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New type of azacyclization: thermal preparation of 4,6-disubstituted 2-piperidinone from *N*-sulfonyldienamide and its substituent effect

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ABSTRACT

The thermal 6-endo cyclization of *N*-sulfonyl-2,4-dienamide compounds to produce 4,6-disubstituted 2-piperidinone is described. The observed remarkable substituent effect due to the *N*-sulfonyl and C3 ethoxycarbonyl groups for acceleration of this 6-endo cyclization strongly suggests that the reaction would proceed via the 6π-azaelectrocyclization of the intermediary imidic acid. On the contrary, the corresponding 5-formyl and 5-acetyl derivatives rapidly cyclized at room temperature to produce the 5-exo cyclized products.

The substituted piperidines can be found as a core structural motif in many naturally occurring alkaloids, and have also been paid much attention because of their attractive pharmacological activities.[1] 2-Piperidinone is known as an effective synthon for substituted piperidines, because the stereocontrolled introduction of the desired functional groups into this cyclic amide is easily realized and produces the desired polysubstituted piperidines.[2,3a] Thus various kinds of methods for the synthesis of substituted 2-piperidinones have been reported.[3–6] They are roughly classified into four groups. The first one is the relatively classical and general method, which is the cyclization of amino acids or esters including the method using chiral bicyclic lactams originally developed by A. I. Meyers as chiral templates.[3] The second method is utilizing the Ring-Closing-Methathesis,[4] in which the stereochemistry of the substrate can be maintained in the product. The amidation reaction using Pd catalysts is classified as the third method.[5] The fourth one is the Diels–Alder reaction catalyzed by Lewis and Brønsted acids.[6] Although various kinds of methods for the synthesis of 2-piperidinone have already been reported, no application of the azaelectrocyclization of azatrienes and their equivalents has been reported. In this Letter, we describe the thermal 6-endo cyclization of *N*-sulfonyldienamides as a new method for the 2-piperidinone synthesis and also the remarkable accelerating effect on the cyclization due to the *N*-sulfonyl and the ester group at the C3 position. This method easily allowed us to obtain 4,6-disubstituted 2-piperidinones by only heating.

We have already developed an efficient synthetic method for multisubstituted chiral piperidine compounds based on the rapid 6π-azaelectrocyclization from 1-azatrienes over the past 10 years.[7] In this reaction, the key azaelectrocyclization step is dramatically accelerated by the C4 ester substituent in the azatriene due to the enhancement of the HOMO–LUMO interaction in the 6π electron system (Fig. 1A).[7j] We have also found that the *N*-sulfonyl group of the 1-azatrienes accelerates the 6π-azaelectrocyclization to produce the stabilized dihydropyridine derivatives by the similar protocol. This method was applied to the one-pot substituted pyridine synthesis in both the solution and solid phases.[7b,e] For further development of our accumulating knowledge on the activation of this system, we next focused on the more challenging variant, the catalytic 6π-azaelectrocyclization. The catalytic asymmetric 6-endo azacyclization of dienamide compounds possessing the ester group at the C3 position was achieved with the aid of the chiral BINAP–Pd complex catalyst to afford the corresponding chiral 2-piperidinone compounds (Fig. 1B).[8] Inspired by these reactions described above, we tried to realize the thermal 6-endo azacyclization of the *N*-sulfonyldienamide compounds that would include the 6π-azaelectrocyclization of the activated intermediary imidic acids, that is, the azatrienes (Fig. 1C).

We first investigated the reaction conditions of the thermal cyclization using the 3-ethoxycarbonyl-5-phenyl-*N*-sulfonyldieneamide derivative **1a** as a substrate for the cyclization (Table 1). It was synthesized by the Migita–Stille coupling of vinylstannane **4a** with vinyl iodide **3**, which was prepared from the acid **2** through

