Facile Intramolecular Carbolithiation Reactions of Alkylthio- and Alkoxyacetylenes by Stabilized Carbanions. A Novel Strategy for the Synthesis of Functionalized Carbocycles

Raymond L. Funk,* Gary L. Bolton, Kay M. Brummond, Karen E. Ellestad, and John B. Stallman

Department of Chemistry
University of Nebraska, Lincoln
Lincoln, Nebraska 68588
Department of Chemistry
The Pennsylvania State University
University Park, Pennsylvania 16802

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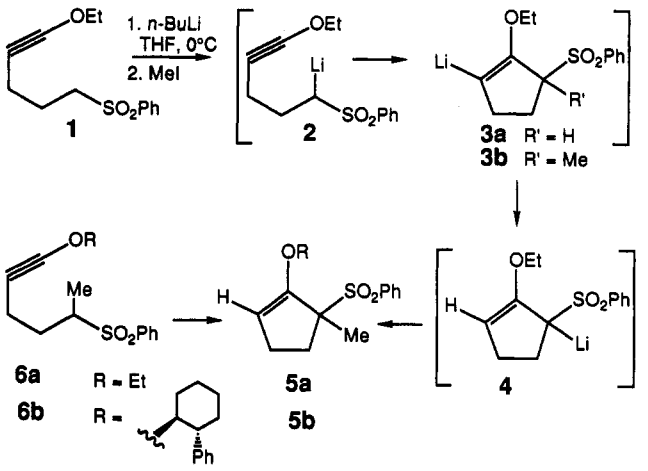
Despite their extensive investigation, intramolecular carbolithiation reactions of alkynes have seen limited application in organic synthesis.[1] This situation, no doubt, reflects the necessity of generating the alkyllithium reagents (which are incompatible with many functional groups of interest)[2] and using "activated" acetylenes (phenyl or trimethylsilyl) in order to effect efficient cyclization reactions. We have made the discovery, albeit serendipitously, that alkylthio- and alkoxyacetylenes smoothly participate in cyclization reactions with a variety of stabilized lithio carbanions to provide functionalized exocyclic and endocyclic enol (thioenol) ethers. We delineate, herein, the scope and limitations of this transformation and document its utility in several carbocycle annelation processes.

The first cyclization reaction of this type was observed during an attempted "routine" preparation of the α-methylated sulfone **6a** from sulfone **1** (Scheme I). Instead of the desired compound,[3] a product was isolated in excellent yield (96%) whose spectral characteristics were consistent with structure **5a**[4] and whose structural assignment was further corroborated by hydrolysis of the enol ether moiety of **5a** to the corresponding cyclopentanone. A reasonable mechanism for this transformation would involve *trans*-carbometalation of the alkoxyacetylene moiety of **2** by the α-phenylsulfonyl anion to afford the vinyl anion **3a**, equilibration to the thermodynamically preferred allyl/α-phenylsulfonyl anion **4**, and regiospecific methylation with methyl iodide to furnish the cyclopentenyl sulfone **5a**.

In order to determine whether this cyclization reaction is driven by formation of the relatively stabile anion **4**, the α-methylated sulfone **6a** was prepared (**1**, 1 equiv of BuLi, *-78 °C*, THF; MeI).

