



Neighbouring effect in the course of the ozonolysis of a hindered bornene derivative

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ARTICLE INFO

Article history:

Received 13 January 2009

Revised 16 February 2009

Accepted 17 February 2009

Available online 21 February 2009

Keywords:

Ozonolysis

Allylic functionalization

Ketone oxides

Cyclization cascade

ABSTRACT

In the course of the ozonolysis of the bicyclo[2.2.1]heptene anhydride **1**, the three bis-lactones **3–5** have been obtained (the structures were confirmed by X-ray crystallographic analysis).

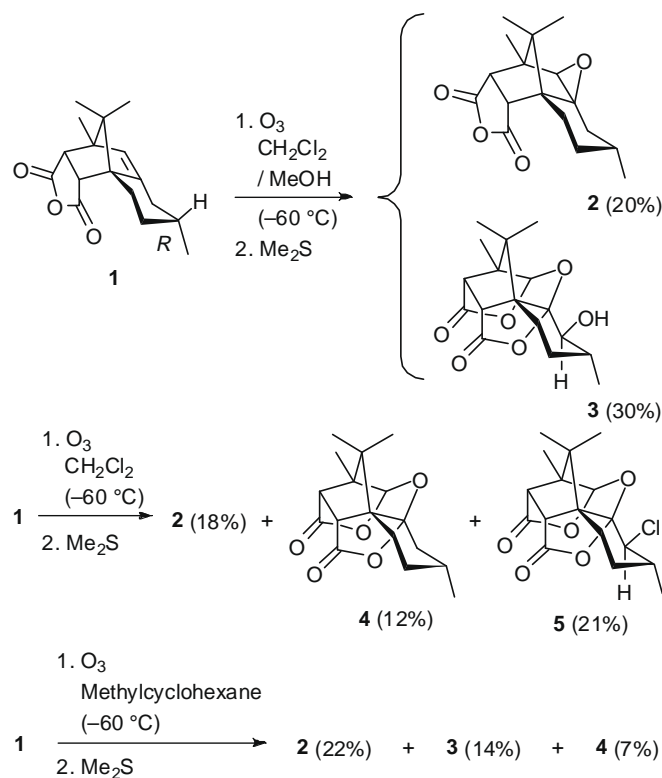
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1. Introduction

Ozonolysis is an important process for oxidations in organic synthesis due to the easy access to ozone and also to the formation of little amount of wastes compared to several other oxidative methodologies.¹ Therefore, a deeper understanding of the reactivity of organic species towards ozone is an important field in organic synthesis. Previous work of our laboratory has shown that the ozonolysis of hindered norbornene derivatives gave rise to unexpected products.² Here, we wish to report that an unprecedented neighbouring effect, in the course of the ozonolysis of such substrates, led to the formation of some unexpected polyoxygenated products.

Depending on the solvent employed, the ozonolysis of anhydride **1** led to compounds **2–5** (Scheme 1).³ Fortunately, crystals of **2–5** were suitable for X-ray analysis⁴ (Figs. 1 and 2).⁵ Concerning the formation of **2**, it is well known that the ozonolysis of hindered alkenes sometimes leads to the epoxide formation as it is the case with longifolene.⁶

But the formation of **3–5** was unexpected, and is more difficult to be explained. First, we can assume that a partial allylic functionalization of anhydride **1** occurs to give allylic alcohol **6** or allylic chloride **7** (not isolated) (Scheme 2). The ozonation of the C–H bonds in hydrocarbons adsorbed on silica gel is a known process.⁷



Scheme 1. Ozonolysis of the anhydride **1**.

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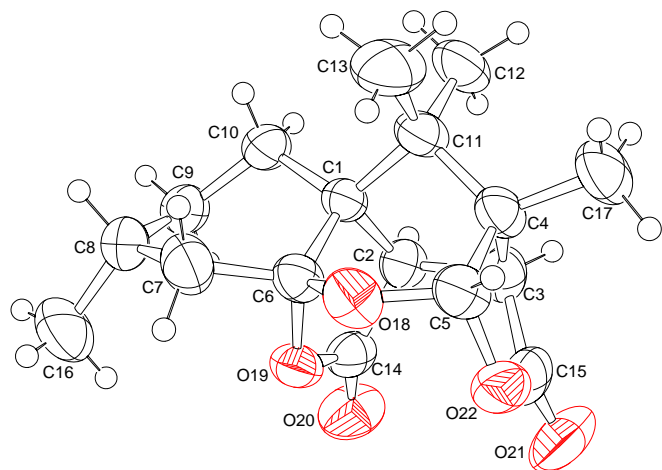


Figure 1. ORTEP drawing for **4**. Non-hydrogen atoms are drawn with 50% probability thermal ellipsoids.

