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Scope of the Inverse Electron Demand Diels-Alder Reactions of 1,2,3-Triazine

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Abstract

An examination of the scope of the inverse electron demand Diels–Alder reactions of the parent unsubstituted 1,2,3-triazine is described including the first report of its unique capabilities for participating in previously unexplored [4 + 2] cycloaddition reactions with heterodienophiles.

The inverse electron demand Diels–Alder reactions of electron-deficient heterocyclic azadienes with electron-rich dienophiles have proven useful in the total synthesis of natural products possessing highly functionalized heteroaromatic ring systems not easily accessed by conventional means.¹ Such reactions have also found widespread use in the synthesis of highly substituted heterocycles not easily accessed by other means,² in the divergent³ synthesis of screening libraries,⁴ and recently for use in bioconjugation reactions.⁵ The most widely studied of these reactions in our own efforts enlist 1,2,4,5-tetrazines,⁶ 1,2,4- or 1,3,5-triazines,^{7,8} 1,3,4-oxadiazoles,⁹ and occasionally 1,2-diazines,¹⁰ often followed by key transformations that now constitute general strategies for the preparation of five-membered¹¹ as well as six-membered heterocyclic ring systems (Figure 1). These reactions are complementary in the nature of the heterocyclic ring systems generated and exhibit a range of relative reactivities that may be predictably modulated by the heterocyclic azadiene substituents (reactivity and regioselectivity). Several studies have demonstrated the ability of selected 1,2,3-triazines to participate in inverse electron demand Diels–Alder reactions with enamine¹² and ynamine¹³ dienophiles. The studies reported to date have been derived largely from the pioneering efforts of Okatani (Sugita)¹² or Igeta and Ohsawa¹³ sometimes suggesting modest utility, and have only rarely^{12e–g,13b} focused on the parent 1,2,3-triazine (**1**)¹⁴ itself. As a result and in a continuation of our efforts to explore heterocyclic and acyclic azadiene Diels–Alder reactions and their applications,^{15–18} herein we report our examination of the scope of the inverse electron demand Diels–Alder reactions of the parent 1,2,3-triazine (**1**) including the first disclosure of its unique capabilities for participating in previously unexplored [4+2] cycloadditions with heterodienophiles.

Consistent with prior reports,¹² the reaction of **1** with enamines (CHCl₃, 60 °C) proved more limited than the analogous reactions of 1,2,4- or 1,3,5-triazines, providing modest yields of the expected pyridine product (equation 1). Products derived from liberated pyrrolidine

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Supporting Information Available. Full experimental details, compound characterizations, and Spectra are provided. This material is available free of charge via the internet at <http://pubs.acs.org>.

addition to the starting 1,2,3-triazine were detected that reflect a slow [4+2] cycloaddition versus aromatization and that may account in part for the modest conversions.

(1)

Similarly, the reaction of **1** with ynamines proceeded well as reported,¹³ but required warming the reaction mixtures at 60 °C (CHCl_3 , 3–12 h) for complete reaction (equation 2). Other dienophiles examined, including ketene acetals ($(\text{EtO})_2\text{C}=\text{CH}_2$, xylene, 140 °C, 24 h), ethoxy-acetylene (dioxane, 100 °C, 24 h), phenylacetylene (dioxane, 100 °C, 24 h), and enol ethers ($\text{Ph}(\text{OMe})\text{C}=\text{CH}_2$ and $\text{Ph}(\text{OTMS})\text{C}=\text{CH}_2$, dioxane, 100 °C, 24 h), failed to react with **1** under the conditions examined.

(2)

More interesting was the reactivity of **1** toward heterodienophiles. Amidines, imidates and related reagents react with heteroaromatic azadienes by a reaction course that is often dependent on the nature of the diene, dienophile, and reaction conditions. Such reagents have been shown to react as either $\text{C}=\text{N}$ or their isomeric N,N - or N,O -ketene acetal dienophiles depending on the heterocyclic azadiene and reaction conditions (equation 3).

(3)

Typically it is not a mixed behavior, but reactions that are characterized as cleanly proceeding through a single pathway. Given the modest reactivity of **1** and like the behavior of 1,3,5-triazines^{8c} versus 1,2,4,5-tetrazines,^{6a} we anticipated that **1** would be a superb candidate for reaction with such reagents through their more reactive, in situ generated N,N -

or N,O-ketene acetal. Remarkably and like 1,2,4,5-tetrazines,^{6a} both aliphatic amidine **6a** and imidate **6b** underwent clean, rapid [4+2] cycloaddition with **1** as C=N dienophiles to provide the pyrimidine **7a** in superb conversions with no evidence of reaction through their in situ generated and more reactive 1,1-diaminoethylene or 1-amino-1-ethoxyethylene tautomers (equation 4). The reaction of **1** with amidine **6a** (CH₃CN, 25 °C, 5 min, 93%) was extraordinarily fast, proceeding in minutes at room temperature, whereas the less reactive imidate **6b** required higher reaction temperatures and longer reaction times (CH₃CN, 80 °C, 24 h, 64%). Although complete conversion to the pyrimidine product required higher reaction temperatures, most remarkable of the initial observations was that **1** reacts with the aliphatic amidine **6a** even at -30 °C in minutes with an instantaneous evolution of N₂ and distinct color change indicative of a remarkably facile [4+2] cycloaddition.

(4)

Similarly, the aryl amidines **6c–6k** as well as the additional aliphatic amidine **6l** provided the corresponding pyrimidines **7c–7l** (90–99%) in superb conversions in reactions where the disappearance of **1** occurs at room temperature (1–10 min) and precedes completion of the reaction, indicating that aromatization with loss of ammonia versus [4+2] cycloaddition is the slow step in the overall reaction sequence (Scheme 1). The reactions were completely regioselective with regard to both the amidine/imidate, providing only the pyrimidine product with no trace of the corresponding pyrazine (1,2-diazine), as well as the 1,2,3-triazine, providing no trace of the 1,2,4-triazine product consistent with cycloaddition only across C4/N1 versus C5/N2. In each case, it was essential to use the amidine or imidate free base rather than their HCl salts, which provided less reproducible and lower yields.

Extensions of these studies to the examination of the impact of key heterocyclic azadiene substituents on the reactivity and regioselectivity of the inverse electron demand Diels–Alder reactions of 1,2,3-triazines is in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Diels–Alder reactions of select heterocyclic azadienes.

6c , R = C ₆ H ₅	dioxane, 25 °C, 6 h	7c , 91%
6d , R = 2-Pyr	dioxane, 60 °C, 2 h	7d , 98%
6e , R = 4-MeOC ₆ H ₄	dioxane, 60 °C, 2 h	7e , 93%
6f , R = 4-BrC ₆ H ₄	CH ₃ CN, 60 °C, 4 h	7f , 99%
6g , R = 4-FC ₆ H ₄	CH ₃ CN, 60 °C, 2 h	7g , 99%
6h , R = 3-NO ₂ C ₆ H ₄	CH ₃ CN, 60 °C, 5 h	7h , 99%
6i , R = 2,6-Cl ₂ C ₆ H ₄ CH ₂	CH ₃ CN, 60 °C, 2 h	7i , 90%
6j , R = 2-pyrimidinyl	CH ₃ CN, 60 °C, 5 h	7j , 99%
6k , R = 2-thienyl	CH ₃ CN, 60 °C, 2 h	7k , 95%
6l , R = cyclopropyl	CH ₃ CN, 60 °C, 1 h	7l , 95%

Scheme 1.