Cycloadditions of 1,2,3-Triazines Bearing C5-Electron Donating Substituents: Robust Pyrimidine Synthesis

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Abstract
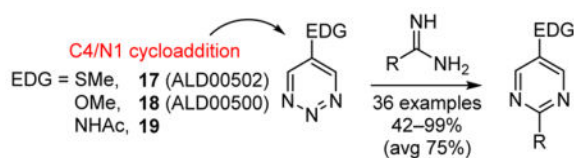
The examination of the cycloaddition reactions of 1,2,3-triazines **17**–**19**, bearing electron-donating substituents at C5, are described. Despite the noncomplementary 1,2,3-triazine C5 substituents, amidines were found to undergo a powerful cycloaddition to provide 2,5-disubstituted pyrimidines in excellent yields (42–99%; EDG = SMe > OMe > NHAc). Even select ynamines and enamines were capable of cycloadditions with **17**, but not **18** or **19**, to provide trisubstituted pyridines in modest yields (37–40% and 33% respectively).

The inverse electron demand Diels–Alder reaction of electron-deficient heterocyclic azadienes is a highly effective method for the synthesis of challenging heterocyclic ring systems.[1] In efforts that have expanded the range of heterocycles accessible by this powerful cycloaddition strategy, we have systematically explored the reactions of 1,2,4,5-tetrazines,[2] 1,2,4-triazines,[3] 1,3,5-triazines,[4] 1,3,4-oxadiazoles,[5] and 1,2-diazines.[6] Frequently, these methodological studies were inspired by their use as the key steps in the total synthesis of complex natural products, providing non-obvious or effective solutions to the preparation of their core structures.[7–10] Additional applications include their reactions with strained olefins and alkynes as bioorthogonal bioconjugation reagents because of their extraordinarily efficient and rapid rates of cycloaddition.[11] Recently, our efforts extended to 1,2,3-triazines, examining the synthesis and cycloaddition reaction scope of the parent 1,2,3-triazine and a series of 1,2,3-triazines that contain electron-withdrawing groups at sites where their electronic impact was both consonant and dissonant to that innate to the 1,2,3-triazine core (Figure 1).[12] In addition to defining the scope of the 1,2,3-triazine cycloaddition reactions, these studies have also found application in the total syntheses of (−)-pyrimidoblamic acid and P-3A[13] as well as the late-stage divergent total syntheses of dihydrolysergic acid, dihydrolysergol, and a series of heterocyclic derivatives[14].

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Perhaps the most remarkable of the cycloaddition reactions of 1,2,3-triazines and the most effective of those examined to date is their reactions with amidines to provide pyrimidines. The efficiency and robust nature of these reactions led to our further study of 1,2,3-triazines that contain electron-donating groups at C5. It was expected that this modification would decrease the overall reactivity of the 1,2,3-triazines, perhaps even to the point of preventing the anticipated cycloaddition chemistry. Herein, we show that while such substituents do slow the rate of reaction of the 1,2,3-triazines, their reaction with amidines remained remarkably effective, providing the product pyrimidines in excellent yields. In selected cases, even less effective dienophiles, such as ynamines and enamines, were found to be capable of cycloaddition, albeit in more modest yields.

Three previously unreported 1,2,3-triazines were chosen to probe the effects of electron-donating substituents on the reactivity and regioselectivity of the cycloaddition reactions with amidines, ynamines, and enamines. These 1,2,3-triazines, 5-(methylthio)-1,2,3-triazine (**17**), 5-methoxy-1,2,3-triazine (**18**), and 5-(*N*-acetylamino)-1,2,3-triazine (**19**), were selected to provide a range of electronic effects on which to base an analysis (Scheme 1).

