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Facile Preparation of Allenic Hydroxyketones via Rearrangement of Propargylic Alcohols

Michael E. Jung* and Joseph Pontillo[1]

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569

jung@chem.ucla.edu

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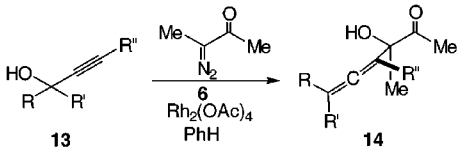
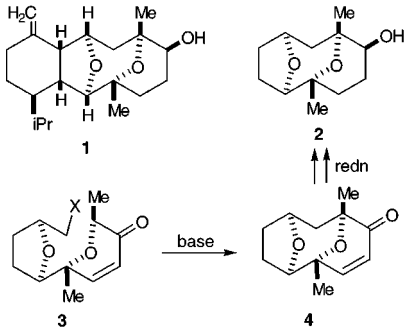
ABSTRACT



Treatment of tertiary propargylic alcohols 13 with 3-diazo-2-butanone 6 and catalytic dirhodium tetraacetate in benzene gave good yields of the diastereomeric allenic hydroxyketones 14, with, in some cases, good diastereocontrol. These products are presumably formed via the [2,3]-sigmatropic rearrangement of an α-propargyloxy enol derivative. This reaction has been extended to the preparation of homoallylic hydroxyketones from allylic alcohols by reaction with 6 and the rhodium catalyst.

For a proposed synthesis of the right-hand portion **2** of the strongly cytotoxic agent sclerophytin A, **1**,[1,2] the unusual cyclodecane ring having two oxygen bridges, we envisioned a procedure in which the anion of a 2,6-dimethyl-3-pyranone would displace a nearby leaving group, e.g., **3** → **4**. Reduction of the enone would then afford the desired target **2**. To test this internal alkylation procedure, we sought to



prepare simple 2,6,6-trisubstituted 3-pyranones. One method for doing so involved reaction of the tertiary propargylic alcohol **5** with the readily available[3] diazoketone **6** in the presence of a rhodium(II) catalyst to give the product of insertion of the carbenoid into the O−H bond **7**.[4]

We report herein the unusual course of this reaction which allows a general entry into allenic hydroxyketones.

Lithium (trimethylsilyl)acetylide was added to commercially available 1-phenoxyacetone **8** to give, after desilylation, the propargylic alcohol **5** in 95% yield. Reaction of 1 equiv of **5** with 2 equiv of the diazoketone **6** in the presence of 5 mol % of rhodium diacetate dimer in benzene did not give any of the expected products of O−H insertion **7** but rather a 9:1 mixture of the diastereomeric allenic hydroxyketones **9** and **10** in 58% yield (76% based on recovered starting material). These unusual products are presumably formed via interaction of the metal carbenoid **I** with the hydroxyl group of **5** to give the intermediates **II** and **III** which prefer to react via a [2,3] sigmatropic rearrangement[5] to generate the allene rather than by simple O−H insertion. Of the two possible diastereomeric inter-

(1) Recipient of UCLA Distinguished Teaching Assistant Award.

(2) (a) Sharma, P.; Alam, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2537. (b) Alam, M.; Sharma, P.; Zektzer, A. S.; Martin, G. E.; Ji, X.; Van der Helm, D. *J. Org. Chem.* **1989**, *54*, 1896.

(3) Cooke, M. P., Jr. *J. Org. Chem.* **1979**, *44*, 2461.

(4) a) Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssié, P. *Tetrahedron Lett.* **1973**, *24*, 2233. (b) Miller, D. J.; Moody, C. J. *Tetrahedron* **1995**, *51*, 10811. (c) This reaction has been reported on propargylic alcohols using diazoacetates: Noels, A. F.; Demonceau, A.; Petiniot, N.; Hubert, A. J.; Teyssié, P. *Tetrahedron* **1982**, *38*, 2733.

(5) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263.

