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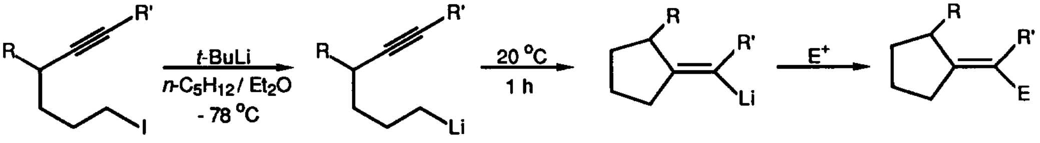
INTRAMOLECULAR ADDITION OF ALKYLLITHIUMS TO ACETYLENES: REGIOSPECIFIC 4-, 5-, and 6-*EXO-DIG* CYCLIZATIONS

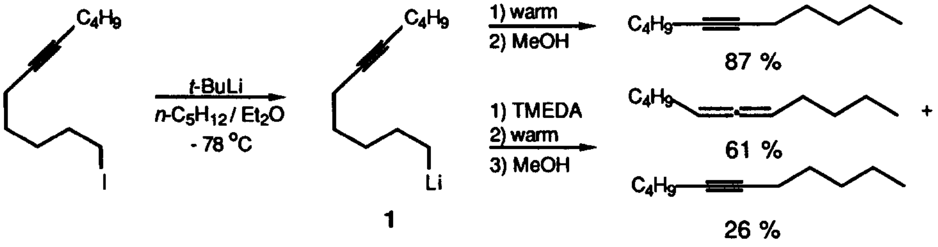
William F. Bailey* and Timo V. Ovaska
Department of Chemistry, University of Connecticut, Storrs, Connecticut 06269-3060

Summary: Primary acetylenic alkyllithiums bearing a phenyl substituent on the triple bond, which may be prepared in virtually quantitative yield by low-temperature lithium-iodine interchange, undergo regiospecific *exo-dig* cyclization via stereoselective syn-addition of CH_2Li to the carbon-carbon triple bond to give four-, five-, and six-membered carbocycles bearing an easily functionalized exocyclic lithiomethylidene moiety. Cyclization of the analogous alkyl substituted acetylenic alkyllithiums is confined to the 5-*exo-dig* mode.

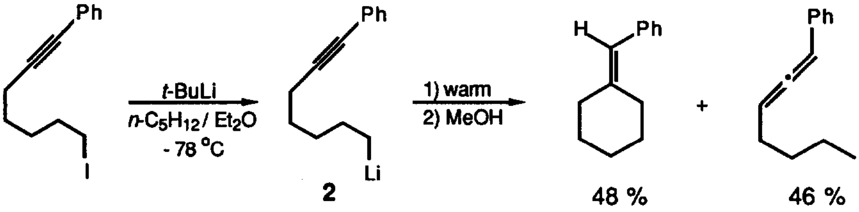
We recently described the generation and facile cyclization of 5-alkyn-1-yllithiums to give functionalized cyclopentylidene-containing products.[1] As shown below,[2] this anionic cyclization is a regiospecific 5-*exo-dig* process involving stereoselectively *syn*- addition to the triple bond. The formation of 5-membered rings by intramolecular addition of a C-Li bond to an acetylenic moiety appears to be a rather general phenomenon: cyclization of acetylenic aryllithiums was first reported over 20 years ago[3] and Negishi's group has recently observed 5-*exo-dig* isomerization of acetylenic organolithiums having lithium bound to sp²-hybridized carbon.[4] Herein we describe extension of this methology to the construction of four- and six-membered rings by cyclization of appropriately substituted acetylenic alkyllithiums.



Acetylenic alkyllithiums are easily and cleanly prepared in a solution of *n*-pentane-diethyl ether (3:2 by vol) by treatment of the appropriate primary iodides with 2 equiv of *t*-BuLi at -78°C using our general protocol for low-temperature lithium-iodine interchange.[1,5-7] Alkyl substituted 6-heptyn-1-yllithiums such as **1** are stable for extended periods of time at +20°C, while in the presence of TMEDA, which has been found to facilitate cyclization of olefinic alkyllithiums,[6] extensive prototropic rearrangement ensues and the allene is the major product. Indeed, we have been unable to find conditions that result in a synthetically useful cyclization of such alkyl-substituted substrates. The phenyl substituted analog, **2**, behaves quite differently: as shown on the following page, quench of a



reaction mixture that had been warmed at +20°C for 1h afforded an approximately 1:1 mixture of allene and benzylidene-cyclohexane.