Scheme I



Nonetheless, the cyclization of **6a** also proceeded smoothly (1 equiv of BuLi, -78 °C to 0 °C, THF; NH_4Cl), if HMPA (2 equiv) was present, to afford **5a** (88%). This result suggested that the vinyl anion **3b** produced in this reaction might be stable and capable of interception. However, upon warming of the reaction mixture to 0 °C and addition of methyl iodide, a 1:1 mixture (86%) of **5a** and the *o*-tolyl sulfone analogous to **5a** was isolated. Apparently, deprotonation of the solvent (THF) and ortho-metalation of the phenylsulfonyl moiety is the thermodynamic driving force of this particular reaction. All subsequent efforts to trap related vinyl anion intermediates using either a *tert*-butyl sulfone analogous to **6a** or an alkoxyacetylene capable of chelating the lithium atom of the putative vinyl anion intermediate (**6a**, R = $CH_2CH_2OCH_2CH_2OCH_2CH_3$) have been equally unsuccessful. Finally, useful levels of relative asymmetric induction by chiral alkoxyacetylenes[5] have been observed in these cyclizations. For example, the enantiomerically pure *trans*-2-phenylcyclohexyloxyacetylene **6b** gave an 89:11 mixture of diastereomers **5b** (65%) and warrants further development as a novel strategy for the enantioselective synthesis of carbocycles.

The regioselectivity of the cyclization reactions of alkoxyacetylene homologs of **1**, as well as the analogous alkylthioacetylenes, is presented in Table I. As shown in entries **a** and **c**, the preference for nucleophilic addition at the α-carbon of the alkoxyacetylene moiety[3] is insufficient to overcome a kinetically favored attack at the β-carbon leading to the smaller ring system. However, the preferred site of intermolecular attack by nucleophiles on thioalkoxyacetylenes is at the β-carbon,[7] and, consequently, these cyclizations are completely regioselective (entries **b** and **d**). It should be further noted that only one alkene stereoisomer was observed for each of the *exo*-adducts. It is presently unclear whether the (*Z*)-olefin stereochemistry[8] results from an atypical *trans*-carbometalation[1] reaction or, alter-

(1) For recent examples wherein radical intermediates have been excluded and leading references therein, see: (a) Bailey, W. F.; Ovaska, T. V.; Leipert, T. K. *Tetrahedron Lett.* **1989**, *30*, 3901. (b) Bailey, W. F.; Ovaska, T. V. *Ibid.* **1990**, *31*, 627. (c) Negishi, E.-I.; Wu, G.; Cederbaum, F. E. *Ibid.* **1990**, *31*, 493. For recent carbometalation reactions of alkynes by Grignard or organotitanium reagents, see: (d) Fujikura, S.; Inoue, M.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 1999. (e) Stille, J. R.; Harms, A. E. *Ibid.* **1992**, *33*, 6565.

(2) However, intramolecular carbometalation reactions of copper–zinc organometallics and palladium-catalyzed cyclizations are more tolerant of functionality, see: (a) Knochel, P.; Rao, S. A. *J. Am. Chem. Soc.* **1991**, *113*, 5735. (b) Crandall, J. K.; Ayers, T. A. *Organometallics* **1992**, *11*, 463. (c) Monteiro, N.; Balme, G.; Gore, J. *Synlett* **1992**, 227. (d) Negishi, E.; Zhang, Y.; Wu, G.-Z.; Agnel, G. *J. Am. Chem. Soc.* **1990**, *112*, 8590. (e) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. (f) Gore, J.; Fournet, G.; Balme, G. *Tetrahedron* **1991**, *47*, 6293.

(3) This result was not totally unanticipated since we were well aware of the fact that alkyllithium reagents undergo addition–elimination reactions with alkoxyacetylenes to provide disubstituted acetylenes, see: (a) Kooyman, J. G.; Hendriks, H. P. G.; Montijn, P. P.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim.* **1968**, *87*, 69. For the addition of organocopper reagents, see: (b) Normant, J. F.; Alexakis, A.; Cahiez, G. *Tetrahedron* **1980**, *36*, 1961. (c) Wijkens, P.; Vermeer, P. *J. Organomet. Chem.* **1986**, *301*, 247.

(4) All cyclization products reported herein exhibit satisfactory spectral (IR, NMR), analytical and/or high-resolution mass spectral characteristics.

