhar, R.; Dietrich, S. *Arch. Pharm.* **1983**, *316*, 472. Boger, D. L.; Panek, J. S. *Tetrahedron Lett.* **1983**, *24*, 4511. Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1983**, *48*, 621. Seitz, G.; Dhar, R.; Mohr, R.; Overheu, W. *Arch. Pharm.* **1984**, *317*, 237. See also ref 2.

0022-3263/94/1959-4950$04.50/0

Scheme 1



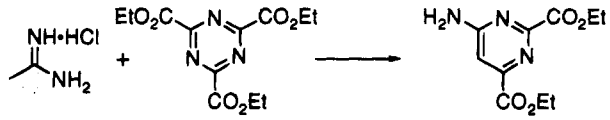
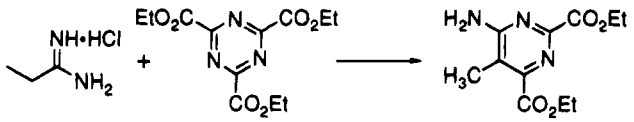
N- versus O-elimination observed with *N,O*-ketene acetals. Herein, we report a full study of the scope and limitations of the amidine Diels–Alder reaction with 1,3,5-triazines.

General Reaction Parameters. In an initial survey of reaction conditions that might prove successful for promoting the reversible, in situ tautomerization of an amidine to its corresponding 1,1-diaminoethene[20] and its subsequent [4 + 2] cycloaddition trap with a 1,3,5-triazine, a range of potential solvents and thermal conditions were examined. In these studies, the [4 + 2] cycloaddition reactions of acetamidine hydrochloride (**2a**)[9] and propionamidine hydrochloride (**2b**)[10] with 2,4,6-tris-(ethoxycarbonyl)-1,3,5-triazine (**1a**)[21] were found to proceed best in polar aprotic solvents including DMF under modest thermal reaction conditions (80–120 °C), Table 1. The use of both a polar, aprotic solvent and the thermal reaction conditions (>80 °C) promote amidine tautomerization and, consistent with past observations,[18] the thermal conditions of >80 °C are generally required for effecting the retro Diels–Alder loss of ethyl cyanoformate with aromatization of a 1,3,5-triazine Diels–Alder adduct.

With these observations in hand, a representative range of acyclic and cyclic amidines were examined for their capabilities of participating in a [4 + 2] cycloaddition reaction with the 1,3,5-triazine **1a**, and the results of this survey are summarized in Table 2. Acyclic amidines (entries 1–4) were found to react regiospecifically with **1a** to afford high yields of the 4-aminopyrimidine products. The reaction proved relatively insensitive to the amidine structure (R = H, alkyl, phenyl, methylthio), allowing the incorporation of a variety of substituents at C5 of the 4-aminopyrimidine products. Cyclic amidines (entries 5–7) were also found to react with **1a** with complete regiospecificity, albeit with somewhat reduced efficiency. In all cases detailed in Table 2, the substituted or annulated pyrimidines were isolated as the primary or sole cycloaddition products.[22]

In the course of conducting this survey, a number of reaction parameters were found to subtly affect the optimized conversions, and each of these factors is discussed individually in the following sections.

Table 1. Survey of Reaction Conditions for the Amidine–1,3,5-Triazine Diels–Alder Reaction

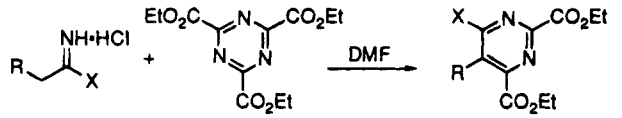
entry	reaction conditions	yield (%)
		
	2a **1a** **6a**	
1a	dioxane, 101°C, 48 h	0
b	CH_3CN, 84°C, 48 h	0
c	pyridine, 60°C, 28 h	20
d	pyridine, 115°C, 30 h	55
e	DMF, 80°C, 22 h	70
f	DMF, 90°C, 22 h	85
g	DMF, 100°C, 22 h	81
h	DMF, 110°C, 22 h	73
i	DMF, 120°C, 22 h	50
j	DMF, 130°C, 26 h	35
		
	2b **1a** **6b**	
2a	toluene-HOAc (1:1) 100°C, 24 h	7
b	4M HCl-dioxane, 101°C, 48 h	0
c	DMF, 90°C, 29 h	75
d	DMF, 100°C, 72 h	80
e	DMF, 110°C, 22 h	65
f	DMF, 120°C, 48 h	53
g	DMF, 130°C, 29 h	46
h	DMF, 140°C, 26 h	44

