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Isomerization–Cyclization Approach to the Synthesis of 2-Hydroxy-5-alkylidene-cyclopent-2-enones

Jeremy Forest, Cisco Bee, Frank Cordaro, and Marcus A. Tius*

Department of Chemistry, 2545 The Mall, University of Hawaii, Honolulu, Hawaii 96822, and The Cancer Research Center of Hawaii, 1236 Lauhala Street, Honolulu, Hawaii 96813

tius@gold.chem.hawaii.edu

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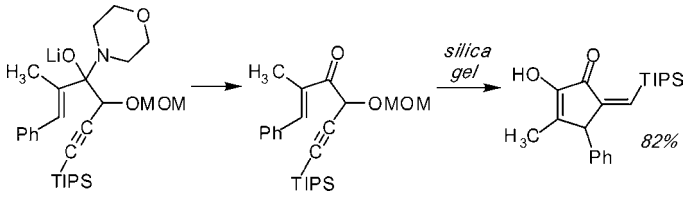
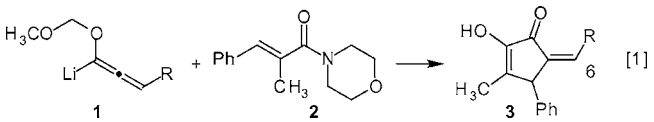
ABSTRACT



Propargyl vinyl ketones that are derived from the addition of 1-lithio-1-methoxymethoxy-2-ynes to morpholino enamides undergo isomerization followed by cyclization to α-methylene cyclopentenones upon exposure to silica gel.

The variant of the Nazarov reaction[1] that makes use of an allenyl ketone has been the focus of our research for some time.[2] The reaction as originally conceived takes place between an allenyllithium species **1** (eq 1) and a morpholino enamide such as **2**. The tetrahedral intermediate of this addition reaction collapses during workup, and the allenyl vinyl ketone is never isolated, as it undergoes cyclization to 2-hydroxy-5-alkylidene-cyclopent-2-enones **3** spontaneously. The reaction is successful both for the unsubstituted allene **1** (R = H) as well as for allenes in which R is alkyl. Lithioallenes **1** are readily prepared by deprotonation of the neutral allenes, which are derived from isomerization of the corresponding propargyl ethers.



1 2 3 [1]

In the case of the unsubstituted allene **1** (R = H), this isomerization reaction is accomplished very easily by following Brandsma's method.[3] When R = alkyl, the isomerization is more difficult and generally leads to mixtures of allene and acetylene. An alternative method for preparing the γ-substituted allenes, uncontaminated by the isomeric acetylene, requires several steps.[4] Because neither method for preparing substituted allenes is completely satisfactory, we recently described an alternative protocol for preparing C6-substituted cyclopentenones that avoids the use of γ-substituted allenes. The outline of this method is shown in eq 2. The tetrahedral intermediate **4** can be deprotonated by *sec*-butyllithium to produce γ-lithioallene **5**. Trapping of this species with electrophiles leads to **6**, which undergoes cyclization to C6-substituted α-methylene cyclopentenone **3**.

This approach is triply convergent,[5] as it brings together allene **1**, morpholino enamide **2**, and electrophile. Moreover, since the electrophile is not present during the isomerization step that leads to allene **1** (R = H), one can introduce groups

(1) (a) Jacobi, P. A.; Armacost, L. M.; Kravitz, J. I.; Martinelli, M. J.; Selnick, H. G. *Tetrahedron Lett.* **1988**, *29*, 6865−6868, et seq. (b) Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443−7444. (c) Hashmi, A. S. K.; Bats, J. W.; Choi, J.-H.; Scharz, L. *Tetrahedron Lett.* **1998**, *39*, 7491−7494. (d) Schultz-Fademrecht, C.; Tius, M. A.; Grimme, S.; Wibbeling, B.; Hoppe, D. *Ang. Chem. Int. Ed.* **2002**, *41*, 1532−1535. For a review of the Nazarov reaction, see: Habermas, K. L.; Denmark, S.; Jones, T. K. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1994; Vol. 45, pp 1−158.

(2) For an overview of our work in this area, see: Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284−290 and references cited therein.

(3) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 916−924.

(4) Tius, M. A.; Busch-Petersen, J.; Yamashita, M. *Tetrahedron Lett.* **1998**, *39*, 4219−4222.

