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5-Aminopyrazoles as Dienophiles in the Inverse Electron Demand Diels−Alder Reactions of 2,4,6-Tris(ethoxycarbonyl)-1,3,5-triazine: Syntheses of Pyrazolopyrimidines†

Qun Dang,* Brian S. Brown, and Mark D. Erion

Department of Medicinal Chemistry, Gensia, Inc.,
9360 Towne Centre Drive, San Diego, California 92121

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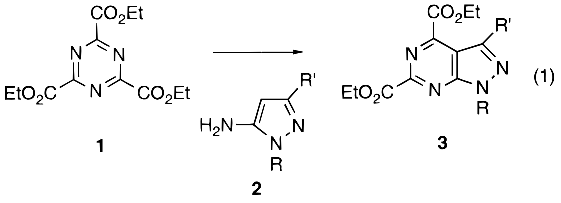
Recently, the development of the inverse electron demand Diels−Alder reactions of 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine (**1**) has led to the total syntheses of bleomycin A_2, P-3A,[1] and the syntheses of many other bleomycin-related agents.[2] It has been shown that triazine (**1**) undergoes [4 + 2] cycloaddition reactions with electron-rich alkenes and alkynes as dienophiles to efficiently generate highly substituted and highly functionalized pyrimidines.[3,4] Although many five-membered aromatic heterocycles have been reported to participate in Diels−Alder reactions as the diene component,[5] few of them have been reported as dienophiles.[6] Five-membered aromatic heterocycles bearing an amino group can be viewed as possible electron-rich dienophiles. Their successful participation in the inverse electron demand Diels−Alder reaction with triazine (**1**) should produce a wide range of highly substituted and highly functionalized five-membered ring fused pyrimidine derivatives. Many five-membered ring fused pyrimidine-containing compounds posses interesting biological properties. For example, allopurinol and oxypurinol (pyrazolopyrimidines) are used for gout therapy, and tubercidin and toyocamycin (pyrrolopyrimidines) and aristeromycin (an imidazopyrimidine) are known antibiotics (Figure 1). The heterocyclic nucleus of these molecules can be potentially prepared from the Diels−Alder reaction of triazine (**1**) with the appropriate dienophile. Herein we report our preliminary studies on the [4 + 2] cycloaddition reaction of triazine (**1**) with various 5-aminopyrazoles[7] and the use of this reaction in a one-step synthesis of pyrazolo[3,4-*d*]pyrimidines, eq 1.



a: R = R' = H b: R = H, R' = Me
c: R = Et, R' = H d: R = R' = Me
e: R = Me, R' = 2-thienyl f: R = Me, R' = c-propyl
g: R = Me, R' = Ph

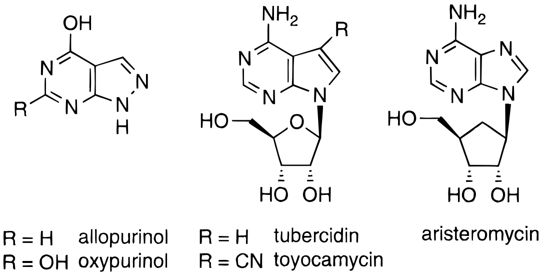


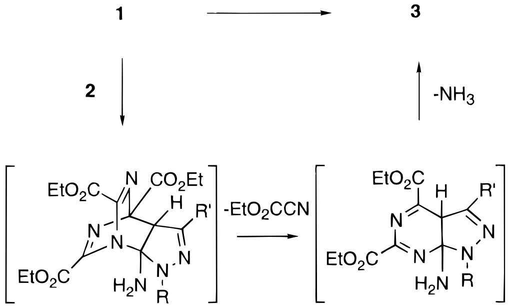
Figure 1.

Table 1. [4 + 2] Cycloaddition Reactions of Triazine (1) with 2a−g

entry	dienophile[4]	conditions[a] (*T* (°C), time (h))	product	yield[b] (%)
1	**2a**, R = R′ = H	100/16	**3a**	41
2	**2b**, R = H, R′ = Me	100/30	**3b**	30
		100/42	**3b**	42[c]
		100/24	**3b**	46[d]
3	**2c**, R = Et, R′ = H	100/20	**3c**	57
4	**2d**, R = R′ = Me	90/18	**3d**	62
5	**2e**, R = Me, R′ = 2-thienyl	110/16	**3e**	33
6	**2f**, R = Me, R′ = c-propyl	100/16	**3f**	45
7	**2g**, R = Me, R′ = Ph	100/20	**3g**	70[e]

[a] All reactions were conducted with 2.0 equiv of dienophiles in anhydrous DMF under nitrogen. [b] Yields were not optimized. [c] Acetic acid was used as cosolvent. [d] The hydrogen chloride salt of **2b** was used. [e] Addition of acetic acid showed no effect on the reaction.

Scheme 1



5-Aminopyrazoles, viewed as cyclic amidines, proved to be sufficiently reactive dienophiles to participate in efficient [4 + 2] cycloaddition reactions with triazine (**1**) under mild thermal conditions (90−100 °C) (Table 1). Analogous to the well-defined Diels−Alder reactions between triazine (**1**) and amidines,[4] 5-aminopyrazoles participate in [4 + 2] cycloaddition reactions with triazine (**1**) to provide the [4 + 2] cycloadducts, which undergo a retro Diels−Alder reaction and subsequent aromatization to regioselectively produce the pyrazolo[3,4-*d*]pyrimidines, Scheme 1. The Diels−Alder reactions of 5-aminopyrazoles bearing an N-1 alkyl substituent generate pyrazolopyrimidines in higher yields than reactions using the N-1 unsubstituted 5-aminopyrazoles. This difference in reactivity may be due to the electron-donating effect of the alkyl group. A variety of groups are tolerated at the 3-position of the pyrazoles, e.g., methyl, 2-thienyl,

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cyclopropyl, and phenyl. However, 3-cyclopropyl and 3-(2-thienyl)pyrazoles (**2e**,**f**) give low yields of the [4 + 2] cycloadducts, possibly due to the instability of the functional groups (entries 5 and 6, Table 1). Consistent with the [4 + 2] cycloaddition reactions of triazine (**1**) with amidines[4] and enamines,[3] the addition of acid proved to be beneficial in some cases (entry 2, Table 1) but not in others (entry 7, Table 1). Pyrazole itself was found to be too unreactive to participate in the [4 + 2] cycloaddition reaction with triazine (**1**), suggesting that the 5-amino group on the pyrazole is required for efficeint reaction with triazine (**1**).

In summary, we have demonstrated that 5-aminopyrazoles can be used as dienophiles in *s*-triazine Diels−Alder reactions for the one-step syntheses of pyrazalopyrimidines. To the best of our knowledge, this is the first report of a five-membered aromatic heterocycle acting as a dienophile in a Diels−Alder reaction with *s*-triazine as diene. The investigation of the [4 + 2] cycloaddition reactions of furans, pyrroles, imidazoles, thiazoles, and other aromatic heterocycles with triazines is currently in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for **3a**−**g** (4 pages).

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(7) **2a,d**−**e** were purchased from Lancaster, and **2b,c** were purchased from Aldrich and used as received.