(5) (a) Greene, A. E.; Moyano, A.; Charbonnier, F. *J. Org. Chem.* **1987**, *52*, 2919. For asymmetric Pauson–Khand cyclizations using chiral alkoxyacetylenes and enol ethers derived from them, see: (b) Greene, A. E.; Poch, M.; Valentí, E.; Moyano, A.; Pericàs, M. A.; Castro, J.; DeNicola, A. *Tetrahedron Lett.* **1990**, *31*, 7505. (c) Castro, J.; Sörensen, H.; Riera, A.; Morin, C.; Moyano, A.; Pericàs, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 9388.

(6) These substrates were prepared by alkylation of ethoxyacetylene or ethylthioacetylene with the appropriate 1-bromo-ω-chloroalkane (1 equiv of BuLi, 1 equiv of dihalide, 1 equiv of HMPA, THF, room temperature, 6 h) followed by treatment with sodium benzenesulfinate (2 equiv, DMF).

(7) Viehe, H. G. *Chemistry of Acetylenes*; Marcel Dekker, Inc.: New York, 1969; p 788.

(8) The stereochemical assignment for the *exo*-adduct of entry **a** is based on an X-ray crystallographic analysis. The stereochemical assignment for the *exo*-adduct of entry **c** is based on its partial isomerization ($CHCl_3$, 7 days) to a new isomer. A 7% NOE was observed for the α-phenylsulfonyl proton resonance upon irradiation of the olefinic proton resonance of this new isomer, whereas irradiation of the analogous proton resonance in the original isomer gave no enhancement of the α-phenylsulfonyl proton resonance.

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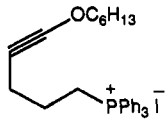
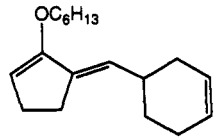
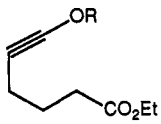
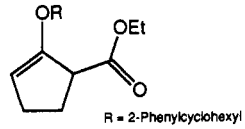
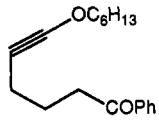
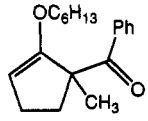
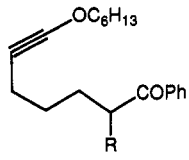
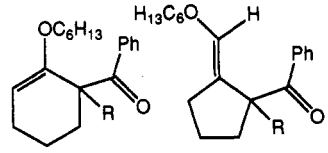
Table I. Regiochemistry of Cyclizations of Alkoxy- and Thioalkoxyacetylenes with Phenylsulfonyl Anions[a]

entry	alkoxyacetylene or thioalkoxyacetylene	ratio *exo*-adduct		*endo*-adduct	yield (%)
a	X = O	75	:	25	53
b	X = S	100	:	0	75
c	X = O	66	:	34	54
d	X = S	100	:	0	57

[a] 2 equiv of BuLi, 2 equiv of HMPA, THF, −78 °C to room temperature, 30 min; aqueous NH_4Cl.

Table II. Additional Stabilized Carbanions which Participate in Cyclizations with Alkoxyacetylenes

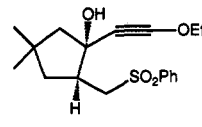
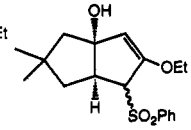
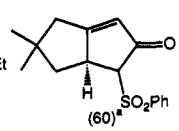
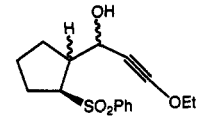
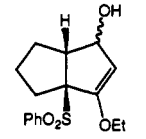
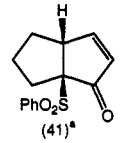
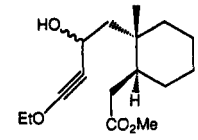
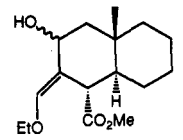
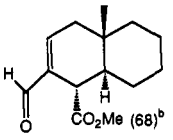
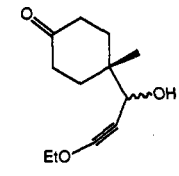
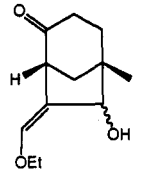
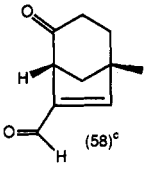
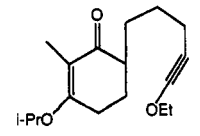
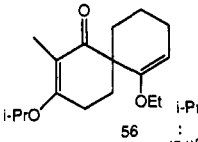
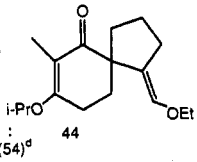
entry	alkoxyacetylene	product	yield (%)
a			69[a]
b		 R = 2-Phenylcyclohexyl	72[b]
c			72[c]
d			88 : 12[d] 76[e]
e	R = Me		19 : 81 73[e]