5-(Methylthio)-1,2,3-triazine (**17**, ALD00502) was accessed by the simultaneous deprotonation and lithium–halogen exchange of commercially available 4-bromopyrazole (**8**) with subsequent trap of the *C*-lithiate by dimethyl disulfide to provide pyrazole **11** (91%).[15] Subsequent *N*-amination of **11** with monochloramine[16] provided a mixture of *N*-amino pyrazole **14** and starting **11** (74%, 98% brsm, ~3.4:1) that was inseparable by chromatography. Nevertheless, when the mixture of *N*-amino pyrazole **14** and pyrazole **11** was treated with $NaIO_4$ under biphasic oxidative ring expansion conditions[17], 5-(methylthio)-1,2,3-triazine (**17**) (56–74%) was obtained in good yield and was readily separable from products derived from pyrazole **11**.

Preparation of 5-methoxy-1,2,3-triazine (**18**, ALD00500) was achieved starting with 4-methoxypyrazole (**12**), which was prepared from **9** in a known 3-step sequence (56% overall).[18] This pyrazole **12** was subjected to *N*-amination with monochloramine[16] (56%) and the subsequent $NaIO_4$ oxidative ring expansion[17] to provide **18** in good yield (70–88%).

The synthesis of 5-(*N*-acetylamino)-1,2,3-triazine (**19**) began with the reduction of commercially available 4-nitropyrazole (**10**) (quant.) followed by bisacylation (83%) of 4-aminopyrazole and subsequent monodeacylation (94%) to provide **13**.[19] While it is reported that 4-aminopyrazole can be monoacylated selectively (vs N1),[20] doing so was found to be challenging, frequently providing mixtures of des-, mono-, and bisacylation products in our hands. *N*-amination of pyrazole **13** with monochloramine[16] provided the penultimate substrate **16** in good yield (62%). Oxidative ring expansion under biphasic conditions[17] generates 1,2,3-triazine **19**, but the solubility of the compound did not allow its extraction from the aqueous phase. As such, a new monophasic protocol, utilizing $NaIO_4$ in acetonitrile under sonication, was developed and optimized to provide a modest yield (34%) of 5-(*N*-acetylamino)-1,2,3-triazine (**19**).

Based on previous studies[12], it was expected that the reactions of 1,2,3-triazines **17**–**19** with free-based amidines would proceed with a C4/N1 regioselectivity to furnish symmetrical

pyrimidine products. The electron-donating substituents raise the $LUMO_{diene}$ relative to 1,2,3-triazine and suggest they should slow or even preclude the cycloaddition reaction (reactivity: MeS > MeO > AcNH). Initial studies with **17** revealed that reactions at 25 °C typically required 24–90 h to achieve full consumption of the limiting reagent, but that product pyrimidine was produced even under such mild reaction conditions (Figure 2, entries 1,2). Although increases in reaction time provided further yield improvements (Figure 2, entry 3), simply warming the reactions in which the amidine was the limiting reagent at 40 °C, provided acceptable reaction times and superb isolated yields (Figure 2, entry 4). Since the most valuable component of reactions is likely to be the amidine, further studies focused on a reaction stoichiometry of 1.0 equivalent of amidine and 1.5 equivalents of 1,2,3-triazine.

Finally, although not extensively examined and unlike previously disclosed examples, the inclusion of molecular sieves served neither to increase the reaction rate or yield. In fact, their inclusion was observed to decrease the isolated yield of cycloaddition products in some cases (Figure 2, entries 4,5). As a result, molecular sieves were omitted from the optimized reaction conditions.

With effective conditions in hand and with use of an extended reaction time of 24 h, the reaction of 1,2,3-triazine **17** with a wide variety of aliphatic and aryl amidines was explored (Figure 3). The cycloadditions proceeded smoothly at 40 °C to afford the 2-substituted-5-(methylthio)pyrimidines in excellent yields (generally >90%). Qualitatively, the relative reaction rates tracked with the amidine electronic character, with the electron-rich amidines (e.g. **20j**) reacting most rapidly (ca. 2 h) and the electron-poor amidines (e.g. **20b** and **20e**) requiring the full 24 h to achieve comparable conversions. Even the sterically encumbered amidine **20k** provided a superb conversion to pyrimidine **21k**.

