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The Synthesis, Characterization, and Rapid Cycloadditions of 5-Nitro-1,2,3-Triazine

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Abstract

The synthesis, characterization, and a study of the cycloaddition reactions of 5-nitro-1,2,3-triazine (**3**) are reported. The electron-deficient nature of **3** permits rapid cycloaddition with a variety of electron-rich dienophiles including amidines, enamines, enol ethers, ynamines, and ketene acetals in high to moderate yields. ¹H NMR studies of a representative cycloaddition reaction between **3** and an amidine revealed a remarkable reaction rate and efficiency (1 mM, <60 s, CD₃CN, 23 °C, >95%).

Graphical Abstract

The inverse electron demand Diels–Alder reaction of heterocyclic azadienes often provides an effective strategy for the preparation of highly substituted heterocyclic scaffolds of synthetic and medicinal chemistry interest.¹ Over the course of the years, we have systematically explored the cycloaddition 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 resulting in the development of cycloaddition methodology that is now widely employed.^{7–9} The facility of these cycloadditions coupled with the prevalence of heterocyclic motifs in important natural products led to our use of the reactions as the key steps in a series of natural product total syntheses, including the antitumor antibiotics streptonigrin¹⁰ and lavendamycin.¹¹

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Notes

The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: XX.

Full experimental details and ¹H NMR spectra (PDF)

Crystallographic data for 5-nitro-1,2,3-triazine (**3**) (CIF)

prodigiosin,¹² isochrysohermidin,¹³ ningalin A,¹⁴ CC-1065,¹⁵ bleomycin A2,¹⁶ and vinblastine.¹⁷ More recently, the inverse electron demand Diels–Alder reactions of such heterocyclic azadienes have become a cornerstone of modern bioorthogonal bioconjugation techniques along with click chemistry.¹⁸

Recently, our efforts have begun to define the previously unexplored rich cycloaddition chemistry available to 1,2,3-triazines (Figure 1).¹⁹ These studies have included an examination of the synthesis and reaction scope of 1,2,3-triazines bearing electron-rich and electron-deficient substituents with electronically consonant and dissonant positioning, in addition to that of the parent 1,2,3-triazine.^{19a–d} Their use as key steps in the total syntheses of P-3A,¹⁶ (–)-pyrimidoblamic acid,¹⁶ dihydrolysergic acid,^{19e} dihydrolysergol,^{19e} methoxatin,^{19f} and their heterocyclic analogues have been reported. In the course of these studies, the first general method for catalysis of the inverse electron demand Diels–Alder reaction of heterocyclic azadienes by solvent hydrogen bonding was disclosed.^{19f}

A growing though still limited number of electron-deficient 1,2,3-triazines have now been synthesized and examined, although 5-nitro-1,2,3-triazine (**3**) had yet to be prepared. Only one reference to nitrated 1,2,3-triazines was found in which the as-yet theoretical compounds were computationally examined.²⁰ Our own simple semiempirical computational studies (AM1, MNDO) of 5-nitro-1,2,3-triazine (**3**) revealed its extraordinarily low LUMO energy (–1.70 to –1.59 eV) compared to those of both the parent 1,2,3-triazine **1** and **2**, the most reactive 1,2,3-triazine disclosed to date.¹⁹ This suggested that **3**, if capable of being prepared, would be highly reactive in inverse electron demand Diels–Alder reactions (Figure 2). Additionally, Mulliken population analysis also revealed a high degree of polarization, predicting a susceptibility to C4 nucleophilic attack.

As part of an effort to expand the number of accessible monocyclic 1,2,3-triazines, and to more clearly define their stability characteristics, herein we disclose the successful synthesis of 5-nitro-1,2,3-triazine (**3**), its spectroscopic and X-ray characterization, and an initial survey of its cycloaddition reaction scope and rapid cycloaddition reaction rate.

Multi-gram scale *N*-amination of 4-nitropyrazole (**4**) was accomplished according to the procedure of Vinogradov and coworkers,²¹ which takes advantage of a borate buffer system to ensure the deprotonation of starting material in the presence of the acidic aminating reagent (Scheme 1). Recrystallization of the crude residue from water afforded the *N*-aminopyrazole **5**, which could be stored indefinitely at –30 °C without incident. Upon submission of **5** to Igeta's biphasic oxidative ring expansion conditions,²² only trace quantities of 5-nitro-1,2,3-triazine (**3**) could be observed by ¹H NMR. Although **3** was rapidly formed under the reaction conditions, its extended exposure to the reaction aqueous phase appeared to result in its consumption. After significant optimization efforts, a modified oxidative ring expansion protocol was developed, which minimized the exposure of **3** to water. This protocol, which involves shaking the biphasic reaction mixture in a separatory funnel for 3 min, followed by rapid phase separation and drying of the organic layer, was successful in providing crude residues consisting largely of the desired 1,2,3-triazine **3**. Elution of the crude material through a short plug of SiO₂ afforded an acceptable yield of pure 5-nitro-1,2,3-triazine (**3**), provided that the exposure of **3** to SiO₂ was

minimized (< 5 min). 5-Nitro-1,2,3-triazine (**3**), whose structure was characterized spectroscopically as well as in a single crystal X-ray structure determination, exists as a moisture-sensitive yellow crystalline solid that can be stored under N₂ or Ar at 4 °C for up to 100 days without observable decomposition (¹H NMR).²³