(20) For examples of amidines, imidates, thioimidates, and imines reacting through their enamine tautomer as 2π C=C dienophiles in [4 + 2] cycloaddition reactions with the more reactive 1,2,4,5-tetrazines: Seitz, G.; Overheu, W. *Arch. Pharm.* **1977**, *310*, 936. Figeys, H. P.; Mathy, A.; Dralants, A. *Synth. Commun.* **1981**, *11*, 655. Seitz, G.; Dhar, R.; Mohr, R. *Chem.-Ztg.* **1983**, *107*, 172. Overheu, W.; Seitz, G.; Wassmuth, H. *Chem.-Ztg.* **1989**, *113*, 188. Seitz, G.; Wassmuth, H. *Arch. Pharm.* **1990**, *323*, 89.

(21) 1,3,5-Triazine (**1b**) is commercially available from Aldrich. 2,4,6-Tris(ethoxycarbonyl)-1,3,5-triazine (**1a**) is prepared in one step through acid-catalyzed trimerization of commercially available ethyl cyanoformate (95–100%): Ott, E. *Chem. Ber.* **1919**, *52*, 656. 2,4,6-Tris-(methylthio)-1,3,5-triazine (**1c**) is prepared in one step through methylation (NaOH, CH_3I) of commercially available trithiocyanuric acid (88%): ref 18 and Tosato, M. L.; Paoloni, L. *J. Chem. Soc. C* **1966**, 909.

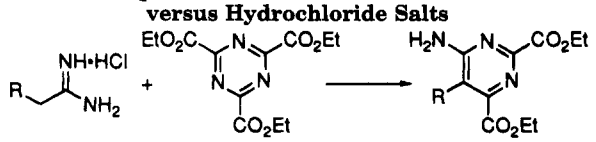
(22) In one instance to date, we have observed a competitive reaction of an amidine as a 2π C=N dienophile with **1a** to provide the corresponding unsymmetrical 1,3,5-triazine Diels–Alder product. These and related studies will be disclosed in due time: Boger, D. L.; Cai, H. Unpublished studies.

Table 2. Inverse Electron Demand Diels–Alder Reaction of Amidines with Triazine 1a



entry	amidine	R	X	reaction conditions	product, yield (%)
acyclic amidines					
1	**2a**	H	NH_2	100°C, 24 h	**6a**, 85
2	**2b**	CH_3	NH_2	100°C, 72 h	**6b**, 80
3	**2c**	CH_3S	NH_2	90°C, 48 h	**6c**, 90
4	**2d**	Ph	NH_2	100°C, 24 h	**6d**, 82
cyclic amidines					
5	**2e**	$-CH_2CH_2NH-$		100°C, 36 h	**6e**, 52
6	**2f**	$-CH_2CH_2CH_2NH-$		100°C, 24 h	**6f**, 75
7	**2g**	$-CH_2CH_2CH_2CH_2NH-$		100°C, 36 h	**6g**, 28

Table 3. Comparison of Reaction of Amidine Free Bases versus Hydrochloride Salts

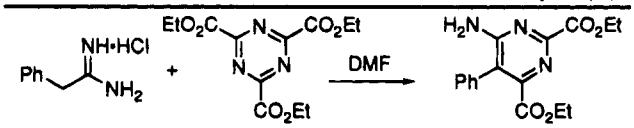
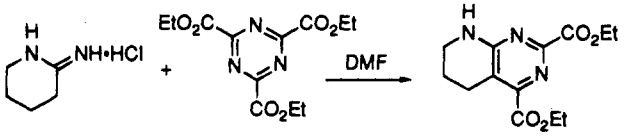


entry	R	reaction conditions	yield (%)
1a	H	DMF, 100°C, 22 h	82
b		DMF, K_2CO_3, 100°C, 48 h	42
2a	CH_3	DMF, 100°C, 72 h	85
b		DMF, K_2CO_3, 100°C, 48 h	45

Amidine Hydrochloride versus Amidine Free Base. The most surprising factor identified in the conduct of the studies was the general observation that the amidine hydrochloride salts routinely provided higher conversions to the product pyrimidines than the corresponding free base, Table 3. In preceding studies of the [4 + 2] cycloaddition reactions of 1,3,5-triazines with ynamines and enamines, acid catalysts proved to accelerate both the retro Diels–Alder reaction and, in the case of enamines, a subsequent aromatization reaction.[18] Although this was not unambiguously established in the present study, it is likely that the retro Diels–Alder reaction of **5** and the tautomerization of **2** are facilitated by the presence of HCl derived from the use of the amidine hydrochloride.

