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Synthesis of fused bicyclic pyridines with microwave-assisted intramolecular hetero-Diels–Alder cycloaddition of acetylenic pyrimidines

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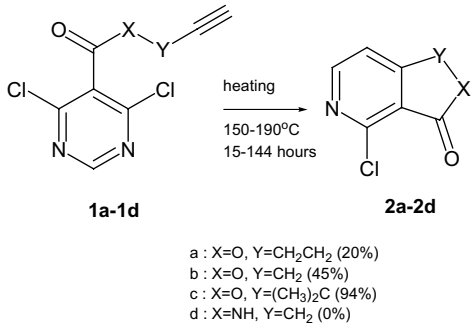
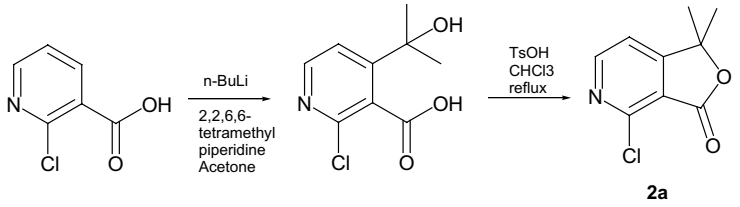
Abstract—A series of acetylenic pyrimidines was synthesized and subjected to microwave irradiation. In contrast to conventional heating, the microwave irradiations generally gave clean conversion to fused bicyclic pyridines for all substrates reported with shorter reaction time. This method has been successfully applied to the synthesis of both fused lactones and lactams.

As part of a program in search for antagonists for the mGluR5 receptor, we were confronted with a need for an efficient synthesis of fused bicyclic pyridines.[1] Two relevant methods were thoroughly investigated after careful review of the literature.[2,3] One of the methods is the alkylation of the dianion of 2-chloronicotinic acid with acetone as electrophile at low temperature, followed by acid-catalyzed lactone formation (Scheme 1). This sequence does provide an entry to the desired series of analogs. However, the unacceptable low yields for other analogs of the series limit its potential application. The second method is based on the results published by Dehaen and co-workers, in which an intramolecular hetero-Diels–Alder cycloaddition reaction was utilized to introduce a fused lactone ring (Scheme 2). This could potentially provide a general method for all of our planned analogs. However, the authors reported that the thermal cyclization required an extended reaction time and gave low yields for several lactone products.



Scheme 2. Hetero-Diels–Alder cycloadditions with conventional heating conditions.



Scheme 1. Dianion alkylation and intramolecular lactonization.

Keywords: Heterocycle; Hetero-Diels–Alder cycloaddition; Microwave; Pyrimidine; Acetylene; Intramolecular.
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Further, the attempted extension of this method to the synthesis of the fused lactam was unsuccessful.

