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Synthesis of pyrazolo[1,5-*a*]pyridines by thermal intramolecular cyclization

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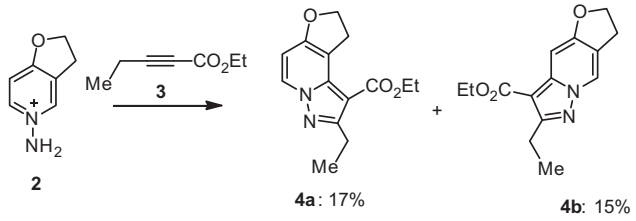
ABSTRACT

Thermal intramolecular cyclization of *N*-amino-2-alkynylpyridines was developed for facile and versatile synthesis of pyrazolo[1,5-*a*]pyridines. Simply heating *N*-amino-2-alkynylpyridines in acetic acid provided pyrazolo[1,5-*a*]pyridines in excellent yield.

Heterocycles with bridgehead nitrogen atoms play an important role as core structures of therapeutic agents. Among them, pyrazolo[1,5-*a*]pyridine derivatives such as an antiplatelet agent KC-764,[1] an antiallergic agent FK 838[2] and a melatonin receptor agonist **1**[3] have attracted considerable interest due to their efficacious biological activity (Fig. 1).

Pyrazolo[1,5-*a*]pyridines are generally synthesized by *intermolecular* cyclization reactions of *N*-aminopyridine derivatives with alkene or alkyne derivatives;[3–5] however, synthesis from asymmetric *N*-aminopyridines is usually accompanied by undesirable production of their corresponding regioisomers with poor selectivity.[3,4b,5] In our efforts to synthesize **1**, the [3+2] cycloaddition of the asymmetric *N*-aminopyridine **2** with an alkyne **3** provided both the desired regioisomer **4a**, which was converted to **1**, and the undesired regioisomer **4b** with poor selectivity (Scheme 1).[3] On the other hand, some *intramolecular* cyclization reactions without production of the regioisomers have been reported.[6–11] Of the reactions, cyclization of *N*-amino-2-alkynylpyridines under basic conditions[6] is reported to be a relatively versatile synthetic method for pyrazolo[1,5-*a*]pyridines in comparison with the other *intramolecular* cyclization reactions.[8–11] However, this reaction still remains a challenge due to the low yield of the practical examples.[7] These synthetic drawbacks have made the synthesis of a wide variety of pyrazolo[1,5-*a*]pyridines, especially structurally complex ones such as **1**, difficult and limited their medicinal potential.

In this Letter, we describe the development of thermal intramolecular cyclization of *N*-amino-2-alkynylpyridines to allow for facile and versatile synthesis of pyrazolo[1,5-*a*]pyridines including highly substituted ones such as the melatonin receptor agonist **1**.



Scheme 1. [3+2] cycloaddition of asymmetric *N*-aminopyridine.

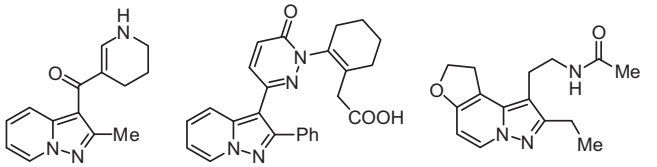


Figure 1. Chemical structures of biologically active pyrazolo[1,5-*a*]pyridines.

Our initial efforts were directed at exploring the reaction conditions for the cyclization of a model compound **5a** prepared by the amination of 2-(phenylbutynyl)pyridine with *O*-(mesitylsulfonyl)hydroxylamine ($MesONH_2$).[12] As per the reported procedure,[6] potassium carbonate was added to a solution of **5a** in *N*,*N*-dimethylformamide, and trace amounts of the desired product with large

