



Cyclohexynes as Intermediates in a Novel *endo*-Cyclization of Alkynylzincates Derived from 5-Hexynyl Tosylates

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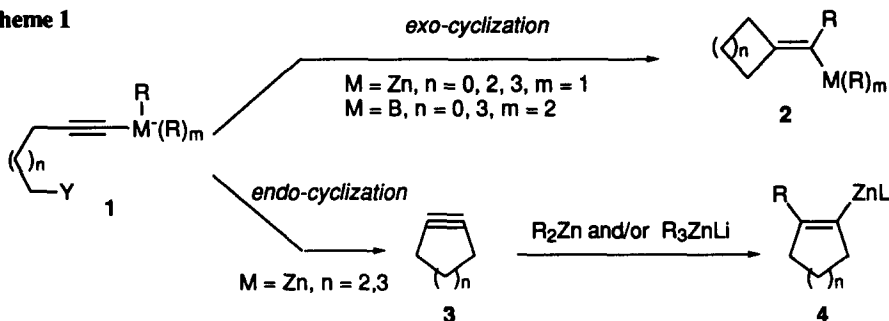
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Abstract: The π -type *endo*-cyclization of metal acetylides to form cyclohexynes was observed for the first time in the reaction of alkynylzincates derived from 5-hexynyl tosylates. The *endo*-cyclization took place in competition with *exo*-cyclization, leading to the formation of 1-(cyclopentylidene)alkylzincs.

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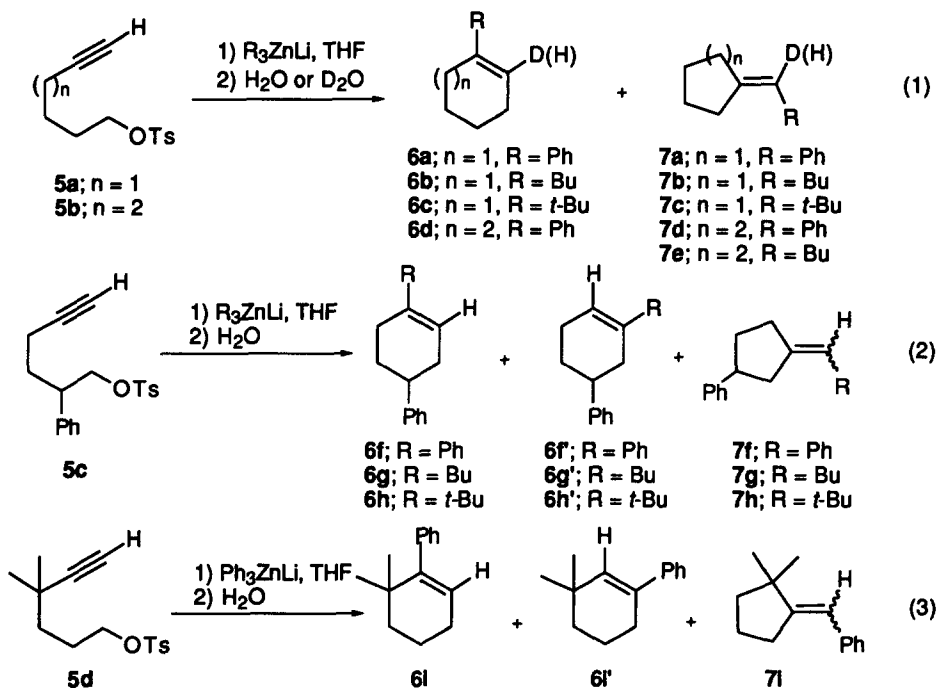
Alkynyltrialkylborates **1** ($M = B, m = 2, n = 0$ or 3) bearing a remote electrophilic center undergo *exo*-cyclization with 1,2-migration of the alkyl ligand to give organoboron derivatives of alkylidenecycloalkanes **2** (Scheme 1).^{1,2} We have recently shown that alkynylzincates **1** ($M = Zn, m = 1, n = 0$) derived from homopropargylic arenesulfonates undergo a similar *exo*-cyclization to afford synthetically useful 1-(cyclopropylidene)alkylzincs **2**.³ Herein, we wish to report a novel *endo*-cyclization of homologous alkynylzincates **1** ($M = Zn, n = 2, 3$) leading to cycloalkenylzincs **4** through the intermediacy of strained cycloalkynes **3**. Although alkylation of metal acetylides is a well-established process and the intramolecular version of the reaction has often been used for the synthesis of medium- and large-ring cycloalkynes,⁴ the formation of smaller-ring, strained cycloalkynes has been considered to be stereoelectronically unfavorable. To our knowledge, this is the first example of cyclization of metal acetylides to form strained cycloalkynes.^{3,4}

