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1,2,4-TRIAZINE PREPARATION VIA THERMAL CYCLOADDITION OF DIMETHYL 1,2,4,5-TETRAZINE-3,6-DICARBOXYLATE WITH ARYL THIOIMIDATES

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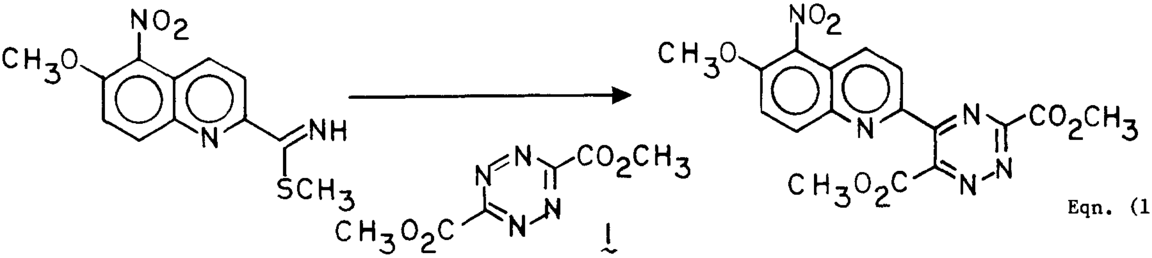
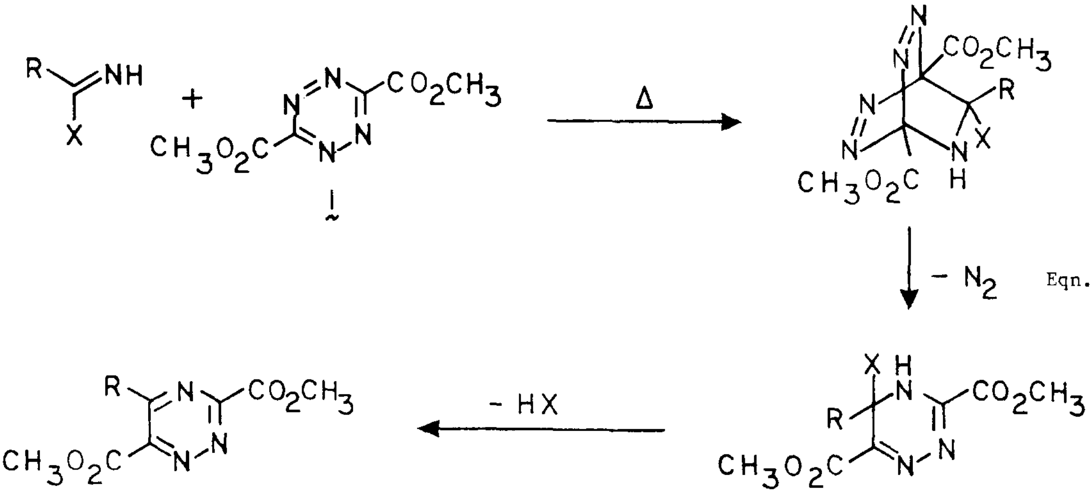
Summary: A short approach to 1,2,4-triazine preparation based on the inverse electron demand Diels-Alder reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with aryl thioimidates is described.

In a preceding communication[2] we described an effective, formal total synthesis of streptonigrin,[3] an antitumor antibiotic isolated from cultures of Streptomyces flocculus, based on the sequential implementation of two azadiene inverse electron demand Diels-Alder reactions.[4] The first of these being the thermal cycloaddition of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (1)[5] with a S-methyl thioimidate for the preparation of a 1,2,4-triazine used in the construction of the streptonigrin ABC ring system, equation 1.



Eqn. (1)

Investigations on the cycloaddition reaction of substituted 1,2,4,5-tetrazines with heterodienophiles have been reported[6] and short accounts of their reaction with imidates[7a] and amidines[7b] illustrated the application and potential of this approach for the preparation of 1,2,4-triazines. However, each study has been characterized typically by low yields, complex product mixtures, limited scope and, in some instances, surprising reaction products.[7, 8, 9] In addition, the reactivity of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (1) precludes its successful use in many cycloaddition reactions.[9] In the course of



1

Eqn. (2)

investigations of the scope of the cycloaddition reactions of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (1) with heterodienophiles possessing a carbon-nitrogen double bond that could lead to 1,2,4-triazine products we have found that the success of the reaction is sensitive to the nucleophilic character of the dienophile and the leaving group ability of X, equation 2. Table I summarizes typical results of this investigation.

Initial efforts employing aryl nitriles and aryl amidines were unsuccessful. 2-Cyanopyridine (2) failed to react with tetrazine 1 and no identifiable products could be isolated from the reaction of 1 with aryl amidines 3c and 3d under a range of reaction conditions. Aryl imidates 3b, 5b, and 7b were found to react in the desired fashion with 1 to afford the 1,2,4-triazine products 4, 6, and 8, albeit in modest yields. In sharp contrast, dependable results were obtained employing aryl S-methyl thioimidates. The cycloaddition reactions of 3a, 5a, 7a, 9 and 11 with 1 take place under mild conditions (45-90°C) in a controllable manner. In no instance was there evidence of the product triazine 4, 6, 8, 10, or 12 participating, or competing with 1, in a subsequent Diels-Alder reaction with unreacted thioimidate. The success of the cycloaddition reaction of aryl S-methyl thioimidates with 1 can be attributed to the optimal combination of nucleophilic character of the carbon-nitrogen double bond and the leaving group ability of X (equation 2, $X = SCH_3$).