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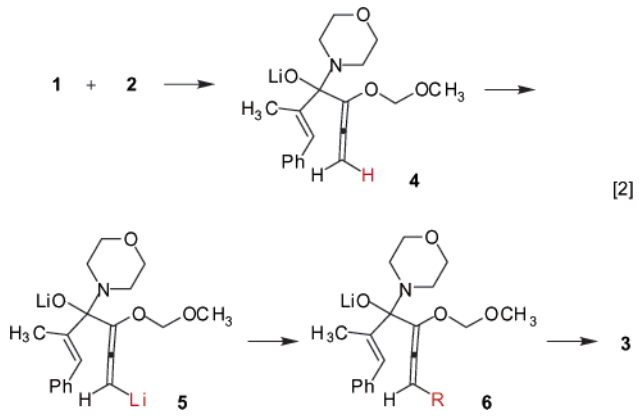
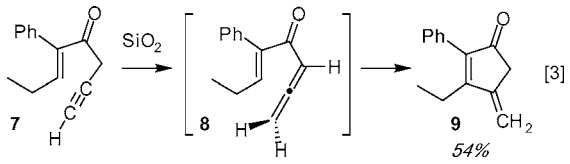
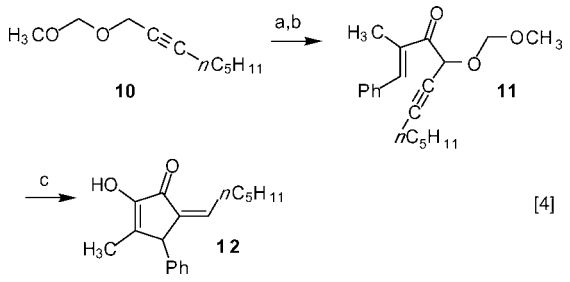


on the allene that are incompatible with the strongly basic conditions for the acetylene to allene conversion.[6]



After the completion of this work, we wondered whether there might be a way to avoid having to prepare and manipulate the allenes *completely*. Our inspiration for this work was provided by Hashmi's results (eq 3).[1c] When Hashmi and co-workers subjected propargyl vinyl ketone **7** to chromatography on silica gel, they isolated cyclopentenone **9**, which is presumably derived from allenyl vinyl ketone **8**. We postulated that the approach of eq 3 could be modified so as to provide an easy access to 2-hydroxy-5-alkylidene-cyclopent-2-enones **3**. Our first effort (Scheme 1, eq 4) was

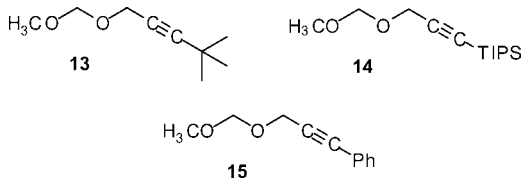
Scheme 1 [a]



[a] Conditions: (a) 0.9 equiv *sec*-BuLi, THF, −78 °C, 15 min; (b) 0.4 equiv **2**; (c) SiO_2 chromatography column, 12 h; 56% overall from **2**.

successful. Exposure of propargyl ether **10** to strong base, followed by a deficiency of enamide **2** led to the expected propargyl vinyl ketone **11** following workup. This material was introduced to a chromatography column packed with 200−400 mesh silica gel in 5% ethyl acetate and hexanes and allowed to stand for 12 h. Elution of the column provided 5-hexylidene-2-hydroxy-3-methyl-4-phenyl-cyclopent-2-enone **12** in 56% yield. Long contact times with the stationary phase are critical to the success of the process. It is noteworthy that the preference for the (*Z*)-isomer of the exocyclic double bond that is expressed in the solution-phase cyclizations is also observed in the reactions on silica gel.[7] This suggests that the cyclizations in the presence of silica gel can also be represented as 4 π conrotations.[8]

To determine the scope and limitations of the method, propargyl ethers **13**−**15** were prepared and their reactions with a series of morpholino enamides were examined. The results are summarized in Figure 1. The yields of products derived from propargyl ethers **13** and **14** were good or excellent, whereas products **26** and **27**, derived from **15**, were isolated in poorer yield.



