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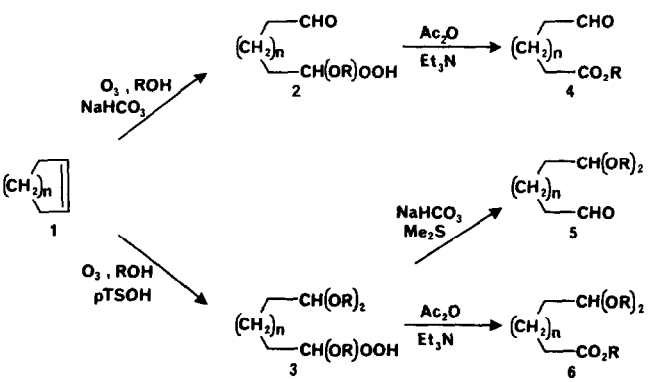
OZONOLYTIC CLEAVAGE OF CYCLOALKENES TO TERMINALLY DIFFERENTIATED PRODUCTS

Stuart L. Schreiber,*[1] Ronald E. Claus, Jeff Reagan
Sterling Chemistry Laboratory, Yale University
New Haven, Connecticut, 06511

Abstract. Conditions are reported which convert cycloalkenes to terminally differentiated products through the intermediacy of α-alkoxy hydroperoxides.

The ozonolytic cleavage of cycloalkenes in the presence of an alcohol affords a chain with an aldehyde and an α-alkoxy hydroperoxide at the termini.[2] We report that simple modifications of ozonolytic workup procedures on these peroxides give rise to a variety of products with differentiated terminal functionality.

Scheme 1

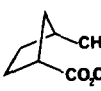
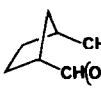
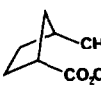


Scheme 1 depicts the reaction conditions which are employed to cleave an olefin in an unsymmetrical fashion[3] and the products generated. The ozonolysis is carried out at -78° in 5:1 CH_2Cl_2-alcohol buffered with $NaHCO_3$[4] and affords an aldehyde-alkoxy hydroperoxide, 2.[5] After dilution with benzene and rotary evaporation of the azeotrope, the peroxide is dehydrated with acetic anhydride and triethylamine[6] to produce an aldehyde-ester, 4, in a one-pot sequence.

Alternatively, addition of p-toluenesulfonic acid to the ozonolysis reaction medium leads to the formation of an acetal-alkoxy hydroperoxide, 3.[7] Neutralization of the acid with $NaHCO_3$[8] followed by reduction with dimethylsulfide[9] yields an acetal-aldehyde, 5, in a one-pot operation. Dehydration of the peroxyacetal, 3, in the same fashion as with 2, affords an acetal-ester, 6.

Table 1 summarizes the results of carrying out these procedures on a variety of symmetrical cyclic olefins.[10] Methanol was most commonly used as the source of alcohol but entry 2 demonstrates that other types of esters (i.e., t-butyl instead of methyl) can be

Table 1

entry	alkene	alcohol	aldehyde-ester	yield	acetal-aldehyde	yield	acetal-ester	yield
1		MeOH	$MeO_2C(CH_2)_4CHO$	96	$(MeO)_2CH(CH_2)_4CHO$	93	$(MeO)_2CH(CH_2)_4CO_2Me$	83
2		tBuOH	$tBuO_2C(CH_2)_4CHO$	91	———		———	
3		MeOH	$MeO_2C(CH_2)_3CHO$[12]	47	$(MeO)_2CH(CH_2)_3CHO$	48	$(MeO)_2CH(CH_2)_3CO_2Me$	72
4		MeOH	$MeO_2C(CH_2)_5CHO$	93	$(MeO)_2CH(CH_2)_5CHO$	95	$(MeO)_2CH(CH_2)_5CO_2Me$	100
5		MeOH	$MeO_2C(CH_2)_{10}CHO$	94	$(MeO)_2CH(CH_2)_{10}CHO$	95	$(MeO)_2CH(CH_2)_{10}CO_2Me$	83
6		MeOH	 12	90		90		92

produced by the appropriate choice of alcohol in the ozonolysis reaction. Compounds of the type 4, 5, and 6 were formed directly from the corresponding cycloalkene without purification of the intermediate peroxide. The aldehyde-alkoxy hydroperoxides, 2, were often oligomeric[5] and tended to be difficult to purify. However, the acetal-alkoxy hydroperoxides, 3, were monomeric and could be obtained in high yield after flash chromatography.[11]