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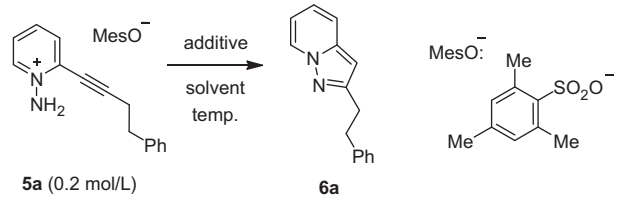
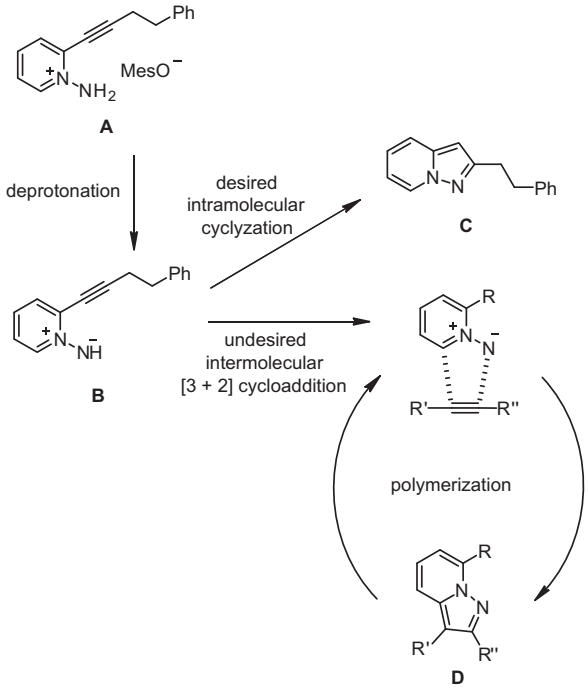
Table 1
Exploration of intramolecular cyclization



5a (0.2 mol/L) **6a**

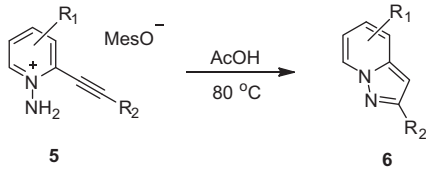
Entry	Additive	Solvent	Temp (°C)	Time (h)	Yield (%)
1	K_2CO_3 (2.0 equiv)	DMF	rt	5	Trace
2	Phosphate buffer (pH 7.3)	EtOH	rt	24	49
3	None	DMF	rt	24	No reaction
4	None	AcOH	rt	24	No reaction
5	H_2SO_4 (1.0 equiv)	DMF	rt	24	No reaction
6	None	DMF	80	24	63
7	None	AcOH	80	24	94



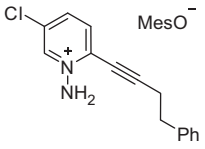
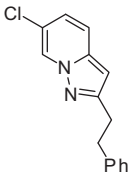
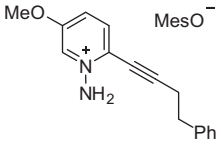
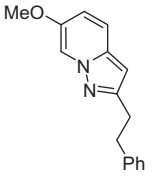
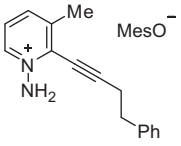
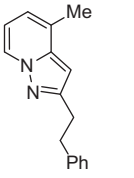
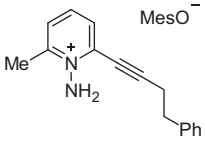
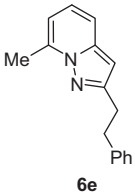
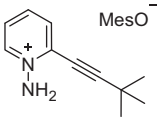
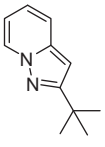
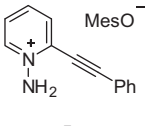
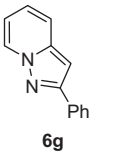
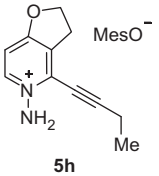
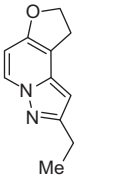
Scheme 2. Plausible reaction pathway through the 1,3-dipole **B**.