The yield of **12** (56%) was comparable to the yields of **26** and **27**. The methoxymethyl ether of 2-butynol was prepared, however, the reaction of the derived anion with **2** gave none of the anticipated cyclopentenone. A trend therefore appears to emerge: the best results are obtained from propargyl ethers **13** and **14** that are terminally substituted by sterically demanding groups. Although we are not completely certain why poorer yields of products were obtained from propargyl ethers **10** and **15**, it is conceivable that in each case a nonregioselective reaction of the anion with the enamide is responsible. For example, deprotonation of **13** or **14** generates the corresponding propargyl anion that reacts with the enamide carbonyl group only at the α-carbon atom. In these cases, undesired γ-attack is inhibited by the steric bulk of the *tert*-butyl group and the triisopropylsilyl (TIPS) group, respectively. In the case of the propargyl anions that are generated from ethers **10** and **15**, there is no overwhelming steric bias to favor α-attack, and in the case of **15**, reaction at the undesired γ-carbon atom may be electronically favored as well. The contrasting results that were observed in the case of **20** and **25** also deserve comment. In the absence of a non-hydrogen substituent at C4, the kinetic preference for the (*Z*)-isomer of the exocyclic double bond may not be observed.[9] This rationalizes the observed (*E*)-stereochemistry

(5) Tius, M. A.; Gomez-Galeno, J.; Gu, X.-Q.; Zaidi, J. H. *J. Am. Chem. Soc.*, **1991**, *113*, 5775−5783.

(6) Bee, C.; Tius, M. A. *Org. Lett.* **2003**, *5*, 1681−1684.

(7) Signal for the C6 methine proton of the (*Z*)-isomers appears near 6.1 ppm in the ^{1}H NMR spectrum ($CDCl_3$), whereas in the (*E*)-isomers, the C6 methine proton appears near 6.6 ppm.

(8) Hu, H.; Smith, D.; Cramer, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 9895−9896.

(9) Configuration in **20** and **25** was established unambiguously on the basis of a positive NOE, in the case of **20** between the *tert*-butyl and the C4 methylene protons, and in the case of **25** between the C6 methine and the C4 methylene protons. The stereochemistry of **26** and **27** was also determined on the basis of the NOE between C4 and C6 methine protons.

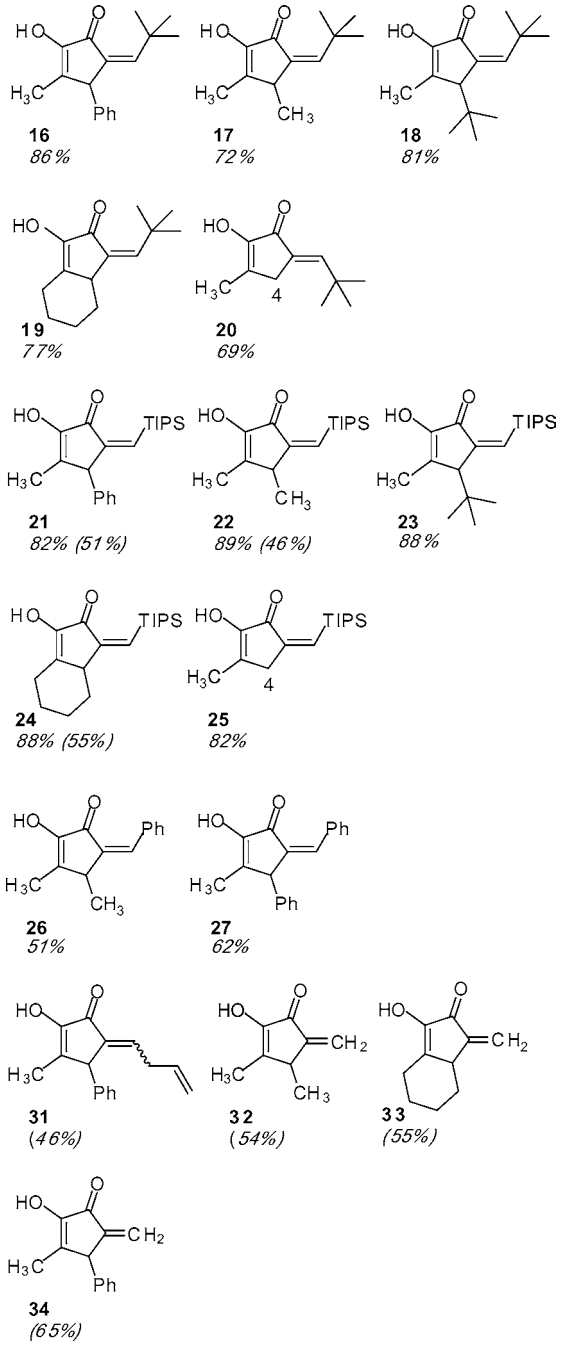
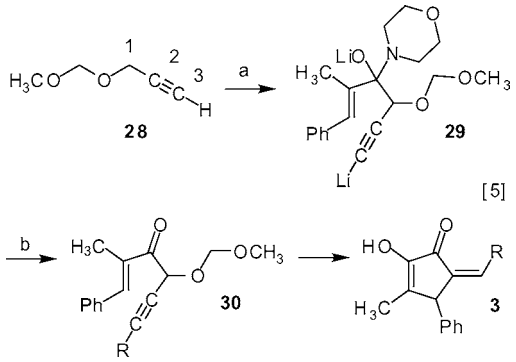