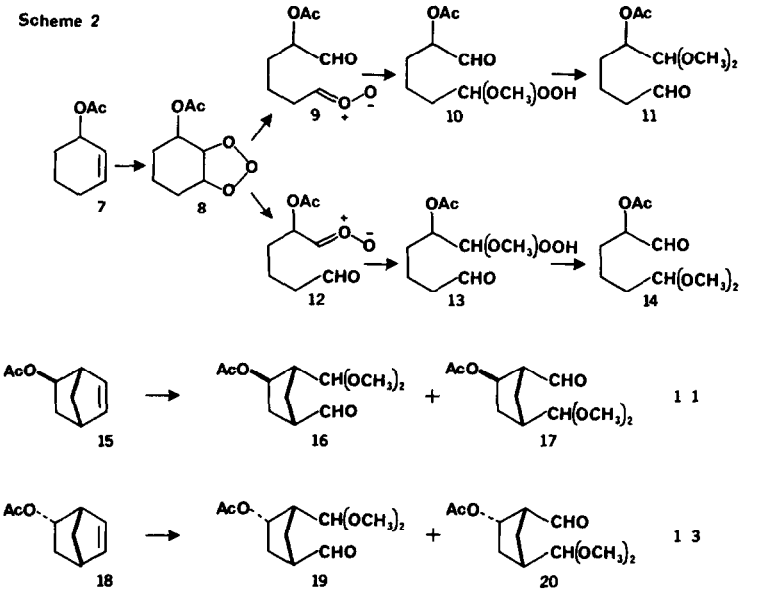
Application of these reactions to substituted unsymmetrical cycloalkenes requires a knowledge of the effect of substituents on the direction of cleavage of the primary ozonide. Fortunately, considerable attention has been given to this problem.[13] The ozonolysis of enol ethers exemplifies the effects of substitution at the olefinic carbon of a cycloalkene, this results in a highly regioselective cleavage to yield an ester and an alkoxy hydroperoxide at the β-carbon of the enol ether.[14] Thus, ozonolysis of 1-methoxycyclohexene in 5:1 CH_2Cl_2-methanol produced the corresponding methoxy hydroperoxide-ester which upon dehydration afforded dimethyl adipate in 85% yield.[10]

Previous studies indicated that simple inductive arguments should reliably predict the effect of substitution at a saturated carbon of an unsymmetrical cycloalkene.[15] Scheme 2 illustrates the two possible regioisomeric acetal-aldehydes that can result from cleavage of cyclohexen-3-ol acetate.

Breakdown *via* retro 2+3 cycloaddition of the primary ozonide, 8, could occur in two directions to give the carbonyl oxides, 9 or 12. 1,3-addition of methanol would yield 10 or 13. Workup as previously described would then generate the monoprotected dialdehydes, 11 or 14. Since the identity of the final product is determined at the retro 2+3 stage,[16] it would be expected that 11 would be formed in preference to 14, since the electron withdrawing acetyloxy substituent is more remote to the electrophilic carbon center of the carbonyl oxide in 9 relative to 12.

In the event, the expected acetal-aldehyde, 11, was obtained in 74% isolated yield, free of any regioisomeric material as determined by careful analysis of the crude reaction

Scheme 2



mixture.[17] Subjection of exo-5-norbornen-2-ol acetate, 15, to the identical conditions, however, led to the formation of a 1:1 mixture of 16 and 17 in 84-87% yield. The more remote acetyloxy substituent now fails to exert any control in the regiochemical outcome. Cleavage of the endo isomer, 18, resulted in the formation of a 1·3 ratio of 19 and 20 in comparable yield.[18] Since the preferred direction of cleavage[16] of 18 is opposite to that predicted by consideration of the inductive effect of the acetyloxy substituent, it is apparent that other factors must be operative.

Further studies of the utility of peroxides in organic synthesis[14c] are underway and will be reported in the future.

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References and Notes

1. Searle Scholar, 1982-1985.

2. For an excellent discussion, see Philip S. Bailey, "Ozonation in Organic Chemistry," Academic Press, New York, 1978, Vol. 1.

