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PREPARATION AND FACILE CYCLIZATION OF 5-ALKYN-1-YLLITHIUMS

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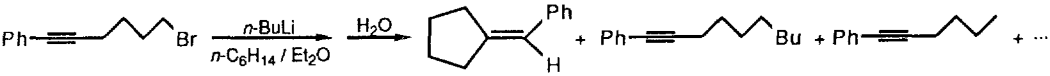
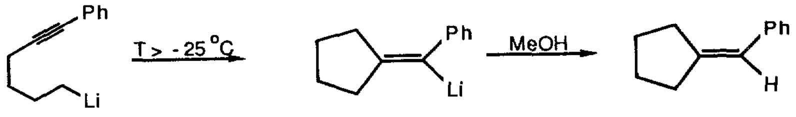
Abstract: Primary 5-hexyn-1-yllithiums, which may be generated in virtually quantitative yield by low-temperature lithium-iodine interchange, undergo regiospecific 5-exo-dig cyclization via stereoselectively syn-addition of CH_2Li to the alkyne moiety to give vinyllithiums that may be trapped with any of a variety of electrophiles to deliver functionalized cyclopentylidene- containing products.

Some twenty years ago, Ward reported[1] that treatment of 6-bromo-1-phenyl- 1-hexyne with n-butyllithium (n-BuLi) in hexane-ether (5:1 by vol) at room temperature, followed by hydrolysis with water, gave a mixture of products that included 60% of benzylidenecyclopentane. Ward[1] and others[2] have presented convincing arguments that these products resulted from radical intermediates generated in the reaction of n -BuLi with the bromide. This analysis is consistent with a body of recent evidence[3-5] which suggests that the lithium-bromine interchange reaction between an alkyllithium and a primary alkyl bromide is an outer sphere process involving single-electron transfer (SET). Since the lithium-iodine interchange, by contrast, is an inner sphere reaction that does not involve radical intermediates when conducted under appropriate conditions,[3,5,6] it occurred to us that the use of an acetylenic alkyl iodide rather than the bromide should allow for the preparation of the corresponding lithio derivative. Indeed, treatment of 6-iodo 1-phenyl-1-hexyne (**1**) in n-pentane-diethyl ether (3:2 by vol) at -78°C with 2.2 equiv of t-BuLi in n-pentane served to cleanly generate the acetylenic alkyllithium, **2** . Quench of the cold reaction mixture with deoxygenated methanol afforded the hydrocarbon quantitatively (96% isolated yield; d_1 content of 91% above natural abundance upon quench with MeOD).



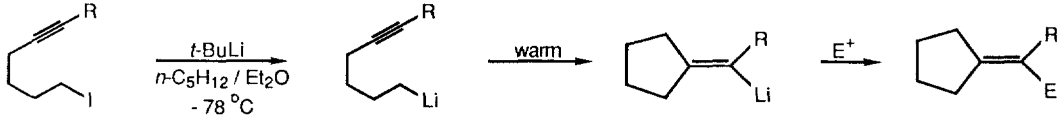
1 **2**

At temperatures above ca. -25°C, **2** undergoes fairly rapid isomerization to vinyllithium **3** via a 5-exo-dig cyclization. Quench of a reaction mixture that had been warmed briefly at room temperature gave benzylidenecyclopentane in 94% isolated yield.



2 **3**

While intramolecular cyclizations of various organometallic derivatives of the 5-hexynyl system are known,[8,9] the facile isomerization of **2** to **3** is unprecedented.[10] Herein we describe the results of an exploratory study of such anionic cyclization as a route to functionalized cyclopentylidene-containing products. As shown below, clean 5-exo-dig cyclization in easily accomplished upon warming solutions of either phenyl substituted (**2**→**3**) or alkyl substituted (**5**→**6**) 5-hexyn-1-yllithiums. The vinyllithium product, moreover, may be trapped in synthetically useful yield by addition of electrophiles.

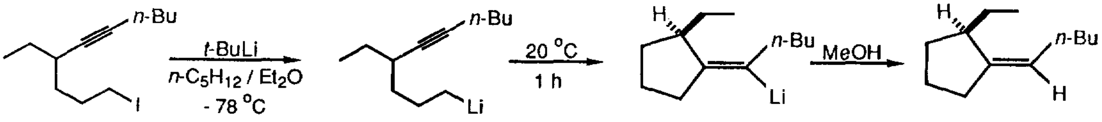


1 R = Ph　　**2** R = Ph　　**3** R = Ph

4 R = *n*-Bu　　**5** R = *n*-Bu　　**6** R = *n*-Bu

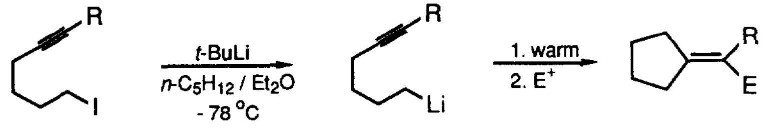
Dropwise addition of 2.0-2.2 equiv of t-BuLi in n-pentane to 0.1 *M* solutions of either **1** or **4** in n-pentane-diethyl ether (3:2 by vol) at -78°C results in rapid (< 5 min) lithium-iodine interchange to produce the corresponding 5-hexyn-1-yllithiums, **2** or **5** . Isomerization of **2** to **3** , or of **5** to **6** , is most easily effected by simply removing the cooling bath, and upon reaching ca. +20°C, allowing the reaction mixture to sit for a period of time at ambient temperature under a blanket of dry argon (typically: 15 min for **2**→**3**; 1h for **5**→**6**).[11] As demonstrated by the results summarized in **Table I** , the resulting vinyllithium (**3** or **6**) may be trapped with any of a variety of electrophiles to deliver good to excellent isolated yields (60-90%) of functionalized product that is easily purified by flash chromatography or bulb-to-bulb distillation.[13] The only by-product detected in greater than trace amounts from these reactions was 5-10% of the easily removed *unfunctionalized open-chain alkyne* produced in the initial lithium-halogen interchange.[14]

