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

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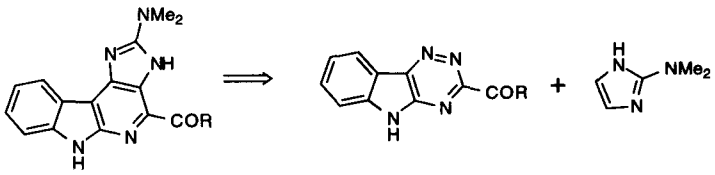
Abstract: Intermolecular cycloadditions between trialkyl 1,2,4-triazine-4,5,6-tricarboxylates and protected 2-aminoimidazole gave 1*H*-imidazo[4,5-c]pyridines (3-deazapurines) and the rearranged 3*H*-pyrido[3,2-d]pyrimid-4-ones (8-deazapteridines). No cycloadditions were observed with imidazole and 2-phenylimidazole. © 1997 Elsevier Science Ltd.

The ability of electron rich heterocycles with latent enamine functionalities to participate in inverse electron demand Diels-Alder reactions with electron deficient dienes has been the focus of research for some time.[1] A prominent example is the chemistry of indole in reactions with electron deficient heteroaromatic azadienes which has been probed by several groups.[2] Recently, we have become interested in utilizing imidazole as a dienophile in such reactions with 1,2,4-triazines as a potential means to prepare 3-deazapurines[3] and alkaloids bearing similar subunits such as the grossularines.[4] Such chemistry evokes a conceptually simple route to these marine natural products (Scheme 1). The reactivity of imidazole in cycloaddition chemistry, however, has not been reported to a great extent in the literature. Seitz has reported the reaction of imidazole and derivatives with 1,2,4,5-tetrazines to give imidazo[4,5-d]pyridazines in modest yields, among other products,[5] while more recently Horne has demonstrated the condensation of 2-aminoimidazole with aldehydes by a concerted cycloaddition route to give tetrahydropurine analogues.[6] Since there are no reports, to the best of our knowledge, concerning the dienophilicity of imidazoles with 1,2,4-triazines, we began by exploring this basic chemistry, and now report our preliminary results in this and the following communication.

Scheme 1



Grossularine-1: R = *p*-hydroxyphenyl
Grossularine-2: R = 3-indolyl

Initially the reactivity of imidazole [**1a**], 2-phenylimidazole [**1b**] and 2-aminoimidazole [**1c**] with triethyl 1,2,4-triazine-3,4,6-tricarboxylate [**2a**],[7] one of the best triazine-based azadienes for inverse electron demand Diels-Alder reactions,[1c,8] was probed. However, no cycloadducts were observed from the numerous reactions attempted; **1a** and **1b** proved too unreactive while **1c** gave only an intractable mess when stirred with **2a** at or below room temperature. Protection of **1c** as the aminoimine **1d**,[9] and subsequent reaction of **1d** with triazine **2a** (1.2 eq) produced a mixture of the anticipated [4+2]-cycloadduct, imidazo[4,5-c]pyridine **3a**, and the

rearranged[10] pyridopyrimidones **4a** and **5a**,[11] one of which was produced in only trace amounts (Scheme 2); all three compounds were separable by flash chromatography. In order to distinguish pyrido[3,2-d]pyrimid-4-one **4a** and pyrido[4,3-d]pyrimid-4-one **5a**, regioisomeric rearrangement products of common cycloadduct intermediate **A**, 5,6-dimethyl-3-ethyl 1,2,4-triazine-3,5,6-tricarboxylate **2b** was prepared[12] and reacted with **1d**, producing **3b** along with the dominant rearrangement product **4b** and trace amounts of **5b**. The **3b**:**4b** ratio was strikingly dependent upon the temperature (Table 1). Thus, increasing the reaction temperature led to increasing amounts of the pyrido[3,2-d]pyrimidone **4b** at the expense of **3b**. Running the reaction under ambient atmosphere or under argon had no impact upon the outcome.