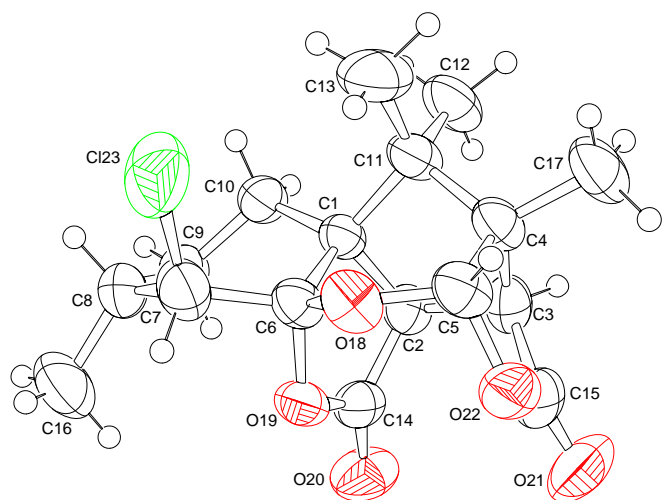
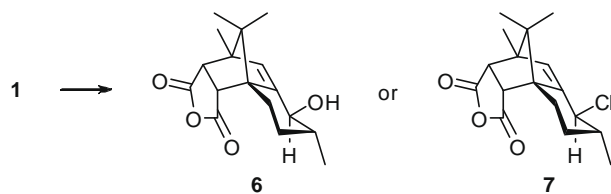


Figure 2. ORTEP drawing for **5**.

Plesničar reported that HOOO radicals are most likely involved in the ozonation of saturated hydrocarbons and cumene.⁸ Moreover, ozonolysis of norbornane in CCl₄ afforded 2-chloronorbornanes (8.2% at 30% conversion).⁹ However, to the best of our knowledge, no example of allylic functionalization in the course of an ozonolysis reaction has been reported so far.

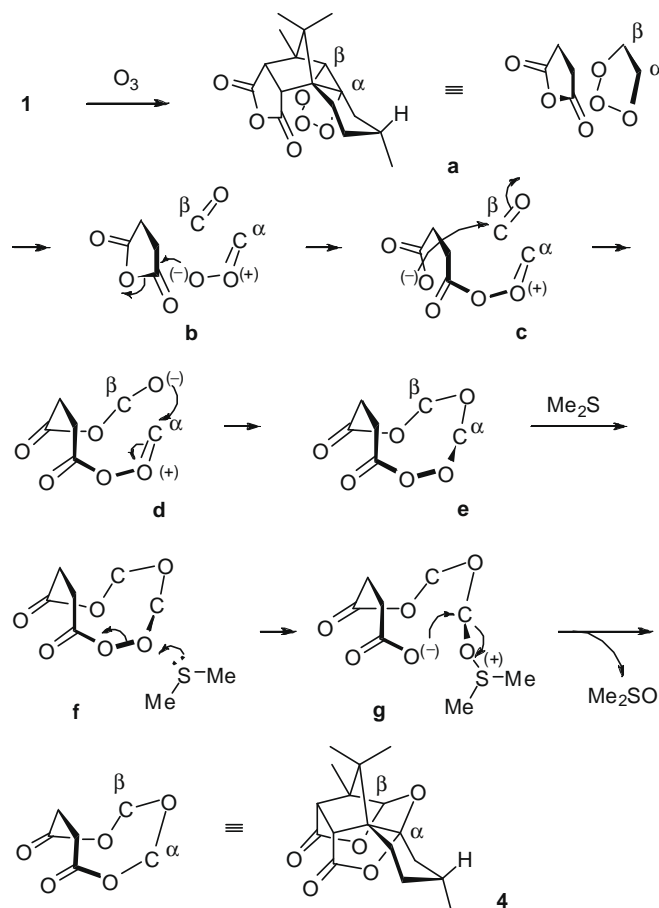
Then, the ozonolysis of compounds **6** and **7** would form **3** or **5**, respectively. The most striking result in the course of the ozonolysis of the carbon–carbon double bond of **1**, **6** or **7** is the formation of a bislactone moiety with an additional ether bridge in **3–5**. A reasonable mechanistic hypothesis which explains such anomalous oxidation reaction involves the formation of the *endo* primary ozonide (1,2,3-trioxolane) **a**,¹⁰ its fragmentation into aldehyde and