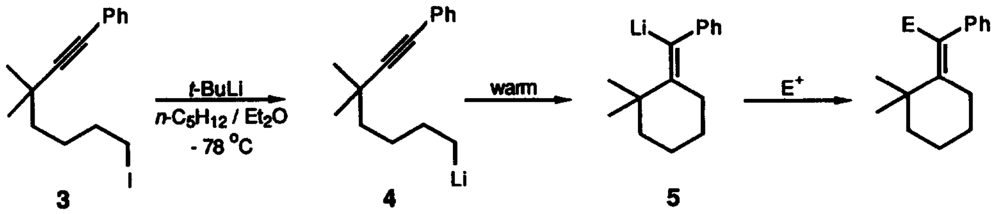


Allene formation can of course be entirely supressed by introduction of gem-dialkyl groups at the propargylic position and the rate of cyclization of such substrates would be expected , moreover, to benefit from operation of the Thorpe-Ingold effect.[9] Indeed, as shown in **Scheme I**, organolithium **4**, which is prepared from iodide **3** in virtually quantitative yield,[7] undergoes clean 6-*exo-dig* isomerization upon warming at room temperature for 1h to deliver a vinyllithium that may be trapped by addition of electrophiles to give high isolated yields of functionalized products (**6 a-c**).[10] As indicated in **Scheme I**, the products are stereoisomerically pure and were derived from reaction of the electrophiles with the E-isomer of the vinyllithium (**5**). This stereochemical outcome is consistent with either: (1) an *anti*-addition of the CH_2Li to the alkyne moiety or, (2) a *syn*-addition followed by rapid and complete isomerization of the configurationally labile Z-vinyllithium[11] to the thermodynamically more stable E-isomer[12] at the elevated temperatures (ca.+20°C) needed to effect cyclization. In an effort to distinguish between these two scenarios, we investigated the more rapid[1] 5-*exo-dig* cyclization of an analogously substituted 5-hexyn-1-yllithium, **8**, at various temperatures. The results of these experiments, summarized in **Scheme II**, clearly indicate that, while the cyclization proceeds in a stereoselectively *syn*-manner, isomerization of the initially generated Z-vinyllithium to the more stable E-isomer[12] is a very facile process at elevated temperatures.[11] On this basis, the formation of products derived from a formally *anti*-addition in the 6-*exo-dig* cyclization is seen as a consequence of equilibration of an initially formed Z-vinyllithium to the E-isomer under the conditions of the cyclization reaction.

The relatively rapid 5-*exo-dig* cyclization of **8** at -78°C coupled with the configurational stability of the initially formed Z-vinyllithium (**12**) at these low temperatures can be exploited for the preparation of functionalized products. As illustrated in **Scheme III**, vinyllithium **12** may be trapped with electrophiles prior to *cis-trans* isomerization to give stereoisomerically pure products (**9** and **13 a-c**) in good yield.[10] Unfortunately, due to the higher temperatures needed to effect cyclization of **4**, it has not proved possible to trap the putative Z-vinyllithium intermediate in the 6-*exo-dig* reaction.

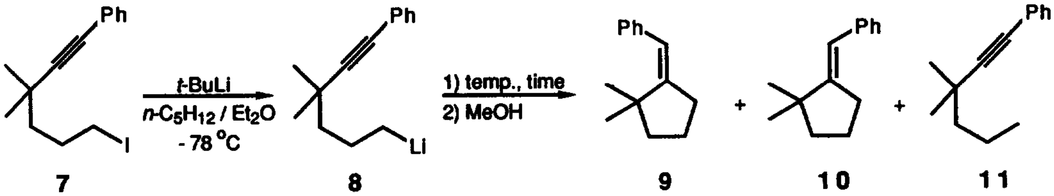
The formation of four-membered rings by 4-*exo-dig* cyclization of a 6-phenyl-5-pentyn-1-yllithium is an unexpectedly rapid and clean process as demonstrated by the results presented below. While we have been unable to successfully isomerize an alkyl-substituted substrate, the cyclization of **15** to **16** is complete within 15 min at +20°C and addition of any of a variety of electrophiles provides functionalized benzylidenecyclobutanes (**17 a-d**) in good to excellent isolated yields.[10]

Scheme I



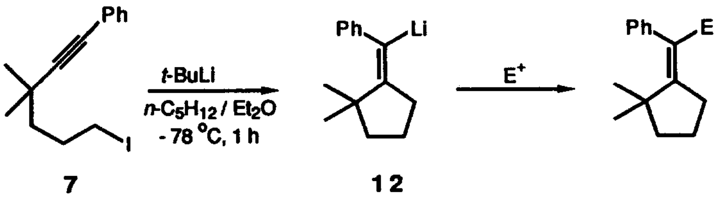
E^+	E	Product	Yield, %
CH_3OH	H	**6 a**	86
CH_3CHO	CH_3CHOH	**6 b**	81
$CH_3(CH_2)_2CHO$	$CH_3(CH_2)_2CHOH$	**6 c**	78

