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Synthesis of fused pyridopyrrolidine dione derivatives using hetero Diels–Alder reactions

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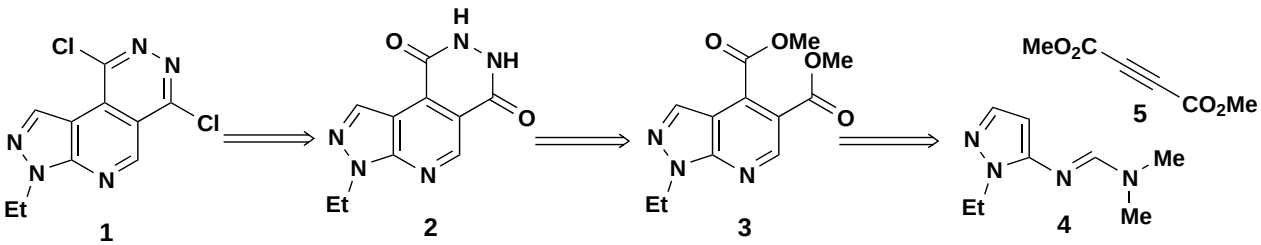
Abstract—Hetero Diels–Alder reactions of heteroaromatic amidines and maleimide afforded novel fused pyridopyrrolidine dione scaffolds in moderate to good yields under mild conditions.

Hetero Diels–Alder reactions have been extensively utilized in the construction of heterocyclic rings, such as substituted pyridines.[1] However, use of this methodology has not been as well established for the synthesis of fused pyridine derivatives. Several reports have recently appeared applying hetero Diels–Alder chemistry to the synthesis of fused pyridine derivatives.[2] These reports provided novel entries into highly substituted, fused pyridine scaffolds. In this communication, we wish to report our new approaches to fused pyridines using hetero Diels–Alder reactions under mild conditions forming versatile substrates.

In our studies of the synthesis of pyrazolopyridopyridazine PDE5 inhibitors,[3] we required large quantities of intermediate **1** (Scheme 1). Our original synthesis of **1** took five steps to reach intermediate **2** in 18% overall yield starting from 5-amino-1-ethylpyrazole. This pathway failed to supply sufficient amounts of intermediate **1** for detailed SAR studies and subsequent compound scale-up.[3]

The use of conjugated amidines as azadienes, or as heterodienophiles is well documented in the literature.[1] Retrosynthetic analysis from **2** leads to diester **3** (Scheme 1), which we reasoned should be available from the reaction of the amidine **4** and DMAD (**5**, Scheme 1).[4] Hetero Diels–Alder cyclization of **4** and **5** proceeded smoothly in an acetic acid solution at ambient temperature to generate dihydropyridine **6** (Scheme 2). Instead of eliminating dimethylamine to form **3**, **6** persisted in the solution and was observed as its methanol adduct **7** by LC-MS analysis (methanol in the eluent) whose regiochemistry was not defined. We assumed that the elimination was retarded by the *cis* geometry of the hydrogen and the dimethylamino group, thus preventing the 1,4-conjugate elimination from occurring.[5] Elevated temperature and/or the addi-



Scheme 1.

Keywords: hetero Diels–Alder reaction; maleimide; pyridine; pyridopyrrolidine dione.

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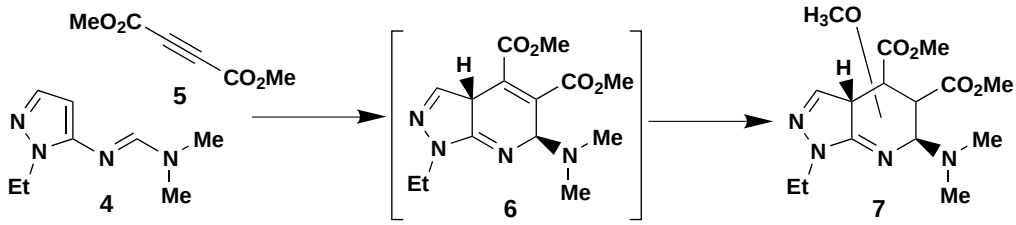


Scheme 2.

tion of oxidizing agents, such as *m*-CPBA to oxidize the dimethylamino moiety in order to facilitate elimination, also failed to produce **3**.[5]

Based on these observations, we hypothesized that by using a dienophile in a lower oxidation state, such as maleimide (**8**), the resultant Diels–Alder product **9** would have a hydrogen *anti* to the leaving dimethylamino group (Scheme 3). E2 elimination of dimethylamine would afford the intermediate **10**. Aromatization of **10** forming **11** should be accomplished by air oxidation. As anticipated, pyridine **11** was produced in a 50% yield when 2 equiv. of maleimide was used in acetic acid at 60°C (Scheme 3).

