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Dienophilicity of Imidazole in Inverse Electron Demand Diels-Alder Reactions; Intramolecular Reactions with 1,2,4-Triazines.

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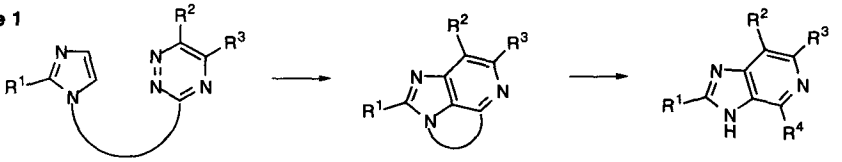
Abstract: Imidazole and 2-phenylimidazole undergo intramolecular cycloadditions with 1,2,4-triazines tethered between an imidazole nitrogen and the triazinyl C3 position with a trimethylene chain to produce tetrahydro-1,5-naphthyridines following loss of N_2 and a nitrile.

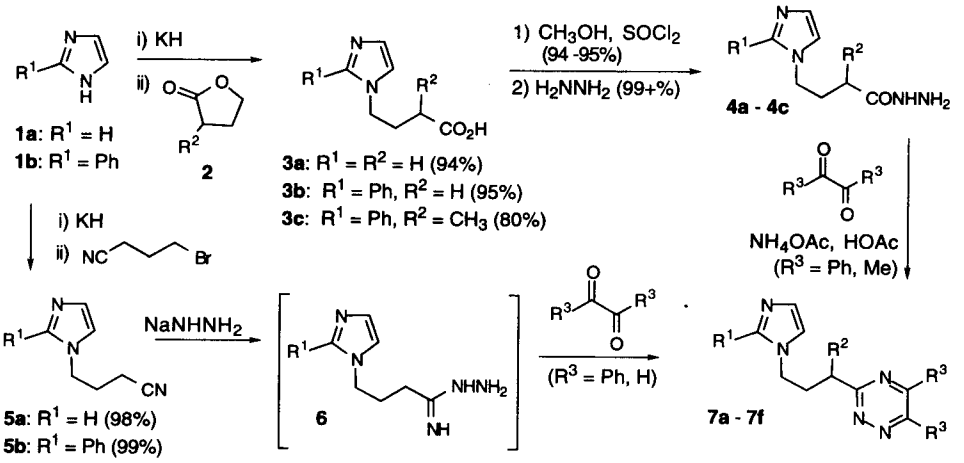
In the previous communication,[1] preliminary results with intermolecular inverse electron demand Diels-Alder reactions of imidazoles with 1,2,4-triazines were presented. Cycloadditions of protected 2-aminoimidazole with alkyl 1,2,4-triazine-3-carboxylates yielded a product mixture consisting primarily of 1*H*-imidazo[3,4-d]-pyridines and 3*H*-pyrido[2,3-d]pyrimid-4-ones. Increasing the reaction temperature favored the production of the pyrido[2,3-d]pyrimid-4-ones at the expense of the imidazopyridines. Since imidazole itself, as well as 2-phenylimidazole, were unreactive in this intermolecular chemistry, we sought to extend the cycloaddition chemistry of imidazoles to these less electron-rich dienophiles using an intramolecular strategy.[2] We had envisioned that such chemistry would lead to the 1*H*-imidazo[4,5-c]pyridine skeleton, a 3-deazapurine system of considerable biological interest (Scheme 1).[3]

Scheme 1



In work parallel to our previous studies with indole[4] and pyrrole,[5] the intramolecular cycloadditions of imidazoles with tethered 1,2,4-triazines were examined. As with these earlier experiments, the tethered triazines were initially prepared by two routes: via acyl hydrazides **4** or amidrazones **6**, depending upon the identity of R^2 and R^3 (Scheme 2). Carboxylic acids **3a** - **3c** were obtained by treating **1a** and **1b** with KH, followed by addition of the appropriate γ–butyrolactones **2** (R^2 = H, CH_3).[4-6] Esterfication ($SOCl_2$/MeOH, ≥94%) followed by treatment with hydrazine in ethanol gave "crude" acylhydrazides **4a** - **4c** in nearly pure form (99+%). As previously reported, heating the relatively unstable acylhydrazides without further purification, with the 1,2-dicarbonyl compound (R^3 = Ph, Me) in HOAc/NH_4OAc produced the triazines **7a** - **7c** in modest to excellent yields (Table 1). This acylhydrazide route, though convenient, did not work for all triazines (R^3 = H, for example), and gave a poor yield of tethered triazine **7d** (30%). Thus, the alternative amidrazone route was also pursued.

Scheme 2



In an improvement over our previous preparations of similar amidrazone-precursor nitriles which relied upon amide dehydration,[4,5] deprotonation of **1a** and **1b** with NaH, then addition of commercially available 4-bromobutyronitrile in DMF produced **5a** and **5b** in 98% and 99% yields, respectively. Subsequent treatment with sodium hydrazide generated amidrazones **6** which were immediately treated with the desired 1,2-dicarbonyl compounds (R^3 = H, Ph) to produce tethered triazines **7** (Table 1). For unsubstituted trimethylene tethers (**7**, R^2 = H) this is now the preferred route due to its simplicity.

