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Direct Synthesis of β -Aminoenals through Reaction of 1,2,3-Triazine with Secondary Amines

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Abstract

Simple and direct nucleophilic addition of secondary amines, including imidazole, to 1,2,3-triazine under mild reaction conditions (THF, 25–65 °C, 12–48 h), requiring no additives, cleanly provides β -aminoenals **4** in good yields (21 examples, 31–79%). The reaction proceeds by amine nucleophilic addition to C4 of the 1,2,3-triazine, in situ loss of N₂, and subsequent imine hydrolysis to provide **4**.

Graphical abstract

The inverse electron demand Diels–Alder reaction of electron-deficient heterocyclic azadienes has been employed as powerful methodology for the synthesis of complex heterocyclic targets.¹ Extensive efforts have now detailed the wide range of cycloaddition reactions and applications 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 These reactions have been, and continue to be, inspired by their synthetic applications, enabling concise routes to challenging target molecules with the rapid construction of highly substituted or functionalized heterocyclic cores.^{7–10} Recent applications of 1,2,4,5-tetrazines in bioorthogonal reactions have capitalized on their unusually rapid and efficient cycloaddition reactions with select dienophiles.¹¹

We recently described a series of such studies on 1,2,3-triazines, an untapped class of heterocyclic azadienes, exploring their synthesis, defining the scope of their cycloaddition reactions with various classes of dienophiles, and illustrating pronounced substituent electronic effects on their reactivity, regioselectivity, or mode of cycloaddition.¹² The exploration and development of the 1,2,3-triazine cycloaddition reactions was inspired by

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We dedicate this article to Professor A. Padwa (Emory University) on the occasion of his 80th birthday.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publication website at DOI: 10.1021/acs.orglett.xxxxxxx. Full experimental details, ¹H and ¹³C NMR spectra, and the CIF file for the X-ray structure determination are provided (PDF).

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their projected use in the total syntheses of natural products that now include dihydrolysergic acid,¹³ pyrimidoblamic acid,¹⁴ P-3A,¹⁴ and methoxatin.¹⁵

In the course of our studies, the susceptibility of the more reactive 1,2,3-triazines toward nucleophiles was noted. Much like studies of the heterocycle itself, prior investigations on the addition of nucleophiles to 1,2,3-triazine (**1**) are limited. The C4 addition of methoxide has been reported, addition of Grignard reagents at C4 (PhMgBr) or C5 (MeMgI) has been disclosed, and the reaction of a lithium reagent (PhLi) at C4 has been described.¹⁶ C4 and C6 disubstitution (methyl) on 1,2,3-triazine has been reported to redirect the addition of a nucleophile to C5 and, remarkably, N2 as well.¹⁶ Like the work detailed herein, C4 addition in these studies has been reported to proceed with in situ loss of nitrogen (N₂) and hydrolysis of the resulting imine, providing the corresponding α,β -unsaturated aldehyde.

As part of our continuing interest in heterocyclic azadienes, we elected to investigate this underexplored reactivity of 1,2,3-triazines. In our studies on the cycloaddition of 1,2,3-triazine with pyrrolidine enamines, we occasionally observed that the pyrrolidine liberated in the aromatization step consumed the starting triazine. Thus, secondary amines were chosen as a representative class of nucleophiles with which to examine this reactivity with the parent 1,2,3-triazine (**1**). Herein, we describe studies on this intrinsic electrophilic reactivity of 1,2,3-triazine and its effective use in reactions with secondary amines, providing β -aminoenals **4** (β -enaminals, Figure 1). Formally, the reagent 1,2,3-triazine (**1**) behaves in such reactions as an equivalent of **2** or as a stable alternative the unmanageable malondialdehyde (**3**) in reactions toward secondary amines.

Nucleophilic addition of secondary amines to 1,2,3-triazine was found to proceed under mild, easily reproducible reaction conditions. In initial surveys of the reaction, it was found to be relatively insensitive to the choice of non-protic solvent and proceeded at room temperature without the need of additives, such as a base. Only addition at C4 was observed, and was followed by in situ loss of nitrogen (N₂) without detection (MS, ¹H NMR) of an intermediate dihydro-1,2,3-triazine. The intermediate imine was observable by mass spectrometry (MS) of the reaction mixture, with hydrolysis to the corresponding aldehyde also observable (MS) over time by using “wet” THF as the reaction solvent. However, the initial dihydro adduct was not observed, nor was competitive addition at C5 (MS, ¹H NMR). Interestingly, a second condensation of excess amine onto the product was also detected (MS), and it is conceivable that further manipulation at this step, such as reductive amination, can provide a route to additional products.

