Tetrahedron Letters, Vol. 33, No. 40, pp. 5917-5920, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

THE CO-OXIDATION OF CONJUGATED ENYNES. A CONVENIENT SYNTHESIS OF β-SULFOXY ACETYLENIC CARBINOLS

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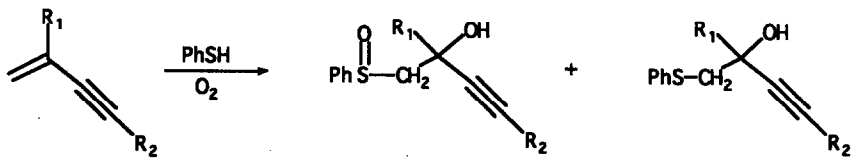
Abstract: Several β-sulfoxy substituted acetylenic carbinols were prepared by the addition of thiyl radicals and oxygen to conjugated enynes.

The unusual structure and the outstanding biological activity of antitumor antibiotics such as neocarzinostatin,[1] calichemicin,[2] esperamicin[3] and dynemicin[4] have recently provided new incentives for studying the synthesis and chemistry of unsaturated diyne systems.[5] In this regard, acetylenic carbinols are of current interest because they serve as key intermediates for the synthesis of these conjugated enynes.[6] Acetylenic alcohols also represent versatile reagents in organic synthesis and can be converted to allenes, cumulenes, ketones and aldehydes *via* rearrangement reaction sequences.[7] In connection with our efforts towards the development of new methodology using sulfonyl substituted allenes,[8] we required an efficient construction of β-sulfur substituted ynols. While several useful syntheses of acetylenic carbinols have been recorded,[7] a simple and general method for the preparation of sulfoxy substituted ynols has not been established. In this communication we describe an approach to these compounds which is based on the addition of thiyl radicals and oxygen to conjugated enynes.

The addition of thiyl radicals and oxygen to olefins, a process termed co-oxidation, is known to produce β-sulfoxy alcohols.[9] Our synthetic plan was based on the assumption that thiyl radical attack would occur at the terminal olefinic carbon.[10] This assumption was made on the basis of earlier reports on the regiochemical outcome of thiyl radical additions to conjugated enynes.[10] Our results show that this indeed is the case and we obtain β-sulfoxy and β-thio substituted acetylenic alcohols in good yields (50-70%). A typical experimental



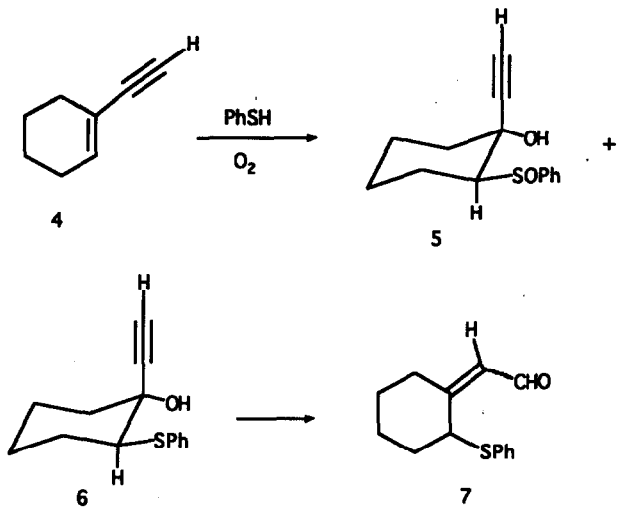
1a; R_1=Me; R_2=H
1b; R_1=Me; R_2=Ph

2

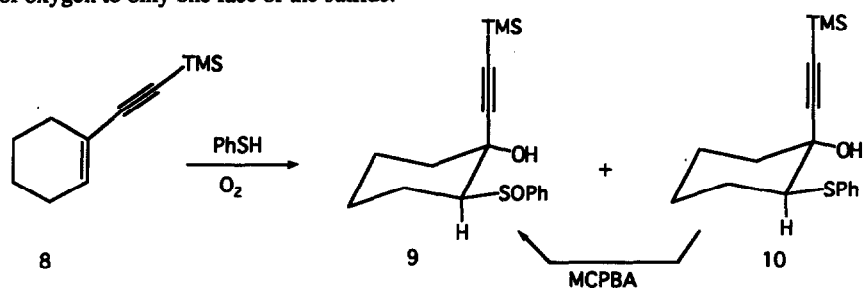
3

procedure consists of adding a heptane solution of thiophenol (1 mmol) over a course of 5-10 h to an oxygenated heptane solution of the enyne (1 mmol). The product mixture obtained was readily separated by flash chromatography. When enyne **1a** was co-oxidized, the major sulfoxy carbinol **2a** (67%) was obtained as a 2:1 mixture of diastereomers which were readily separated by silica gel chromatography. Similar results were obtained with enyne **1b**.

The co-oxidation of enyne **4** gave sulfoxy carbinol **5** (26%) as a single diastereomer as well as a lesser amount (14%) of sulfide **6**. The structure of **5** has both the sulfoxy and hydroxyl groups in the equatorial position (*trans*). This assignment is based on an axial coupling constant of J=12.9 Hz for the C_2-hydrogen.[11] The fact that out of four possible diastereomers only one is observed is worth noting and suggests an intramolecular oxygen atom transfer process (*vide infra*). When left standing for several days, sulfide **6** undergoes a Rupe rearrangement[12] to give a mixture of *E/Z* aldehydes **7**.