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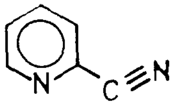
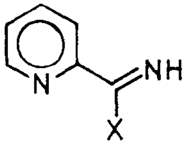
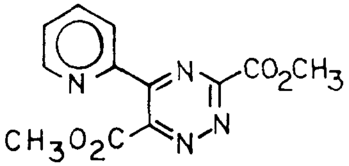
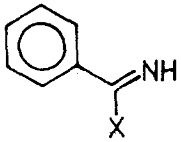
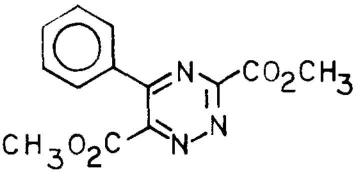
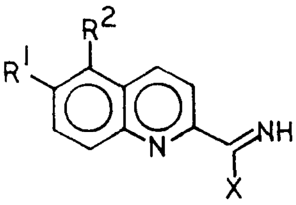
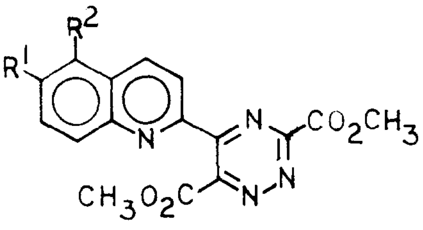
Table I. Diels-Alder Reaction of Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (1) with Heterodienophiles.

	Substrate	Conditions[a] Solvent, Temp. C (Time h)	Product[b]	% Yield
2		dioxane, 80-100 (15-42) o-$Cl_2C_6H_4$, 150 (10)		---[c]
				
3a	X = SCH_3	dioxane, 80 (20)	4	68%
3b	X = OEt	dioxane, 80 (8-12)		37%
3c	X = NH_2	dioxane, 25 (5)		---[d]
3d	X = NEt_2	dioxane, 25-50 (25)		---[d]
				
5a	X = SCH_3	dioxane, 80 (24)	6	64%
5b	X = OEt	dioxane, 60 (10)		27%[7a]
5c	X = NH_2	-----------		0%[7b]
				
7a	$R^1=R^2=H$ X = SCH_3	dioxane, 80 (4)	8 $R^1=R^2=H$	70%
7b	$R^1=R^2=H$ X = OEt	dioxane, 80 (20)	8	33%
9	$R^1=OCH_3$, $R^2=H$ X = SCH_3	dioxane, 80 (4)	10 $R^1=OCH_3$, $R^2=H$	78%
11	$R^1=OCH_3$, $R^2=NO_2$ X = SCH_3	dioxane, 80 (20-24)	12 $R^1=OCH_3$, $R^2=NO_2$	72%

[a] Each reaction was run under nitrogen in the presence of 2.0 equivalents of 1. [b] Yield of purified product isolated by column chromatography (SiO_2). All products exhibited the reported or expected ^{1}H-NMR, IR, and mass spectral characteristics consistent with the assigned structure. All new compounds gave satisfactory C,H,N analysis (±0.40%) or high resolution mass spectral information. [c] No detectable reaction. [d] Rapid exothermic reaction accompanied by the evolution of nitrogen, no detectable 1,2,4-triazine product.

References and Notes.

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3. For a recent review on streptonigrin, see: (a) Gould, S. J.; Weinreb, S. M. *Fortschr. Chem. Org. Natur.*, **1982**, *41*, 77. For completed total syntheses, see: (b) Kende, A. S.; Lorah, D. P.; Boatman, R. J. *J. Am. Chem. Soc.*, **1981**, *103*, 1271; (c) Basha, F. Z.; Hibino, S.; Kim, D.; Pye, W. E.; Wu, T.-T.; Weinreb, S. M. *J. Am. Chem. Soc.*, **1980**, *102*, 3962; Weinreb, S. M.; Basha, F. Z.; Hibino, S.; Khatri, N. A.; Kim, D.; Pye, W. E.; Wu, T.-T. *J. Am. Chem. Soc.*, **1982**, *104*, 536. For related work, see: (d) Martin, J. C. *J. Org. Chem.*, **1982**, *47*, 3761.
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8. For instance: alkyl imidates, amidines and ketone N,N-dimethylhydrazones react with 1,2,4,5-tetrazines through their isomerized N,O-ketene acetal, N,N-ketene acetal and enamine tautomers respectively; see references 7a-c and Seitz, G.; Overheu, W. *Arch. Pharm.*, **1977**, *310*, 936.
9. For instance, aryl amidines react with aryl substituted 1,2,4,5-tetrazines to afford mixtures of 1,2,4- and 1,3,5-triazines yet little or no triazine product was observed upon reaction with 3; see reference 7b.

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