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# Ring-Closing Reaction of Allenic/Propargylic Anions Generated by Base Treatment of Sulfonylallenes

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# Ring-Closing Reaction of Allenic/Propargylic Anions Generated by Base Treatment of Sulfonylallenes

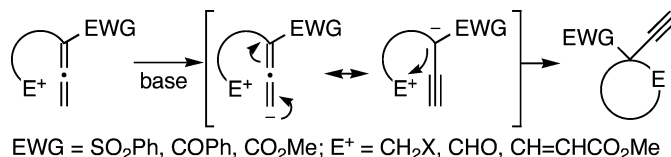
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## ABSTRACT



The intramolecular trapping of allenyl/propargyl anions generated by base treatment of sulfonylallenes was investigated. Treatment of 1-( $\omega$ -iodoalkyl)-1-(phenylsulfonyl)allenes with TBAF or NaH in DMF efficiently produced three- to seven-membered 1-ethynyl-1-(phenylsulfonyl)substituted carbocycles. The allenyl/propargyl anions could also be intramolecularly trapped using a terminal aldehyde or  $\alpha,\beta$ -unsaturated ester. The phenylsulfonyl group was found to be replaced by other electron-withdrawing functionalities like ketone and ester groups but not by an alkyl group for this novel ring-closing reaction.

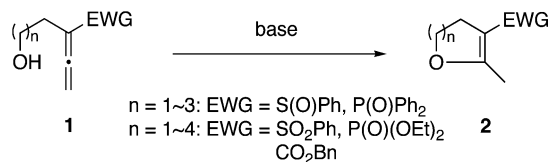
It is well-known that the  $\gamma$ -proton of an allyl functionality possessing an electron-withdrawing group (EWG) at the  $\alpha$ -position is acidic enough to be abstracted by strong amide bases, such as lithium diisopropylamide (LDA), at low temperature. The allyl anion species, thus generated, could be used for a variety of carbon–carbon bond formations, exemplified by the vinylogous aldol reaction, in organic synthesis.<sup>1</sup> On the other hand, the  $\gamma$ -allenic proton having an EWG at the  $\alpha$ -position, namely the proton of the sp<sup>2</sup>-hybridized carbon of the 1-EWG-allene species, would be anticipated to be more acidic than that of the sp<sup>3</sup>-hybridized carbon of the 1-EWG-allyl species owing to the following two factors. One is that the C–H  $\sigma$  bond of the  $\gamma$ -carbon is strictly eclipsed by the  $\pi$  bond between the  $\alpha$ - and  $\beta$ -carbons, thereby introduction of an EWG at the  $\alpha$ -position would markedly increase its acidity, and the other factor is an inherently higher s character of the allenic  $\gamma$ -carbon (sp<sup>2</sup>-hybridized carbon) than the allylic carbon (sp<sup>3</sup>-hybridized carbon).

As a part of our studies<sup>2</sup> on the development of novel and efficient methods for ring-closing reactions by taking advantage of the intrinsic property of allenes, we have demonstrated that allenes **1** having an EWG and an  $\omega$ -hydroxyalkyl group at the same allenic terminus easily underwent the endo–dig mode ring-closing reaction to produce the five- to eight-membered oxacycles **2** (Scheme 1).<sup>2a,f,n</sup> We now envisaged, on the basis of the above prediction regarding the acidity of the  $\gamma$ -allenic proton having an EWG at the  $\alpha$ -position, that replacing the terminal hydroxy group of **1**

(1) For reviews, see: (a) Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682–4698. (b) Kalesse, M. *Top. Curr. Chem.* **2005**, *244*, 43–76. (c) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929–1972.