Reaction Temperature. A significant effect of the temperature on the reactions was observed. For **1a**, temperatures lower than 80 °C resulted in only slow and low conversion to the pyrimidine product, and at the higher reaction temperatures (>120 °C) the conversion to the pyrimidine [4 + 2] cycloadduct diminished considerably. Presumably at the lower reaction temperatures, the in situ amidine tautomerization to the reactive dienophile, the effective [4 + 2] cycloaddition trap with **1a**, as well as the subsequent reaction cascade leading to **6** including a documented[18] slow retro Diels–Alder conversion of **5** to **6** are less effective. At the higher reaction temperatures, competitive reactions of the substrates, reaction intermediates, and the reaction products including the liberated ethyl cyanoformate intervene to diminish the desired conversion. Notably, each of the amidines examined reacted with **1a** with optimal conversions observed between 90 and 110 °C despite the apparent structural differences that would affect tautomerization, Tables 1 and 4. Monitoring the course of reaction of phenylacetamidine hydrochloride (**2d**) and iminopiperidine hydrochloride (**2f**) with **1a** by ^1H NMR revealed the buildup of significant amounts of uncharacterized intermediates during the conversion to pyrimidines **6d** and **6f** although the complete disappearance of the starting 1,3,5-triazine was not observed prior to appearance of products. The buildup of intermediates was diminished at 100 °C relative to 90 °C, indicating that at higher reaction temperatures the latter steps ($-NH_3$, tautomerization, retro [4 + 2]) more effectively compete with the initial amidine tautomerization and [4 + 2] cycloaddition.

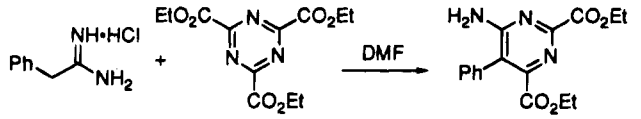
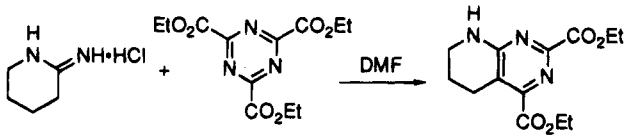
Table 4. Effect of Reaction Temperature on Conversion

entry	reaction conditions	yield (%)
		
	2d + **1a**	**6d**
1a	DMF, 90°C, 24 h	76
b	DMF, 100°C, 24 h	82
c	DMF, 110°C, 12 h	80
d	DMF, 120°C, 12 h	67
		
	2f + **1a**	**6f**
2a	DMF, 90°C, 24 h	69
b	DMF, 100°C, 24 h	75
c	DMF, 110°C, 12 h	73
d	DMF, 120°C, 12 h	68

Diene–Dienophile Ratio. Contrary to initial expectations but significant to the scope of the amidine [4 + 2] cycloaddition reaction with 1,3,5-triazines, the efficiency of conversion to the product pyrimidine proved to be relatively independent of the ratio of diene–dienophile employed, Table 5. Diene to dienophile ratios of 1:2, 2:1, or 1:1 provided comparable conversions based on the limiting reagent, although slightly higher conversions were observed with excess amidine. However, the comparisons clearly illustrate that the [4 + 2] cycloaddition trap of the in situ generated and reactive 1,1-diaminoethenes is both effective and efficient under the prescribed reaction conditions. Importantly, either the diene or dienophile may be employed as the limiting reagent depending on their relative value as synthetic intermediates without sacrificing the conversion efficiency.

Amidine Structure: Acyclic and Cyclic Amidines. The scope of the [4 + 2] cycloaddition reaction was

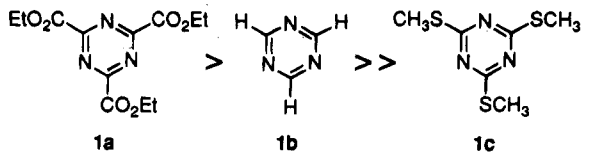
Table 5. Effect of Reactant Ratio on Conversion

entry	amidine:triazine ratio	reaction conditions	yield (%)
			
2d + 1a → 6d			
1a	2 : 1	90°C, 24 h	76
b		100°C, 24 h	82
c	1 : 2	90°C, 24 h	68
d		100°C, 24 h	60
e	1 : 1	100°C, 72 h	70
			
