Tetrahedron Letters,Vol.24,No.23,pp 2363-2366,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

CRIEGEE REARRANGEMENT OF α-ALKOXY HYDROPEROXIDES A SYNTHESIS OF ESTERS AND LACTONES THAT COMPLEMENTS THE BAEYER-VILLIGER OXIDATION OF KETONES

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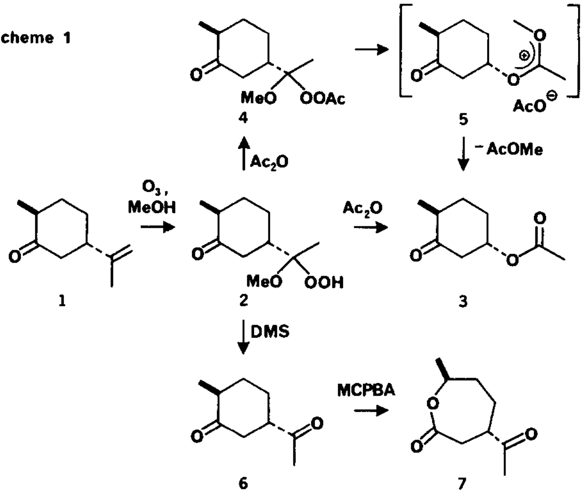
Abstract: α-Alkoxy hydroperoxides undergo Criegee rearrangment upon treatment with $(CH_3CO)_2O$ to provide esters or lactones.

The acylation of hydroperoxides results in the formation of peroxyesters which can undergo the Criegee rearrangement to afford ketones or ketals.[2] We have studied the acylation of an α-alkoxyhydroperoxide to furnish a peroxyester that is related to the intermediate produced in the Baeyer-Villiger reaction.[3] The peroxyester undergoes the Criegee rearrangement to a dioxenium ion that suffers dealkylation or hydrolysis to provide an ester or a lactone. The α-alkoxy hydroperoxide can be obtained from a variety of conditions including the ozonolysis of an olefin[4] or the addition of hydrogen peroxide to an enol ether. Thus, the transformation of the peroxide into an ester can provide chemoselectivity that may not be observed in the Baeyer-Villiger oxidation of the corresponding ketone.[5,6]

Ozonolysis (O_3, 5:1 CH_2Cl_2-MeOH, -78°C) of (+)-trans-dihydrocarvone afforded the α-methoxy hydroperoxide 2 as a 1:1 mixture of diastereomers in 86% isolated yield.[7,8] The regioselective breakdown of the presumed primary ozonide favors formation of the more substituted carbonyl oxide which is trapped by 1,3-addition of methanol.[4] Acetylation and rearrangement (Ac_2O, ET_3N, DMAP, CH_2Cl_2, 40°) provided trans-5-acetoxy-2-methylcyclohexanone 3, $[\alpha]^{20}_{D}$ 7.9°, in 61% yield and the corresponding alcohol in 20% yield after an aqueous workup.

Acetylation of the alcohol gave the acetate 3 (combined yield of 3=79%). The intermediate peroxyacetate 4 can be isolated (84% yield) and purified by flash chromatography[7]. When warmed in deuteriochloroform (35°) concomitant formation of 3 and methyl acetate was observed. Presumably, the dioxenium ion 5 suffers acetate dealkylation of the methyl substituent[9] to afford 3 and hydrolysis to produce the corresponding alcohol. Similarly, trifluoroacetylation (($(CF_3CO)_2O$, K_2CO_3, $CHCl_3$,-50°→25°(30min)) of 2 provided 3 and methyl trifluoroacetate, but in diminished yield.

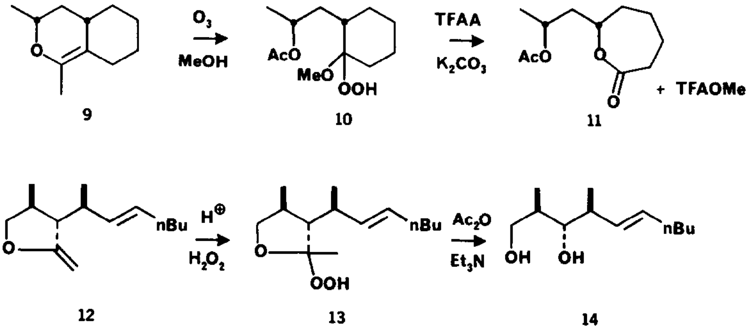
Scheme 1



To illustrate the chemoselectivity available to this oxygen insertion reaction, the Baeyer-Villiger oxidation of the diketone 6 was examined. Reduction (Me_2S)[10] of 2 afforded the diketone 6 which undergoes chemoselective Baeyer-Villiger oxidation (MCPBA (1 eq.), CH_2Cl_2, 25°) to provide a single product, the lactone 7 in 79% yield.

