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Stereoselective synthesis of 1,6-diazecanes by a tandem aza-Prins type dimerization and cyclization process†

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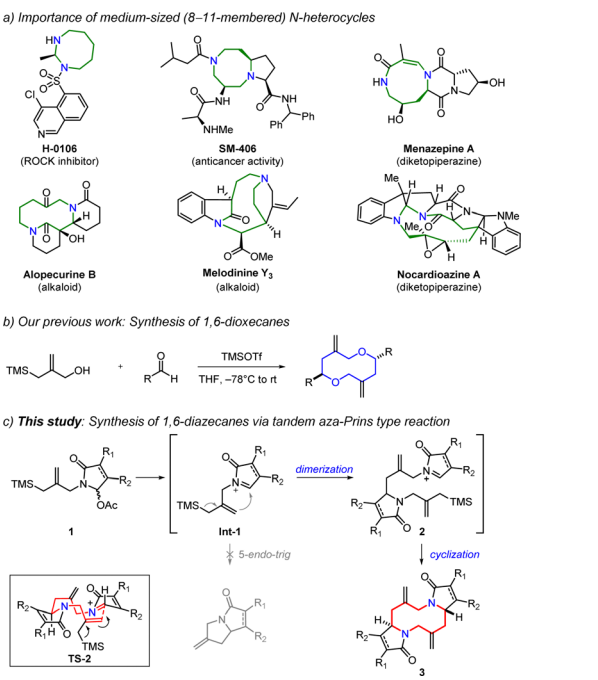
We report the stereocontrolled synthesis of 1,6-diazecanes *via* a tandem aza-Prins type reaction of *N*-acyliminium ions with allylsilanes. It involves an aza-Prins type dimerization and cyclization in a single-step operation. This reaction represents the first example of 10-membered N-heterocycle synthesis using an aza-Prins reaction. Also, the interesting formation of an unusual tetracyclic compound through further cyclization of 1,6-diazecane and bicyclic compounds by the intramolecular cyclization of linear allylsilane are described. This tandem aza-Prins protocol provides a new synthetic strategy for the direct synthesis of medium-sized nitrogen heterocycles.

Medium-sized (8–11-membered) heterocycles[1] are widely found in medicinally important molecules and natural products (Scheme 1a).[2] The unique 3D spatial shapes and conformational constraints of medium-sized rings provide improved biological properties.[3] However, medium-sized ring systems are hard to find in drug molecules and compound libraries,[4] probably due to their synthetic challenge.[5] The synthesis of medium-sized rings *via* cyclization is difficult because of transannular interactions and entropic factors.[6] Although there are diverse approaches for the synthesis of medium-sized rings,[7] the development of new strategies is still in high demand to investigate underexplored chemical space.

Aza-Prins cyclization is a powerful strategy to generate a wide range of N-heterocycles through intramolecular trapping of the *in situ* formed iminium or *N*-acyliminium ion intermediates.[8,9] Aza-Prins cyclization has been broadly utilized to form 5- and 6-membered rings such as pyrrolidines and piperidines.[10] A number of complex natural products have also been synthesized using this method.[11] Nevertheless, there are very scarce examples to form larger (*e.g.*, 7- and 8-membered) rings through this reaction.[12] Herein, we describe the tandem aza-Prins type dimerization and cyclization strategy for the stereoselective synthesis of 1,6-diazecanes (Scheme 1c). Notably, the present protocol is the first example of a 10-membered N-heterocycle synthesis using an aza-Prins reaction.

Previously, we reported the synthesis of 1,6-dioxecanes *via* a Prins type cyclization of allylsilane with an aromatic aldehyde (Scheme 1b).[13] It involves an inter- and intramolecular Prins



Scheme 1 Synthesis of 1,6-diazecanes *via* an aza-Prins type reaction.