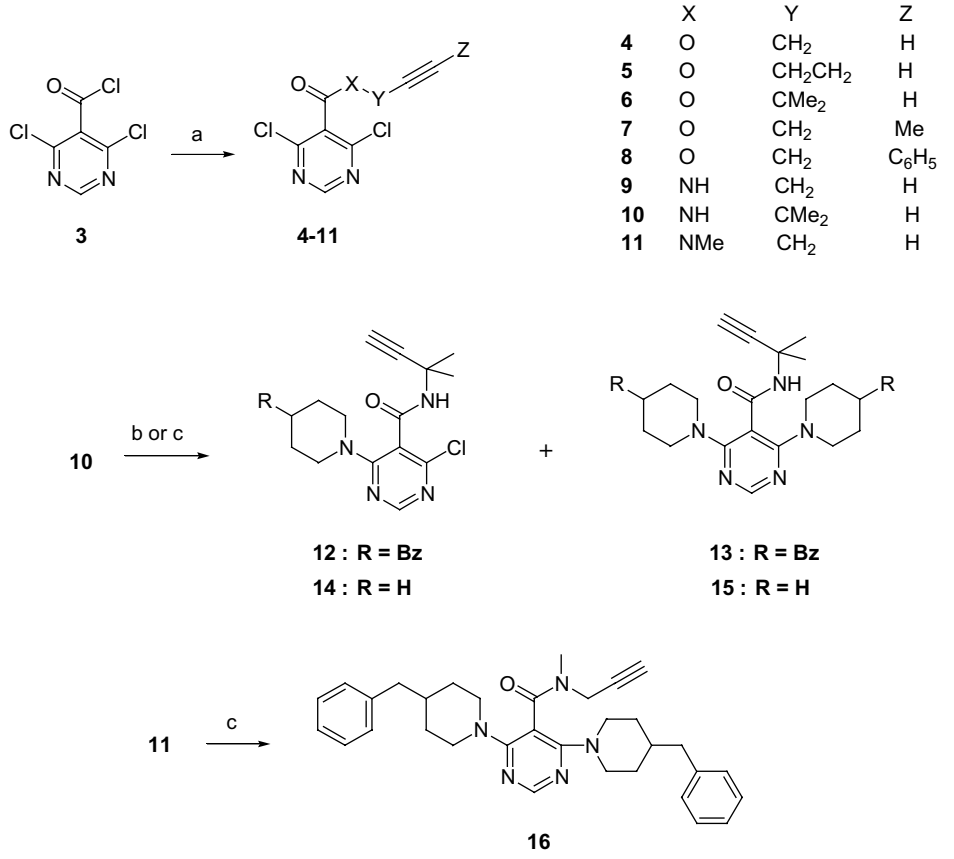
We envisioned that the failure encountered by Dehaen and co-workers most likely originated from the potential degradation of either reactants or products under the harsh thermal conditions reported (150–190 °C, 15–144 h). Therefore, if we were able to find an alternate method that avoids such conditions, that is, extended heating, but still facilitates the cyclization, we could expand the scope of this useful cyclization and provide a general route to the fused bicyclic pyridines. Microwave irradiation represents an excellent alternative. Several successful applications of microwaves in organic synthesis have been reported.[4–7] Microwave irradiation can achieve 'flash' heating at high temperature within a very short period, and therefore provide enough energy for the desired reaction to occur without any significant degradation of reactants or products.

In this communication we report the microwave-assisted hetero-Diels–Alder cycloaddition reaction of a series of acetylenic pyrimidines. In addition, we have successfully extended these conditions to the synthesis of the fused lactam analogs. These reaction generally gave high isolated yields of products and provided a practical general method for the preparation of fused bicyclic pyridines.

Scheme 3 illustrates the general reaction sequence for the compounds reported here. The synthesis of the substrate started with **3**, which was efficiently obtained according to literature procedures.[8] After treatment with the appropriate commercial alcohols or amines, the desired substrates **4**–**11** were synthesized and isolated in good to excellent yields.

The low yield of **6** is most likely due to the steric hindrance of the geminal dimethyl group and the relatively lower nucleophilicity of the oxygen atom. It is worth noting that in order to obtain **9**–**11**, the reaction is generally run at −78 °C to avoid reaction of amines with the chlorine on the pyrimidine ring. When the reaction temperature was raised to 0 °C, one of the chlorines on the pyrimidine ring was replaced by amine nucleophiles. At room temperature, the remaining chlorine can also be replaced in moderate to good yield. By controlling the reaction temperature, **12**–**16** were synthesized and isolated in good yields.

A list of non-nucleophilic polar aprotic solvents with high boiling point were investigated as potential reaction media under microwave conditions. From these, nitrobenzene was selected because we found it can be easily removed after the reaction. A sealed reaction vessel containing the solution of substrate in nitrobenzene was



Scheme 3. Reagents and conditions: (a) Et_3N (**6**: NaH), propargyl alcohols, 0 °C to rt; or Et_3N, propargyl amines, −78 °C; **4** (97%), **5** (>99%), **6** (12%), **7** (>99%), **8** (>99%), **9** (>99%), **10** (>99%), **11** (>99%); (b) Et_3N, piperidine, 0 °C; **12** (70%), **14** (87%); (c) Et_3N, piperidine, rt; **13** (35%), **15** (40%), **16** (65%).

