Annulative Ring Expansions. Direct Conversion of ω-Alkynyl Acetals to Polycyclic Unsaturated Ketones

Joseph Sisko,[1a] Aaron Balog, and Dennis P. Curran*,[1b]

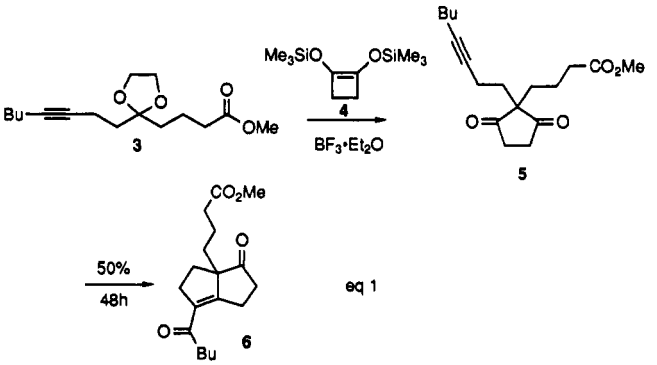
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received May 19, 1992

Summary: Geminal acylation of ω-acetylenic acetals and bis(silyloxy)cycloalkenes under Lewis acid conditions preceded cationic cyclization of the alkyne onto the ketone to produce polycyclic unsaturated ketones.

Cationic cyclizations of alkynes have recently been exploited in a variety of transformations including polyene cyclizations[2] and reactions with alkoxonium ions,[3] *N*-acyliminium ions,[4] and iminium ions.[5] In contrast, the addition of alkynes to carbonyl compounds has been much less studied. In one of the few known examples, Harding[6,7] found that treatment of ynone **1** with BF_3 etherate for 10 d provided the enones **2a** and **2b** in a ratio of 55:45 (Scheme I). Enone **2a** derives from a 5-*exo-dig* ring closure of 1 (path A) while enone **2b** is formed from a 6-*endo-dig* ring closure (path B). We now report the first examples of a new class of annulative ring expansions involving related cyclizations of alkynyl ketones.

We recently attempted to prepare cyclopentanedione **5** by Burnell and Wu's modification[8] of Kuwajima's geminal acylation procedure.[9] When we treated acetal **3** and bis-silylated succinoin **4** with 15 equiv of BF_3 etherate for 16 h at 25 °C, we isolated not only the desired dione **5** but also the bicyclic enone **6** in a 1:1 ratio (eq 1). Exposing



the reaction mixture to excess BF_3 etherate in CH_2Cl_2 for 48 h at 25 °C led to a 50% yield of enone **6**. Dione **5** was no longer detected, apparently because it suffered nucleophilic addition of the alkyne in a manner similar to that depicted in Scheme I, path A. Indeed, isolation of dione

Scheme I

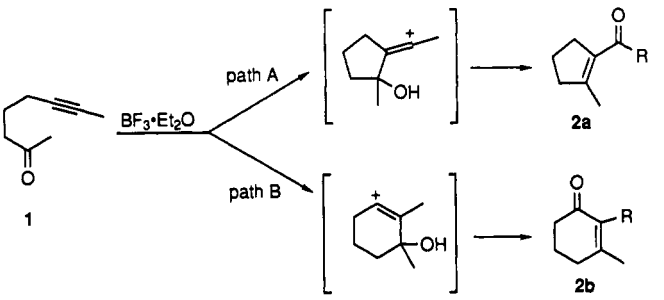
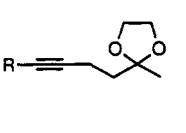
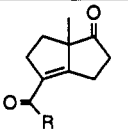
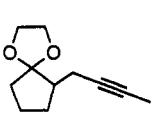
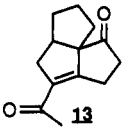
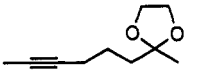
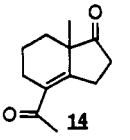
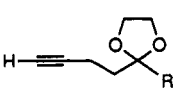
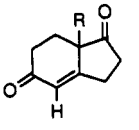
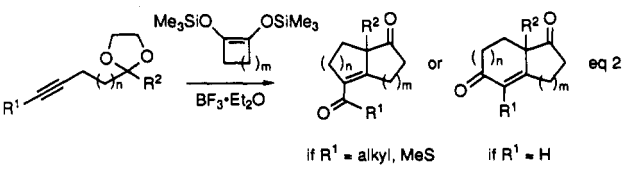


