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LDA-Catalyzed Cycloisomerization of 2-(2-Propynyloxy)ethyl Iodides Leading to 3-(Iodomethylene)tetrahydrofurans

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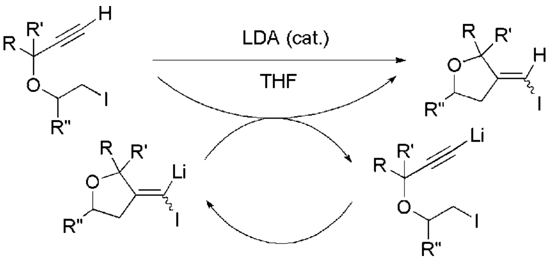
ABSTRACT



LDA catalyzes cycloisomerization of 2-(2-propynyloxy)ethyl iodides to give 3-(iodomethylene)tetrahydrofurans. The reaction is proposed to proceed through a mechanism involving *exo*-cyclization of an alkynyllithium intermediate and protonation of the resulting alkylidene carbenoid by the starting iodide.

Iodine-containing organic compounds are frequently utilized as reactive carbon electrophiles in organic synthesis. In their reactions, the substrate iodine atom is usually lost as an iodide salt and not incorporated into the product. Carbon−carbon bond forming reactions that give products with incorporation of the iodine atom would provide a useful means for constructing complex carbon frameworks through a subsequent bond forming reaction of the iodine-containing products. Indeed, the atom transfer radical cyclization of hex-5-enyl and hex-5-ynyl halides leading to the formation of the five-membered ring cycloisomerization product has been the focus of recent research and several reagents mediating this useful reaction have been developed.[1−3]

Alkynylmetal ate complexes such as alkynylboronates[4,5] and -zincates[6] are known to react at the β position with simultaneous migration of the ate ligand to the α position. That alkynylmetals (M = Li, Na, K) also exhibit nucleophilic reactivity at the β position was recently disclosed.[7] Alkynylmetals **3** bearing a remote leaving group undergo facile *exo*-cyclization at the β position to generate cycloalkylidene carbenoids **4** (Scheme 1).[8] A tandem cyclization of io-

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[1] (a) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc*. **1986**, *108*, 2489. (b) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc*. **1989**, *111*, 6265. (c) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140−3157.

[2] (a) Ichinose, Y.; Matsunaga, S.; Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1989**, *30*, 3155. (b) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem*. **1998**, *63*, 8604. (c) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc*. **2000**, *122*, 11041.

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[7] Harada, T.; Iwazaki, K.; Otani, T.; Oku, A. *J. Org. Chem.* **1998**, *63*, 9007.

[8] Some transition metal acetylides are known to react with electrophiles at the β position to form vinylidene complexes: Bruce, M. I. *Chem. Rev.* **1991**, *91*, 197.

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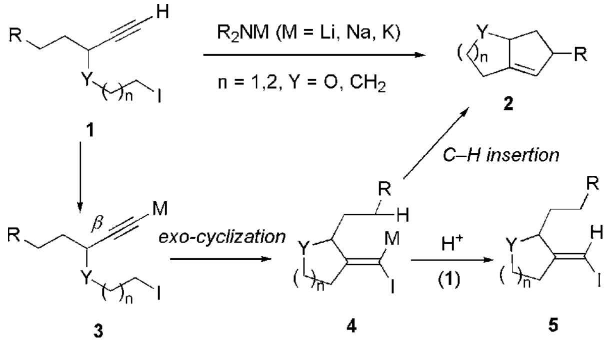
Scheme 1. Tandem Cyclization of Iodoalkynes **1**

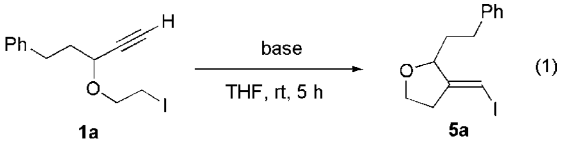


doalkynes **1** leading to bicyclic products **2** was developed by the use of regioselective intramolecular C−H insertion of thus-generated cycloalkylidene carbenoids.[9]

If the protonation of carbenoid intermediate **4** occurred before decomposition to the reactive carbenic species,[10] this might produce the desired iodine-containing product **5**. Such a possibility was examined in the reaction of iodoalkynes **1** in the presence of a catalytic amount of a base with the anticipation that the terminal alkyne moiety of **1** serves as a proton source for intermediate **4**. Herein is reported an unusual LDA-catalyzed cyclization of iodoalkynes leading to a product without the loss of the iodo functional group.