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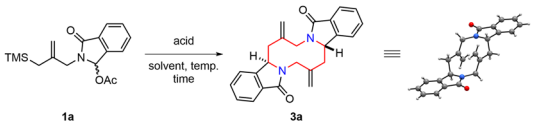
Table 1 Optimization of reaction conditions[a]



Entry	Acid (equiv.)	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1	TfOH (1.1)	CH_2Cl_2	−78 to rt	6	ND
2	$Bi(OTf)_3$ (1.1)	CH_2Cl_2	−78 to rt	6	ND
3	$TiCl_4$ (1.1)	CH_2Cl_2	−78 to rt	6	ND
4	TMSOTf (1.1)	CH_2Cl_2	−78 to rt	6	67
5	TMSOTf (1.1)	Et_2O	−78 to rt	6	47
6	TMSOTf (1.1)	THF	−78 to rt	6	—[c]
7	TMSOTf (1.1)	CH_3CN	−40 to rt	6	78
8	TMSOTf (1.1)	CH_3CN	−40 to 0	2	81
9	TMSOTf (0.50)	CH_3CN	−40 to 0	2	92
10	TMSOTf (0.20)	CH_3CN	−40 to 0	2	83
11	TfOH (0.50)	CH_3CN	−40 to 0	2	81
12	$Bi(OTf)_3$ (0.50)	CH_3CN	−40 to 0	2	42

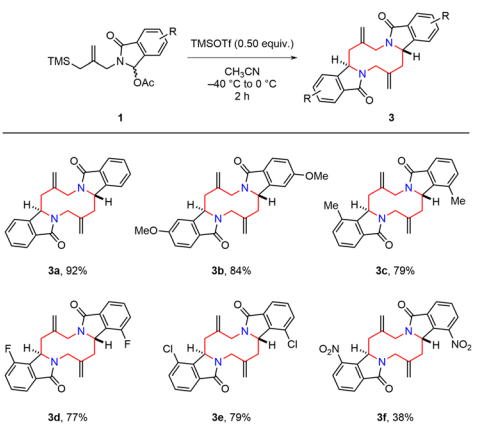
[a] Reactions performed with substrate (0.60 mmol) and acid in solvent (6.0 mL) at the indicated temperature for the indicated time. the temperature was slowly elevated over the indicated time. [b] Isolated yield. [c] The reaction mixture became viscous; ND = not detected.

type reaction in a single-step operation. On the basis of this study, we envisioned a new synthetic strategy to form a 1,6-diazecane ring system using an aza-Prins type reaction. An *N*-acyliminium ion intermediate **2** would be generated by an intermolecular aza-Prins type reaction between an *in situ* formed *N*-acyliminium ion and an allylsilane since intramolecular 5-*endo-trig* cyclization of **Int-1** is stereoelectronically unfavourable. Next, the subsequent aza-Prins type intramolecular cyclization of **2** would occur to provide the desired 1,6-diazecane **3**. In this process, 2,7-*trans* stereochemistry would be expected if the cyclization reaction takes place through the transition state **TS-2**.

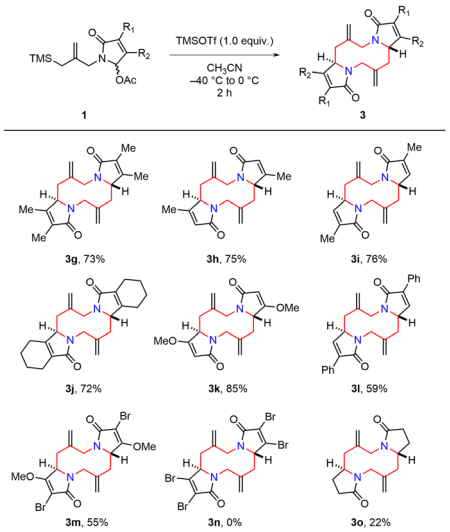
In order to explore the tandem aza-Prins type reaction, the *N*-acyliminium ion precursor **1a** was chosen as a model substrate to perform the reaction under various conditions (Table 1). Among the various acids screened (entries 1–4), only TMSOTf gave the desired 1,6-diazecane product **3a** in 67% yield. Other acids such as TfOH, $Bi(OTf)_3$ and $TiCl_4$ failed to give the product. We next examined the effect of solvent on the reaction (entries 4–7). The desired product was obtained in lower yield when we used diethyl ether (entry 5). In the case of THF, the reaction mixture became viscous probably due to cationic polymerization of THF (entry 6).[14] We observed the desired product and polyTHF in an aliquot of the reaction mixture by NMR, but we could not isolate the product from the viscous reaction mixture. The yield of **3a** was improved when the reaction was carried out in acetonitrile (entry 7). A further increased yield was observed by modifying the reaction time and temperature (entry 8). To our delight, decreasing the amount of TMSOTf to 0.50 equiv. remarkably enhanced the yield to 92% (entry 9). Further decreasing the amount to 0.20 equiv. also led to the desired product albeit in slightly lower yield (entry 10, 83%). Interestingly, TfOH (0.50 equiv.) and $Bi(OTf)_3$ (0.50 equiv.) were also affective when we used acetonitrile as a solvent (entries 11 and 12), although no desired product was observed in dichloromethane. It suggests that the use of acetonitrile as a solvent is crucial for the successful transformation. These results may be explained by the acetonitrile influence on the iminium cation separation from the ion pair[15] and stabilization. It was noteworthy that only a single diastereomer of **3a** was observed in all cases through the transition state **TS-2** in Scheme 1. The structure and stereochemistry of the product (**3a**) was unambiguously determined by X-ray crystallographic analysis.