Table 1. Hetero-Diels–Alder cycloadditions with microwave irradiation

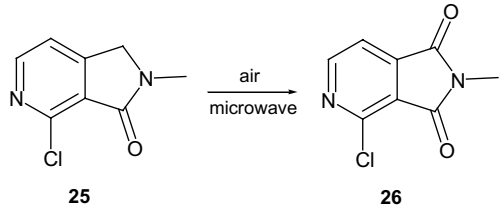
Substrates	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**14**	**16**
Products	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**25**	**23**	**28**	**29** **30**
Lit. yields (%)	45	20	94	—	—	0	0	—	—	—	—
m.w. yields (%)	96	30	96	38	69	96	96	96[a]	85[b]	83[b]	63
Ratio								1:1[c] (**25/26**)	6:1[c] (**23/27**)	5:1[c] (**23/28**)	10:1[c] (**30/29**)

[a] **26** was not observed if the reaction was run under argon.
[b] **27** and **28** were not isolated.
[c] Ratio were determined by HPLC for reactions under air.

subjected to microwave irradiation under preset conditions.[9] In order to minimize potential side reactions, we intended to subject the reactants to the high temperature with the shortest reaction period possible. The progress of the reaction was carefully monitored by LC/MS. When no more starting material was detected, the reaction was cooled to room temperature, then poured onto a silica gel column. Elution with methylene chloride removed nitrobenzene. Subsequent elution with 5–10% methanol in methylene chloride yielded the pure cyclization product in moderate to high yield.

Table 1 summarizes the yields of the cyclization products of various substrates.[10] As anticipated, the microwave-assisted hetero-Diels–Alder cycloaddition reactions tend to be much cleaner than those using conventional thermal conditions, resulting in higher isolated yields of the desired product. This is consistent with the 'flash' heating characteristic of the microwave. The conditions of very high temperatures for a very short period clearly facilitate the reaction while minimizing the decomposition of reactants or products. However, this obvious advantage does have its limitation, as exemplified by substrate **5**. It was noted that the microwave-assisted Diels–Alder reaction of **5** was considerably more sluggish than others. The reported yield for **18** represents the best obtained. Extended reaction time gave lower isolated yields of product (**18**) and low recovery of **5**, presumably as a result of decomposition. At higher temperature, only tar was observed, while at lower temperature the reaction conversion was too slow to be practical. It is concluded that neither substrate **5**, nor corresponding product **18** survives extended high temperature.

In contrast to the results reported when conventional heating was applied,[3] the Diels–Alder cycloaddition of **10** under microwave irradiation gave a high yield of desired fused lactam **23**, therefore expanding the scope of this reaction. It was noted that when the geminal dimethyl group was absent in the amide substrates, such as **9**, **11**, and **16**, the oxidized cyclization products **24**, **26**, and **30** were observed in various yields by LC/MS. It was later discovered that the extent of the formation of **24**, **26**, and **30** decreased if the solution of the reactants in nitrobenzene was deoxygenated prior to heating by bubbling an inert gas (argon) through the solution. When pure **25** was subjected to the same microwave irradiation conditions, it was found that a mixture of **25** and **26** was obtained. At 260 °C for 2 min, the ratio of **25** verses **26** became 2:1; additional heating at 280 °C for 2 min changed the ratio of **25** verses **26** to



Scheme 4. Air oxidation of **25** under microwave condition.