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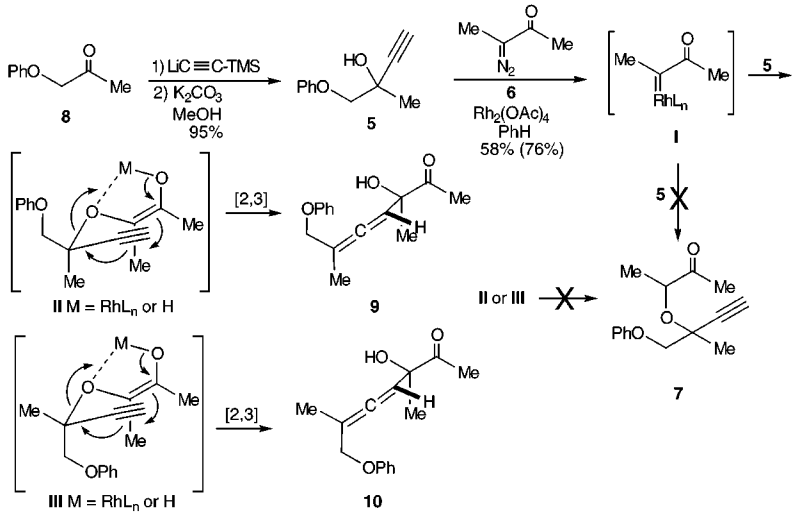
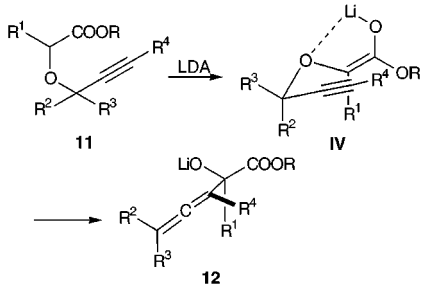
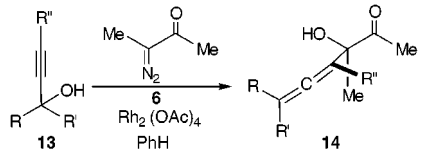


mediates **II** and **III**, the former is presumably favored due to the difference in size between the methyl and phenoxymethyl which results in differential steric hindrance between one of these groups and the olefinic methyl group. The stereochemistry of the major diastereomer was assigned on the basis of analogy to the work of Marshall[6] who reported a conceptually similar rearrangement of the anion of α-(propargyloxy) esters **11** to give the allenic hydroxyesters **12**. The closest analogy to the current rearrangement is the work of Doyle,[7] namely, reaction of propargyl methyl ethers with diazoketones in the presence of catalytic rhodium complexes to give mixtures of the cyclopropenes and the corresponding methoxy allenic ketones. Curiously, contrary to our case, $Rh_2(OAc)_4$ gave predominately the cyclopropenes via C=C insertion while $Rh_2(pfb)_4$ afforded the allenes via the [2,3] sigmatropic rearrangement.



We have determined the generality and scope of this rearrangement by carrying out several additional examples (Table 1). Secondary and primary propargylic alcohols, e.g., **13abc**, give generally higher yields than do tertiary alcohols, e.g., **13d**. Substitution of an alkyl group on the alkyne does



not stop the rearrangement although the yield is lower (**13e**). In this case, the product of O−H insertion (corresponding to **7**) is isolated as a byproduct in 19% yield. The diastereomeric ratios are poorer in these cases for some unexplained reason. We have also extended this reaction to the preparation of homoallylic hydroxyketones from allylic alcohols. Thus treatment of the allylic alcohol **15** with **6** and Rh(II) gave a 67% yield (92% based on recovered starting material) of a 7:1 mixture of the hydroxyketones **16** and **17**, presumably via the intermediate **V**. The stereochemistry of the major diastereomer was assigned by the use of NOE experiments. As in the case of **5**, the diastereomeric ratio is quite high, implying a reasonable energy difference between the two diastereomeric transition states.

Table 1. Reaction of Alcohols **13** with **6** To Give **14**

compd	R	R′	R″	yield, %	ratio
13a	Ph	H	H	75	3:1
13b	H	H	H	68	
13c	Me	H	H	62	3:2
13d	Me	Et	H	45	3:2
13e	H	H	Me	44[a]	

[a] In addition, 19% of the O−H insertion product corresponding to **7** was obtained.