Scheme 1



Treatment of tosylates **5a,b** with lithium triorganozincates (2.0 equiv) in THF at temperatures from -80 °C to rt and quenching of the mixture with D_2O and/or H_2O gave a mixture of *endo*-cyclization products **6a-d** and *exo*-cyclization products **7a-d** (eq 1, Table 1).⁵⁻⁷ 1H NMR analyses of the products obtained by D_2O -quench (entries 1 and 2) showed quantitative ($>95\%$) incorporation of deuterium at the olefinic carbons, demonstrating generation of the corresponding organozinc species. In the reaction of 5-hexynyl tosylate **5a**, the series of zincates, Ph_3ZnLi , Bu_3ZnLi , and $t-Bu_3ZnLi$, led to a decrease of the **6**:**7** ratio. The ratio was also influenced by the methylene-chain length of the substrates. As reported previously, *exo*-cyclization took place exclusively in the reaction of 3-butylnyl arenesulfonates.³ The reaction of 4-pentylnyl *p*-fluorobenzenesulfonate

with Bu_3ZnLi was sluggish and neither *exo*- nor *endo*-cyclization product was formed.⁸ Upon treatment with Bu_3ZnLi , 5-heptynyl tosylate **5b** underwent selective *exo*-cyclization while *endo*-cyclization product **6d** was formed as a minor product in the reaction with Ph_3ZnLi (entries 4 and 5).



We previously showed that 1-(cyclopropylidene)alkylzinc **2** ($M = \text{Zn}$, $n = 0$) undergoes ring opening at temperatures above -20°C to be converted to homopropargylic zinc $\text{RC}\equiv\text{CCH}_2\text{CH}_2\text{ZnL}$.³ Cycloalkenylzinc **10** may be obtained by a similar ring opening of (cycloalkylidene)alkylzinc **8** and intramolecular carbometalation of the resulting organozinc **9** (Scheme 2).⁹ However, the possibility was ruled out by the following experiment. 1-(Cyclopentylidene)alkylzinc **8** ($R = \text{Ph}$, $n = 1$) was prepared separately by the reaction of (1-iodobenzylidene)cyclopentane and $t\text{-BuLi}$ (THF, -85°C) followed by treatment with Bu_2Zn (2 equiv). Protonation of the mixture after standing at rt for 17 h gave **7a** (56%) but no **6a** was detected.

In order to gain further information on the mechanism of *endo*-cyclization, reactions were examined for substituted 5-hexynyl tosylates **5c,d** (eqs 2 and 3, entries 6-9). Surprisingly, two isomeric *endo*-cyclization products **6f-i** and **6f'-i'** were produced as well as *exo*-cyclization products *E*- and *Z*-**7f-i**. The ratios of *endo*- vs *exo*-cyclization [(**6+6'**):**7**] are quite similar to those observed in the reaction of **5a** and the corresponding zincates. In the reaction of **5c**, two *endo*-cyclization products were formed in nearly equal amounts but, in the reaction of **5d**, the formation of the less sterically encumbered product **6i'** was predominant.

