Nucleophilic 5-*endo-trig* cyclizations of N-homoallylic sulfonamides: a facile method for the construction of pyrrolidine rings[†]

Junji Ichikawa,* Guillaume Lapointe and Yu Iwai

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Normally disfavored 5-*endo-trig* cyclizations proceed in *N*-homoallylsulfonamides bearing a CF₃, CCl₃, CO₂Et or CN group at the C-3 position, *via* an intramolecular S_N2' -type or addition reaction to construct pyrrolidine rings, even though the system allows a more favorable 5-*exo-trig* pathway.

It has long been considered, following Baldwin's rules,¹ that the 5-*endo-trig* cyclization is a geometrically disfavored process. These ring closures can be classified into three categories: nucleophile-driven,² electrophile-driven,³ and radical-initiated⁴ cyclizations. Among them, the nucleophile-driven 5-*endo-trig* cyclization has rarely been observed in synthetic chemistry and is still a challenge in organic synthesis.

Recently, we have accomplished the disfavored 5-endo-trig cyclization in 2-trifluoromethyl-1-alkenes 1 bearing a 4-methylbenzenesulfonamide (tosylamide: TsNH–) moiety as an intramolecular nucleophile (Scheme 1).⁵ The nitrogen anion attacked the alkene in an S_N2' fashion with elimination of a fluoride ion to afford difluoromethylene-substituted pyrrolidines 2. In this cyclization, the 5-endo-trig products were obtained without any products of the favored 5-exo-tet ring closure. These results show that (i) the trifluoromethyl group activates the C–C double bond in 1 to allow the normally disfavored 5-endo-trig cyclization and (ii) this reaction has a high potential in the synthesis of substituted pyrrolidines.⁶

To expand the scope of this synthetic method for functionalized pyrrolidines, the reactions of other types of electrophilic moieties with intramolecular *N*-nucleophiles have been investigated. Herein, we wish to report the nucleophilic 5-endo-trig cyclization of *N*-homoallylic sulfonamides containing an electron-withdrawing group at the C-3 position.

We first set our goal on 3-halomethyl-substituted analogs of *N*-homoallylsulfonamides (Table 1). Such substrates were expected



Scheme 1 Nucleophilic 5-endo-trig cyclization of *N*-(3-trifluoromethyl-homoallyl)sulfonamides **1**.

Department of Chemistry, Graduate School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo, Japan. E-mail: junji@chem.s.u-tokyo.ac.jp; Fax: +81-3-5841-4345;

Tel: +81-3-5841-4345

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to possess an S_N2'-type reactivity similar to that of 2-trifluoromethyl-1-alkenes. Their reaction with nucleophiles would occur at the terminal vinylic carbon, followed by elimination. Before investigating other 2-halomethyl-1-alkene systems, we confirmed that the substituent (R) at the homoallylic position did not affect the course of the reaction, because substrate 1b gave the 5-endo-trig product, pyrrolidine 2b, albeit in diminished yield (entry 2). When trichloromethyl-substituted alkene 1c was treated with NaH in DMF (N,N-dimethylformamide), cyclization readily proceeded in a 5-endo-trig fashion at 80 °C, a lower temperature than that of the trifluoromethyl counterpart, affording dichloromethylenesubstituted pyrrolidine 2c in 89% yield (entry 3). To evaluate the advantage of trihalomethyl (CX₃) groups in the 5-endo-trig process, we employed alkene substrates with a 2-monohalomethyl (CHDX) group, whose deuterium atom was introduced to differentiate between the 5-endo-trig and the 5-exo-tet products. In contrast to the trihalomethylated substrates, fluoromethyl-, chloromethyl- and bromomethyl-1-alkenes 1d-f underwent direct substitution without allylic rearrangement, leading to the 5-exo-tet product 3d exclusively (Table 1, entries 4-6).

The preference in **1a–c** for the 5-endo-trig cyclization over the normally favored 5-exo-tet cyclization can be explained as follows. The sulfonamidate, in the 5-exo-tet approach, meets severe electrostatic and steric repulsions from the halogens present on the trihalomethyl group, which consequently retards the normally favored 5-exo-trig process. On the other hand, the 5-endo-trig approach, while geometrically disfavored, has no such repulsions. Because the steric and electrostatic repulsions dominate over the geometric distortion, only the 5-endo-trig cyclization proceeds in the trihalomethyl substrates.