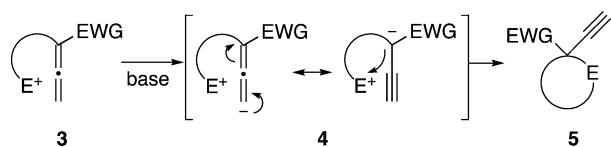
(2) (a) Mukai, C.; Yamashita, H.; Hanaoka, M. *Org. Lett.* **2001**, *3*, 3385–3387. (b) Mukai, C.; Nomura, I.; Yamanishi, K.; Hanaoka, M. *Org. Lett.* **2002**, *4*, 1755–1758. (c) Mukai, C.; Ukon, R.; Kuroda, N. *Tetrahedron Lett.* **2003**, *44*, 1583–1586. (d) Mukai, C.; Inagaki, F.; Yoshida, T.; Kitagaki, S. *Tetrahedron Lett.* **2004**, *45*, 4117–4121. (e) Mukai, C.; Kobayashi, M.; Kubota, S.; Takahashi, Y.; Kitagaki, S. *J. Org. Chem.* **2004**, *69*, 2128–2136. (f) Mukai, C.; Ohta, M.; Yamashita, H.; Kitagaki, S. *J. Org. Chem.* **2004**, *69*, 6867–6873. (g) Mukai, C.; Kuroda, N.; Ukon, R.; Itoh, R. *J. Org. Chem.* **2005**, *70*, 6282–6290. (h) Mukai, C.; Takahashi, Y. *Org. Lett.* **2005**, *7*, 5793–5796. (i) Kitagaki, S.; Ohdachi, K.; Katoh, K.; Mukai, C. *Org. Lett.* **2006**, *8*, 95–98. (j) Inagaki, F.; Mukai, C. *Org. Lett.* **2006**, *8*, 1217–1220. (k) Kuroda, N.; Takahashi, Y.; Yoshinaga, K.; Mukai, C. *Org. Lett.* **2006**, *8*, 1843–1845. (l) Kitagaki, S.; Okumura, Y.; Mukai, C. *Tetrahedron Lett.* **2006**, *47*, 1849–1852. (m) Mukai, C.; Itoh, R. *Tetrahedron Lett.* **2006**, *47*, 3971–3974. (n) Kitagaki, S.; Shibata, D.; Mukai, C. *Tetrahedron Lett.* **2007**, *48*, 1735–1738.

**Scheme 1.** Ring-Closing Reaction of Electron-Withdrawing Group Substituted Allenes **1**



by the proper electrophilic functionality and its base treatment might result in the unprecedented ring-closing reaction via intramolecular trapping of the allenic/propargylic anion **4** to form 1-ethynyl-1-sulfonyl substituted carbocycles **5** (Scheme 2). To the best of our knowledge, a reaction based on such

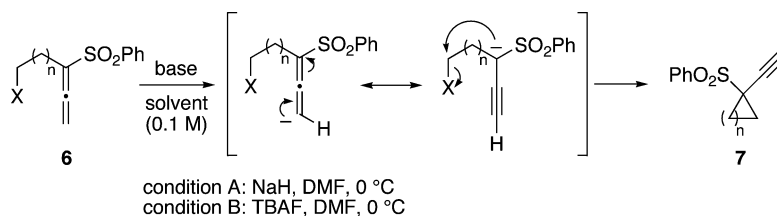
**Scheme 2.** Ring-Closing Reaction of Allenyl/Propargyl Anion



a consideration has not yet been reported.<sup>3–6</sup> We now report a novel ring-closing reaction based on the easy abstraction of the  $\gamma$ -allenic proton activated by the sulfonyl and other EWGs.

We first examined the construction of a three-membered ring from 1-(phenylsulfonyl)-1-(tosyloxyethyl)allene (**6a**). Thus, a 0.1 M THF solution of **6a** was treated with a commercially available 1.0 M THF solution of TBAF at 0 °C for 0.5 h to afford 1-ethynyl-1-(phenylsulfonyl)cyclopropane (**7a**) in 97% yield (Table 1, entry 1).<sup>7</sup> Treatment with NaH produced a similar result (entry 2). Interestingly, the ring-closing product was obtained in 71% yield even using K<sub>2</sub>CO<sub>3</sub>, although a fairly prolonged reaction time was needed (46 h, starting material 17% recovery) (entry 3). No reaction occurred when triethylamine was used (entry 4). The ring-closing conditions, which provided excellent results for the formation of the cyclopropane skeleton, could not be applied to the construction of the six-membered one. Indeed, the reaction of tosyloxypentallene **6b** with NaH in THF formed the cyclohexane derivative **7b** in only 17% yield (entry 5). The use of DMF as a solvent resulted in a similar level of efficiency, though consumption of the starting material was markedly fast (entry 6). Changing the leaving group from the tosyloxy to iodo group brought about a drastic improvement in the chemical yield. Upon treatment of iodopentallene **6b'** with NaH, the reaction in DMF at 0 °C (condition A) smoothly proceeded to give the cyclohexane derivative **7b** in 92% yield (entry 8). TBAF in DMF at 0 °C (condition B) was also effective for this conversion (91% yield) (entry 9), but the use of THF at 0 °C gave poor results (entry 7). These two conditions (conditions A and B) could be applicable for the construction of not only the five-