Figure 1. 2-Hydroxy-5-alkylidene-cyclopent-2-enones. Yields calculated from the enamide. Yields in parentheses are for compounds prepared through **28** according to the procedure that is summarized in eq 5 (Scheme 2).

in the case of **20**, but it fails to explain why only (*Z*)-**25** was isolated under identical conditions. The stereochemistry in this case may be influenced by intramolecular donation of a nonbonding electron pair from the carbonyl oxygen atom to the exocyclic silicon atom.[10]

(10) There is precedent for such donor−acceptor interactions: Macharashvili, A. A.; Shklover, V. E.; Struchkov, Yu. T.; Baukov, Yu. I.; Kramarova, E. P.; Oleneva, G. I. *J. Organomet. Chem.* **1987**, *327*, 167−172.

Scheme 2 [a]



[a] Conditions: (a) 2.5 equiv *sec*-BuLi, THF, −78 °C, 20 min; 0.4 equiv **2**; (b) R−X, excess; SiO_2 column chromatography.

It occurred to us that it might be possible to further reduce the labor of preparing C6-substituted cyclopentenones. The methoxymethyl ether **28** of propargyl alcohol, the starting material for allene **4**, is easily converted into a C3 nucleophile by deprotonating the acetylene. It is also very easy to convert **28** into a 1,3-dianion by exposure to a small excess of *sec*-butyllithium (Scheme 2). The dianion can be trapped at C1 with enamide **2** to give intermediate **29**. The acetylide function in **29** can subsequently be trapped by electrophiles, leading to **30**. Exposure of **30** to silica gel, as before, results in the formation of 2-hydroxy-5-alkylidene-cyclopent-2-enones.

This approach immediately led to positive results. The results are summarized in Figure 1 (yields in parentheses). A comparison of the yields of **21**, **22**, and **24** indicates that they are somewhat lower through the protocol of eq 5. The yields are nonetheless serviceable, especially when one takes into account the number of transformations that take place in one operation. Quenching the acetylenic anion (viz. **29**) with allyl bromide led to **31** in 46% overall yield as a ca. 17/83 mixture of (*E*)- and (*Z*)-isomers. Quenching the reaction of eq 5 without adding an electrophile led to 5-methylene cyclopentenones **32**−**34** in the yields indicated in Figure 1.

In summary, we have developed a greatly simplified procedure for performing the cationic cyclopentannelation reaction that avoids the use of allenes altogether. A three-component process has been demonstrated (eq 5) in which enamide, propargyl ether **28**, and an electrophile are combined in a single operation to produce 2-hydroxy-5-alkylidene-cyclopent-2-enones. Although yields of cyclic products appear to be somewhat lower by this method than they are when the allenes are used, the convenience and the brevity of the current method recommend it, especially for the assembly of diverse libraries of small molecules.[11]

Acknowledgment. We thank the National Institutes of Health (GM57873) for generous support and Dr. Conchi Fernandez-Garcia for having suggested this approach many years ago.

(11) Jang, W. B.; Hu, H.; Lieberman, M. M.; Morgan, J. A.; Stergiades, I. A.; Clark, D. S. Tius, M. A. *J. Comb. Chem.* **2001**, *3*, 346−353.

Supporting Information Available: General procedures for the synthesis of **18**, **24**, and **34**; spectroscopic data and reproductions of ^{1}H NMR spectra for **16**−**27** and **31**−**34**; and reproductions of ^{13}C NMR, IR, and mass spectra of **18**, **24** and **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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