Scheme II

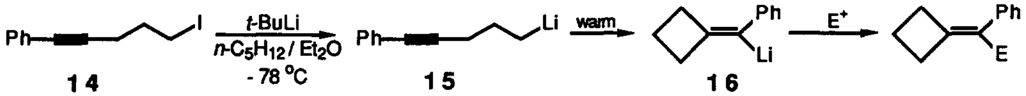


Temperature, °C	Time, min	**9**, %	**10**, %	**11**, %
- 100	5	2	–	98
- 78	5	31	3	66
- 78	60	88	6	6
- 55	30	85	10	5
+ 20	15	32	63	5
+ 20	60	29	67	4

Scheme III



E^+	E	Product	Yield, %
CH_3OH	H	**9**	88
CH_3CHO	CH_3CHOH	**13 a**	82
PhCHO	PhCHOH	**13 b**	78
t-BuCHO	t-BuCHOH	**13 c**	84



14 15 16

E$^+$	E	Product	Yield, %
MeOH	H	**17 a**	93
DMF	CHO	**17 b**	90
PhCHO	PhCHOH	**17 c**	84
H$_2$CO	CH$_2$OH	**17 d**	62

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References and Notes

1. Bailey, W. F.; Ovaska, T. V.; Leipert, T. K. *Tetrahedron Lett.* **1989**, *30*, 3901.
2. For the sake of clarity, organolithiums are represented as monomers in the schemes.
3. (a) Kandil, S. A.; Dessy, R. E. *J. Am. Chem. Soc.* **1966**, *97*, 7171.
   (b) Johnson, F.; Subramanian, R. *J. Org. Chem.* **1986**, *51*, 5040.
4. Wu, G.; Cederbaum, F. E.; Negishi, E. *Tetrahedron Lett.* accompanying article.
5. (a) Bailey, W. F.; Patricia, J. J.; Nurmi, T. T.; Wang, W. *Tetrahedron Lett.* **1986**, *27*, 1861.
   (b) Bailey, W. F.; Patricia, J. J.; Nurmi, T. T. *Tetrahedron Lett.* **1986**, *27*, 1865.
6. (a) Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. *J. Am. Chem. Soc.* **1987**, *109*, 2442.
   (b) Bailey, W. F.; Rossi, K. *J. Am. Chem. Soc.* **1989**, *111*, 765.
7. The general procedure used for the preparation of acetylenic alkyllithiums is as follows. A 0.1 M solution of the appropriate primary iodide in *n*-pentane-diethyl ether (3:2 by volume) was cooled to -78°C under an atmosphere of dry, oxygen-free argon and 2.0-2.2 molar equivalents of *t*-BuLi in *n*-pentane was added dropwise via syringe over a 5-min period. The lithium-iodine exchange is complete within minutes at -78°C and the yield of the acetylenic alkyllithium is typically 90-98%. It is to be noted that the lithium-iodine interchange reaction between a primary alkyl iodide and *t*-BuLi invariably results in the formation of a small but non-negligible quantity of hydrocarbon (typically 2-10%) formally derived from reduction of the halide. As noted elsewhere,[6,8] this side-product is an unavoidable consequence of rapid reaction between the RLi and the cogenerated *t*-BuI to give RH and isobutylene.
8. For a critical review of mechanistic studies of the metal-halogen interchange reaction, see: Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1.
9. Allinger, N. L.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701.
10. Exact mass spectroscopic molecular weights have been determined for previously unreported compounds and their IR, ^{1}H NMR and ^{13}C NMR are fully in accord with the assigned structures. Assignment of configuration to the olefinic products was based for the most part on chemical shift analysis. When necessary, difference-NOE experiments were performed to confirm assignments.
11. The configurational lability of a vinyllithium bearing an α-aryl substituent is well known. See, for example: (a) Curtin, D. Y.; Koehl, W. J., Jr. *J. Am. Chem. Soc.* **1962**, *84*, 1967. (b) Panek, E. J.; Neff, B. L.; Chu, H.; Panek, M. G. *J. Am. Chem. Soc.* **1975**, *97*, 3996.
12. Molecular mechanics calculations indicate that 1,1-dimethyl-2-(E)-benzylidene-cyclohexane (**6a**) is some 1.3 kcal/mol more stable than its Z-isomer. This energy difference, which is mirrored in the relative stabilities of the analogous vinyllithiums, serves to account for the essentially complete isomerization of the initially formed Z-vinyllithium to **5**. By way of contrast, 1,1-dimethyl-2-(E)-benzylidenecyclopentane is calculated to be only ca. 0.25 kcal/mol more stable than its Z-isomer (9).

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