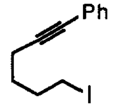
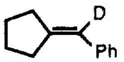
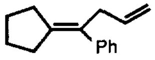
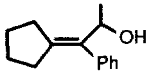
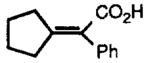
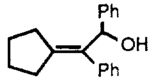
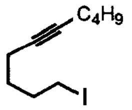
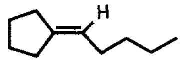
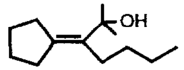
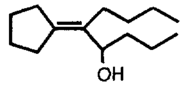
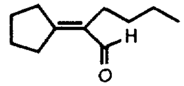
The stereochemistry of the cyclization was probed by investigation of the isomerization of the hexynyllithium derived from 1-iodo-4-ethyl-5-decyne. As shown below, the cyclization proceeds in a totally stereoselective fashion to give the configurationally stable Z-vinyllithium via syn-addition of the CH_2Li to the alkyne moiety. Quench of the reaction mixture with deoxygenated methanol gave a single diastereoisomer, assigned the Z-configuration,[15] in 75% yield. The balance of the product (24%) was uncyclized 4-ethyl-5-decyne; no trace of the E-isomer could be detected by GLC or ^1H NMR.



We are exploring the utility of regio- and stereoselective anionic cyclization of acetylenic alkyllithiums as a route to other types of substituted carbocycles and plan to report the results of these studies in the near future.

Table I. Cyclization of 5-Alkyn-1-yllithiums



Entry	Iodide	E^+	Product	Yield[a], %
1		D_2O		88
2		$CH_2=CHCH_2Br$		57[b]
3		CH_3CHO		86
4		CO_2		76
5		PhCHO		90
6		MeOH		84
7		CH_3COCH_3		69
8		$CH_3(CH_2)_2CHO$		83
9		$(CH_3)_2NCHO$		68

[a] Isolated yield of purified product. [b] This reaction also produced ~25 % of the vinyl bromide generated by lithium-bromine exchange between **3** and allyl bromide.

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References and Notes

1. Ward, H. R. *J. Am. Chem. Soc.* **1967** , *89* , 5517.
2. Ohnuki, T.; Yoshida, M.; Simamura, O.; Fukuyama, M. *Chem. Letters* **1972** , 999.
3. (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.
4. Ashby, E. C.; Pham, T. N. *J. Org. Chem.* **1987,** *52* , 1291
5. For a recent review of the literature dealing with the mechanism of the lithium-halogen interchange, see: Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988,** *352* , 1.
6. Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. *J. Am. Chem. Soc.* **1987** , *109* , 2442.
7. For the sake of pictorial clarity, organolithiums are represented as monomers in the schemes. The degree of aggregation of the acetylenic allyllithiums under the reaction conditions is unknown.
8. Cyclization of 5-hexynyl Grignards: (a) Fujikura, S.; Inoue, M.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984,** *25* , 1999. (b) Hill, E. A. *J. Organomet. Chem.* **1975,** *91* 123. (c) Richey, H. G., Jr.; Rothman, A. M. *Tetrahedron Lett* **1968** , 1457. (d) Kossa, W. C., Jr.; Rees, T. C.; Richey, H. G., Jr. *Tetrahedron Lett.* **1971,** 3455.
9. Cyclization of 5-hexynyl cuprates: (a) Crandall, J. K.; Battioni, P.; Wehlacz, J. T.; Bindra, R. *J. Am. Chem. Soc.* **1975,** *97* , 7171. (b) Normant, J. F.; Alexakis, A. *Synthesis* **1981,** 841.
10. We are aware of only two reports of the intramolecular additon of an organolithium to a proximate alkyne and both involve cyclization of aryllithiums: (a) Kandil, S. A.; Dessy, R. E. *J. Am. Chem. Soc.* **1966,** *88* , 3027. (b) Johnson, F.; Subramanian, R. *J. Org. Chem.* **1986,** *51* , 5040.
11. Cyclization of the phenyl derivative (**2**→**3**) is more rapid than that of the alkyl derivative (**5**→**6**). Although quantitative kinetic data have not yet been obtained for these rearrangments, isomerization of a 5-hexyn-1-yllithium appears to be a more facile process than the analogous 5-exo-trig cyclization of a 5-hexen-1-yllithium.[12]
12. Bailey, W. F.; Patricia, J. J.; DelGobbo, V. C.; Jarret, R. M.; Okarma, P. J. *J. Org. Chem.* **1985,** *50* , 1999.
13. Exact mass spectroscopic molecular weights have been determined for all new compounds and their IR, ^{1}H NMR and ^{13}C NMR spectra are in accord with the assigned structures.
14. As noted elsewhere,[5,6] lithium-iodine interchange between a primary iodide and t-BuLi invariably results in the formation of a small but non-negligible amount of hydrocarbon formally derived from reduction of the halide. This phenomenon is a consequence of the reaction of RLi with the t-BuI generated in the interchange to give RH and $CH_2=C(CH_3)_2$.
15. Proton and carbon-13 1D NMR spectra were used in conjunction with homonuclear 2D J-resolved, H,H-COSY and heteronuclear COSY to assign the chemical shifts of all protons and carbons. The stereochemical assignment was then made on the basis of difference-NOE experiments.

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