**Table 1.** Ring-Closing Reaction of Allenes **6**



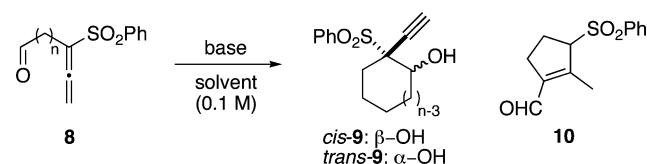
entry	substrate			conditions	yield of <b>7</b> (%)
	<b>6</b>	n	X		
1	<b>6a</b>	1	OTs	TBAF, THF, 0 °C, 0.5 h	97
2	<b>6a</b>	1	OTs	NaH, THF, 0 °C, 0.5 h	94
3	<b>6a</b>	1	OTs	K <sub>2</sub> CO <sub>3</sub> , THF, 0 °C → rt, 46 h	71 <sup>a</sup>
4	<b>6a</b>	1	OTs	Et <sub>3</sub> N, THF, 0 °C → rt, 24 h	<i>b</i>
5	<b>6b</b>	4	OTs	NaH, THF, 0 °C, 6 h	17
6	<b>6b</b>	4	OTs	A, 0.5 h	21
7	<b>6b'</b>	4	I	NaH, THF, 0 °C, 5 h	30
8	<b>6b'</b>	4	I	A, 0.5 h	92
9	<b>6b'</b>	4	I	B, 0.5 h	91
10	<b>6c</b>	3	I	A, 0.5 h	quant
11	<b>6c</b>	3	I	B, 0.5 h	90
12	<b>6d</b>	2	I	A, 0.5 h	88
13	<b>6d</b>	2	I	B, 0.5 h	87
14	<b>6e</b>	5	I	B, 0.5 h	53
15	<b>6e</b>	5	I	A, 0.5 h	51
16	<b>6e</b>	5	I	A, 0.5 h <sup>c</sup>	85

<sup>a</sup> Starting material **6a** was recovered in 17% yield. <sup>b</sup> Starting material **6a** was recovered in 96% yield. <sup>c</sup> Reaction was performed in 0.01 M solution.

membered ring but also a four-membered one (entries 10–13). Furthermore, the efficient formation of a seven-membered ring was achieved under a diluted condition (0.01 M) (entry 16). The eight-membered carbocycle, however, was not obtained under any conditions.

To establish the availability of the allenic/propargylic anion, generated by treatment with a base, we extended the present protocol to sulfonylallenes having an aldehyde moiety as an electrophilic partner (Table 2). While the reaction of

**Table 2.** Ring-Closing Reaction of Allenes **8**



entry	substrate	n	conditions	yield of <b>9</b> (%)	(cis:trans) <sup>a</sup>
1	<b>8a</b>	4	NaH, DMF, 0 °C (condition A)	<i>b</i>	
2	<b>8a</b>	4	NaH, DMF, –78 °C	81	(5:4)
3	<b>8a</b>	4	K <sub>2</sub> CO <sub>3</sub> , DMF, 0 °C	85	(3:1)
4	<b>8a</b>	4	DBU, DMF, 0 °C	85	(2:1)
5	<b>8a</b>	4	LHMDS, THF, –78 °C	37	(2:1)
6	<b>8a</b>	4	<i>t</i> BuOK, THF, –78 °C	80	(5:1)
7	<b>8a</b>	4	TBAF, DMF, 0 °C (condition B)	92	(5:1)
8	<b>8a</b>	4	TBAF, DMF, –20 °C	88	(5:1)
9	<b>8a</b>	4	TBAF, DMF, –40 °C	85	(5:1)
10	<b>8a</b>	4	TBAF, DMF, –60 °C	73	(3:4)
11	<b>8a</b>	4	TBAF, THF, 0 °C	90	(3:1)
12	<b>8a</b>	4	TBAF, CH <sub>2</sub> Cl <sub>2</sub> , 0 °C	90	(5:2)
13	<b>8a</b>	4	TBAF, toluene, 0 °C	92	(2:1)
14	<b>8b</b>	3	condition B	<i>c</i>	
15	<b>8b</b>	3	TBAF, DMF, –40 °C	62	(1:0)
16	<b>8b</b>	3	TBAF, DMF, –60 °C	69	(1:0)