With the optimized conditions in hand (Table 1, entry 9), we first investigated the substrate scope of *N*-acyliminium ion precursors synthesized from phthalimide derivatives (Scheme 2). Substrates having electron-donating groups, such as methyl and methoxy groups, smoothly reacted under the optimized conditions to afford 1,6-diazecanes **3b** (84%) and **3c** (79%). Halogen-substituted substrates were also applied to the present procedure to give the products **3d** (77%) and **3e** (79%). However, a low yield (**3f**, 38%) was observed when an electron-deficient group substituted substrate was used. These results indicated that electron-donating substituents (**3b** and **3c**) were more suitable for this reaction than electron-withdrawing substituent (**3f**), probably related to the stability of the highly reactive *N*-acyliminium ion intermediate.

To expand the scope of the tandem aza-Prins type reaction, we next explored the *N*-acyliminium ion precursors derived from pyrrole-2,5-dione derivatives (Scheme 3). Unlike substrates **1a–1f** derived from phthalimide derivatives, we often encountered low reproducibility with substrates **1g–1o** under the optimized reaction conditions. We used 1.0 equiv. of TMSOTf for these substrate **1g–1o** because reproducible results were obtained when we simply used an increased amount of acid. Alkyl group substituted substrates **1g–1j** produced the corresponding 1,6-diazecanes **3g–3j** in good yields (72–76%) regardless of the substitution patterns. Substrate **1k** bearing an electron-donating methoxy group at R_2 gave **3k** in higher yield (85%). When electron-withdrawing phenyl or bromide groups were substituted at R_1, the reactions suffered from relatively lower yields (**3l** and **3m**) even in the presence of the methoxy



Scheme 2 Substrate scope of **1** derived from phthalimide derivatives.



Scheme 3 Substrate scope of **1** derived from pyrrole-2,5-dione derivatives.

group at R_2 (**3m**). Furthermore, the dihalogen-substituted substrate **1n** failed to give the product. The desired 1,6-diazecane **3n** was not observed in the complex crude mixture. In the case of substrate **1o** prepared from pyrrolidine-2,5-dione, the yield of 1,6-diazecane **3o** was only 22%. It implies that the conjugated olefin system stabilizes the highly reactive *N*-acyliminium ion intermediate during the reaction.

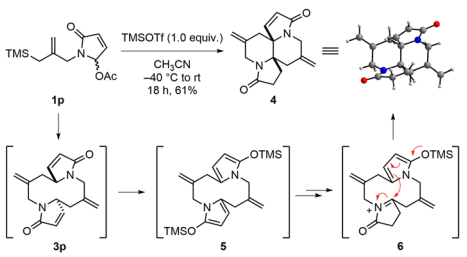
In the course of investigating the substrate scope, we also tested substrate **1p** prepared from pyrrole-2,5-dione (Scheme 4). We could not observe the desired 1,6-diazecane **3p** under the optimized conditions. However, very interestingly, we obtained an unusual tetracyclic compound **4** in 61% yield instead of **3p** under modified reaction conditions. The structure of tetracyclic product **4** was clearly confirmed by X-ray crystallographic analysis. The substrate **1p** would be first converted to the corresponding 1,6-diazecane **3p**, and then 2-silyloxy dienes **5** could be formed from **3p** under the same conditions. It is well known that pyrrole-based 2-silyloxy diene can be generated from a 1,5-dihydropyrrol-2-one moiety in the presence of silyl triflate. The 2-silyloxy diene can act as either a nucleophile or an electrophile to functionalize the 5-position of 1,5-dihydropyrrol-2-one.[16] Based on this aspect, one of the 2-silyloxy dienes of **5** would generate the *N*-acyliminium ion intermediate **6** which could be trapped by the other 2-silyloxy diene intramolecularly to form the tetracyclic compound **4**.