2f + 1a → 6f			
2a	2 : 1	90°C, 24 h	69
b		100°C, 24 h	75
c	1 : 2	90°C, 36 h	65
d		100°C, 24 h	61
e	1 : 1	100°C, 31 h	54

expanded considerably with the demonstration that the cyclic amidines **2e–g** may participate effectively in the Diels–Alder reaction, Table 2. Notably, **2e–g** react with **1a** under conditions comparable to those observed with acyclic amidines and generally with comparable conversions. Because the rate of [4 + 2] cycloaddition of the olefin derived from **2e–g** versus that of the acyclic amidines **2a–d** would be expected to be considerably slower due to destabilizing steric interactions encountered in the [4 + 2] cycloaddition transition state, the comparable rates and conversions observed with **2a–g** suggest the [4 + 2] cycloaddition reaction is not the rate-limiting step in the conversions to **6e–g**. In addition, the clean generation of **6e–f** requires preferential and selective elimination of ammonia versus the *N*-alkylamine from **3**. The alternative products derived from elimination of the *N*-alkylamine were not detected or isolated but their generation may have been masked by further reactions of the liberated basic amine under the conditions of cycloaddition and, particularly in the case of **6g**, may be the origin of the lower conversions. Thus, similar to past observations,[15] the ease of elimination/aromatization of the initial cycloadducts to the corresponding pyrimidines such as those derived from **2e–g** and consequently the yields of the final pyrimidines proved to be dependent on the cyclic amidine ring size (6 > 5 > 7).

1,3,5-Triazine Substituent Effects. Consistent with expectations, the reaction exhibited 1,3,5-triazine substituent effects characteristic of an inverse electron demand Diels–Alder reaction (CO_2Et > H >> SCH_3), Figure 1. The parent 1,3,5-triazine (**1b**)[21] proved to participate effectively in the amidine Diels–Alder reaction but required slightly more vigorous reaction conditions than 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine (**1a**) for comparable conversions (120–125 °C versus 90–100 °C), Table 6. In contrast, 2,4,6-tris(methylthio)-1,3,5-triazine[21] (**1c**) failed to react with amidines even under vigorous reaction conditions.

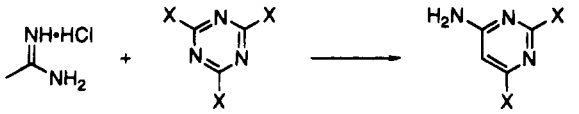
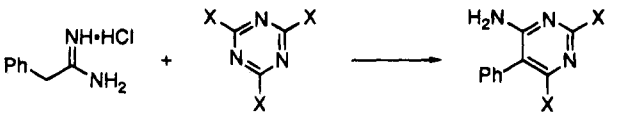
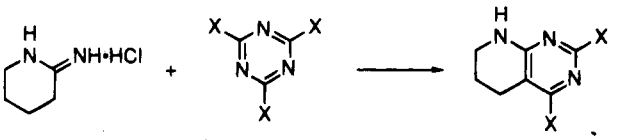
Relative Reactivity:



1a **1b** **1c**

Figure 1.

Table 6. Effect of Substituents on Triazine Reactivity

entry	amidine	1,3,5-triazine	reaction conditions	product, yield (%)
				
1	**2a**	**1a**, X=CO_2Et	DMF, 100°C, 24 h	**6a**, 85
2a	**2a**	**1c**, X=SCH_3	DMF, 100°C, 24 h	**7a**, 0
b			DMF, 150°C, 24 h	**7a**, 0
				
3	**2d**	**1a**, X=CO_2Et	DMF, 100°C, 24 h	**6d**, 82
4a	**2d**	**1b**, X=H	DMF, 120°C, 24 h	**8d**, 47
b			DMF, 120°C, 48 h	**8d**, 64
				
5	**2f**	**1a**, X=CO_2Et	DMF, 100°C, 24 h	**6f**, 75
6a	**2f**	**1b**, X=H	DMF, 100°C, 48 h	**8f**, 44
b			DMF, 125°C, 48 h	**8f**, 64
c			DMF, 125°C, 96 h	**8f**, 63
7a	**2f**	**1c**, X=SCH_3	DMF, 150°C, 24 h	**7f**, 0
b			N-methylpyrrolidinone, 180°C, 24 h	**7f**, 0