When iodoalkyne **1a** was treated with 0.2 equiv of LDA in THF at 0.1 M for 5 h at room temperature, cycloisomerization product (*E*)-**5a** was obtained stereoselectively (*E*/*Z* = 10:1) in 30% yield together with the recovery of **1a** (60%) (Table 1, entry 1). Similar reactions at higher concentration of 0.5 and 1.0 M gave (*E*)-**5a** in the improved yields of 74% and 70%, respectively, demonstrating the catalytic nature of the cycloisomerization reaction (entries 2 and 3). The use of a reduced amount of the base resulted in lower conversion of the reaction (entry 4) whereas an increased amount of the base did not give a better result owing to the formation of byproducts (entry 5).[11] The formation of (*E*)-**5a**, albeit in low yield, was also observed with NaN(TMS)$_2$ (entry 6) but not with KN(TMS)$_2$. No reaction took place when the LDA-catalyzed reaction of **1a** was carried out in ether.

Table 1. Cycloisomerization of **1a** under Various Conditions



(1)

entry	base	equiv	conc (M)	yield[a] (%)	*E*/*Z*[b]
1	LDA	0.2	0.1	30	10:1
2	LDA	0.2	0.5	74	9.1:1
3	LDA	0.2	1.0	70	9.0:1
4	LDA	0.1	0.5	30	8.1:1
5	LDA	0.4	0.5	54	5.3:1
6	NaN(TMS)$_2$	0.2	0.5	10	4.2:1

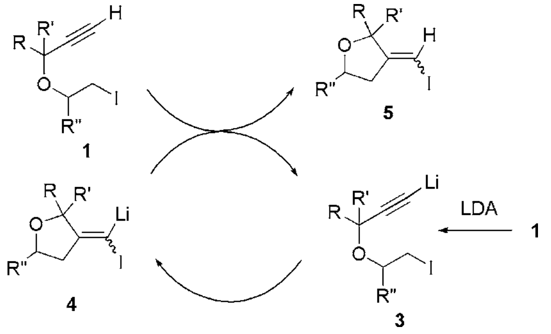
[a] Isolated as an *E*/*Z* mixture after flash chromatography. [b] Determined by a capillary GC analysis. The structure of (*E*)-**5a** was determined by NOESY analysis.

Under the optimized conditions using LDA (0.2 equiv) as a base in THF at 0.5 M at room temperature, the reaction of cyclohexyl derivative **1c** gave stereoselectively (*E*)-**5c** (Table 2, entry 3). On the other hand, iodoalkyne **1d** with the phenyl group *β* to the iodine atom was found to be less reactive. The reaction using 0.4 equiv of LDA at 65 °C afforded **5e** as a mixture of stereoisomers in 30% yield (entry 4). Bromoalkyne **1b** did not undergo similar cyclization leading to bromide **5b** even at 65 °C (entry 2).

The present cycloisomerization was found to be successfully applied to acetal derivatives **1e**−**j**. Acetal **1e**, not bearing substituents at the propargylic position, was slightly less reactive but the corresponding cycloisomerization product **5e** was obtained in 81% yield by carrying out the reaction at 40 °C (entry 5). Efficient and *E*-selective cycloisomerization was observed at 25−35 °C for acetal **1f**−**i** bearing substituents at the propargylic position (entries 6−10). A smooth reaction took place for gem-disubstituted **1h** even in the presence of 0.1 equiv of LDA (entry 9). Although extremely sluggish even at 65 °C, the reaction of the *trans*-cyclic secondary iodide **1j** selectively afforded *cis*-fused bicyclic product (*Z*)-**5j** at (entry 11), albeit in only ca. 7% conversion. The stereochemical outcome of the reaction may imply that the *exo*-cyclization proceeds with the inversion of the carbon attached by the iodine atom.

Scheme 1 suggests a mechanism involving the protonation of alkylidene carbenoid intermediate **4** by iodoalkyne **1** in the catalytic cycle for the present cycloisomerization reaction depicted in Scheme 2. Thus, alkynyllithium **3**, generated by the lithiation of **1** with LDA, undergoes *exo*-cyclization to give carbenoid **4**, which is basic enough to abstract the

Scheme 2. Proposed Catalytic Cycle for Cycloisomerization of **1**



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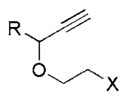
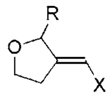
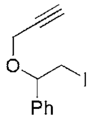
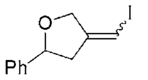
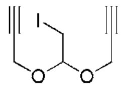
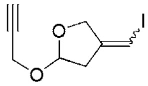
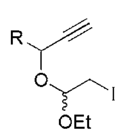
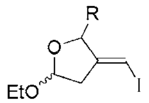
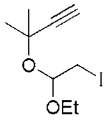
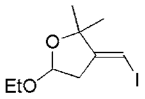
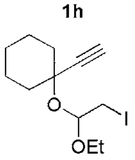
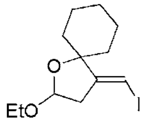
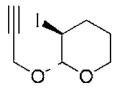
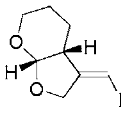
(10) Knorr, R. *Chem. Rev.* **2004**, *104*, 3795.