3. Other methods for the unsymmetrical cleavage of olefins have been reported· a) T. Sato, K. Maemoto, and A. Kohda, J. Chem. Soc., Chem. Commun., 1116, (1981); b) RZhKhim, 24H, 68, (1977), c) V.N. Odinokov, G.A. Tolstikov, R.I. Galeyeva, and T.A. Karagapoktseva, Tetrahedron Lett., 1371, (1982), d) Philip S. Bailey and R.E. Erickson, Organic Syntheses, Vol. 41, 41 (19); e) P.S. Bailey, S.S. Bath, F. Dobinson, F.J. Garcia-Sharp, and C.D. Johnson, J. Org. Chem., 29, 697, (1964), f) I.E.D. Besten, and T.H. Kinstle, J. Am. Chem. Soc., 102, 5968 (1980).

4. The buffer serves to prevent acetal formation, see· R.B. Woodward, K. Sakan, et al., J. Am. Chem. Soc., 103, 3210, (1981).

5. Compounds of this type have been reported previously; cyclohexene. P S Bailey, J Org Chem , 22, 1548 (1957), P S Bailey, Ind Eng Chem , 50, 993 (1958), J E. Franz, W S. Knowles, and C Osuch, J Org Chem , 30, 4328, (1965), norbornene R H Perry, Jr , J Org. Chem , 24, 829 (1959), phenanthrene P S Bailey, and S B. Mainthia, J. Org. Chem , 23, 1089 (1958), P S. Bailey, J Am Chem Soc , 78, 3811 (1956). For other examples, see P S Bailey, 'Ozonation in Organic Chemistry," Academic Press, New York, 1978, Vol 1, Chapter 4, pg 37-43

6 The direct dehydration of certain alkoxy hydroperoxides with amines (without acetylation) has been reported, see R M. Ellam and J.M Padbury, J Chem Soc., Chem Commun , 1086, (1972)

7 In a typical experiment, 10% pTSOH (w/w) is added after ozonolysis and the reaction mixture is stirred for 1 5 hr at R T. to assure complete acetal formation. Under these conditions, the alkoxy hydroperoxide is stable to acetal exchange

8 Neutralization prevents bisacetal formation on subsequent reduction

9 J J Pappas, W P Keaveney, E Gancher, and M Berger, Tetrahedron Lett , 4273 (1966)

10. Yields are based on the starting cycloalkene and refer to materials purified by flash chromatography[11] All compounds were characterized by their ^{1}H nmr, ^{13}C nmr, gc-ms, and ir spectral data

11 W C Still, M Kahn and A Mitra, J Org Chem., 43, 2923 (1978).

12 Formation of the ester occurred partially via acetylation of the hydroxyl of the cyclic nemiperoxyacetal form of 2, followed by fragmentation The use of two equivalents of triethylamine and stirring at room temperature for 24 hours was necessary to insure complete conversion to the ester

13. For a review, see ref 1, Ch 7, pg 119-129

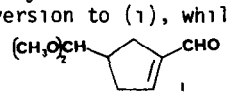
14 a) Q E Thompson, J Org Chem , 27, 4498 (1962), b) P S Bailey, S B Mainthia, and C J Abshire, J Am Chem Soc , 82, 6136, (1960); c) S.L Schreiber, J Am Chem Soc , 102, 6163 (1980)

15 a) P S Bailey, Chem Rev , 58, 925 (1958), b) S Fliszár, Tetrahedron Lett , 6083, (1966), c) S Fliszár and J Renard, Can. J Chem , 45, 533 (1967), d) S Fliszár and M Granger, J Am Chem Soc , 91, 3330 (1969), e) S Fliszár and M Granger, J. Am Chem. Soc , 92, 3361 (1970), f) S Fliszar and J. Renard, Can J. Chem , 48, 3002, (1970), g) S Fliszár, J. Renard and D Z Simon, J Am Chem Soc., 93, 6953, (1971)

16 This argument assumes there is no scrambling during acetal formation, which we feel is a reasonable assumption since the previous examples demonstrate the stability of the alkoxy hydroperoxide to acetal exchange Determination of the regiochemistry of 11 and its corresponding acetal-methoxy hydroperoxide was straightforward by ^{1}H nmr, but the oligomeric nature of 10 precluded a similar analysis

17. In addition to the absence of 14, we could not identify any products which might arise from "anomalous" fragmentation of the peroxide 13, e g , see K Aoki, M Kato, M Suzuki, Y. Hayakawa, H Nukamura, K Yamada, and Y Hirata, J Chem Soc , Chem Commun , 618 (1973)

18 The regiochemical identity of 19 and 20 could be unambiguously determined by ^{1}H nmr decoupling studies at 500 MHz and by the observation that treatment of 20 with SiO_2 resulted inthe quantitative conversion to (1), while similar treatment of 19 failed to cause any elimination



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