Table I. Annulative Ring Expansion Products with Succinoin Derivative 4

entry	acetal	product	isolated yield (%)	reaction time (h)
				
1	R = Me	**7** R = Me	58	24
2	R = Bu	**8** R = Bu	56	48
3	R = Ph	**9** R = Ph	0	48
4	R = CO_2Me	**10** R = CO_2Me	0	144
5	R = PhS	**11** R = PhS	0	48
6	R = MeS	**12** R = MeS	50	24
7		 **13**	69	48
8		 **14**	87	144
				
9	R = Me	**15** R = Me	66	48
10	R = $(CH_2)_3CO_2Et$	**16** R = $(CH_2)_3CO_2Et$	41	96

5 and subsequent treatment with BF_3 etherate led to near-quantitative conversion to enone **6** over several hours.



A series of preliminary experiments shows that this powerful annulative ring expansion succeeds with a variety

(1) (a) National Institutes of Health Postdoctoral Fellow, 1991-93. (b) National Institutes of Health Research Career Development Awardee, 1987-92.

(2) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. Johnson, W. S.; Ward, C. E.; Boots, S. G.; Gravestock, M. B.; Markezich, R. L.; McCarry, B. E.; Okorie, D. A.; Parry, R. J. *J. Am. Chem. Soc.* **1981**, *103*, 88.

(3) Johnson, T. O.; Overman, L. E. *Tetrahedron Lett.* **1991**, *32*, 7361.

(4) Shoemaker, H. E.; Boer-Terpstra, T.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1980**, *36*, 143. Boer-Terpstra, T.; Dijkink, J.; Shoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1977**, 939.

(5) Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612. Overman, L. E.; Sharp, M. J. *Tetrahedron Lett.* **1988**, *29*, 901.

(6) Harding, C. E.; Hanack, M. *Tetrahedron Lett.* **1971**, 1253.

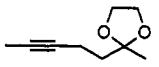
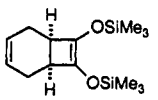
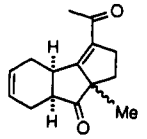
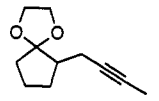
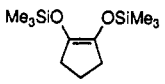
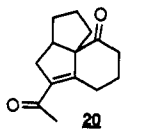
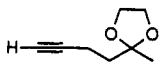
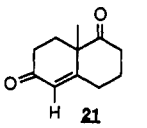
(7) For recent discussions of the mechanism of such cyclizations, see: Harding, C. E.; Stanford, G. R., Jr. *J. Org. Chem.* **1989**, *54*, 3054. Harding, C. E.; King, S. L. *J. Org. Chem.* **1992**, *57*, 883.

(8) Wu, Y.-J.; Burnell, D. J. *Tetrahedron Lett.* **1988**, *29*, 4369.

(9) Shimada, J.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759.

0022-3263/92/1957-4341$03.00/0

Table II. Annulative Ring Expansion Products Using Other Bis(silyloxy)cycloalkenes

acetal	bis(silyloxy)-cycloalkene	product	isolated yield (%)	reaction time (h)
	 17	 1:1 18	44	48
	 19	 20	64	48
	19	 21	55	48

of substrates. The basic transformation is outlined in eq 2, and specific examples are reported in Tables I and II. The reactions were conducted by addition of the bis-silylated succinoin 4 to a premixed solution of the acetal and 15 equivalents of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −78 °C. After 3 h, the reaction mixture was slowly warmed to 25 °C and monitored by TLC or GC until completion (see indicated reaction times in Tables I and II). The products were isolated by flash chromatography in yields ranging from 41 to 87%.

In contrast to Harding's observations with 1 (Scheme I), the reactions of 4 with disubstituted alkynes led exclusively to acylbicyclo[3.3.0]octenones derived from path A cyclizations (Table I, entries 1, 2). The isomeric bicyclo[4.3.0]nonenediones were not detected. The cyclization of a single homologated acetal (entry 8) also proceeded via path A to the corresponding acylbicyclo[4.3.0]nonenone 14 in 87% yield despite the prolonged reaction time. In addition, more complex ring systems could be prepared by using alkynyl acetals in which one ring was already present (Table I, entry 7).

