ORGANIC
LETTERS

2007
Vol. 9, No. 13
2549−2552

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

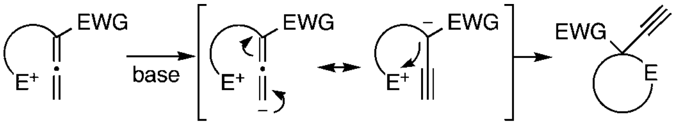
Shinji Kitagaki, Satoshi Teramoto, and Chisato Mukai*

Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

cmukai@kenroku.kanazawa-u.ac.jp

Received April 20, 2007

ABSTRACT



EWG = SO_2Ph, COPh, CO_2Me; E^+ = CH_2X, CHO, $CH{=}CHCO_2Me$

The intramolecular trapping of allenyl/propargyl anions generated by base treatment of sulfonylallenes was investigated. Treatment of 1-(*ω*-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 α,*β*-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 γ-proton of an allyl functionality possessing an electron-withdrawing group (EWG) at the α-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.[1] On the other hand, the γ-allenic proton having an EWG at the α-position, namely the proton of the sp^2-hybridized carbon of the 1-EWG-allene species, would be anticipated to be more acidic than that of the sp^3-hybridized carbon of the 1-EWG-allyl species owing to the following two factors. One is that the C−H σ bond of the γ-carbon is strictly eclipsed by the π bond between the α- and β-carbons, thereby introduction of an EWG at the α-position would markedly increase its acidity, and the other factor is an inherently higher s character of the allenic γ-carbon (sp^2-hybridized carbon) than the allylic carbon (sp^3-hybridized carbon).

As a part of our studies[2] 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 ω-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).[2a,f,n] We now envisaged, on the basis of the above prediction regarding the acidity of the γ-allenic proton having an EWG at the α-position, that replacing the terminal hydroxy group of **1**

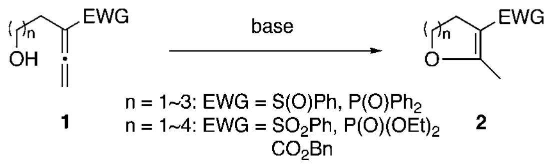
---

(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.

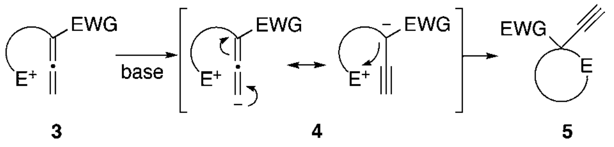
10.1021/ol0709329 CCC: $37.00

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



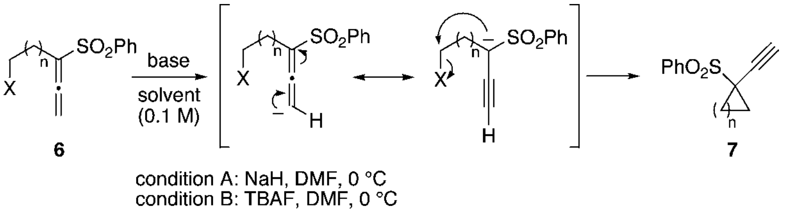
by the proper electrophilic functionality and its base treatment might result in the unprecedented ring-closing reaction via intramolecular trapping of the allenic/propargylic anion **4** to form 1-ethynyl-1-sulfonyl substituted carbocycles **5** (Scheme 2). To the best of our knowledge, a reaction based on such a consideration has not yet been reported.[3−6] We now report a novel ring-closing reaction based on the easy abstraction of the γ-allenic proton activated by the sulfonyl and other EWGs.

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



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).[7] Treatment with NaH produced a similar result (entry 2). Interestingly, the ring-closing product was obtained in 71% yield even using K_2CO_3, 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 tosyloxypentylallene **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 iodopentylallene **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**



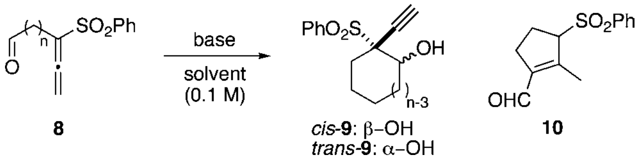
entry	substrate 6	n	X	conditions	yield of **7** (%)
1	**6a**	1	OTs	TBAF, THF, 0 °C, 0.5 h	97
2	**6a**	1	OTs	NaH, THF, 0 °C, 0.5 h	94
3	**6a**	1	OTs	K_2CO_3, THF, 0 °C → rt, 46 h	71[a]
4	**6a**	1	OTs	Et_3N, THF, 0 °C → rt, 24 h	[b]
5	**6b**	4	OTs	NaH, THF, 0 °C, 6 h	17
6	**6b**	4	OTs	A, 0.5 h	21
7	**6b′**	4	I	NaH, THF, 0 °C, 5 h	30
8	**6b′**	4	I	A, 0.5 h	92
9	**6b′**	4	I	B, 0.5 h	91
10	**6c**	3	I	A, 0.5 h	quant
11	**6c**	3	I	B, 0.5 h	90
12	**6d**	2	I	A, 0.5 h	88
13	**6d**	2	I	B, 0.5 h	87
14	**6e**	5	I	B, 0.5 h	53
15	**6e**	5	I	A, 0.5 h	51
16	**6e**	5	I	A, 0.5 h[c]	85

[a] Starting material **6a** was recovered in 17% yield. [b] Starting material **6a** was recovered in 96% yield. [c] 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 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 2-ethynylcyclohexanol **9a** in a 5:4 ratio of *cis* and *trans* isomers[8] (entries 1 and 2). The use of K_2CO_3 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_2Cl_2, 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,[2a,c,e−h,k,n] 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 allenyl/propargyl anion **A** kinetically attacks the aldehyde moiety, whereas **10** must be the thermodynamically controlled product.