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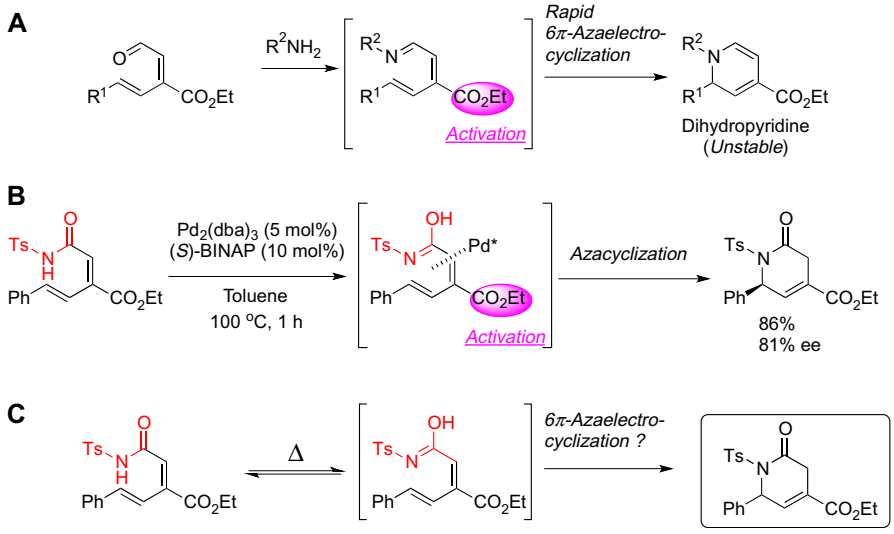
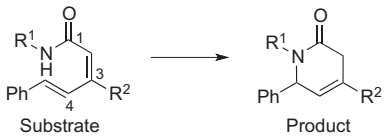
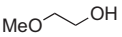
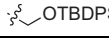


Figure 1. Azacyclization reaction accelerated by substituent effect.

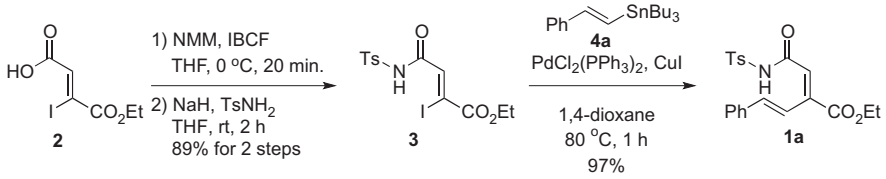
Table 1
Thermal 6-endo cyclization of dienamides **1a**, **6** and **8**



Entry	Substrate	R^1	R^2	Solvent	Condition	Product	Result
1	**1a**	Ts		Toluene	100 °C, 16 h	**5a**	No reaction
2	**1a**	Ts	As above	o-Xylene	130 °C, 4 h	**5a**	Quant.
3	**1a**	Ts	As above		130 °C, 4 h	**5a**	Trace
4	**1a**	Ts	As above	DMSO	130 °C, 4 h	**5a**	Trace
5	**6**	Bn	As above	o-Xylene	130 °C, 4 h	**7**	No reaction
6	**8**	Ts		o-Xylene	130 °C, 4 h	**9**	40% (32% recovered)

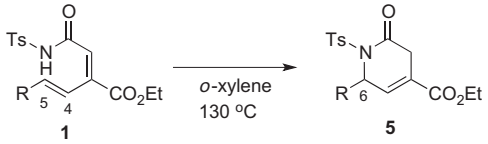
a mixed anhydride of isobutyl chloroformate (IBCF) in the presence of *N*-methylmorpholine (NMM) followed by sulfonamidation (Scheme 1).

Although the dienamide **1a** was stirred at 100 °C in toluene for 16 h only to give the starting material (entry 1), we admitted that the reaction of **1a** slightly proceeded at 110 °C in xylene after stirring for 1 h, however, it was not completed after 3 h at the same temperature. We then stirred the solution at 130 °C for 4 h. The reaction went to completion and the expected cyclized product **5a** was quantitatively obtained (entry 2).[9] 2-Methoxyethanol and dimethyl sulfoxide as a polar solvent were not suitable for this reaction (entries 3 and 4). Next, we investigated the substituent effect at the amide nitrogen and the C3 position. When the tosyl group attached at the amide nitrogen was replaced by a benzyl group, the thermal cyclization did not proceed at all (entry 5). Meanwhile, compound **8** afforded the cyclized product **9** in a 40% yield along with 32% of the starting material under the same reaction conditions (entry 6). This compound **8** possessed the bulky siloxymethyl group instead of the electron-withdrawing ethoxycarbonyl group in order to keep the *s-cis* conformation at the C3–4 bond. Thus, we found that the *N*-sulfonyl group was very important for this new thermal 6-endo cyclization reaction[10] and the ester group at the C3 position obviously accelerated this cyclization reaction.



Scheme 1. Synthesis of *N*-sulfonyldienamide.