The annulative ring expansion of phenyl-substituted alkynes (entry 3) unexpectedly failed to give any discernable products. While alkynoate esters have recently been shown to cyclize with acetals,[3] the alkynoate ester shown in entry 4 (Table I) progressed only to the stage of the corresponding cyclopentanedione analogous to 5. This cyclopentanedione was recovered after exposure for 6 d to 15 equiv of $BF_3{\cdot}Et_2O$. An acetal containing a trisubstituted olefinic nucleophile was also examined, but failed to undergo the desired Prins cyclization under our reaction conditions.[10] While the reaction of a phenylthio alkynyl ether (entry 5) failed to give any characterizable products, we were gratified to find that α,β-unsaturated thioester 12 was cleanly formed from the corresponding alkynyl thiomethyl ether (entry 6) in 50% yield. The ready accessibility of alkynyl thioethers[11,12] makes them excellent substrates for our annulative ring expansion strategy to generate products which are in the carboxylic acid oxidation state.

In contrast to disubstituted alkynes, the reactions of acetals containing a terminal alkyne with bis-silylated succinoin 4 yielded products arising exclusively from path B cyclizations. Apparently, the putative primary vinyl cations resulting from path A cyclizations are sufficiently less stable and inhibit this pathway. This change of reaction pathway was confirmed by isolation of the known cyclohexenone 15[13] and cyclohexenone 16 (Table I, entries 8, 9) which were readily identified by characteristic doublets (J = 2 Hz) at 5.9 ppm in the ^1H NMR spectra.

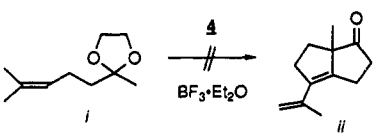
Varying the bis(silyloxy)cycloalkene component was effective in producing carbocycles of varying ring size and complexity (Table II). The cyclohexene derivative 17[14] was successfully employed in the preparation of the tricyclic enone 18 as a 1:1 mixture of diastereomers. Burnell and Wu have shown that 1,2-bis[(trimethylsilyl)oxy]cyclopentene (19) undergoes the Kuwajima geminal acylation reaction for the preparation of 1,3-cyclohexanediones.[15] We have found that acetylenic acetals react with 19 to produce ring-enlarged polycyclic enones via our annulative ring expansion process. As before, the disubstituted alkyne reacted via path A to form enone 20 while the terminal acetylene followed path B to produce the known enone 21.[16]

We have described here a versatile, one-pot procedure for the preparation of highly functionalized, polycyclic enones and thioesters from readily available acetals. The reactions are simple to conduct, and the method is useful in the preparation of carbocycles of varying ring size and complexity. More detailed studies on the scope and usefulness of this new annulative ring expansion are in progress.

Acknowledgment. We thank the National Institutes of Health for funding of this work.

Supplementary Material Available: General experimental procedure and complete spectroscopic characterization ($^1H/^{13}C$, IR, and MS) of all new compounds (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(10) The expected transformation of *i* to *ii* failed to produce any characterizable products.



(11) The thioether was readily prepared by alkylation of the lithium acetylide of the acetal in entry 9 with $(MeS)_2$; see: Abrams, S. R. *Can. J. Chem.* **1983**, *61*, 2423.

(12) The addition of alkynyl ethers to ketones to give α,β-unsaturated esters is known; see: Vieregge, H.; Bos, H. J. T.; Arens, J. F. *Recl. Trav. Chem. Pays-Bas* **1959**, *78*, 664. Vieregge, H.; Schmidt, H. M.; Renema, J.; Bos, H. J. T.; Arens, J. F. *Recl. Trav. Chem. Pays-Bas* **1966**, *84*, 929.

(13) Boyce, C. B. C.; Whitehurst, J. S. *J. Chem. Soc.* **1959**, 2022.

(14) Ruhlmann, K. *Synthesis* **1971**, 236.

(15) Wu, Y.-J.; Burnell, D. *J. Tetrahedron Lett.* **1989**, *30*, 1021.

(16) This compound is commercially available from The Aldrich Chemical Co.