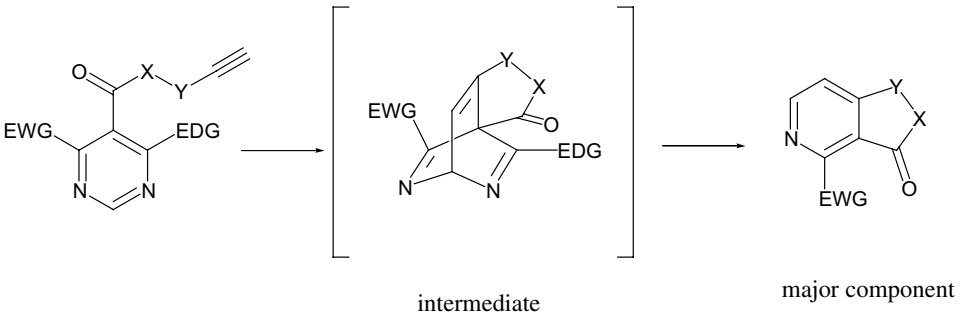


Figure 1. Formation of fused lactones and lactams.

1:2. It is most likely that the oxygen in the vessel oxidized the methylene adjacent to nitrogen atom at high temperature (Scheme 4).

We have found that the electronic properties of the pyrimidine dictate the ratio of the final products. After cycloaddition occurs across the pyrimidine, the more electronically rich moiety is selectively extruded from the intermediate (Fig. 1). This was observed in the microwave-mediated cycloadditions of both **12** and **14**, where **23** was isolated as the major component and **27** and **28** were minor products, respectively. It was believed that compounds like **27** and **28** could be accessible by coupling between **23** and the corresponding amines. However, several attempts of such direct coupling reaction failed due to the inert characteristic of **23** even at high temperature under argon. When **22** and **25** were subjected to the same direct coupling thermally with an amine under argon, no desired products were observed by LC/MS. Compounds **27** and **28** were eventually synthesized and isolated in 40% and 69% yields from **13** and **15**, where both chlorine atoms were replaced with the same amine nucleophile. Similarly, **29** was synthesized and isolated.

In summary, application of microwave conditions to the hetero-Diels–Alder cycloaddition reaction of acetylenic pyrimidines increases yields and broadens the utility to the preparation of pyrido-fused lactams.

Supplementary data

Proton NMRs of compounds **20**, **21**, **22**, **23**, **25**, **26**, **27**, **28**, **29**, **30**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.03.098.