Table 2
Generality of C5 substituent in thermal 6-endo cyclization



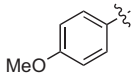
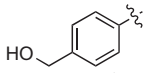
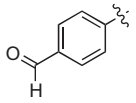
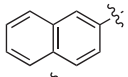
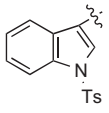
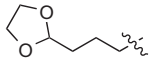
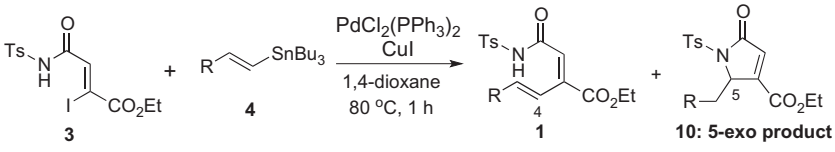
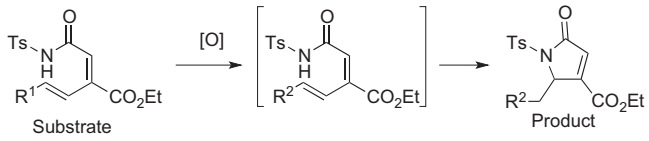
Entry	Substrate	R	Time (h)	Product	Yield (%)
1	**1a**		4	**5a**	Quant.
2	**1b**		2.5	**5b**	76
3	**1c**		4	**5c**	56
4	**1d**		4	**5d**	76
5	**1e**		4	**5e**	96
6	**1f**		3	**5f**	66
7	**1g**		4	**5g**	69
8	**1h**		4	**5h**	74
9	**1i**		4	**5i**	33
10	**1j**		4	**5j**	16

Table 3
One-pot 5-exo cyclization of C5 carbonyl-substituted dienamide



Entry	**4**	R	Result	
			1	10
1	**4k**		–	**10k**: 60%
2	**4l**		–	**10l**: 75%
3	**4m**		**1m**: 51%	**10m**: 13%
4	**4n**		**1n**: 75%	–
5	**4o**		**1o**: 65%	–

Table 4
5-Exo cyclization of C5 carbonyl-substituted dienamide



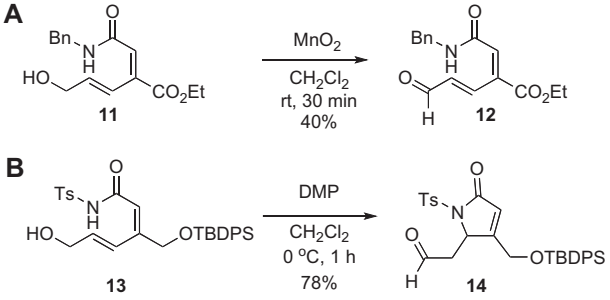
Entry	Substrate	R^1	Condition	Product	R^2	Yield (%)
1	**1n**	MnO2, CH_2Cl_2, rt, 30 min.		**10k**		58
2	**1o**	DMP, CH_2Cl_2, 0 °C, 30 min.		**10l**		96

To investigate the generality of the thermal 2-piperidinone synthesis resulting from the 6-endo cyclization, we next examined the cyclization using dienamide substrates having various C-5 substituents (Table 2). Substituted benzene derivatives, such as *p*-methoxyphenyl, *p*-hydroxymethylphenyl, *p*-formylphenyl, and *o*-tolyl derivatives (entries 2–5) allowed the cyclization to produce the 2-piperidinone compounds in good yields. Furthermore, the reaction of the various aromatic derivatives such as 2-naphthalenyl, 3-thiophenyl, and *N*-*p*-toluenesulfonyl-3-indolyl derivatives (entries 6–8), also produced the cyclized products in moderate yields. Additionally, alkyl derivatives, which were rather unstable at the reaction conditions at 130 °C, also gave the cyclized products in relatively lower yields (entries 9 and 10).

On the contrary, the coupling reaction of formyl vinylstannane **4k** with vinyl iodide **3** under the same reaction conditions as that of compound **3**–**1a** (Scheme 1) directly produced the 5-exo cyclized product **10k** in a 60% yield and not the corresponding dienamide and the 6-endo cyclized product (Table 3, entry 1). We then attempted a similar coupling reaction using the corresponding ketone **4l** with the same vinyl iodide **3** under the same reaction conditions, and also obtained the similar 5-exo cyclized product **10l** in a 75% yield (entry 2).[9] Meanwhile, in the case of ester **4m**, the coupling reaction gave the cyclized product **10m** and the uncyclized dienamide derivative **1m** in an 13% and a 51% yields, respectively, (entry 3). The stereochemistry of the 5-exo cyclized products was determined by the detailed NMR analysis (^{13}C, COSY, HMQC, HMBC, NOE). These results strongly suggested that the 5-exo cyclization, namely the Michael-type addition at the C4 position by the amide nitrogen, proceeded from the intermediary C5-formyl- and C5-acyl-2,4-dienamide derivatives resulting from the Migita–Stille coupling.