Table 1Nucleophilic cyclization of N-(3-halomethylhomoallyl)-
sulfonamides 1

Z TSHN	x	NaH /[(1.3 eq DMF))	N R	or Y	N R
1a–f					2a–c	3d	
Entry	1	CYZ	Х	R	Conditions	2 (%)	3 (%)
1 2 3 4 5 6	1a 1b 1c 1d 1e 1f	$\begin{array}{c} CF_2\\ CF_2\\ CCl_2\\ CHD\\ CHD\\ CHD\\ CHD \end{array}$	F F Cl F Cl Br	Ph H Ph Ph Ph Ph	130 °C, 3 h 130 °C, 4 h 80 °C, 1 h 110 °C, 2 h 50 °C, 1 h rt, 0.25 h	91 67 89 	91 86 89



Scheme 2 Nucleophilic 5-endo-trig cyclization of N-(3-trichlororomethylhomoallyl)sulfonamide 1g.

(Trichloromethyl)alkene 1g bearing a nosyl group (Ns: $o-NO_2C_6H_4SO_2$)⁷ on the nitrogen instead of a tosyl group also underwent the 5-endo-trig cyclization to afford pyrrolidine 2g (Scheme 2). However, other examined (trichloromethyl)alkenes with an intramolecular nitrogen nucleophile failed to cyclize. The substrates with a free amine (NH2-) or a benzylamine (PhCH₂NH-) moiety resulted in decomposition upon heating, probably due to the strongly basic conditions. The cyclization of the substrates with a benzamide (PhCONH-) or a carbamate (t-BuOCONH-) moiety gave poor results. This fact might be due to the partial pyramidalization of the sulfonamidate in the transition state,8 which could help the geometrically unfavorable cyclization, when compared with the planar amide and carbamate nitrogen anions. The relative stability of the N-sulfonamide nitrogen anions may also prevent decomposition prior to the cyclization.

Then, taking into account the relative electrophilicity of the trihalomethyl-substituted alkene moiety, we examined different electrophiles, such as α , β -unsaturated esters and nitriles (Table 2). Baldwin et al. previously reported that the 5-exo-trig cyclization proceeded more favorably than the 5-endo-trig pathway in an α,β -unsaturated ester bearing an amino group.¹ Pursuing the goal of 5-endo-trig cyclization, we adopted the aforementioned sulfonamide moiety as an N-nucleophile. Whereas treatment of ethyl ester 4a with 1 equiv. of NaH gave the expected 5-endo-trig product 5a only in 12% yield (entry 1), a catalytic amount (0.1 equiv.) of NaH^{2d} raised the yield to 87% (entry 2).[‡] When ethyl ester 4b and nitrile 4c were subjected to similar reaction conditions, the 5-endo-trig products 5b and 5c were obtained in high vield (entries 3 and 4). In contrast to ethyl esters, phenyl esters 4d and 4e afforded the 5-exo-trig cyclization products 6d and 6e exclusively (entries 5 and 6).§

 Table 2
 Nucleophilic cyclization of 2-functionalized 1-alkenes 4

EWC	G R	NaH	(0.1 e		R or OF	N Ts R
4ae				5a–c		6d–e
Entry	4	EWG	R	Conditions	5 (%) (anti:syn	b^{b} 6 (%)
1 ^{<i>a</i>} 2 3 4 5 6	4a 4b 4c 4d 4e	$\begin{array}{c} CO_2Et\\ CO_2Et\\ CO_2Et\\ CN\\ CO_2Ph\\ CO_2Ph\\ CO_2Ph \end{array}$	Ph Ph H Ph Ph H	110 °C, 3 h 110 °C, 3 h 110 °C, 4 h 50 °C, 4 h 100 °C, 1 h 100 °C, 1 h	$ \begin{array}{c} 12\\ 87\\ (59:41)^c\\ 72\\ 88\\ (37:63)^c\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\$	 90 76
^{<i>a</i>} NaH footnot	(1.0 e.¶	eq.) wa	ıs us	ed. ^b Determi	ined by ¹ H N	MR. ^c See



Scheme 3 Nucleophilic 5-endo-trig and 5-exo-trig cyclizations of α , β -unsaturated esters 4.

Thus, not only trihalomethyl groups (CF₃ and CCl₃) but other electron-withdrawing groups (CO₂Et and CN) also promote the 5-*endo-trig* cyclization. Moreover, both 5-*endo-trig* and 5-*exo-trig* cyclization products can be obtained by choosing an appropriate alkoxy group in the starting esters (CO₂Et or CO₂Ph).