It was anticipated that **3** would react with free-based amidines with C4/N1 regioselectivity to afford the corresponding pyrimidines in high yields.¹⁹ Indeed, reaction of **3** with amidine **6f** under typical conditions (1.5 equiv **3**, CH₃CN (0.15 M), 23 °C, 5 min, 50%) afforded the corresponding pyrimidine product **7f**, albeit in moderate yield with immediate evolution of N₂ and obvious nonproductive consumption of **3**. Exploration of reaction conditions designed to exert more control over the vigorous reaction revealed that either low temperature or more dilute reaction conditions improved the conversions, with dilute conditions providing superior, near quantitative yields of the product pyrimidine in mere seconds.

With effective conditions for the cycloaddition of **3** and amidines defined, an examination of the reaction scope was conducted (Figure 3). The cycloadditions proceeded rapidly and afforded the product pyrimidines **7a–k** in excellent yields under extraordinarily mild reaction conditions (CH₃CN, 13 mM, 23 °C, < 10 min).²⁴ While the remarkable reaction rates make even relative rate comparisons challenging, there does appear to be at least a qualitative relationship where electron-rich amidines (e.g., **6g**) react most rapidly.

The remarkably rapid rate of cycloaddition between 5-nitro-1,2,3-triazine (**3**) and amidines was examined in greater detail with **6f**. As shown in Figure 4, the cycloaddition reaction proceeded in near-quantitative yield at concentrations as low as 100 μM, with a 10 μM reaction still capable of providing detectable amounts of pyrimidine product. Further qualitative study of the reaction conducted at 1 mM (CD₃CN) by ¹H NMR revealed that the reaction is nearly complete within 10 s and fully complete in ca. 60 s, a rate well beyond the acceptable range for even bioorthogonal bioconjugation reactions.¹⁸ Although it is not clear whether the reactions represent direct [4+2] cycloadditions or stepwise addition-cyclization reactions, the rates, and especially, the efficiencies of the reactions are extraordinary.

Enamines represent a second useful class of electron-rich dienophiles capable of reaction with 1,2,3-triazines to afford substituted pyridine products derived from regioselective cycloaddition across C4/N1.¹⁹ Exploration of the reaction of 5-nitro-1,2,3-triazine (**3**) with enamine **8** established the optimized reaction conditions, which were applied to a suite of representative enamine cycloadditions (Figure 5). The reactions proceed smoothly to afford the corresponding pyridines (**13–15**, **19–21**, **23**) in good to moderate yields.²⁵ It is important to note that the elevated reaction temperature and extended reaction times are unnecessary to observe the initial cycloaddition of **3** with enamines, but rather are required to promote the elimination of pyrrolidine or morpholine to afford the product pyridines. Efforts to improve the cycloaddition yields through solvent hydrogen bond catalysis^{19f} were not successful, as **3** rapidly and nonproductively reacts with protic solvents.

Additional dienophiles known to react with 1,2,3-triazines were also examined (Figure 6).¹⁹ Ketene acetals and ynamines undergo rapid reaction with **3** to afford the product pyridines

derived from regioselective cycloaddition across C4/N1.²⁶ *O*-Methyl enol ethers also undergo reaction with **3**, but only under more forcing thermal conditions.²⁵

Herein, the synthesis, characterization, and survey of the cycloaddition reactions of 5-nitro-1,2,3-triazine (**3**) are disclosed. In spite of its anticipated reactivity, **3** could be prepared, purified by chromatography, fully characterized, and stored at -40°C for several months. 1,2,3-Triazine **3** was found to participate in cycloaddition reactions with amidines, enamines, enol ethers, ynamines, and ketene acetals in high to moderate yields. The qualitative rate of the amidine cycloaddition reaction with **3** was examined and found to be extraordinarily fast and efficient, being competitive with even the tetrazine reactions used in bioorthogonal ligation reactions.¹⁸

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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23. Differential scanning calorimetric measurement (Supporting Information page S61) at 5 °C min⁻¹ indicate that 3 does not melt prior to decomposition and has an onset decomposition temperature of 66 °C. From 66–90 °C, only a small fraction of the compound's total energy is released. Peak heat flow occurs at 113 °C. Overall, 3 releases 4342 J/g of energy over the full temperature range of decomposition (66–272 °C).
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Methodology **Synthesis**

Figure 1.
Selected previous studies of 1,2,3-triazines.

Figure 2.
Computational studies.

Figure 3.
Reaction of **3** with amidines.

Figure 4. Concentration (top) and ^1H NMR studies at 1 mM and 23 $^{\circ}\text{C}$ (bottom) of the reaction of **6f** (1 equiv) and **3** (1 equiv) in CD_3CN .

Figure 5.
Reaction of **3** with enamines.

Figure 6.
Reaction of **3** with other dienophiles.

Scheme 1.
Synthesis of 5-nitro-1,2,3-triazine (**3**).