With 5-methoxy-1,2,3-triazine (**18**), the reaction rate decreased and a reoptimization of the reaction temperature was conducted. It was determined that a reaction temperature of 90 °C was effective in promoting the cycloaddition in high yields (42–97%) over a convenient timeframe (24 h) (Figure 4). Consistent with observations made with 1,2,3-triazine **17**, the rate of cycloaddition of **18** tracked closely with the electronic character of the amidine and those bearing aromatic substituents generally provided higher yields of the 2-substituted-5-methoxypyrimidines than those bearing aliphatic substituents.

The introduction of a C5 *N*-acetylamino substituent resulted in a further decrease in reaction rate with **19**, which required reexamination of the reaction parameters. Unlike 1,2,3-triazine **18**, further increasing the reaction temperature was ineffective. Instead, extended reaction times (72 h) at 90 °C were found to afford moderate to good isolated yields (43–79%) of the pyrimidine products (Figure 5).

It is possible, even likely, that the reactions of amidines with 1,2,3-triazines represent stepwise addition-cyclization reactions proceeding through polar intermediates, although we have not yet detected such intermediates or isolated intercepted products diagnostic of their intermediacy. As a result, we conducted the reaction of 1,2,3-triazines **17** and **4** (ALD00106) with amidine **[15]N-20g** doubly labeled with [15]N. Each reaction produced the pyrimidine

product in superb yields (97–98%) and each was generated with incorporation of a single ^{15}N label (Figure 6). This is consistent with a single-step cycloaddition and, while not ruling out stepwise addition-cyclization mechanisms, the latter would have been expected to provide at least mixtures of singly and doubly ^{15}N labeled pyrimidine products perhaps even favoring the doubly labeled product.

We also examined the reactivity of **17**–**19** toward other candidate dienophiles including ynamines and enamines. Since both classes are less reactive in their cycloaddition reactions with 1,2,3-triazines than amidines, it was anticipated that their cycloadditions might be difficult to promote. An extensive survey of the reaction conditions for both ynamines and enamines was undertaken and included the exploration of the solvent, reaction time, temperature, additives, concentration, and stoichiometry. In the case of ynamines, the optimal reaction conditions identified were modestly effective in promoting the cycloaddition reaction of 1,2,3-triazine **17** (37–40%), providing the product of cycloaddition across C4/N1, whereas the 1,2,3-triazines **18** and **19** failed to react to an appreciable extent (Figure 7). Similarly, the cycloaddition reaction of selected enamines were only moderately effective in the case of 1,2,3-triazine **17** (33%) (Figure 7).