Nature of the Dienophile: Amidine versus Thioimidate and Imidate. In efforts to further extend or explore the scope of the inverse electron demand Diels–Alder reaction of the 1,3,5-triazines **1a–b**, the potential use of the HCl and HI salts of imidates and thioimidates was investigated, Table 7. Unlike amidines, both imidates and thioimidates, like *N,O*-ketene acetals, may suffer from competitive amine versus alcohol or thiol elimination in the reaction cascade leading to the pyrimidine products. Nonetheless, it was of interest to determine the relative ease with which they would participate in a comparable [4 + 2] cycloaddition reaction cascade with 1,3,5-triazines. Imidates **9** and **12** afforded

Table 7. Reactivity of Amidines versus Imidates and Thioimidates

entry	dienophile[a]	triazine	reaction conditions	product	yield (%)
1	**2a**, X=NH_2	**1a**	DMF, 100°C, 24 h	**6a**, X=NH_2	85
2	**9**, X=OCH_3	**1a**	DMF, 100°C, 24 h	--	0
3	**10**, X=SCH_3	**1a**	DMF, 100°C, 24 h	**11**, X=SCH_3	73
4	**2f**, X=NH_2	**1a**	DMF, 100°C, 24 h	**6f**	75
5a	**12**, X=OCH_3	**1a**	DMF, 90°C, 24 h	--	0
b			toluene, 90°C, 24 h	--	0
c			dioxane, 101°C, 24 h	--	0
d			pyridine, 115°C, 36 h	--	0
6	**13**, X=SCH_3	**1a**	DMF, 100°C, 48 h	**6f**	11
7	**2f**, X=NH_2	**1b**	DMF, 125°C, 48 h	**8f**	64
8	**12**, X=OCH_3	**1b**	DMF, 125°C, 48 h	--	0
9	**13**, X=SCH_3	**1b**	DMF, 120°C, 48 h	**8f**	36

[a] Amidine and imidate hydrochloride salts. Thioimidate hydroiodide salts.

none of the desired pyrimidine products under conditions optimal for reaction of the corresponding amidines and provided only the recovered starting triazines unchanged. In contrast, the thioimidates **10** and **13** reacted with the 1,3,5-triazines **1a** and **1b** under the established conditions with varying results. Methyl thioacetimidate hydroiodide reacted with 1,3,5-triazine **1a** to afford a high yield of the corresponding 4-(methylthio)pyrimidine **11** (73%) derived from preferential elimination of ammonia. None of the corresponding 4-aminopyrimidine resulting from methanethiol elimination was observed. Although this confirms the in situ thioimidate tautomerization and subsequent 1,3,5-triazine [4 + 2] cycloaddition trap analogous to that observed with amidines (Scheme 1), the preferential elimination of ammonia provides a useful complementary but not identical reaction process leading to 4-(alkylthio)pyrimidines. This result contrasts with the reaction of *N,S*-ketene acetals with 1,2,4,5-tetrazines and 1,2,4-triazines which have been observed to provide products derived from preferential elimination of methanethiol.[23,24] In contrast and similar to observations

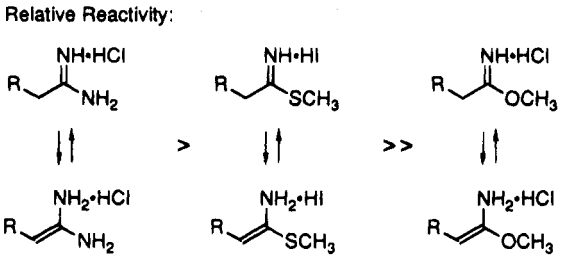


Figure 2.

made in the reaction of cyclic thioimidates with 1,2,4,5-tetrazines,[25] the cyclic thioimidate **13** reacted with triazines **1a** and **1b** to afford the annulated pyrimidines resulting from methanethiol elimination although the yields were significantly lower than those obtained with the corresponding amidine. While these latter results may be potentially attributed in part to the undetected competitive elimination of the amine, the lower conversions also reflect a slower, less effective [4 + 2] cycloaddition reaction as judged by the time required for disappearance of the starting 1,3,5-triazine.

Thus, thioimidates may participate in a comparable [4 + 2] cycloaddition reaction cascade but suffer inherent limitations due to unpredictable and competing amine and thiol elimination reactions while imidates were found to be unreactive under the reaction conditions examined, Figure 2.