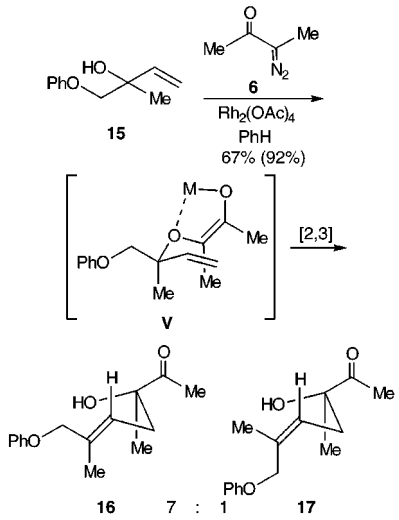
Finally it is important to point out that these rearrangements could proceed by either a [2,3]- or a [3,3]-sigmatropic rearrangement pathway. Wood and co-workers have shown that the [3,3] pathway is favored for allylic alcohols[8,9] and also for propargylic alcohols under certain conditions.[10] However, under the conditions reported here, namely, the

(6) (a) Marshall, J. A.; Wang, X. *J. Org. Chem.* **1991**, *56*, 4913. (b) Marshall, J. A.; Robinson, E. D.; Zapata, A. *J. Org. Chem.* **1989**, *54*, 5854.

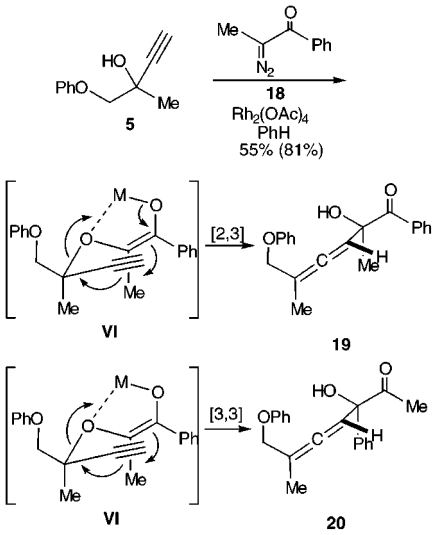
(7) Doyle, M. P.; Bagheri, V.; Claxton, E. E. *J. Chem. Soc., Chem. Commun.* **1990**, 46.

(8) For a different rearrangement of a secondary allylic alcohol with methyl diazoacetoacetate, see: Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J.; Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc.* **1995**, *117*, 10413. In this case, an intermediate very similar to **V** undergoes a [3,3] sigmatropic shift rather than the [2,3] shift we observe here.

(9) Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stoltz, B. M.; Holubec, A. A.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1999**, *121*, 1748.



addition of the diazoketone quickly to a solution of the propargyl alcohol and the rhodium catalyst in benzene at 25 °C, we are convinced that the rearrangement proceeds via a [2,3]- rather than a [3,3]-sigmatropic pathway. The use of 3-diazo-2-butanone **6** does not allow one to choose between the two possibilities since the product is the same. However, treatment of the alcohol **5** with diazopropiophenone **18** afforded in 55% isolated yield (81% based on recovered starting material) only the product of the [2,3] pathway, compound **19**, with none of the product of the corresponding [3,3] pathway **20** being isolated. Thus under our conditions, the [2,3] sigmatropic rearrangement pathway is favored. However, under slightly modified conditions,[10] e.g., addition of the rhodium catalyst to a solution of the diazoketone **18** and the alcohol **5** in benzene at 25 °C, the [3,3] product **20** was afforded as the major (>15:1) product in 52% yield (75% based on recovered starting material).



Further work on these rearrangements and the synthesis of sclerophytin A and its analogues is currently underway and will be reported in due course.

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Supporting Information Available: Full experimental procedures and proton and carbon NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9900257

(10) See following Letter (Wood, J. L.; Moniz, G. A. *Org. Lett.* **1999**, *1*, 371). We thank Professor Wood for communication of these results prior to publication.