References and notes

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9. The microwave-assisted reactions were carried out in a Microsynth from Milestone with maximum power output of 1000 W. The reaction temperature profiles used were: 22–280 °C in 1 min, hold at 280 °C for 2.5 min then power off to cool down to room temperature. For substrate **5** only, 22–265 °C in 1 min, hold at 265 °C for 45 min, then power off to cool down to room temperature.
10. Satisfactory spectroscopic data (proton NMR, 400 MHz, MS and elemental analysis) have been obtained for all new compounds. Compound **20**: ($CDCl_3$) δ 8.43 (q, 1H, J = 0.8Hz); 5.25 (d, 2H, J = 0.4 Hz); 2.38 (m, 3H). MS: 184 (MH^+), 206 (M^++Na^+). Found: C, 52.23; H, 3.19; N, 7.55. $C_8H_6ClNO_2$ requires C, 52.34; H, 3.29; N, 7.63. Compound **21**: ($CDCl_3$) δ 8.68 (s, 1H); 7.54 (m, 3H); 7.43 (m, 2H); 5.40 (s, 2H). MS: 246 (MH^+), 268 (M+Na). Found: C, 63.16; H, 3.15; N, 5.72. $C_{13}H_8ClNO_2$ requires C, 63.56; H, 3.28; N, 5.70. Compound **22**: ($CDCl_3$) δ 8.56 (d, J = 4.8 Hz, 1H); 7.42 (dt, J = 0.4, 5.0 Hz, 1H); 6.82 (br s, 1H); 4.49 (t, J = 0.8 Hz, 2H). MS: 169 (MH^+), 191 (M^++Na^+). Found: C, 49.72; H, 3.01; N, 16.32. $C_7H_5ClN_2O$ requires C, 49.87; H, 2.99; N, 16.62. Compound **23**: ($CDCl_3$) δ 8.57 (d, 1H, J = 4.8 Hz); 8.01 (br s, 1H, NH); 7.35 (d, 1H, J = 4.8 Hz); 1.60 (s, 6H). MS: 219 (MH^+). Found: C, 54.20; H, 4.58; N, 14.13. $C_9H_9ClN_2O$ requires C, 54.97; H, 4.61; N, 14.25. Compound **25**: ($CDCl_3$) δ 8.51 (d, J = 4.8 Hz, 1H); 7.37 (dt, J = 0.4, 4.8 Hz, 1H); 4.40 (s, 2H); 3.20 (s, 3H). MS: 183.1 (MH^+); 205 (M+Na). Found: C, 51.94; H, 3.76; N, 14.99. $C_8H_7ClN_2O$ requires C, 52.62; H, 3.86; N, 15.34. Compound **26**: ($CDCl_3$) δ 8.83 (d, J = 4.8 Hz, 1H); 7.73 (d, J = 4.8 Hz, 1H); 3.23 (s, 3H). MS: 197.0 (MH^+). Found: C, 49.45; H, 2.61; N, 13.90. $C_8H_5ClN_2O_2$ requires C, 48.88; H, 2.56; N, 14.25. Compound **27**: ($CDCl_3$) δ 8.27 (d, 1H, J = 4.8 Hz); 7.28 (m, 2H); 7.19 (m, 3H); 6.68 (d, 1H, J = 4.8 Hz); 6.26 (br s, 1H, NH); 4.41 (m, 2H); 2.89 (t, 2H, J = 12 Hz); 2.60 (d, 2H, J = 6.8 Hz); 1.4–1.8 (m, 5H). MS: 336 (MH^+), 358 (M^++Na^+). Found: C, 74.51; H, 7.51; N, 12.37. $C_{21}H_{25}N_3O$ requires C, 75.19; H, 7.51; N, 12.53. Compound **28**: ($CDCl_3$) δ 8.28 (d, 1H, J = 4.8 Hz); 6.67 (d, 1H, J = 4.8 Hz); 3.66 (t, 4H, J = 5.2 Hz); 1.73 (m, 4H); 1.62 (m, 2H); 1.48 (s, 6H). MS: 246 (MH^+). Found: C, 67.75; H, 7.84; N, 16.90. $C_{14}H_{19}N_3O$ requires C, 68.54; H, 7.81; N, 17.13. Compound **29**: ($CDCl_3$)δ 8.15 (d, 1H, J = 4.8 Hz); 7.21 (m, 2H); 7.12 (m, 3H); 6.67 (d, 1H, J = 4.8 Hz); 4.30 (br d, 2H, J = 12 Hz); 4.20 (s, 2H); 3.06

(s, 3H); 2.79 (t, 2H, J = 12 Hz); 2.52 (d, 2H, J = 6.4 Hz); 1.72–1.40 (m, 5H). Compound **30**: ($CDCl_3$) δ 8.53 (d, 1H, J = 4.4 Hz); 7.32 (t, 2H, J = 7.6 Hz); 7.21 (m, 3H); 7.06 (d, 1H, J = 4.4 Hz); 4.53 (d, 2H, J = 13 Hz); 3.15 (s, 3H); 3.00 (t, 2H, J = 13 Hz); 2.61 (d, 2H, J = 6.8 Hz); 1.84 (m, 3H); 1.43 (m, 2H). MS: 336 (MH^+). Found: C, 71.21; H, 6.07; N, 12.41. $C_{20}H_{21}N_3O_2$ requires C, 71.62; H, 6.31; N, 12.53.