(11) The corresponding tandem cyclization product **2** (R = Ph, X = O, *n* = 1) was obtained in 10% yield.

Table 2. LDA-Catalyzed Cycloisomerization of Iodoalkynes **1**[a]

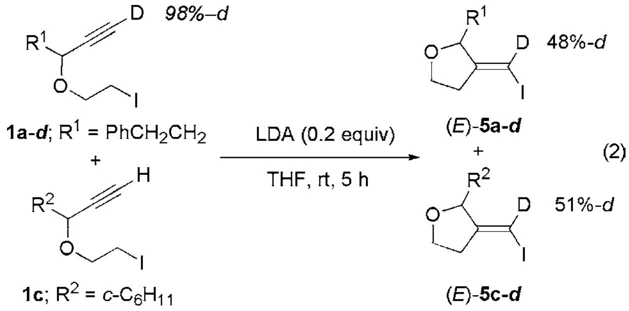
entry	iodoalkyne	product	yield[b] (%)	E:Z[c]
				
1	**1a**; R = $PhCH_2CH_2$, X = I	**5a**	74	9.1:1
2[d]	**1b**; R = $PhCH_2CH_2$, X = Br	**5b**	0	-
3	**1c**; R = c-C_6H_{11}, X = I	**5c**	69	7.0:1
4[d,e]	 **1d**	 **5d**	30	1:1.3
5[f]	 **1e**	 **5e**	81	1:1.3
				
6	**1f**;[g] R = $PhCH_2CH_2$	**5f**[h]	76	8.5:1[i]
7	**1g**;[g] R = $C_6H_{13}CH{=}CH$	**5g**[h]	62	5.5:1[i]
8	 **1h**	 (*E*)-**5h**	63	*j*
9[k]			62	*j*
10	 **1i**	 (*E*)-**5i**	81	*j*
11[d,e]	 **1j**	 (*Z*)-**5j**	7	*j*

[a] Unless otherwise noted, the reactions were carried out by using 0.2 equiv of LDA in THF at 25−30 °C for 4−7 h. [b] Isolated as an *E*/*Z* mixture after flash chromatography. [c] Unless otherwise noted, *E*/*Z* ratio was determined by a capillary GC analysis. [d] The reaction was carried out at 65 °C. [e] LDA (0.4 equiv) was used. [f] The reaction was carried out at 40° for 18 h. [g] A 1:1 mixture of diastereomers. [h] *E* and *Z* isomers were obtained as a mixture of diastereomers. [i] Determined by ^{1}H NMR analysis. [j] The geometrical isomer was not detected by ^{1}H NMR analysis. [k] The reaction was carried out by using 0.1 equiv of LDA.

terminal acetylenic proton of **1** to give cycloisomerization product **5** with simultaneous generation alkynyllithium **3**.

The atom transfer radical cyclization of analogous hex-5-ynyl iodides giving rise to cycloisomerization products has been reported.[1−3] Alternatively, the present reaction may proceed through the radical mechanism if LDA acts as an initiator. However, such mechanism is less likely judging from the following observations. Low stereoselectivity has been reported for the radical cyclization of hex-5-hexynyl iodides in general.[1−3] When **1a** was treated with radical initiator Et_3B in hexane at room-temperature according to the procedure reported by Oshima et al.,[2a] **5a** was obtained with low stereoselectivity ($E/Z = 2.7{:}1$) in 49% yield. The result is in contrast to the high *E* selectivity (9.1:1) observed in the LDA-catalyzed reaction. In the LDA-catalyzed reaction of **1h** possessing both hex-5-ynyl and hex-5-enyl iodide structures (Table 2, entry 7), no product derived from cyclization on the olefinic moiety was formed.

Further support for the proposed base-catalyzed mechanism was provided by deuterium labeling experiments. The reaction of **1a-*d*** (98% *d*) with LDA (0.2 equiv) gave (*E*)-**5a-*d*** (90%-*d*) in 70% yield. When a 1:1 mixture of **1a-*d*** and **1c** were treated with LDA, deuterium incorporation was observed not only into (*E*)-**5a-*d*** (48% *d*) (65% yield) but also into (*E*)-**5c-*d*** (51% *d*) (58% yield) (eq 2). The result of the deuterium scrambling experiment is well in accord with an intermolecular deuterium (and proton) transfer during the cycloisomerization process.



(2)

In summary, a LDA-catalyzed cycloisomerization of 2-(2-propynyloxy)ethyl iodides **1** to give 3-(iodomethylene)-tetrahydrofuran derivatives **5** has been discovered. The carbocyclization took place with incorporation of iodine atom into the products, which may serve as synthetically useful intermediates for the construction of complex carbon frameworks. In comparison with the radical mediated reactions, the LDA-catalyzed reaction showed higher stereoselectivity for the formation of sterically less hindered *E* products.

Supporting Information Available: Experimental procedure and spectra data for cycloisomerization products **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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