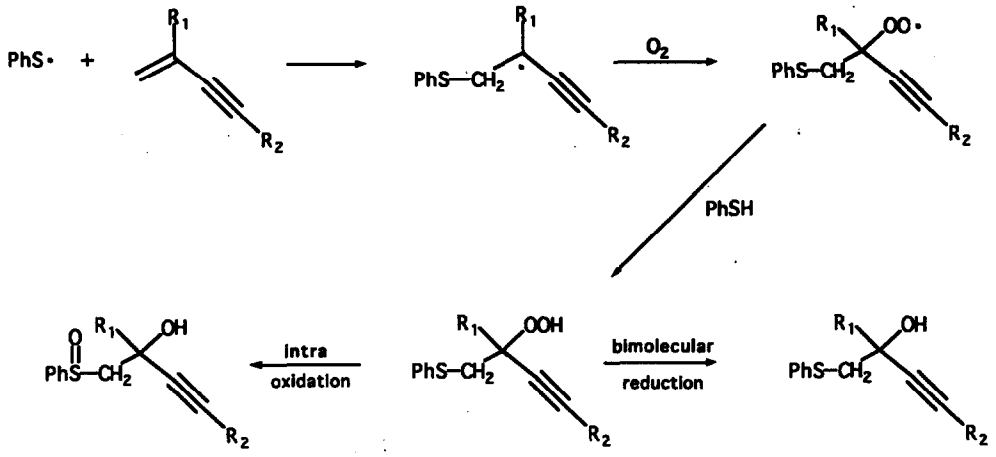


When the silyl protected enyne **8** was co-oxidized, sulfoxide **9** and sulfide **10** were obtained in a 3:2 ratio. Once again, sulfoxy carbinol **9** was obtained as a single diastereomer even though four are possible. Desilylation of **9** with fluoride ion gave sulfoxide **5**, the same product obtained from the co-oxidation of enyne **4**. When sulfide **10** is treated with MCPBA, sulfoxide **9** is formed exclusively. The sole formation of **9** from the bimolecular oxidation is undoubtedly related to hydrogen bonding of the OH group with the peracid and delivery of oxygen to only one face of the sulfide.

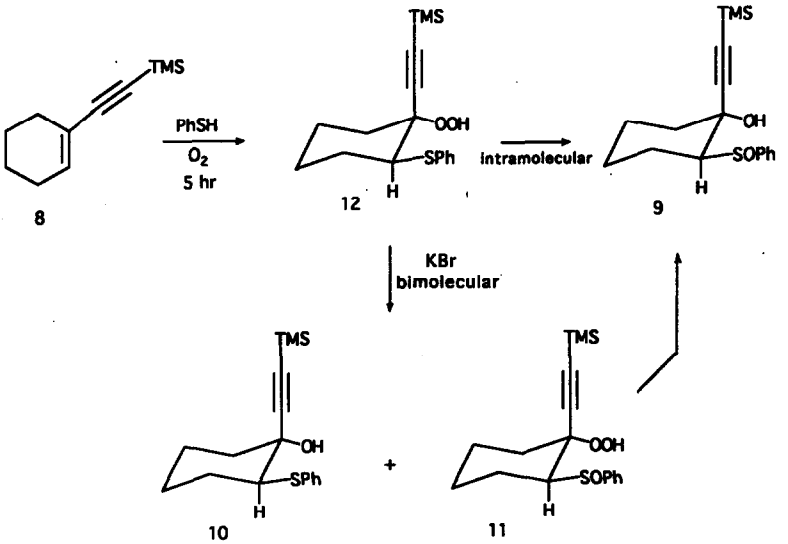


Our results are consistent with the co-oxidation mechanism previously postulated for alkenes and which we now extend to conjugated enynes (Scheme I).[9] Initial thiyl radical attack occurs exclusively at the double bond to generate a propargylic radical. Capture of the radical by oxygen followed by hydrogen atom transfer from thiophenol gives a hydroperoxide intermediate. This species has two available options; it can transfer an oxygen atom either by an intramolecular[13] or intermolecular[14] pathway. In support of this proposal are the following observations. When triphenylphosphine is added to the reaction mixture in the co-oxidation of enyne

Scheme I



8, only sulfide **10** is obtained and no sulfoxide product is observed. This indicates that the oxygen atom donor species must be the hydroperoxide intermediate since reduction of this intermediate with the added triphenylphosphine suppresses the formation of sulfoxide **9**. It has been reported that the absorption rate of oxygen is significantly accelerated in the presence of chloride or bromide ion.[15] When the co-oxidation of **8** was carried out in the presence of KBr and stopped after 5 h of reaction, four products were observed by NMR analysis (sulfoxide **9**, sulfide **10**, sulfoxy hydroperoxide **11** and sulfide hydroperoxide **12** in a 1:1:1:1 ratio). Hydroperoxide **11** could be isolated from the reaction mixture and was reduced to **9** by Ph_3P but hydroperoxide **12** was too unstable for isolation. Sulfoxide **11** was not detected in the absence of KBr and could only have arisen from an intermolecular oxygen transfer process since it still contains the hydroperoxide moiety. After an



additional 12 h of reaction, hydroperoxide **12** is no longer present and has been converted to **9** *via* the intramolecular pathway and at a slower rate to **10** and **11** by a bimolecular disproportionation process.

Acknowledgment: Support from the National Science Foundation (CHE-9014435), U. S. Army CRDEC (#DAAA15-90-C-1076), the National Institute of Health (CA-26750) and the RCMI program of Clark Atlanta University (NIH #RR03062) is gratefully acknowledged.

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11. NMR **5**: ($CDCl_3$, 300 MHz) δ 0.95-2.20 (m, 8H), 2.78 (dd, 1H, J=12.9 and 3.9 Hz), 2.77 (s, 1H), 6.27 (s, 1H) and 7.50-7.80 (m, 5H).
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(Received in USA 28 May 1992)