We then tried to confirm the possibility of a conjugated addition-type reaction. The corresponding allylic alcohols **1n** and **1o** were prepared by the coupling of **3** with the hydroxyl stannanes, **4n** and **4o**, respectively (Table 3, entries 4 and 5). Oxidation of the obtained primary alcohol **1n** with MnO_2 directly produced the cyclized compound **10k** at room temperature for 30 min in a 58% yield (Table 4, entry 1). Oxidation of the secondary alcohol **1o** with DMP at 0 °C cleanly produced the corresponding cyclized product **10l** in a 96% yield (entry 2). In both cases, the intermediate aldehyde and ketone were not admitted. Thus, the 6-endo and 5-exo cyclizations were clearly distinguished by the C-5 substituent.

Since we encountered the pronounced effect of the cyclization reaction due to the aldehyde and ketone groups at the C5 position, we investigated this substituent effect. When the allylic alcohol **11** possessing a *N*-benzyl group instead of a *N*-sulfonyl group was oxidized with MnO_2, the corresponding aldehyde **12** was isolated without cyclization (Scheme 2A). Meanwhile, for the compound having a bulky siloxy group instead of an ester group at the C3 position similar to the reaction from **8** to **9** (Table 1, entry 6), oxidation of the allylic alcohol **13** with DMP smoothly proceeded to produce the cyclized **14** at 0 °C in a 78% yield (Scheme 2B). Thus, the *N*-sufonyl group of the dienamide compounds was again essential for the 5-exo cyclization. On the other hand, the ester group at the C3 position during the 5-exo cyclization would not play a significant role.



Scheme 2. Substituent effect in 5-exo cyclization.

As a plausible mechanism of this thermal 6-endo cyclization reaction, two pathways would be possible. One is the 6π-azaelectrocyclization from the azatriene of the imidic acid form as shown in Figure 1C, which would be present in a solution resulting from the equilibrium of *N*-sulfonyldienamide. The *N*-sufonyl group must assist the imidic acid form of the dienamide, and the C3 ester group would activate the resulting azatriene equivalent leading to the easy cyclization. The other is the conjugated addition of nitrogen in the dienamide form or the imidic acid form to the diene. Considering the apparent contribution by the C3 ester group to the acceleration of the 6-endo cyclization reaction, the former mechanism is favorable because a similar substituent effect has been clearly observed in the previous 6π-azaelectrocyclization.[7j] We believe that our obtained results would be the first example of the thermal 6π-azaelectrocyclization of a dienamide as shown in Figure 1C.

In conclusion, we found a new thermal cyclization reaction of *N*-sulfonyldienamide, which would be the first example of the 6π-azaelectrocyclization of a dienamide. Meanwhile, for the compounds substituted by formyl and acetyl groups at the C5 position, the rapid 5-exo cyclization reaction proceeded resulting from the Michael type addition reaction. The application of this simple and easy thermal cyclization providing 4,6-disubstituted-2-piperidinones to natural product synthesis is now under way in our laboratory.

Acknowledgments

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Reaction Integration' (No.2105) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. This work was also supported by a Matching Fund Subsidy for a Private University.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.014.

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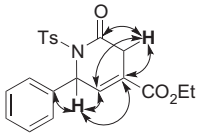
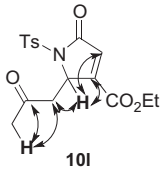
8. The paper describes the Pd catalyzed asymmetric 6-endo azacyclization of dienamides that has been submitted and is currently under evaluation.
9. The structures of compound **5a** and **10l** were determined by the detailed analyses of the corresponding NMR spectra (^{1}H, ^{13}C, COSY, HMQC, HMBC, NOE), in particular based on HMBC as shown in the following figures.

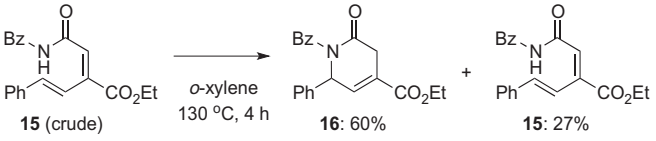


5a



10l

10. We tried to synthesize the *N*-benzoyl derivative **15** to examine the thermal cyclization reaction. However, compound **15** was relatively unstable and could not be obtained in the pure form. The attempts of the thermal cyclization of the crude **15** under the same reaction conditions to those of *N*-sulfonyl compound. gave the cyclized product **16** in roughly 60% yield along with the starting **15** in about 27% yield.



15 (crude) **16**: 60% **15**: 27%