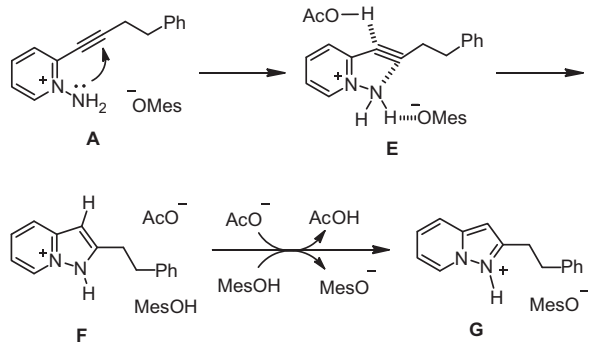
amounts of byproducts were produced (Table 1, entry 1). LCMS analysis detected dimer and trimer products of **5a** in the crude reaction mixture,[13] indicating that intermolecular [3+2] cycloaddition of the activated substrate **B** preceded the desired intramolecular cyclization and that the remaining 1,3-dipole and alkyne moiety of the cycloaddition products **D** caused additional cycloaddition and subsequent polymerization (Scheme 2).[14] The low yield of the reported examples[7] might also be due to this side reaction. To suppress the intermolecular [3+2] cycloaddition and efficiently obtain the targeting product **C**, we carried out this reaction using a mixture of ethanol and aqueous phosphate buffer (pH 7.3). Under the neutral buffered conditions, maintenance of a low concentration of the 1,3-dipole **B** prioritized the intramolecular cyclization over the intermolecular [3+2] cycloaddition, and the desired product **6a** was obtained in improved yield (49%, entry 2). Because the undesirable cycloaddition products **D** were produced even

Table 2
Scope and limitation of substituents

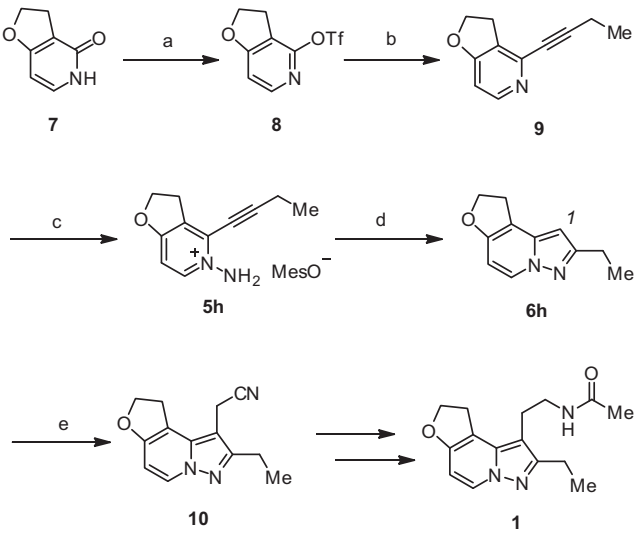


5 **6**

Entry	Substrate	Product	Yield (%)
1	 **5b**	 **6b**	91
2	 **5c**	 **6c**	91
3	 **5d**	 **6d**	88
4	 **5e**	 **6e**	92
5	 **5f**	 **6f**	97
6	 **5g**	 **6g**	90
7	 **5h**	 **6h**	88



Scheme 3. Plausible reaction mechanism.



Scheme 4. Synthesis of melatonin agonist **1**. Reagents and conditions: (a) trifluoromethanesulfonic anhydride, pyridine, 0 °C, 95%; (b) 1-butyne, $PdCl_2$ $(PPh_3)_2$, CuI, Et_3N, rt, 86%; (c) $MesONH_2$, MeCN, 0 °C, 80%; (d) AcOH, 80 °C, 88%; (e) (1) Eschenmoser's salt, MeCN, rt, (2) MeI, AcOEt, rt, (3) KCN, 18-crown-6, MeCN, 80 °C, 89% from 6 h.

under the buffered conditions, we investigated the reaction conditions without deprotonating reagents, to completely avoid the production of the 1,3-dipole **B**. The reaction without additives (entry 3) and under acidic conditions (entries 4 and 5) did not proceed at room temperature. Surprisingly, however, the cyclization was accomplished by simply heating **5a** in *N*,*N*-dimethylformamide at 80 °C (63%, entry 6).[15] Moreover, changing the solvent to acetic acid provided **6a** in excellent yield (94%, entry 7).[16] This is the first example of obtaining pyrazolo[1,5-*a*]pyridines from *N*-amino-2-alkynylpyridines without the formation of the 1,3-dipolar species.