Scheme 2

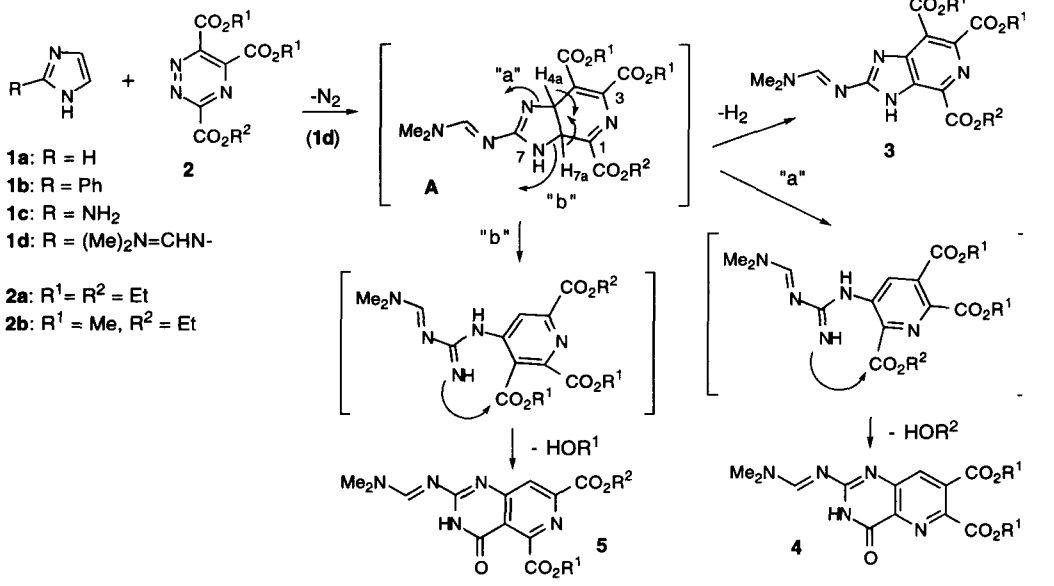


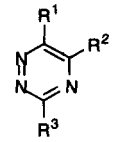
Table 1. Cycloadditions of 1d + 2b

Conditions	3:4:5	Yield[a]
THF, rt, 60 h	1:1.7:trace	87%
dioxane, rt, 60 h	1:1.1:trace	90%
CH_2Cl_2, rt, 60 h	1:2.4:trace	85%
THF ↑↓, 10 h	1:4.1:trace	89%
dioxane ↑↓, 5 h	1:6.2:trace	90%

a) Combined yield: **3** + **4** + **5**

Similar chemistry was observed using the less electron deficient triazines ethyl 5,6-diphenyl-1,2,4-triazine-3-carboxylate [**2c**][13] and ethyl 5-phenyl-1,2,4-triazine-3-carboxylate [**2d**][14] (Scheme 3), though in both cases heating a mixture of the reactants in the absence of solvent to 120-125 °C was required to effect the reactions. Moreover, the yields of cycloadducts were considerably lower than those obtained with **2b**: 44% combined yield of cycloadducts with **2c** (**3c** plus **4c**, 1:2.5), and 40% combined yield with **2d** (**3d** plus **4d**, 3:2). Thus, replacing the electron-withdrawing ester substituents at C5 and C6 of the triazine ring with phenyl rings greatly reduced the reactivity. No reactions occurred between **1d** and ethyl 1,2,4-triazine-3-carboxylate **2e**, nor between **1d** and the methyl triazinyl thioether **2f**. Removal of the aminoimine

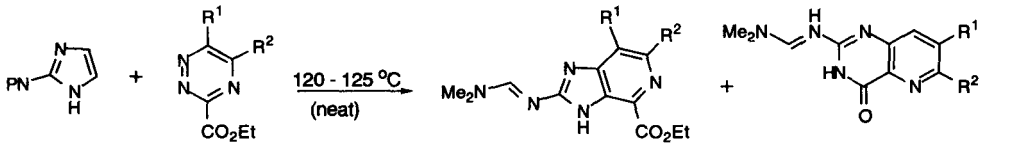
protecting group from **4c** to produce the corresponding primary amine was achieved in near quantiative yield by heating in 50% aqueous DMSO.



2e: $R^1 = R^2 = H$, $R^3 = CO_2Et$
2f: $R^1 = R^2 = CO_2Et$, $R^3 = SMe$

In summary, protected 2-aminoimidazole **1d** has proven to be a good dienophile in intermolecular inverse electron demand Diels-Alder reactions with the highly electron deficient 1,2,4-triazine **2a**, though this intermolecular chemistry appears to be limited to the more electron-rich imidazoles such as **1d**. Comparison of the ratio of imidazo[4,5-c]pyridines **3** to pyrido[3,2-d]pyrimid-4-ones **4** as products from the reactions of **1d** with **2b**, **2c**, and **2d** suggests that increasing acidity of H7a (as influenced by the triazine C6 substituent) of intermediate **A** (Scheme 2) increases the

Scheme 3



1d

2c: $R^1 = R^2 = Ph$
2d: $R^1 = H$, $R^2 = Ph$

3c: $R^1 = R^2 = Ph$ (13%)
3d: $R^1 = H$, $R^2 = Ph$ (24%)

4c: $R^1 = R^2 = Ph$ (31%)
4d: $R^1 = H$, $R^2 = Ph$ (16%)

amount of rearranged **4**. This would also account for the greater amount of **4** in comparison to only trace amounts of **5** observed in the reactions with **2a** and **2b**; H7a would be more acidic than H4a since the conjugate base has a resonance form with the negative charge on N2.[15] Adding 2 equivalents of 2,6-lutidine to the reaction of **1d** with **2c**, however, did not affect the **3c**:**4c** ratio. The good yield of **4b** (77%) in the reaction of **1d** with **2b** at higher temperature (101 °C, refluxing dioxane) suggests a very expedient route to the 8-deazapteridine skeleton.[16] We are attempting to adapt this chemistry to the synthesis of the grossularines, and as reported in the following paper, we are examining the intramolecular cycloadditions of imidazoles and 1,2,4-triazines.

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