A detailed study of the cycloaddition reactions of 1,2,3-triazines bearing C5 electron donating groups was conducted. Despite the unfavorable electronic effects of the substituents, 1,2,3-triazines **17**–**19** were found to participate in a powerful cycloaddition with a wide variety of amidines (reactivity: **17** > **18** > **19**), providing the corresponding pyrimidines in excellent yields (42–99%). Remarkably, 1,2,3-triazine **17**, but not **18** and **19**, was even capable of reaction with a select set of ynamines and enamines, highlighting the highly reactive nature of the 1,2,3-triazine core. In addition to the intrinsic use of such 1,2,3-triazine cycloaddition reactions with amidines for the synthesis of individual substituted pyrimidines, the ability to use virtually any and all readily accessible substituted 1,2,3-triazines in the amidine cycloaddition reaction permits the late-stage divergent synthesis of a series of substituted pyrimidines from a common amidine intermediate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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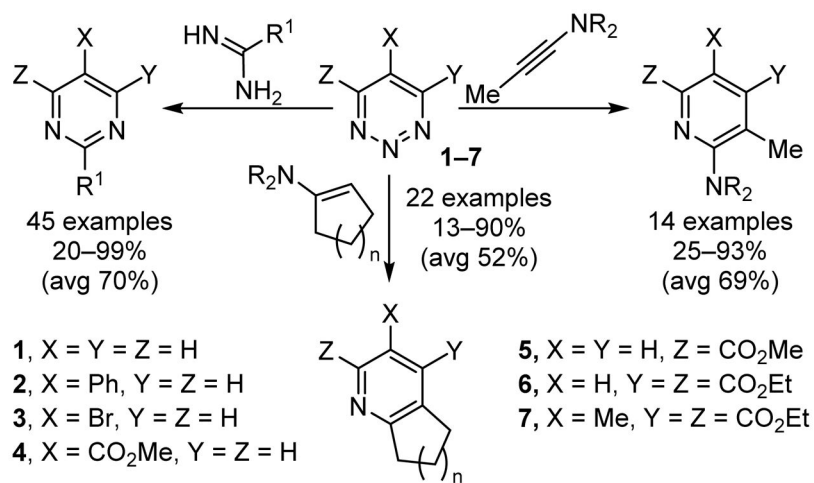
FIGURE 1.
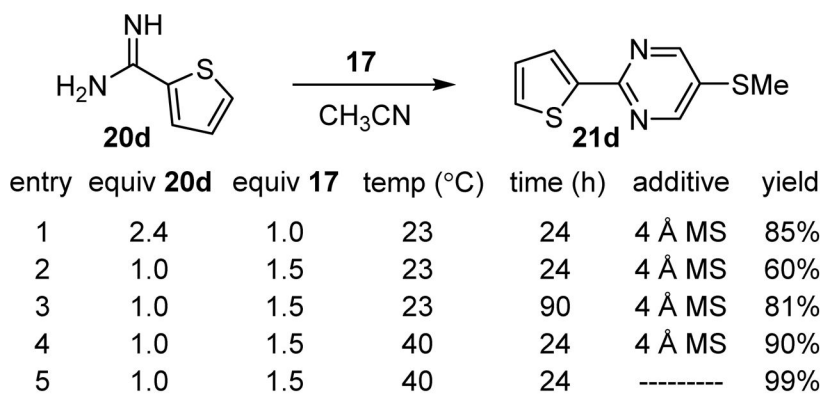Previous studies with 1,2,3-triazines.

FIGURE 2.

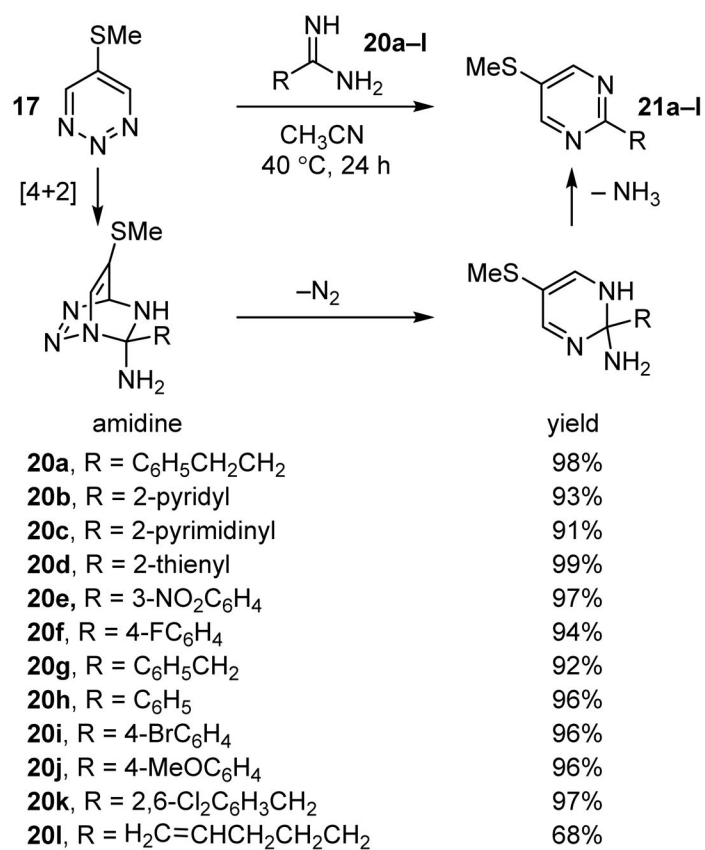Optimization of the reaction of **17** with amidines.