We next investigated the scope and limitation of the R^1 substituents on the pyridine ring and the R^2 substituents at the alkyne terminus (Table 2). Installation of the electron-withdrawing (Cl) and -donating (OMe) groups at the C5 position of the pyridine ring had no effect on the reaction yield (entries 1 and 2), and the C3- and C6-substitution with methyl group also resulted in good yield (entries 3 and 4). The substrates with tertiary butyl and phenyl groups at the alkyne terminus were efficiently cyclized (entries 5 and 6). Finally, the fused pyridine **5h** was applied as a practical example to obtain the tricyclic derivative **6h** in good yield (entry 7). These results suggest that this reaction could allow for the facile synthesis of a wide variety of substituted pyrazolo[1,5-*a*]pyridines.

A plausible reaction mechanism is described in Scheme 3. The cyclization starts with attack of the amino group on the alkyne moiety under heating conditions without activation by deprotonation. Acetic acid and mesitylenesulfonate anion is considered to stabilize the transition state (**E**). Simultaneous deprotonation and protonation provide a protonated form of the pyrazolo[1,5-*a*]pyridine (**F**). This mechanism is consistent with the improved yield obtained by using acetic acid (Table 1, entries 6 vs 7). Proton exchange between acetate anion and mesitylenesulfonic acid yields the pyrazolo[1,5-*a*]pyridine as a salt form with mesitylenesulfonic acid (**G**). Since this product would make the reaction mixture acidic, a suitable alternative for acid-sensitive substrates could be the use of the buffered conditions (Table 1, entry 2).

This reaction was then applied to the synthesis of the melatonin agonist **1**, which has an angularly dihydrofuran-fused pyrazolo[1,5-*a*]pyridine as its core structure (Scheme 4). The reported synthetic route involves the intermolecular [3+2] cycloaddition of *N*-aminopyridine with an alkynoic ester for the construction of pyrazolo[1,5-*a*]pyridine ring.[3] The reaction afforded the desired compound in low yield (Scheme 1 and 17%) with the undesirable regioisomer. The known pyridone **7**[17] was treated with triflic anhydride in pyridine to afford the triflate **8**, which was converted into the alkynylpyridine **9** by the Sonogashira coupling reaction (82% yield over two steps). The key *N*-aminopyridine derivative **5h**, prepared by the amination of **9** with $MesONH_2$ in acetonitrile (80% yield), was cyclized under the heating conditions to yield the 8,9-dihydrofuro[3,2-*c*]pyrazolo[1,5-*a*]pyridine **6h** (Table 2, entry 7). The introduction of the amide side chain at the C1 position of the tricyclic core was achieved by the reported procedure with minor modification.[18] Treatment of **6h** with Eschenmoser's salt yielded a *N*,*N*-dimethylaminomethyl analog, which was converted into the known intermediate **10**[3] by the formation of quaternary amine and subsequent nucleophilic substitution with potassium cyanide (89% yield over three steps). This reaction scheme avoided the production of the regioisomer and improved the chemical yield as compared to the previous one.

In conclusion, we described the development of thermal intramolecular cyclization of *N*-amino-2-alkynylpyridines for the facile and versatile synthesis of pyrazolo[1,5-*a*]pyridines. Exploration of the reaction conditions based on mechanistic consideration revealed that *N*-amino-2-alkynylpyridines are efficiently converted into pyrazolo[1,5-*a*]pyridines by heating at 80 °C in acetic acid. This reaction method provided different types of substituted pyrazolo[1,5-*a*]pyridines in excellent yield and established a superior synthetic route to the melatonin receptor agonist **1**.

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Supplementary data

Supplementary data (experimental procedures and characterization data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.078.

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13. MS (ESI): *m*/*z* 443, 663.
14. Large amounts of insoluble matter which is considered to be derived from polymerization was observed.
15. LCMS analysis confirmed complete consumption of compound **5a**.
16. Typical procedure for thermal intramolecular cyclization: a solution of **5a** (169 mg, 0.400 mmol) in AcOH (2.0 mL) was stirred for 24 h at 80 °C. The reaction mixture was concentrated in vacuo. The residue was diluted with ethyl acetate, washed with aqueous sodium hydrogen carbonate and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/hexane) to afford **6a** (83.8 mg, yield 94%) as colorless solid.
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