Scheme 2

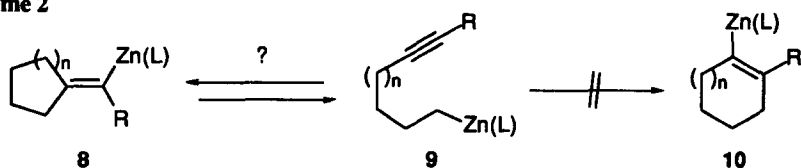
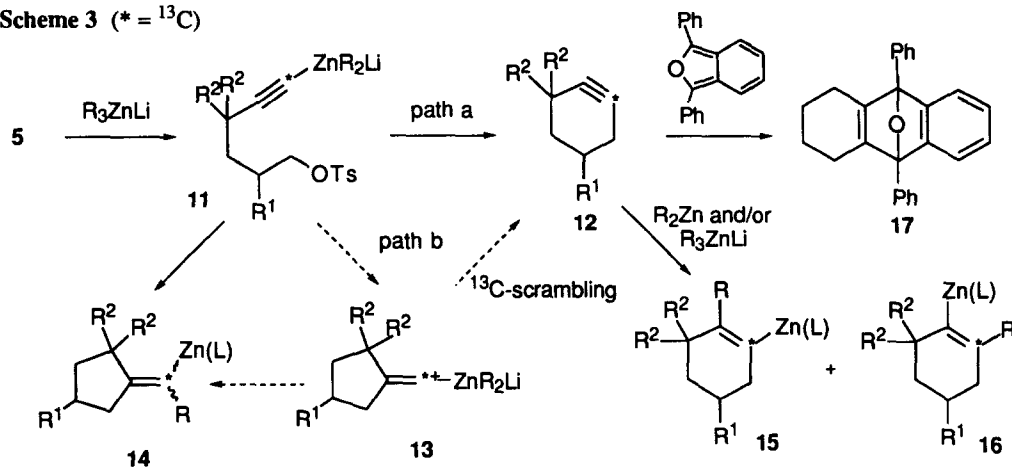


Table 1 Reaction of Alkynyl Tosylates 5a-d with Zincates^a

entry	substrate	zincate	endo-products (rel. %) ^b	exo-products (rel. %) ^b	combined yield (%) ^c
1	5a	Ph ₃ ZnLi	6a (60)	7a (40)	77
2 ^d		Bu ₃ ZnLi	6b (20)	7b (80)	64 ^e
3 ^f		<i>t</i> -Bu ₃ ZnLi	6c (18)	7c (82)	82 ^e
4	5b	Ph ₃ ZnLi	6d (15)	7d (85)	58
5		Bu ₃ ZnLi	-	7e (100)	78
6	5c	Ph ₃ ZnLi	6f (27) 6f' (27)	(<i>Z</i>)-7f (28) (<i>E</i>)-7f (18)	61
7		Bu ₃ ZnLi	6g (7.7) 6g' (7.8)	(<i>Z</i>)-7g (77) (<i>E</i>)-7g (7.5)	77
8		<i>t</i> -Bu ₃ ZnLi	6h (4.8) 6h' (4.5)	(<i>Z</i>)-7g (73) (<i>E</i>)-7g (17)	67
9	5d	Ph ₃ ZnLi	6i (13) 6i' (56)	(<i>Z</i>)-7h (5) (<i>E</i>)-7h (26)	80

^a Unless otherwise noted, reactions were carried out by mixing tosylate 5 and a zincate (2 equiv) in THF at -80 °C. The mixture was allowed to warm to rt during 2 h, stirred further for 3 h, and quenched by the addition of D₂O (entries 1 and 2) or H₂O (entries 3-9). ^b Unless otherwise noted, the product distributions were determined by capillary GC analyses. ^c Isolated yield unless otherwise noted. ^d The product distribution was determined by ¹H NMR analysis. ^e GC yield. ^f The reaction was carried out at temperatures from 0 °C to rt for 4 h.