To test the scope of allylsilane, we tried the tandem aza-Prins type reaction with substrates **7a–7e** having linear allylsilane (Scheme 5). We obtained intramolecularly cyclized products **9a–9e** instead of desired 1,6-diazecanes **10**. The stereoselectivity of **9** regardless of double bond configuration can be explained by electrophilic addition mechanism and stereoelectronic effect in transition state **8**.[17] This results indicated that 5-*endo-trig* cyclization is faster than dimerization in the case of the linear allylsilane substrate **7**.

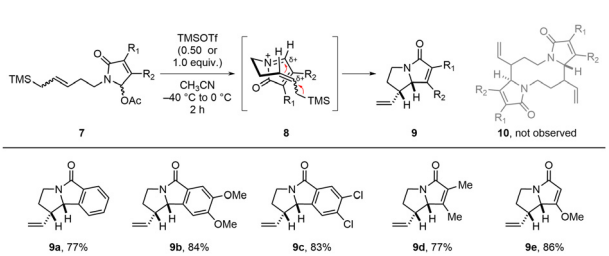
Next, the tandem aza-Prins type reaction of the acyclic iminium ion **15** generated *in situ* from amine **11** and benzaldehyde was examined (Scheme 6). Unexpected intramolecularly cyclized product (**12**) and acetonitrile-involved products (**13** and **14**) were obtained. We also tested the reaction in dichloromethane to avoid a solvent-involved reaction, but we observed an unknown inseparable complex mixture containing the intramolecularly cyclized product **12**. It showed that the *in situ* generated acyclic iminium ion **15** could not provide the desired 1,6-diazecane **16**.

Lastly, a cross-over experiment was performed using a 1 : 1 mixture of **1a** and **1g** in the presence of 2.0 equiv. TMSOTf to check the mechanistic aspect of the tandem aza-Prins type reaction (Scheme 7). All three possible products (**3a**, **3q** and **3g**) were isolated separately in 64% total yield with 1 : 1.1 : 1 ratio. The cross-over product (**3q**) was observed as we expected, supporting the intermolecular dimerization process. Also, the product ratio implied that substrates **1a** and **1g** have similar reactivity. Moreover, this cross-over protocol could be used as an efficient tool for the rapid generation of symmetrical and unsymmetrical 1,6-diazecanes in a single-step process.

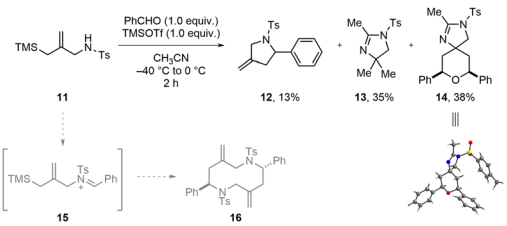
In conclusion, we have described the stereoselective synthesis of 1,6-diazecanes *via* a tandem aza-Prins type dimerization and cyclization reaction of *N*-acyliminium ions with allylsilanes. This is the first method to generate 10-membered azacycles using an aza-Prins reaction and can serve as a tool for the synthesis of complex N-heterocycles. In addition, our study showed the formation of an unusual tetracyclic compound through further cyclization of 1,6-diazecane and bicyclic compounds by intramolecular cyclization of a linear allylsilane. Further investigations towards the Prins type cyclization for different kinds of medium-sized heterocycles are currently underway.



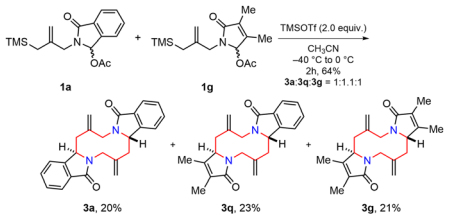
Scheme 4 Unexpected formation of tetracyclic compound **4**.



Scheme 5 Intramolecular cyclization of linear allylsilane **7**.



Scheme 6 Unexpected solvent-involved reaction of **11**.



Scheme 7 Cross-over experiment with mixed substrates **1a** and **1g**.

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Conflicts of interest

There are no conflicts to declare.

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