This successful, novel transformation encouraged us to examine the effect of solvent on this reaction. We found that water was a superior solvent for the reaction, affording the desired pyrazolopyridopyrrolidine dione **11**, even at room temperature.[6] When 4 equiv. of maleimide was used with air bubbling through the aqueous solution for 24 h, **11** was produced in 70–75% optimized yield. The product gradually precipitated from the reaction solution and was collected by filtration. The structure of **11** was subsequently confirmed by X-ray analysis.[7]

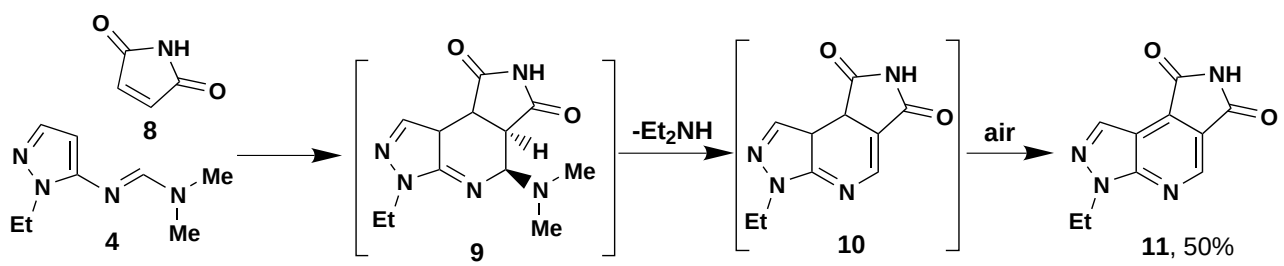
To explore the generality of this reaction, we examined a number of other aminopyrazole analogs, as shown in Table 1. These reactions afforded moderate to good yields of the desired pyrazolopyridopyrrolidine diones (**13**, **15**, **17**, **19** and **21**). Due to the insolubility of the diene precursors in water, acetic acid was used at elevated temperatures.

To extend the application of this hetero Diels–Alder reaction, we investigated the reaction of other commercially available heteroaromatic amines with maleimides (Table 2). Without optimizing each individual reaction condition, we examined aminothiophene, aminoisoxazole and aminobenzothiophene using the reaction conditions described in Table 2. All three substrates afforded the desired pyridopyrrolidine dione products, albeit in lower yields for the simple thiophenylpyridopyrrolidine dione (**23**) and isoxazolopyridopyrrolidine dione (**25**). In view of the complexity of the fused heterocyclic scaffolds formed and the ease of synthesis, this procedure provides a concise, facile route to the formation of these complex fused pyridopyrrolidine dione derivatives.[8] Further optimization of these reactions is the subject of additional studies.

In summary, we have developed a facile methodology for the synthesis of fused pyridopyrrolidine dione derivatives. The chemistry described in this report provides a concise and facile route for rather complicated fused heterocyclic scaffolds. We are currently investigating the scope of this reaction by extending it to other heteroaromatic amidines as the diene precursors and by utilizing other dienophiles. The results of these studies will be reported in due course.

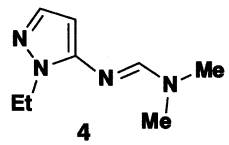
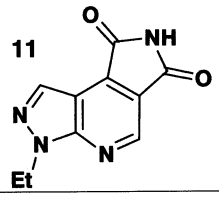
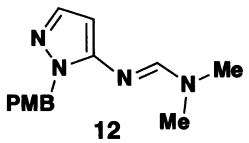
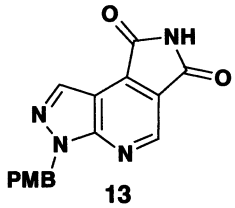
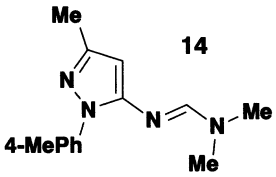
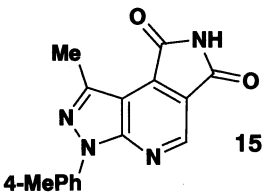
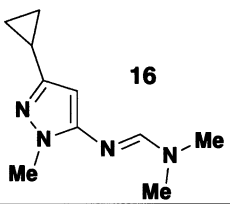
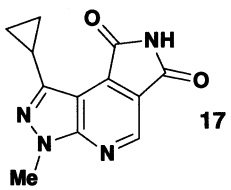
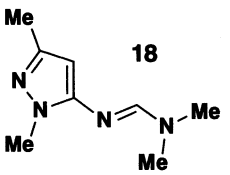
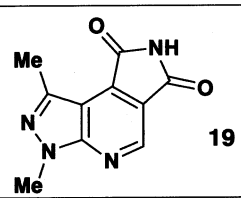
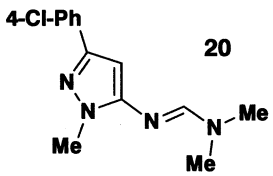
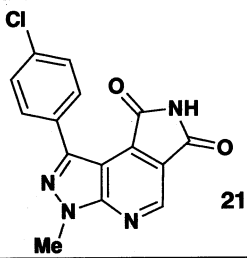
General procedure[9]