Experimental Section[26]

General Procedure for the Diels–Alder Reaction of 2,4,6-Tris(ethoxycarbonyl)-1,3,5-triazine (1a) and 1,3,5-Triazine (1b) with Amidines, Imidates, and Thioimidates: 4-Amino-2,6-bis(ethoxycarbonyl)-5-phenylpyrimidine (6d). A solution of 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine[21] (**1a**, 200 mg, 0.673 mmol) in dry DMF (1.35 mL) under Ar was treated with 2-phenylacetamidine hydrochloride (**2d**, 230 mg, 1.35 mmol, 2.0 equiv), and the resulting solution was warmed at 100 °C for 24 h during which time a precipitate formed. The suspension was cooled, and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL), and the solution was washed with saturated aqueous $NaHCO_3$ (50 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 15 × 2 cm, 2% CH_3OH–CH_2Cl_2 eluant) afforded pure **6d** (173 mg, 212 mg theoretical, 82%) as a yellow solid: mp 156–158 °C (yellow needles, EtOAc–hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 7.28–7.52 (m, 5H), 4.42 (q, J = 7.1 Hz, 2H), 4.07 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 164.9, 163.4, 163.0, 155.2, 154.7, 131.9, 129.4, 129.2, 128.7, 118.6, 62.6, 61.8, 14.1, 13.5; IR (film) ν_{max} 3282, 3183, 2977, 1736, 1623, 1554, 1215, 1033 cm^{-1}; FABHRMS (NBA) m/z 316.1288 (M + H^+, $C_{16}H_{18}N_3O_4$ requires 316.1297).

Anal. Calcd for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.97; H, 5.22; N, 13.69.

6-Amino-2,4-bis(ethoxycarbonyl)pyrimidine (6a):[9] 85%, Table 1; mp 168–169 °C (white needles, EtOAc–hexane); ^1H NMR (200 MHz, DMSO-d_6) δ 7.68 (br s, 2H), 7.13 (s, 1H), 4.31 (q, J = 7.2 Hz, 2H), 4.29 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 165.8, 164.6, 164.3, 158.1, 153.9, 107.6, 62.0, 61.8,

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(26) 2,4,6-Tris(ethoxycarbonyl)-1,3,5-triazine and all amidines, imidates, and thioimidates were dried in vacuo over P_2O_5 for 8–12 h prior to use in the cycloaddition reactions. 1,3,5-Triazine (**1b**), acetamidine hydrochloride (**2a**), and 2-iminopiperidine hydrochloride (**2f**) are commercially available from Aldrich.

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14.2 (2C); IR (KBr) ν_{max} 3442, 3306, 3192, 2980, 1739, 1719, 1650, 1596, 1536, 1435, 1260, 1226, 1026, 972, 866, 746 cm^{-1}; CIHRMS (2-methylpropane) m/z 240.0987 ($M + H^+$, $C_{10}H_{13}N_3O_4$ requires 240.0984).

Anal. Calcd for $C_{10}H_{13}N_3O_4$: C, 50.21; H, 5.44; N, 17.57. Found: C, 50.10; H, 5.82, N, 17.65.

6-Amino-2,4-bis(ethoxycarbonyl)-5-methylpyrimidine (6b):[10] 80%, Table 1; mp 155–156 °C (white needles, EtOAc–hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 6.22 (s, 2H), 4.47 (q, J = 7.1 Hz, 2H), 4.45 (q, J = 7.1 Hz, 2H), 2.30 (s, 3H), 1.44 (t, J = 7.1 Hz, 3H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 164.1, 163.7, 157.9, 153.6, 114.8, 62.5, 62.2, 14.1, 14.0, 12.2; IR (KBr) ν_{max} 3448, 3360, 2980, 2938, 1734, 1720, 1628, 1576 cm^{-1}; EIHRMS m/z 253.1060 (M^+, $C_{11}H_{15}N_3O_4$ requires 253.1062).

Anal. Calcd for $C_{11}H_{15}N_3O_4$: C, 52.12; H, 5.92; N, 16.58. Found: C, 51.91; H, 6.11; N, 16.34.

6-Amino-2,4-bis(ethoxycarbonyl)-5-(methylthio)pyrimidine (6c):[10] 90%, Table 2; mp 148 °C sharp (white needles, EtOAc–hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 4.48 (q, J = 7.2 Hz, 2H), 4.47 (q, J = 7.2 Hz, 2H), 2.35 (s, 3H), 1.43 (t, J = 7.2 Hz, 3H), 1.42 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 164.9, 163.3, 162.6, 155.7, 111.3, 62.8, 62.3, 17.9, 14.1, 14.0; IR ($CHCl_3$) ν_{max} 3500, 3392, 2992, 1739, 1599, 1544, 1448, 1383, 1231, 1199, 1026 cm^{-1}; FABHRMS (NBA) m/z 286.0878 ($M + H^+$, $C_{11}H_{15}N_3O_4S$ requires 286.0861).