[a] 1.1 equiv of BuLi, 2 equiv of HMPA, THF, −78 to 0 °C, 1 h; 1 equiv of 3-cyclohexenecarboxaldehyde, room temperature, 2 h. [b] 1.1 equiv of LDA, 5 equiv of HMPA, THF, −78 to 0 °C, 2 h; aqueous NH_4Cl. [c] 1.1 equiv of LDA, 5 equiv of HMPA, −78 to 40 °C, 3 h; 1.5 equiv of CH_3I. [d] Mixture of (*E*)/(*Z*) stereoisomers (88:12). [e] 1.1 equiv of LDA, 5 equiv of HMPA, THF, −78 to 40 °C, 4 h; aqueous NH_4Cl.

natively, from *cis*-carbometalation followed by equilibration of the intermediate allyl/α-phenylsulfonyl anion, which might prefer the (*Z*)-stereochemistry due to chelation of the lithium atom with the enol ether oxygen (sulfur) atom.

The examples listed in Table II illustrate that this cyclization reaction is not unique to sulfone-stabilized carbanions. Phosphorus ylides (entry **a**), ester enolates (entry **b**), and ketone enolates (entries **c**–**e**) all participate in cyclization reactions with alkoxyacetylenes. The cyclization of a cyano-stabilized carbanion analogous to the ester enolate of entry **b** was also successful, but the cyclization of the analogous malonate carbanion failed. It is of interest to note that the regiochemistry of the cyclization is sensitive to the degree of substitution of the ketone enolate (cf. entries **d** *vs* **e**).

Table III. Carbocyclic Ring Annelation via Alkoxyacetylene Cyclization Reactions

entry	alkoxyacetylene	intermediate adduct	product (yield, %)
a			 (60)[a]
b			 (41)[a]
c			 (68)[b]
d			 (58)[c]
e			 56 : 44 (54)[d]

[a] 2 equiv of BuLi, 2 equiv of HMPA, THF, −78 to 0 °C, 30 min; H_3O^+. [b] 2.1 equiv of LDA, 5 equiv of HMPA, THF, −78 °C to room temperature, 1 h; H_3O^+. [c] 2.1 equiv of LDA, 5 equiv of HMPA, THF, −78 to 40 °C, 3 h; H_3O^+. [d] 1.1 equiv of LDA, 5 equiv of HMPA, −78 °C to room temperature, 6 h.

The potential of this new methodology to impact on organic synthesis is clearly evident in the carbocyclic ring annelation processes enumerated in Table III. Fused bicyclo (entries **a**–**c**), bridged bicyclo (entry **d**), and spiro annelations (entry **e**) can be accomplished via intramolecular carbometalation reactions of various stabilized carbanions with alkoxyacetylenes. The ready accessibility of the alkoxyacetylene substrates shown in Table III and the polyfunctionalized products that ultimately arisefrom these reaction sequences are noteworthy features of this novel strategy for carbocycle synthesis. The further development of this new methodology and its application in natural product synthesis will be reported in due course.

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Supplementary Material Available: Spectral data for all cyclization products (5 pages). Ordering information is given on any current masthead page.