Aminopyrazoles (5.0 mmol) were heated at refluxed in dimethylformamide dimethylacetal (5.5 mmol) for 5 h. The resulting mixture was dissolved in water (20 mL), and maleimide (20.0 mmol) was added. The resulting solution was stirred at ambient temperature with air bubbling through the reaction solution. After about 1 h, solid would begin to form. The product was filtered



Scheme 3.

Table 1.

Diene	Temperature, Solvent, and Reaction time	Product	Yield (%)
 4	Ambient temperature in water for 24 h	 11	70[a]
 12 **PMB: *p*-methoxybenzyl**	50 °C in HOAc for 24 h	 13	50[b]
 14	50 °C in HOAc for 24 h	 15	47[b]
 16	50 °C in HOAc for 24 h	 17	67[b]
 18	50 °C in HOAc for 24 h	 19	42[b]
 20	50 °C in HOAc for 24 h	 21	50[b]

a) Product was characterized by ^{1}H and ^{13}C NMR, HRMS and X-ray analysis.
b) Products were characterized by ^{1}H and ^{13}C NMR and HRMS.

after 24 h and rinsed with ethanol to afford the desired pyridopyrrolidine dione. For reactions performed in acetic acid, the crude reaction products were diluted with water and filtered. For compound **23**, the product was purified by silica gel chromatography.

Acknowledgements

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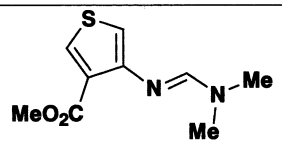
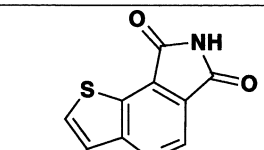
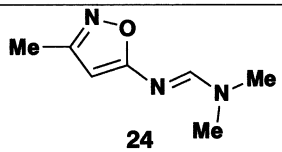
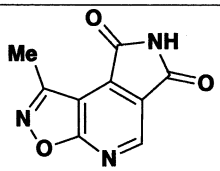
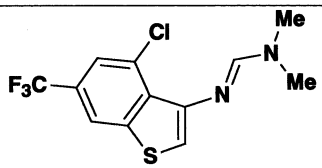
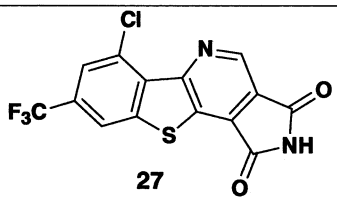
Table 2.

Diene	Product[b]	Yield (%)
 22	 23	25[a]
 24	 25	12[a]
 26	 27	62[a]

a) Products were characterized by ^{1}H and ^{13}C NMR, HRMS and X-ray analysis.
b) All reactions were done in dichloroethane at 80°C for 72 h.

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References

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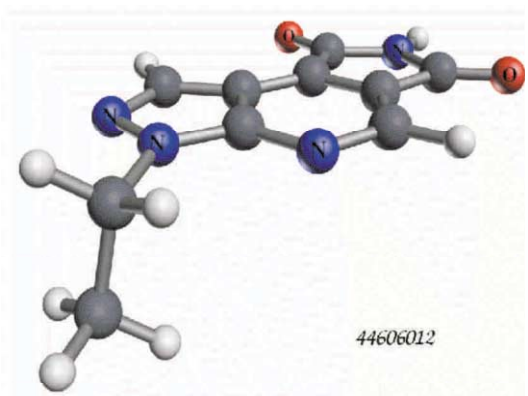
5. Chenard, B. L.; Ronau, R. T.; Schulte, G. K. *J. Org. Chem.* **1988**, *53*, 5175–5177.
6. Use of $CDCl_3$, DMSO-d_6, pyridine-d_5, and CD_3OD as reaction solvents afforded essentially no desired product. Use of CD_3CO_2D afforded products only at elevated temperatures (50–100°C).
7. X-Ray structure of **11**.



8. (a) Elbannany, A. A.; Ibrahiem, L. I.; Chozlan, S. A. S. *Pharmazie* **1988**, *43*, 128–129; (b) Klemm, LeRoy H. *Trends Heterocyclic Chem.* **1997**, *5*, 37–55.
9. All final products have been characterized by ^{1}H, ^{13}C NMR, and elemental analysis.