<sup>a</sup> The ratio was determined by <sup>1</sup>H NMR. <sup>b</sup> Compound **9** could not be detected in the product mixture. <sup>c</sup> Aldehyde **10** was obtained as an isolatable product in 26% yield.

the allenyl aldehyde **8a** under condition A afforded an intractable mixture, the same conditions at a lower temperature (–78 °C) led to the production of the desired

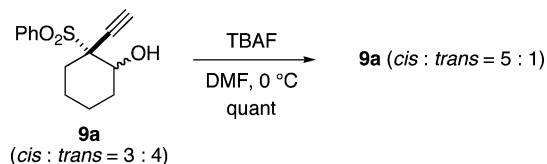
(3) For the generation and reaction of allenyl/propargyl anions, see: (a) Marshall, J. A.; Gung, B. W.; Grachan, M. L. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004, Vol. 1, Chapter 9. (b) Back, T. G. *Tetrahedron* **2001**, *57*, 5263–5301. (c) Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805–2827. (d) Schuster, H. F., Coppola, G. M., Eds. *Allenenes in Organic Syntheses*; Wiley: New York, 1984. (e) Epsztein, R. In *Studies in Organic Chemistry 5, Comprehensive Carbanion Chemistry, Part B*; Buncl, E., Durst, T., Eds.; Elsevier: Amsterdam, The Netherlands, 1984; Chapter 3.

(4) Baudin reported the intermolecular trapping of anions, derived from allenyl sulfoxides and methyl lithium, with some electrophiles: Baudin, J. B.; Julia, S. A.; Lorne, R. *Bull. Soc. Chim., Fr.* **1992**, *129*, 440–456.

(5) Padwa reported the intermolecular reaction of 1-methyl-1-(phenylsulfonyl)allene with methyl vinyl ketone in the presence of sodium benzenesulfonate resulting in the formation of 5-methyl-5-(phenylsulfonyl)-hept-6-yn-2-one. This result could be interpreted on the basis that the benzenesulfonate anion acted as a base and the resulting propargyl anion underwent conjugate addition with methyl vinyl ketone: Padwa, A.; Yeske, P. E. *J. Org. Chem.* **1991**, *56*, 6386–6390.

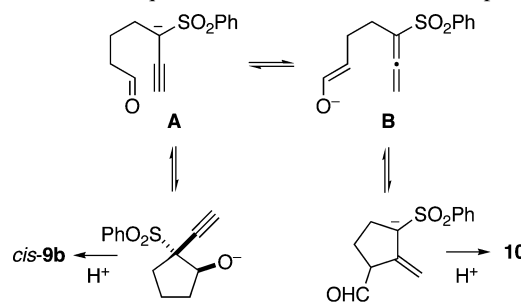
2-ethynylcyclohexanol **9a** in a 5:4 ratio of *cis* and *trans* isomers<sup>8</sup> (entries 1 and 2). The use of K<sub>2</sub>CO<sub>3</sub> and DBU also gave **9a** in a high yield with a modest selectivity, respectively (entries 3 and 4). The anticipated chelation-controlled synthesis of **9a** with the metal bis(trimethylsilyl)amide could not be realized (entry 5). The highest selectivity (5:1) was attained using *t*BuOK in THF at –78 °C and condition B (entries 6 and 7). The lower temperature (–60 °C) under condition B brought about the reverse stereoselectivity (entries 8–10). This temperature-dependent stereoselectivity for the reaction with TBAF in DMF indicates that *cis*-**9a** must be the thermodynamic product under this condition. In fact, the mixture of products [Table 2, entry 10 (*cis*-**9a**/*trans*-**9a** = 3:4)] was exposed to TBAF in DMF at 0 °C (condition B) to give a mixture of *cis*-**9a** and *trans*-**9a** in a ratio of 5:1, which is similar to the product ratio observed in entry 7 (Scheme 3). Less polar solvents (THF, CH<sub>2</sub>Cl<sub>2</sub>,

**Scheme 3.** Recycling of **9** under Condition B



toluene) provided rather low selectivities (entries 11–13). When the one-carbon shorter **8b** was exposed to condition B, cyclopentenecarbaldehyde **10**, presumably formed via the addition of an aldehyde enolate to the allene in an endo-mode ring-closing manner,<sup>2a,c,e–h,k,n</sup> was obtained in 26% yield instead of the expected cyclopentanol **9b** (entry 14). Lowering the reaction temperature to –40 or –60 °C resulted in the selective production of *cis*-**9b** as a single stereoisomer in good yields (entries 15 and 16). Because *cis*-**9b** was isomerized to **10** under condition B, the relation between **9b** and **10** would be rationalized in terms of an equilibrium between anions **A** and **B** as shown in Scheme 4, where the