entry	equiv 20d	equiv 17	temp (°C)	time (h)	additive	yield
1	2.4	1.0	23	24	4 Å MS	85%
2	1.0	1.5	23	24	4 Å MS	60%
3	1.0	1.5	23	90	4 Å MS	81%
4	1.0	1.5	40	24	4 Å MS	90%
5	1.0	1.5	40	24	---------	99%

FIGURE 3.
Reaction of 1,2,3-triazine **17** with amidines.

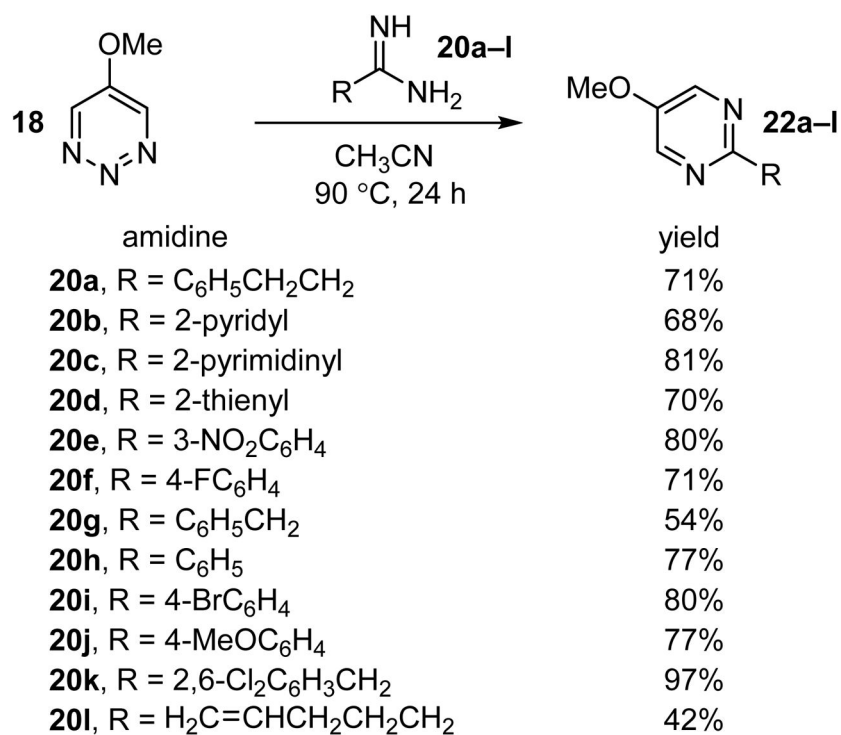| amidine	yield
20a, R = C$_6$H$_5$CH$_2$CH$_2$	71%
20b, R = 2-pyridyl	68%
20c, R = 2-pyrimidinyl	81%
20d, R = 2-thienyl	70%
20e, R = 3-NO$_2$C$_6$H$_4$	80%
20f, R = 4-FC$_6$H$_4$	71%
20g, R = C$_6$H$_5$CH$_2$	54%
20h, R = C$_6$H$_5$	77%
20i, R = 4-BrC$_6$H$_4$	80%
20j, R = 4-MeOC$_6$H$_4$	77%
20k, R = 2,6-Cl$_2$C$_6$H$_3$CH$_2$	97%
20l, R = H$_2$C=CHCH$_2$CH$_2$CH$_2$	42%

FIGURE 4.
Reaction of 1,2,3-triazine **18** with amidines.