Scheme 3 (* = ¹³C)

The result can be rationalized by a mechanism involving cycloalkyne 12 as an intermediate (Scheme 3).^{4,10} Thus, carbometalation of 12 ($R^1 = \text{Ph}$, $R^2 = \text{H}$) derived from 5c should proceed in a nonregioselective manner to give a 1:1 mixture of 15 and 16.^{11,12,9a} On the other hand, the reaction of 12 ($R^1 = \text{H}$, $R^2 = \text{Me}$) derived from 5d should lead to selective formation of 16. Direct evidence for the intermediacy of 12 was obtained by trapping experiments using 1,3-diphenylisobenzofuran. Thus, when the reaction of 5a and Ph₃ZnLi was carried out in the presence of 1,3-diphenylisobenzofuran (3.5 equiv), the Diels-Alder adduct 17¹³ was obtained in 17% yield together with 6a (31%) and 7a (27%).

Cycloalkyne 12 may arise directly with participation of the π -electrons (π -type cyclization)¹⁴ at the α position (path a) or, in a stepwise manner, by a rearrangement of carbenoid intermediate 13 (path b).¹⁵ In order to distinguish between these alternatives, the labeled alkynyl tosylate [6-¹³C]-5c in which the terminal acetylenic carbon is labeled with ¹³C (10%) was prepared and subjected to the reaction with Ph₃ZnLi. Within the limits of NMR (¹H- and ¹³C-) detection, the labeled carbon was found at the 2- and 1-positions of 6f and 6f', respectively. According to path b, the label may distribute at the two acetylenic carbons by a carbene rearrangement leading to ¹³C-scrambling in both 6f and 6f'. Therefore, the experiment clearly showed that the *endo*-cyclization proceeded through path a.

The result discussed above also supports a concerted pathway for *exo*-cyclization leading to **14** rather than a stepwise pathway via **13**. In addition, the stereoselective formation of the *Z*-isomers in the reaction of **5c** is also difficult to be explained by the stepwise pathway. It is most likely that alkynylzincates **11** undergo competitive π -type cyclizations, one in an *endo* manner to **12** and the other in an *exo* manner with the 1,2-migration of the alkyl ligand to **14**. In this regard, origin of the observed variation in *endo*- vs *exo*-cyclization is our current interest.¹⁶