In the α , β -unsaturated ester system, both preferences can be interpreted as follows (Scheme 3). The *5-exo-trig* cyclization of **A** preferentially proceeds up to intermediate **B**, which has two leaving groups, a sulfonamidate and an alkoxide. Because 4-methylbenzenesulfonamidate is a better leaving group than ethoxide, the reaction of ethyl esters **4a** and **4b** (R' = Et) goes back to intermediate **A**. Once the disfavored *5-endo-trig* cyclization proceeds, further protonation of intermediate **C** with the starting sulfonamide **4** occurs to give pyrrolidines **5**. On the other hand, phenyl esters **4d** and **4e** (R' = Ph) undergo elimination of phenoxide, a better leaving group than sulfonamidate, *via* intermediate **B** to give lactams **6**, the *5-exo-trig* products.

In conclusion, we have shown that sulfonamides are good intramolecular nucleophiles for the nucleophilic 5-endo-trig cyclization of electron-deficient alkenes. The normally disfavored 5-endo-trig cyclization is effected in N-homoallylsulfonamides bearing a CF₃, CCl₃, CO₂Et or CN group at the C-3 position, which provides an easy access to functionalized pyrrolidines. Thus, the nucleophilic 5-endo-trig cyclization can be achieved by choosing the right combination of nucleophile, electrophile, and reaction conditions.

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Notes and references

‡ *Representative procedure*: To a solution of *N*-(1-phenyl-3-ethoxycarbonyl-3-buten-1-yl)-4-methylbenzenesulfonamide (**4a**, 234 mg, 0.62 mmol) in DMF (6 mL) was added NaH (1.5 mg, 0.06 mmol) under argon. After the reaction mixture was stirred at 110 °C for 3 h, phosphate buffer (pH 7) was added to quench the reaction. The mixture was then extracted twice with AcOEt and the combined organic extracts were washed with water twice, brine and dried over Na₂SO₄. The solution was filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (AcOEt–hexane–Et₃N 20 : 79 : 1), affording **5a** (203 mg, 87%, *anti* : *syn* = 59 : 41) as a white solid. ¹H NMR (500 MHz, CDCl₃): *anti* **isomer**: δ 1.18 (3H, t, *J* = 7.1 Hz), 2.06 (1H, ddd, *J* = 12.5, 6.7, 3.0 Hz),

2.13–2.20 (1H, m), 2.41 (3H, s), 3.08 (1H, dddd, J = 6.3, 6.3, 6.3, 6.3, Hz), 3.57 (1H, dd, J = 10.1, 8.7 Hz), 3.89 (1H, dd, J = 10.1, 7.9 Hz), 4.00–4.05 (2H, m), 4.90 (1H, dd, J = 8.1, 3.0 Hz), 7.20–7.31 (7H, m), 7.69 (2H, d, J = 8.4 Hz); *syn* isomer: δ 1.15 (3H, t, J = 7.1 Hz), 2.13–2.20 (1H, m), 2.43 (3H, s), 2.49 (1H, ddd, J = 13.0, 7.7, 7.7 Hz), 2.71 (1H, dddd, J = 6.0, 6.0, 6.0, 6.0 Hz), 3.77 (1H, dd, J = 11.3, 8.9 Hz), 3.91 (1H, dd, J = 11.3, 8.0 Hz), 4.00–4.05 (2H, m), 4.74 (1H, dd, J = 7.7, 7.7 Hz), 7.22–7.31 (7H, m), 7.60 (2H, d, J = 8.4 Hz). ¹³C NMR (126 MHz, CDCl₃): *anti* isomer: δ 14.0, 21.5, 38.3, 41.3, 50.8, 61.0, 62.8, 125.9, 126.4, 127.4, 127.5, 128.4, 134.5, 142.0, 143.5, 171.8; *syn* isomer: δ 14.0, 21.5, 39.4, 42.6, 51.1, 61.0, 63.6, 125.9, 126.3, 127.3, 127.5, 128.3, 135.1, 141.5, 143.5, 171.4. IR (neat) 3032, 2920, 2850, 1732, 1348, 1219, 1161, 914 cm⁻¹. Anal. Calcd. for C₂₀H₂₃NO₄S; C, 64.32; H, 6.21; N, 3.75. Found: C, 64.07; H, 6.17; N, 3.55%.

§ The 5-exo-trig cyclization was easily effected also in other active carboxylic acid derivatives, such as acyl chlorides and mixed anhydrides.



¶ The 2,4-*antilsyn* stereochemistry of pyrrolidine **5a** was determined by NOESY experiment. A cross peak between the 2- and 4-protons was not observed in the major product, but in the minor product. The signals of the 2- and 4-protons in the *anti*-isomer were observed at lower field (δ 4.90 and 3.08) than those in the *syn*-isomer (δ 4.74 and 2.71). The configuration of **5c** was determined by analogy with **5a** by comparing the C2- and C4-proton chemical shifts of each isomer.



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