

Cycloadditions between Carbonyl Oxides Generated by the Ozonolyses of Cycloalkenes and Carbonyl Compounds: Novel Method for the Synthesis of Bicyclic 1,2,4,6-Tetroxepanes

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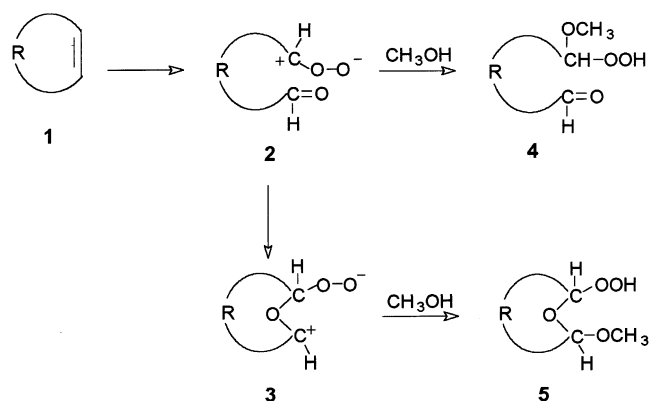
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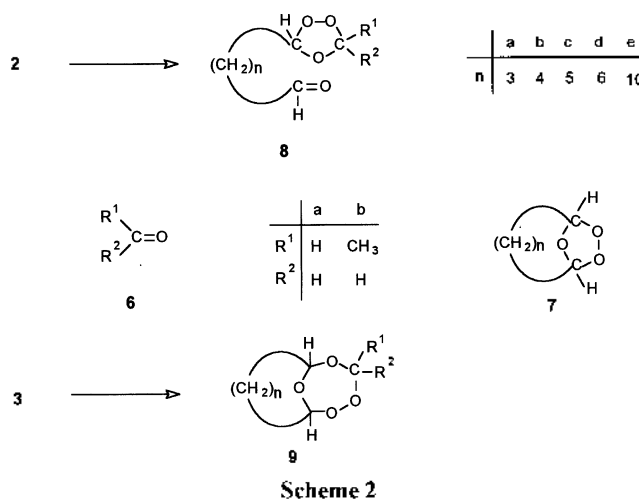
Mono- and polycyclic peroxides have attracted considerable attention as models or analogues of an increasing number of peroxidic natural products, some of which possess attractive pharmacological properties.^{1,2} [3+2] cycloaddition reactions between carbonyl oxides generated in situ by ozonolysis of olefins, and carbonyl oxides are well established. Ozonolyses of certain cycloolefins **1** in methanol, however, revealed a partially anomalous behavior as compared to acyclic olefins. A priori, one would have expected that the primary intermediates of type **2** are trapped by methanol to give compounds of type **4**. But in addition to **4**, variable amounts of the isomeric product of type **5** were obtained.^{1,5} This was explained by an intramolecular reaction between the carbonyl oxide moiety and the aldehyde group of **2** to give intermediate **3**, which is subsequently trapped by methanol to give **5** (Scheme 1).

In the present work, we are interested to find out whether the carbonyl oxide moieties in intermediates of type **3** can be trapped by added aldehydes **6** to give tetroxepanes **9** in addition to cross ozonides of type **8**.⁶⁻⁹ We now report the first examples of bicyclic peroxides **9**, containing the comparatively rare 1,2,4,6-tetroxepane system, derived from cycloadditions between carbonyl oxide **3** generated by the ozonolysis of cycloolefins **1** and aldehydes **6**.

We have ozonized the cyclic olefins **1a-e** in dichloromethane at -78 °C in the presence of two molar equivalents of a formaldehyde **6a**. Ozonolyses of cyclopentene **1a**, cyclohexene **1b**, cycloheptene **1c**, cyclooctene **1d** and cyclododecene **1e** in the presence of formaldehyde **6a** as a good dipolarophile^{10,11} afforded in each case the peroxidic products and the corresponding cross ozonides **8**. Peroxidic



Scheme 1



Scheme 2

products were ozonide **7a** in the ozonolysis of cyclopentene **1a** and the tetroxepanes **9b-9e** in the ozonolyses of **1b**, **1c**, **1d** and **1e**, respectively. These results show that trapping of the carbonyl oxide moiety of intermediates **2** and **3** with formaldehyde can be effectively performed as outlined in Scheme 2.

A normal [3+2] cycloaddition process would provide the cross ozonides **8** via intermediates **2**, whereas the formation of adducts **9** indicates that the intermediate **3** must also be operative. The formation of ozonide **7a** in the ozonolysis of **1a** is in line with the known fact that 5-membered cycloolefins give high yields of monoozonides, i.e. intramolecular reaction of the carbonyl oxide in **2** can compete with the intermolecular reaction with formaldehyde.^{12,13} The lack of formation of ozonides **7b-7e** is in line with the experience that the tendency for intramolecular [3+2] cycloaddition of intermediates of type **2** decreases with increasing ring size of the parent cycloolefin. The formation of **9a-9e**, on the other hand, indicates that intramolecular reactions of the type **2**→**3** can compete with the trapping by formaldehyde **6a**. Ozonolyses of **1a-1e** in the presence of acetaldehyde **6b** also provided the corresponding cross ozonides **8f-8j** and tetroxepanes **9g-9i** of the peroxidic products. The low yields of **9d**, **9e** and **9g-9i** are due to the increasing ring size of cycloolefins and the steric effect of added carbonyl compounds, the maximum yield being obtained for **9b** from the ozonolysis of the cyclohexene **1b**. The results for the ozonolyses of **1a-1e** in the presence of aldehydes **6a** and **6b** are summarized in Table 1.

Table 1. Ozonolysis of cycloalkenes **1a-1e** in the presence of aldehydes **6a** and **6b**

	Structural units			Isolated yield (%) of		
	n	R1	R2	7	8	9
a	3	H	H	16	46	-
b	4	H	H	-	68	36
c	5	H	H	-	74	19
d	6	H	H	-	36	16
e	10	H	H	-	17	10
f	3	H	CH ₃	-	37	-
g	4	H	CH ₃	-	27	10
h	5	H	CH ₃	-	17	8
i	6	H	CH ₃	-	19	8
j	10	H	CH ₃	-	17	-

All of the peroxidic products have been isolated by column chromatography on silica gel and are stable at room temperature. The structural assignments of the tetroxepanes of structure **9** are based on characteristic ¹H and ¹³C NMR signals of the CH₂ groups and of the CH groups in the heterocyclic ring systems. In the ¹H NMR spectra, the CH₂ groups appeared as two singlet signals, in the range of $\delta = 5.02$ - 5.05 and $\delta = 5.17$ - 5.21 , and the CH groups appeared as two triplets, in the range of $\delta = 4.84$ - 4.86 and $\delta = 5.12$ - 5.14 . In the ¹³C NMR spectra, the signals of the CH₂ groups appeared in the range of $\delta = 93.71$ - 94.41 and those of the two magnetically non-equivalent CH groups appeared in the range of $\delta = 100.86$ - 101.96 and $\delta = 103.15$ - 104.19 .

The results in this study provide ample evidences that carbonyl oxides which are formed in the ozonolysis of cyclic olefins can be readily trapped by "foreign" carbonyl com-

pounds like formaldehyde to give cross-ozonides and 1,2,4,6-tetroxepanes. This opens a convenient short-path synthesis for ozonides and novel peroxides, 1,2,4,6-tetroxepanes which were not known previously.

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