As shown in Figure 2, **1** reacts with a variety of secondary amines to provide **4** in good yields. Although some amines required elevated temperatures (65 °C) to drive the reaction to completion, final yields were seemingly not impacted. The reactions were halted once full consumption of **1** was observed by ¹H NMR, with isolation of the product achieved simply by direct chromatographic purification of the concentrated reaction mixture. Although the reactions detailed in Figure 2 were conducted in reagent grade (not anhydrous) THF under otherwise anhydrous conditions, the reaction of **1** with pyrrolidine under a range of THF–H₂O conditions provided **4m** in comparable or even higher yields [THF (53%), 1% H₂O–THF (87%), 5% H₂O–THF (85%), 10% H₂O–THF (80%), 50% H₂O–THF (59%)]. This

indicates that the presence of water does not impede the reaction, does not competitively consume starting 1,2,3-triazine or the product β -aminoenal, and may be used to facilitate hydrolysis the product imine under the reaction conditions and further improve the conversions. Notably, imidazole (THF, 65 °C, 48 h) participated effectively in this reaction. Less nucleophilic secondary arylamines (secondary anilines) failed to effectively participate in the reaction and a primary amine preferentially produced the di-addition product **5**, resulting from amine addition to two molecules of 1,2,3-triazine (eq 1). Finally, no evidence of the participation of the product β -aminoenals **4** in subsequent cycloaddition reactions with **1** was detected under the reaction conditions.

(1)

The reactions proceed cleanly, exclusively generating the *trans* β -aminoenals. The products from symmetrical secondary amines, highlighted in Figure 2, display distinguishable signals for the amine C _{α} protons indicative of restricted rotation on an NMR time scale due to amine conjugation with the enal. The products generated from addition of unsymmetrical secondary amines also display distinguishable rotameric ¹H NMR signals (1–3:1), including the aldehyde signal itself. Although prior disclosures^{18–20} of such β -aminoenals have characterized them as inseparable *cis/trans* isomers because of this doubling of the ¹H NMR signals, variable temperature ¹H NMR (25–45 °C) revealed smooth coalescence of the rotameric, not geometrically isomeric, resonances (Figure 3a). A single crystal X-ray structure of the DNP hydrazone (isolated as the HSO₄[–] salt) of the aldehyde derived from the reaction of dibenzylamine with **1** confirmed the structure (**4h**) and *trans* olefin configuration (Figure 3b).¹⁷

The C4 versus C5 preference for the site of secondary amine nucleophilic attack, like that established for heterocycles in general, can be rationalized as arising from the preferential delocalization of the resulting anion onto two (vs one) ring nitrogens. This site (C4) also constitutes the most electron-deficient center of the reacting molecular orbital (LUMO) of **1** but it is not the center that bears the largest LUMO molecular orbital coefficient.¹⁶

A general, effective, and simple synthesis of β -aminoenals was detailed based on the nucleophilic addition of secondary amines to 1,2,3-triazine (**1**) that complements the existing methods based on the condensation with malondialdehyde or its equivalents (1,1,3,3-tetramethoxypropane),¹⁸ hydroamination of propargylic aldehyde,¹⁹ or dehydrogenative amination of acrolein.²⁰ It is likely this general electrophilic character of 1,2,3-triazine and its ability to serve as a convenient equivalent of **2** may be extended to other classes of nucleophiles and such studies are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 2.
1,2,3-triazine reaction with secondary amines.

(a)

(b)

Figure 3.

(a) VT ^1H NMR (DMSO- d_6) of **4u** showing the coalescence of aldehyde rotomer peaks with increasing temperature. (b) X-ray crystal structure of DNP-hydrazone derived from **4h**, isolated as the HSO_4^- salt, showing the *trans* olefin configuration.