THE FIRST EXCLUSIVE REGIOSELECTIVE FRAGMENTATION OF PRIMARY OZONIDES CONTROLLED BY REMOTE carbonyl GROUPS

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Abstract: Ozonolysis of compounds 1a-1d in CDCl₃ at -78 °C regioselectively and stereoselectively gave the corresponding final ozonides 2a-2d as the sole product, which, after treatment with triethylamine, gave the novel convex tetraquinane oxa-cages 9a-9d in high yields respectively.

Extensive investigation of the mechanism of alkene ozonolysis has confirmed the essential features of the pathway originally proposed by Criegee.¹ Substituent effects on the regioselectivity of primary ozonides (PO) fragmentation have been reported in the cases that the substituents are directly placed on the alkene bond.² The cleavage of PO tends to occur along the path which results in the placement of electron-donating substituents on the carbonyl oxide fragment, while electron-withdrawing substituents are incorporated in the carbonyl product. To our knowledge, the regioselective fragmentation of PO controlled by remote carbonyl groups has not yet been demonstrated.³ We report here the first observation of exclusive regioselective fragmentation of primary ozonides and stereoselective formation of final ozonides controlled by remote different carbonyl groups on ozonolysis of norbornene derivatives.

Ozonolysis of 1a-1d in CDCl₃ at -78 °C gave the final ozonides 2a-2d as the sole product (>95%) respectively, Scheme 1. The ¹H and ¹³C nmr spectra of 2a-2d were taken at -30 °C right after the ozonation process without purification. No detectable amount of the isomeric final ozonides 3a-3d was observed from the ¹H and ¹³C nmr spectra of the crude products of the ozonation of compounds 1a-1d. The ¹H nmr spectrum of 2a reveals two singlets at δ 6.45 and 5.70 for the ozonide ring protons and a singlet at δ 2.21 for the methyl ketone protons,
consistent with structure 2a rather than 3a. The $^{13}$C nmr spectrum of 2a shows two peaks (CH) at δ 103.7 and 101.6 for the two tertiary bridgehead carbons of the ozonide ring indicating no quaternary carbon present at the ozonide ring bridgehead. Ozonolysis of the deuterated compounds 1e and 1f in CDCl$_3$ at -78 °C gave the final ozonides 2e and 2f as the sole product (>95%) respectively. No detectable amount of the isomeric final ozonides 3e and 3f was observed. The crude $^1$H nmr spectra of 2e and 2f reveal that the deuterium atom locates on the bridgehead of the trioxolane ring of 2e and 2f. Thus, these experiments rule out the possibility of the structure of the final ozonides to be 7 or 8.

Scheme 1

A mechanism is proposed for the exclusive formation of the final ozonides 2 from the ozonation of 1, Scheme 1. 1,3-Dipolar cycloaddition of an ozone molecule with the alkene bond of 1 via exo face gave the 1,2,3-trioxolanes 4. A least-motion fragmentation of the 1,2,3-trioxolane ring of the primary ozonides 4 affected by the carbonyl groups led exclusively to the syn-oriented carbonyl oxides 5. Rapid intramolecular 1,3-dipolar cycloaddition of the syn carbonyl oxide group of 5 with the endo formyl group gave the final ozonides 2 with endo stereochemistry. Since no detectable amount of the isomeric final ozonides 3 was obtained, formation of the isomeric carbonyl oxides 6 from 4 would be excluded. The exclusively regioselective fragmentation of the primary ozonides 4 to form the carbonyl oxides 5 is controlled by the two different carbonyl groups. According to the above results, it is the formyl group rather than the acyl group to induce the space-closed trioxolane carbon to form the carbonyl oxide group. If the fragmentation of the primary ozonides 4 was not preferentially
controlled by the *endo* formyl group, both the carbonyl oxides 5 and 6 should be formed. Consequently, both the final ozonides 2 and 3 should be obtained. Since both the formyl group and the acyl group are three $\sigma$ bonds remote to the primary ozonide ring, we propose here that the fragmentation of the trioxolane ring of 4 is induced by the *endo* formyl group through space rather than through bond and that it is the oxygen atom of the formyl group rather than the oxygen atom of the acyl group to adopt a conformation in proximity to the 1,2,3-trioxolane ring of 4.

Ozonolysis of 1a-1d in dichloromethane at -78 °C followed by reaction with triethylamine regioselectively gave the convex tetraquinane oxa-cage compounds 9a-9d in 80-85% yields respectively, Scheme 3. No detectable amount of the other regioisomers 10a-10d was obtained in each case. These results indicate that ozonolysis of 1a-1d in CH$_2$Cl$_2$ or CDCl$_3$ at -78 °C exclusively gives the corresponding final ozonides 2a-2d which, in reaction with triethylamine, give 9a-9d as the sole product respectively. The regiochemistry of the angular alkyl groups of 9a-9d was assigned by H-H COSY 2D spectral analysis. A mechanism is proposed for formation of 9 from 2, Scheme 2. Proton abstraction of the trioxolane ring proton of 2 by triethylamine followed by heterolytic cleavage of the peroxide bond and sequential nucleophilic addition of the newly-formed alkoxide ions to the adjacent carbonyl groups gave the sole product 9. If both the isomeric final ozonides 2 and 3 were formed from ozonolysis of 1, both isomeric compounds 9 and 10 should be obtained via reaction of triethylamine with 2 and 3. Thus, these experimental results support the observation described in Scheme 1.

Scheme 2

![Scheme 2](image)

The final ozonides formed by ozonolysis of 1a-1d in CH$_2$Cl$_2$ or CDCl$_3$ at -78 °C is deduced to be the *endo* isomer 2 instead of the *exo* isomer 11. If the final ozonides were the isomers 11a-11d, with an *exo* stereochemistry, proton abstraction of the trioxolane ring proton of 11 by triethylamine followed by heterolytic cleavage of the peroxide bond could not give the observed
products 9a-9d since the sequential nucleophilic addition of the newly-formed alkoxide ions to the carbonyl groups is stereochemically impossible.

Ozonolysis of 14a and 14b in CDCl₃ at -78 °C exclusively gave the final ozonides 15a and 15b respectively, Scheme 3. Again, no detectable amount of the isomeric final ozonides 16a and 16b was observed from the ¹H and ¹³C nmr spectra of the crude products of the ozonation of compounds 14a and 14b.

Scheme 3

Thus, the order of the preference of various carbonyl groups to control through space the fragmentation of the primary ozonides formed by ozonolysis of norbornene derivatives is as follow: aldehyde carbonyl > ketone carbonyl > thioester. The ability of ester and amide groups to control the fragmentation of the primary ozonides needs to be discovered.

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References


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