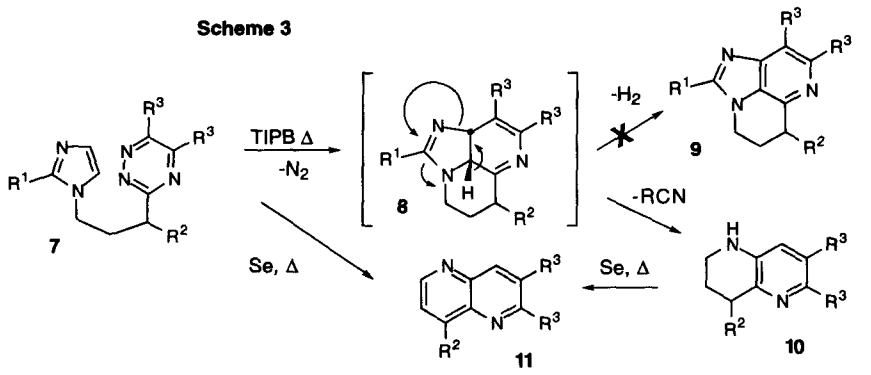
Table 1. Preparation and Cycloadditions of Tethered Triazines **7**.

Item	7	R^1	R^2	R^3	From: %	Cycloaddition Conditions	10%; 11 %	Cycloadducts
1	**7a**	H	H	Ph	**4a**: 76%	TIPB ↑↓, 7.5 h	**10a**: 65%; **11a**: 10%	75%
2	**7b**	Ph	H	Ph	**4b**: 91%	TIPB ↑↓, 9 h	**10a**: 57%; **11a**: 38%	95%
3	"	"	"	"	**5b**: 95%	TIPB ↑↓, BHT (1 eq), 3 h	**10a**: 92%; **11a**: trace	92%
4	"	"	"	"	-	Se melt, 320-340 °C, 10 h	**11a**: 58%	58%
5	**7c**	Ph	Me	Ph	**4c**: 83%	TIPB ↑↓, 48 h	**11c**: 70%; **11a**: 27%	97%
6	**7d**	H	H	Me	**4a**: 30%	TIPB ↑↓, 24 h	**10d**: 52%; **11d**: 25%	77%
7	**7e**	Ph	H	Me	**4b**: 80%	TIPB ↑↓, 7 h	**10d**: 60%; **11d**: 25%	85%
8	**7f**	Ph	H	H	**5b**: 96%	TIPB ↑↓, 42 h	**10f**: 34%; **11f**: 23%	57%

Cycloadditions of the tethered triazines were accomplished by heating in 1,3,5-triisopropylbenzene (TIPB), which gave the tetrahydro-1,5-naphthyridines **10** with lesser amounts of the fully aromatized 1,5-naphthyridines **11**, and not the anticipated tetrahydroimidazo[4,5,1-*de*][1,5]naphthyridines **9** (Scheme 3, Table 1). Presumably the cycloaddition with subsequent loss of nitrogen gives intermediate **8**, then elimination of the nitrile provides **10**, with subsequent aromatization producing **11**. Addition of the antioxidant BHT (1 eq) inhibited aromatization to greatly improve the yield of tetrahydronaphthyridine **10** in the sole example attempted

to-date (92% yield of **10a** compared 57% yield without BHT, Table 1, Items 3 and 2). Cycloaddition of **7c** with the methylated tether, by refluxing in TIPB for 48 h produced aromatized **11c** (70%) with minor, yet significant amounts (27%) of demethylated **11a**. In general, the combined yields of isolable cycloadducts **10** and **11** were excellent.

Scheme 3



Release of RCN has been observed in numerous other inverse electron demand Diels-Alder reactions[7] though in these cases the nitrile elimination proceeds from a bridged system, not fused as observed here. In an attempt to aromatize prior to loss of RCN, **7b** was treated to the classic selenium melt procedure.[8] However, only the fully aromatized 1,5-naphthyridine **11a** was produced. In another attempt to effect the aromatization prior to nitrile loss, sulfur was added to the reaction medium (refluxing TIPB),[9,10] but with no effect on the reaction outcome. Dehydrogenation of **10a** by refluxing in TIPB without protection from oxygen (48 hr, 91%), or heating with selenium (320 - 340 °C, 8 hr, 85%) produced **11a**.

Attention has recently been paid to 1,5-naphthyridine derivatives which have been shown to be potent, relatively nontoxic antimalarials[11] and angiotensin antagonists.[12] As core subunits of these derivatives, 1,5-naphthyridines have almost exclusively been made from 3-aminopyridines,[13] a route which limits substitution patterns on the product naphthyridines due to the difficulty in preparing various substituted 3-aminopyridines.[14] This new, intramolecular inverse electron demand cycloaddition methodology should enable a wider range of substituted 1,5-naphthyridines to become available.

In summary, imidazole and 2-substituted imidazoles have proven to be good dienophiles in intramolecular inverse electron demand Diels-Alder reactions with 1,2,4-triazines, though the intermolecular cycloaddition chemistry appears to be limited to the more electron-rich imidazoles such as protected 2-aminoimidazole. Intramolecular reactions with tethered 1,2,4-triazines proceeded with the loss of N_2 and a nitrile to give 1,2,3,4-tetrahydro-1,5-naphthyridines and the aromatized 1,5-naphthyridines. We are continuing to explore the scope of this chemistry in order to prepare deazapurine analogues, probing applications to other imidazole akaloids, and also examining other tethers for the intramolecular reaction. Specifically, we are investigating tethers which may be lost in the aromatization step prior to losing RCN so that the imidazo[3,4-c]pyridine will be obtained.[15]

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