Anal. Calcd for $C_{11}H_{15}N_3O_4S$: C, 46.31; H, 5.30; N, 14.73; S, 11.24. Found: C, 46.38; H, 5.30; N, 14.70; S, 11.30.

2,4-Bis(ethoxycarbonyl)-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]-pyrimidine (6e). 1,3,5-Triazine **1a** (50 mg, 0.17 mmol) and 2-iminopyrrolidine hydrochloride (**2e**, 41 mg, 0.34 mmol, 2.0 equiv) afforded pure **6e** (23.2 mg, 45 mg theoretical, 52%, Table 2) as a white solid: mp 226–229 °C (powder, EtOAc–hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 8.95 (s, 1H), 4.42 (q, J = 7.1 Hz, 2H), 4.41 (q, J = 7.1 Hz, 2H), 3.94 (t, J = 8.3 Hz, 2H), 3.46 (t, J = 8.3 Hz, 2H), 1.423 (t, J = 7.1 Hz, 3H), 1.420 (t, J = 7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.6, 164.4, 164.0, 155.3, 144.7, 127.3, 62.6, 62.1, 44.5, 27.1, 14.1 (2C); IR (film) ν_{max} 3222, 2975, 1733, 1614, 1587, 1401, 1274, 1221, 1199, 1053, 1027 cm^{-1}; FABHRMS (NBA) m/z 266.1141 ($M + H^+$, $C_{12}H_{16}N_3O_4$ requires 266.1141).

Anal. Calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.10; H, 5.45; N, 15.84.

2,4-Bis(ethoxycarbonyl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (6f). 1,3,5-Triazine **1a** (200 mg, 0.67 mmol) and 2-iminopiperidine hydrochloride (**2f**, 181 mg, 1.34 mmol, 2.0 equiv) afforded pure **6f** (140 mg, 187 mg theoretical, 75%, Table 2) as a white solid: mp 123–125 °C (white needles, EtOAc–hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 6.79 (s, 1H), 4.43 (q, J = 7.1 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 3.45–3.50 (m, 2H), 2.98 (t, J = 6.4 Hz, 2H), 1.92 (p, J = 6.0 Hz, 2H), 1.40 (t, J = 7.1 Hz, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 165.1, 163.8, 161.8, 154.3, 151.3, 115.8, 62.5, 62.1, 40.9, 23.3, 19.8, 14.1 (2C); IR (film) ν_{max} 3253, 2977, 2938, 2859, 1731, 1589, 1431, 1402, 1377, 1234, 1210, 1185, 1112, 1028 cm^{-1}; FABHRMS (NBA-NaI) m/z 302.1106 ($M + Na^+$, $C_{13}H_{17}N_3O_4$ requires 302.1117).

Anal. Calcd for $C_{13}H_{17}N_3O_4$: C, 55.91; H, 6.14; N, 15.04. Found: C, 56.30; H, 6.29; N, 14.98.

Similarly, 1,3,5-triazine **1a** (25 mg, 0.084 mmol) and 6-(methylthio)-2,3,4,5-tetrahydropyridinium iodide (**13**, 43 mg, 0.167 mmol, 2.0 equiv) afforded pure **6f** (2.6 mg, 23 mg theoretical, 11%, Table 7).

2,4-Bis(ethoxycarbonyl)-5,6,7,8-tetrahydro-9*H*-pyrimido[4,5-*b*]azepine (6g). 1,3,5-Triazine **1a** (50 mg, 0.17 mmol) and 2-iminoazepine hydrochloride (**2g**, 50 mg, 0.34 mmol, 2.0 equiv) afforded pure **6g** (14.2 mg, 50 mg theoretical, 28%, Table 2) as a yellow solid: mp 81–83 °C (yellow needles, EtOAc–hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 6.02 (s, 1H), 4.41 (q, J = 7.1 Hz, 2H), 4.37 (q, J = 7.2 Hz, 2H), 3.41–3.48 (m, 2H), 2.82–2.87 (m, 2H), 1.92 (m, 4H), 1.363 (t, J = 7.0 Hz, 3H), 1.361 (t, J = 7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.6, 165.6, 163.5, 155.9, 153.7, 118.8, 62.5, 62.1, 42.8, 27.3, 25.9, 24.4, 14.1, 14.0; IR (film) ν_{max} 3363, 3280, 2971, 2940, 2868, 1733, 1568, 1238, 1212, 1116, 1018 cm^{-1}; FABHRMS (NBA) m/z 294.1459 ($M + H^+$, $C_{14}H_{20}N_3O_4$ requires 294.1454).