Whereas acid-catalyzed addition of hydrogen peroxide to an enol ether affords an α-alkoxy hydroperoxide at the α-carbon of the enol ether, ozonolysis in an alcoholic solvent provides an α-alkoxy hydroperoxide at the β-carbon[4] (Scheme 2). Thus, ozonolysis in methanol of the dihydropyran 9[11] afforded 10 in 90% isolated[7] yield. Trifluoroacetylation ($(CF_3CO)_2O$, K_2CO_3,$CHCl_3$, -50°→25° (30 min) resulted in Criegee rearrangement and dealkylation to afford the lactone 11 in 65% yield and methyl trifluoroacetate. The addition of hydrogen peroxide ((2:1 THF-30%H_2O_2, AcOH) to the enol ether 12[12] resulted in peroxyketalization to afford 13 (quantitative). Rearrangement (($(CH_3CO)_2O$, Et_3N, DMAP, CH_2Cl_2, 40°) gave rise to a mixture of mono- and bis-acetates which was saponified (K_2CO_3, aqueous MeOH) to provide a single diol 14 in 70% yield from 12. Attempted Baeyer-Villiger oxidation (MCPBA) of the hydrolysis product of

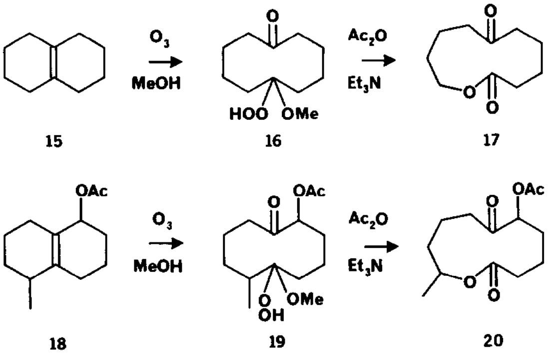
Scheme 2



12 resulted only in epoxidation of the olefin present in the side chain.

The application of this procedure to macrolide formation is depicted in Scheme 3. We have recently reported procedures for the ozonolytic cleavage of cycloalkenes to terminally differentiated products.[13] A related concept can be applied to cycloalkenes 15 and 18. The hydroperoxide 16, prepared from $\Delta^{9,10}$-octalin according to the known procedure[14] (O_3, MeOH, 88% yield), undergoes rearrangement (($(CH_3CO)_2O$, Et_3N, DMAP, CH_2Cl_2, 40°C) to afford the eleven-membered macrolide 17[15] in 74% yield. Regioselective lactone formation from an unsymmetrically substituted cycloalkene can be achieved by employing the directing ability of an acetoxy substitutent.[13] Thus, ozonolysis (O_3, MeOH, -78°C) of 18[16] afforded the hydroperoxide 19. [17] Criegee rearrangement (and dealkylation)[18] proceeded smoothly (($(CH_3CO)_2O$, Et_3N, CH_2Cl_2 40°) to provide the macrolide 20 in 66% yield overall from 18.

Scheme 3



Further studies of the utility of peroxides in organic synthesis[11,13] are underway and will be reported in the future.

Acknowledgement

This investigation was supported by the Institute for General Medical Sciences of the National Institutes of Health (GM-30738) to whom we are grateful. NMR spectra were obtained through the auspices of the Northeast Regional N.S.F./N.M.R. Facility at Yale University which was supported by the N.S.F. Chemistry Division Grant C.H.E. 7916210.

References and Footnotes

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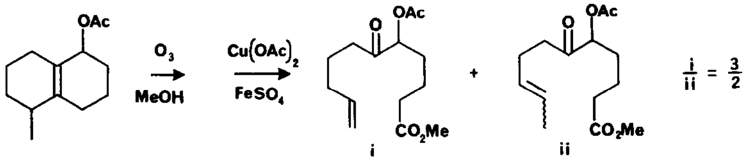
16. Prepared from 5-methoxytetralone by the following sequence: a) MeMgBr, Et_2O, b) MsCl, Et_3N, c) H_2 (50 psi), Pd/C, EtOAc, d) $Li/NH_3/EtOH$, e) 1NHCl, THF,Δ, f) DIBAH, g) Ac_2O, Et_3N, DMAP. The acetates (18) prepared by this procedure are a 3:2 mixture of diastereomers, as are 19 and 20.
17. The absence of the alternative regioisomer was supported by the $Cu(OAc)_2/FeSO_4$ fragmentation[9] of the crude ozonolysis mixture which afforded olefins i and ii in 67% yield.



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18. Selective demethylation of the intermediate dioxenium ions to furnish the macrolide in these two examples is in contrast to small ring dioxenium salts which dealkylate predominantly with ring cleavage.[19] Both alkoxy substituents can adopt the Z configuration in the eleven-membered dioxenium ion so that demethylation can occur to afford a Z lactone.

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(Received in USA 15 March 1983)