FIGURE 5.
Reaction of 1,2,3-triazine **19** with amidines.
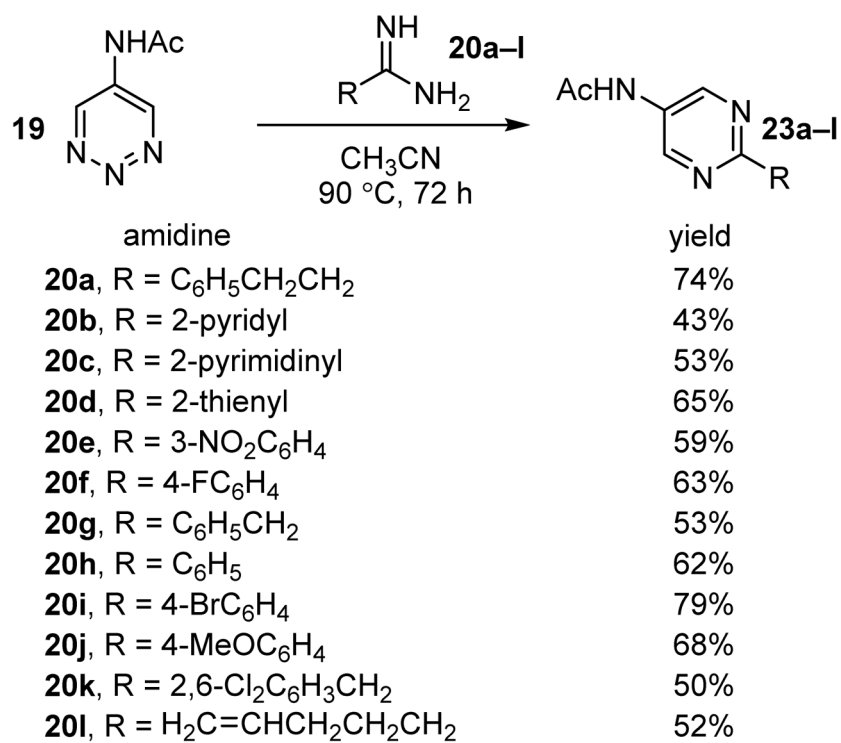
FIGURE 6.
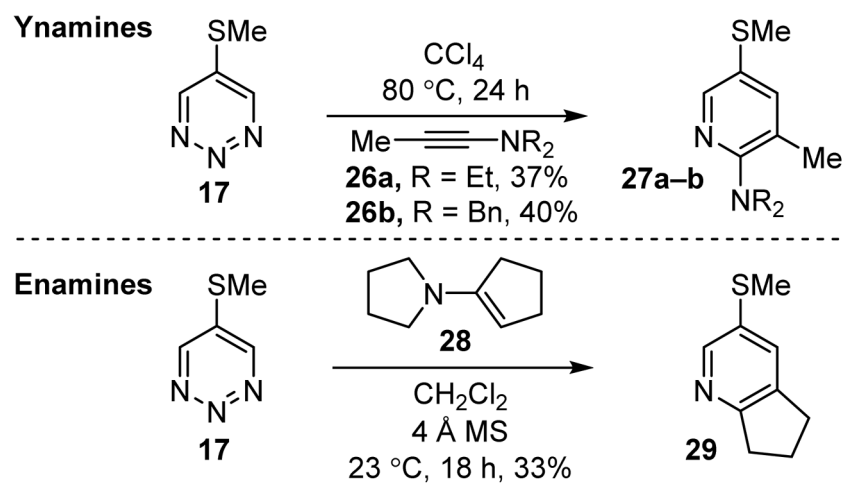Reaction of 1,2,3-triazines with ^{15}N-labeled amidines.

FIGURE 7.
Reaction of **17** with ynamines and enamines.

SCHEME 1.
Synthesis of 1,2,3-triazines **17**–**19**.