Anal. Calcd for $C_{14}H_{19}N_3O_4$: C, 57.33; H, 6.53; N, 14.33. Found: C, 57.30; H, 6.39; N, 14.30.

4-Amino-5-phenylpyrimidine (8d). 1,3,5-Triazine (**1b**, 50 mg, 0.62 mmol) and 2-phenylacetamidine hydrochloride (**2d**, 210 mg, 1.23 mmol, 2.0 equiv) afforded pure **8d** (68 mg, 106 mg theoretical, 64%, Table 6) as a tan solid: mp 155–157 °C (prisms, EtOAc–hexane) (lit.[28] mp 157–158 °C); ^1H NMR (250 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.15 (s, 1H), 7.29–7.53 (m, 5H), 5.29 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 160.4, 157.6, 154.7, 134.2, 129.4, 128.5, 119.0; IR (film) ν_{max} 3332, 3167, 1645, 1583, 1485, 1402, 1341 cm^{-1}; FABHRMS (NBA) m/z 172.0883 ($M + H^+$, $C_{10}H_{10}N_3$ requires 172.0875).

Anal. Calcd for $C_{10}H_9N_3$: C, 70.16; H, 5.30; N, 24.54. Found: C, 70.11; H, 5.32; N, 25.05.

5,6,7,8-Tetrahydropyrido[2,3-*d*]pyrimidine (8f). 1,3,5-Triazine (**1b**, 50 mg, 0.62 mmol) and 2-iminopiperidine hydrochloride (**2f**, 166 mg, 1.24 mmol, 2.0 equiv) afforded pure **8f** (54 mg, 84 mg theoretical, 64%, Table 6) as a white solid: mp 107–109 °C (white needles, EtOAc–hexane) (lit.[27] mp 106–108 °C): ^1H NMR (250 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.88 (s, 1H), 6.34 (s, 1H), 3.41 (m, 2H), 2.63 (t, J = 6.1 Hz, 2H), 1.88 (p, J = 5.9 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 160.0, 156.5, 152.5, 113.0, 40.8, 23.5, 20.1; IR (film) ν_{max} 3204, 3095, 2948, 2859, 1598, 1549, 1402, 1358, 1323, 1229, 1190, 1171, 1112, 1003, 870, 777 cm^{-1}; FABHRMS (NBA) m/z 136.0870 ($M + H^+$, $C_7H_{10}N_3$ requires 136.0875).

Anal. Calcd for $C_7H_9N_3$: C, 62.20; H, 6.71; N, 31.09. Found: C, 61.84; H, 6.67; N, 31.34.

Alternatively, 1,3,5-triazine (**1b**, 22.3 mg, 0.275 mmol) and 6-(methylthio)-2,3,4,5-tetrahydropyridinium iodide (**13**, 140 mg, 0.544 mmol, 2.0 equiv) afforded pure **8f** (13.3 mg, 37 mg theoretical, 36%, Table 7).

2,6-Bis(ethoxycarbonyl)-4-(methylthio)pyrimidine (11). 1,3,5-Triazine **1a** (200 mg, 0.673 mmol) and methyl thioacetimidate hydroiodide (**10**, 292 mg, 1.34 mmol, 2.0 equiv) afforded pure **11** (132 mg, 182 mg theoretical, 73%, Table 7) as a white solid: mp 48–49 °C (white needles, EtOAc–hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 7.90 (s, 1H), 4.47 (q, J = 7.1 Hz, 2H), 4.45 (q, J = 7.1 Hz, 2H), 2.66 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.9, 163.5, 163.1, 156.9, 153.0, 112.0, 62.85, 62.76, 14.0 (2C), 12.8; IR (film) ν_{max} 2981, 2930, 1743, 1563, 1521, 1331, 1310, 1222, 1207, 1186, 1021, 887, 763, 727 cm^{-1}; FABHRMS (NBA) m/z 271.0759 ($M + H^+$, $C_{11}H_{15}N_2O_4S$ requires 271.0753).

Anal. Calcd for $C_{11}H_{14}N_2O_4S$: C, 48.88; H, 5.22; N, 10.36; S, 11.86. Found: C, 48.75; H, 5.20; N, 10.44; S, 11.79.

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