REFERENCES AND NOTES

- (a) Merrill, R. E.; Allen, J. L.; Abramovitch, A.; Negishi, E. *Tetrahedron Lett.* **1977**, 1019. (b) Corey, E. J.; Seibel, W. L. *Tetrahedron Lett.* **1986**, 27, 909.
- For intermolecular reaction of alkynyltrialkylborates ($R^1C\equiv CB(R^2)_3Li$) with electrophiles leading to alkenylborons $R^1(E)C=C(R^2)B(R^2)_2$, see: (a) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: London: 1988; 283. (b) Pelter, A.; Harrison, C. R.; Kirkpatrick, D. *J. Chem. Soc., Chem. Commun.* **1973**, 544. (c) Miyaura, N.; Yoshinari, T.; Itoh, M.; Suzuki, A. *Tetrahedron Lett.* **1974**, 2961. (d) Pelter, A.; Bentley, T. W.; Harrison, C. R.; Subrahmanyam, C.; Laub, R. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2419. (e) Naruse, M.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1974**, 30, 3037. (f) Pelter, A.; Hughes, L.; Rao, J. M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 719.
- Harada, T.; Wada, I.; Oku, A. *J. Org. Chem.* **1995**, 60, 5370.
- The reaction has been used for the synthesis of medium- and large-ring acetylenes; Nakagawa, M. *Cyclic Acetylenes In The Chemistry of Carbon-Carbon Triple Bond*, Patai, S., Ed.; J. Wiley & Sons, New York, 1978, 635.
- The structures of new compounds in Table 1 were fully characterized by spectroscopic and HRMS analysis of the nondeuterated material prepared by separate experiments. In the case when isolation of the isomeric products was difficult, they were identified by comparison of their spectra with those of authentic samples.
- Initial formation of alkynylzincates was confirmed by D_2O trap of the reaction of **5a** and Bu_3ZnLi at $-20^\circ C$ for 22 h, which gives [6-D]-**5a** of 66% deuterium content in 80% yield.
- The use of 2.0 equiv of zincates is not essential to the reaction. Thus, for example, the reaction of **5a** with 1.2 equiv of Ph_3ZnLi gave a 54:46 mixture of **6a** (83% deuterium content) and **7a** (69% deuterium content) in 66% yield. The lower deuterium content of the products is probably due to the protonation of the generated organozinc species by the unreacted starting material in the course of the reaction. When 2.0 equiv of the zincates were used, organozinc species generated by the present reaction (eq 1-3) most probably exists as an equilibrating mixture of diorganozincs ($ZnL = ZnR$) and triorganozincates ($ZnL = ZnR_2Li$).
- Iodine quench of the reaction (rt, 21 h) gave 1-iodo-5-pentyne in 33% yield.
- (a) Meyer, C.; Marek, I.; Courtemanche, G.; Normant, J.-F. *Synlett* **1993**, 266. (b) Bailey, W. F.; Ovaska, T. V. *J. Am. Chem. Soc.* **1994**, 59, 6528.
- For review of strained cycloalkynes, see: (a) Meier, H. *Adv. Strain Org. Chem.* **1991**, 1, 215. (b) Liebman, J. F.; Greenberg, A. *Strained Organic Molecules*; Academic Press: New York, 1978.
- For addition of organolithium compounds to strained cycloalkynes, see ref. 4 and (a) Roberts, J. D. *J. Am. Chem. Soc.* **1960**, 82, 4750. (b) Gassman, P. G.; Valcho, J. J. *J. Am. Chem. Soc.* **1975**, 97, 4768. (c) Samuel S. P.; Niu, T.; Erickson, K. L. *J. Am. Chem. Soc.* **1989**, 111, 1429.
- Carbozincation of alkynes with allylzinc halides has been reported: (a) Coutois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, 69, 1. (b) Mesnard, D.; Miginiac, L. *J. Organomet. Chem.* **1976**, 117, 99. (c) Fernadou, F.; Miginiac, L. *Tetrahedron Lett.* **1976**, 3083.
- Wittig, G.; Pohlke, R. *Chem. Ber.* **1961**, 94, 3276.
- Negishi, E.; Boardman, L. D.; Sawada, H.; Bagheri, V.; Stoll, A. T.; Tour, J. M.; Rand, C. L. *J. Am. Chem. Soc.* **1988**, 110, 5383.
- (a) Erickson, K. L.; Wolinsky, J. *J. Am. Chem. Soc.*, **1965**, 87, 1142. (b) Erickson, K. L.; Vanderwaart, B. E.; Wolinsky, J. *J. Chem. Soc., Chem. Commun.* **1968**, 1031. (c) Fitjer, L.; Kliebisch, U.; Wehle, D.; Modaresi, S. *Tetrahedron Lett.* **1982**, 23, 1661. (d) Fitjer, L.; Modaresi, S. *Tetrahedron Lett.* **1983**, 24, 5495. (e) Gilbert, J. C.; Baze, M. E. *J. Am. Chem. Soc.* **1983**, 105, 664 and **1984**, 106, 1885.
- This work was supported partially by a Grant-in-Aid for Scientific Research on Priority Area of Reactive Organometallics No. 05236101 from the Ministry of Education, Science, Sports, and Culture, Japan.

(Received in Japan 27 January 1997; accepted 7 March 1997)