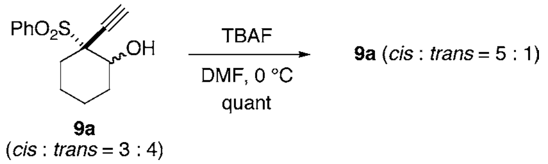
Table 2. Ring-Closing Reaction of Allenes **8**



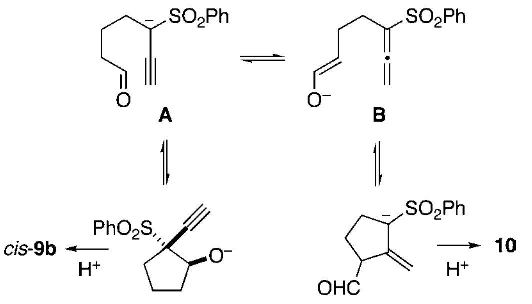
	substrate			yield of **9** (%)	
entry	8	n	conditions	(cis:trans)[a]	
1	**8a**	4	NaH, DMF, 0 °C (condition A)	*b*	
2	**8a**	4	NaH, DMF, −78 °C	81	(5:4)
3	**8a**	4	K_2CO_3, DMF, 0 °C	85	(3:1)
4	**8a**	4	DBU, DMF, 0 °C	85	(2:1)
5	**8a**	4	LHMDS, THF, −78 °C	37	(2:1)
6	**8a**	4	*t*BuOK, THF, −78 °C	80	(5:1)
7	**8a**	4	TBAF, DMF, 0 °C (condition B)	92	(5:1)
8	**8a**	4	TBAF, DMF, −20 °C	88	(5:1)
9	**8a**	4	TBAF, DMF, −40 °C	85	(5:1)
10	**8a**	4	TBAF, DMF, −60 °C	73	(3:4)
11	**8a**	4	TBAF, THF, 0 °C	90	(3:1)
12	**8a**	4	TBAF, CH_2Cl_2, 0 °C	90	(5:2)
13	**8a**	4	TBAF, toluene, 0 °C	92	(2:1)
14	**8b**	3	condition B	*c*	
15	**8b**	3	TBAF, DMF, −40 °C	62	(1:0)
16	**8b**	3	TBAF, DMF, −60 °C	69	(1:0)

[a] The ratio was determined by ^{1}H NMR. [b] Compound **9** could not be detected in the product mixture. [c] Aldehyde **10** was obtained as an isolatable product in 26% yield.

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



Scheme 4. Equilibrium between Some Anion Species



The reaction of the α,*β*-unsaturated ester-containing substrates **11** was the next subject to examine. For the

---

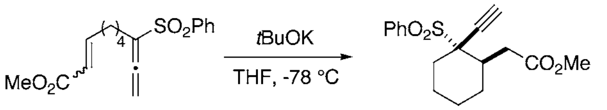
(3) For the generation and reaction of allenyl/propargyl anions, see: (a) Marshall, J. A.; Gung, B. W.; Grachan, M. L. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004, Vol. 1, Chapter 9. (b) Back, T. G. *Tetrahedron* **2001**, *57*, 5263−5301. (c) Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805−2827. (d) Schuster, H. F., Coppola, G. M., Eds. *Allenes in Organic Syntheses*; Wiley: New York, 1984. (e) Epsztein, R. In *Studies in Organic Chemistry 5, Comprehensive Carbanion Chemistry, Part B*; Buncel, 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 benzenesulfinate resulting in the formation of 5-methyl-5-(phenylsulfonyl)-hept-6-yn-2-one. This result could be interpreted on the basis that the benzenesulfinate 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.

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**.[9]

Scheme 5. Ring-Closing Reaction of α,*β*-Unsaturated Esters

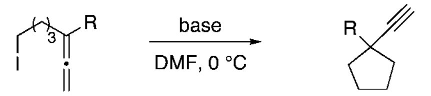


(*E*)-**11** — **12**: 82% (*cis* : *trans* = 5 : 1)

(*Z*)-**11** — 89% (*cis* : *trans* = 30 : 1)

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 (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 α-substituent on the allenyl moiety must play an important role in this ring-closing reaction.

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



13a: R = COPh — **14a**: 93% (TBAF); 97% (NaH)

13b: R = COOMe — **14b**: 47% (TBAF); trace (NaH)

13c: R = CH_2Ph — **14c**: 0% (TBAF); 0% (NaH)

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 α,*β*-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.

Acknowledgment. This work was supported in part by a Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, for which we are grateful.

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

OL0709329

---

(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-(phenylsulfinyl)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 ^{1}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.