**Scheme 4.** Equilibrium between Some Anion Species

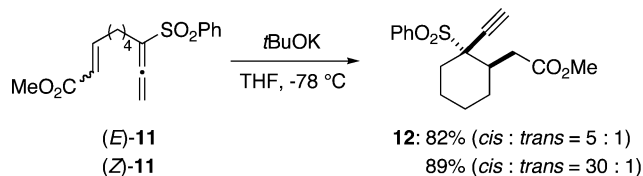


allenyl/propargyl anion **A** kinetically attacks the aldehyde moiety, whereas **10** must be the thermodynamically controlled product.

The reaction of the  $\alpha,\beta$ -unsaturated ester-containing substrates **11** was the next subject to examine. For the

transformation of **11** into the corresponding cyclohexane derivative **12**, *t*BuOK was shown to afford high yields as well as a high stereoselectivity of the ring-closing products **12** (Scheme 5). It is noteworthy that (*Z*)-**11** showed higher diastereoselectivity than (*E*)-**11**.<sup>9</sup>

**Scheme 5.** Ring-Closing Reaction of  $\alpha,\beta$ -Unsaturated Esters



Finally, the effect of the substituents at the allenic position was studied under conditions A and B using iodoallenes **13**. While the result obtained using the benzoyl group substituted allene **13a** was in good accordance with those of **6c**, the ester group substituted **13b** provided a rather low yield

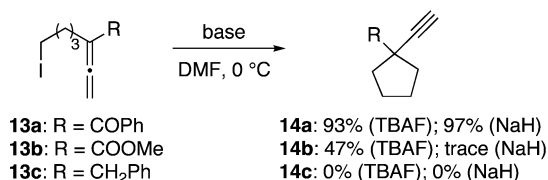
(6) Miesch reported the intramolecular reaction of the propargyl anion, derived from the conjugated acetylenic ester, with the carbonyl function, see: (a) Wendling, F.; Miesch, M. *Org. Lett.* **2001**, 3, 2689–2691. (b) Mota, A. J.; Klein, A.; Wendling, F.; Dedieu, A.; Miesch, M. *Eur. J. Org. Chem.* **2005**, 4346–4358.

(7) TBAF treatment of 1-(phenylsulfonyl)-1-(tosyloxymethyl)allene afforded 2-(phenylsulfonyl)but-1-en-3-yne via 1,4-elimination in 87% yield. Similar reaction using 1-(acetoxymethyl)-1-(phenylsulfonyl)allene and triethylamine was reported by Bridges and Fischer: Bridges, A. J.; Fischer, J. W. *J. Chem. Soc., Chem. Commun.* **1982**, 665–666.

(8) The stereochemical assignments were made by a <sup>1</sup>H NMR consideration. A NOE experiment with 2-vinylcyclohexyl acetate possessing a *trans* relationship between ethynyl group and hydroxy functionality, which was derived from *trans*-**9a** by acetylation and Lindlar reduction, showed an enhancement between the vinyl protons and H-1 of the cyclohexane ring, while the corresponding vinyl derivative, prepared from *cis*-**9a**, showed no enhancement.

(9) The stereoselectivity observed during the production of *cis*-**12** from (*Z*)-**11** was significantly higher than that from (*E*)-**11**. Investigation of the stereoselectivity for this transformation is currently underway.

**Scheme 6.** Ring-Closing Reaction of Allenes **13**



(Scheme 6). For the benzylallene **13c**, the elimination of hydrogen iodide mainly occurred and no ring-closing product was obtained at all. These results strongly suggest that the electron-withdrawing ability of the  $\alpha$ -substituent on the allenyl moiety must play an important role in this ring-closing reaction.

In conclusion, we have described that the sulfonylallenes could be deprotonated by a mild base, exemplified by TBAF, to form the allenic/propargylic anion species, which subsequently reacts with an electrophilic partner such as the haloalkyl group, aldehyde, or  $\alpha,\beta$ -unsaturated ester. In addition, other substituents bearing a strong electron-withdrawing ability comparable to the sulfonyl group were found to be used for this novel ring-closing reaction.

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**Supporting Information Available:** Experimental procedures for preparation and ring-closing reaction of allenes, characterization data for compounds **6–14**, and their <sup>1</sup>H and <sup>13</sup>C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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