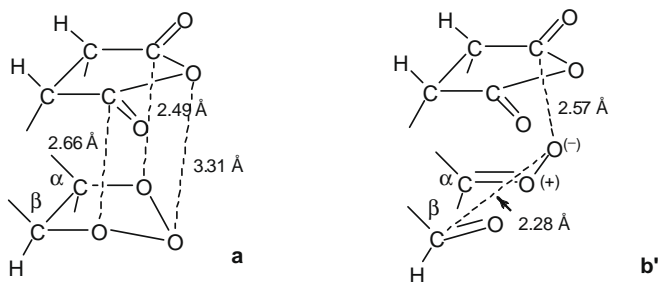
Scheme 2. Allylic functionalization of anhydride **1**.

ketone oxide **b**,^{11,12} followed by a nucleophilic attack of the oxygen of ketone oxide to the adjacent carboxylic group to give carboxylate anion **c** (Scheme 3). Then, a nucleophilic addition of this carboxylate anion to the adjacent aldehyde would give **d**. Finally, the addition of the oxy anion of the tetrahedral intermediate to the *O*-acyloxy ketone gave rise to **e**. Treatment by dimethylsulfur induces the reduction of the peroxy bond of **e** with the release of DMSO and the formation of products **3–5**.¹³

The topochemically controlled structure of **a** and other intermediates **b** and **c** minimizes both the entropic and enthalpic contributions of the free energy of the various transition states.^{14–16} At the RB3LYP/6-311++G(d,p) level of the theory, the calculated structure of **a** reveals that the anhydride and the primary ozonide moieties are very close. Moreover, the conformation **b'** of intermediate **b** where the oxygen of the carbonyl oxide is close to the carboxylic group with a proper orientation is less stable than the fully relaxed conformation **b** of only 3.13 kcal/mol (the distance is slightly longer than the sum of van der Waals radii)¹⁷ ('propinquity' effect) (Scheme 4).¹⁸ The term of near attack conformation (NAC) has been introduced by Bruice and co-workers to define the required conformation for juxtaposed reactants to enter a transition state.¹⁹ NAC structures (NACs) possess the proper geometric juxtaposition of groups for a reaction to proceed directly to a transition state without bond stretching/contraction, angle bending or torsional motion.²⁰ When the ground state consists of only NACs, the rate enhancement can be as large as 10⁸ as it is the case, for example, when a nucleophile is positioned <3 Å above a carbonyl prior to addition.^{21,22} According to Menger, 'the rate of reaction between functionalities A and B is proportional to the time that A and B reside within a critical distance' estimated to ~2.8 Å.²³ In our case,



Scheme 3. Mechanism of the formation of **4** (and similarly, **3** and **5**).



Scheme 4. Calculated structures (at the RB3LYP/6-311++G(d,p) level of the theory) of primary ozonide **a** and carbonyl oxide **b'**.

due to the presence of a congested intramolecular system, the formation of NACs is spontaneous by restricting the configurational space of the reacting groups.

2. Conclusion

Tighter binding of transition state as compared with substrate ground state is the most classical explanation for extremely high efficiency of enzymatic catalysis.²⁴ With our three examples, we have demonstrated that a weak nucleophilic reagent as the terminal oxygen atom of the carbonyl oxide can react with an adjacent anhydride function inducing a pericyclic three-step process leading to a bislactone moiety and an ether bridge. Moreover, these various nucleophilic additions occurred at a low temperature ($\sim -60^\circ\text{C}$) and even in a nonpolar solvent as methylcyclohexane. We believe that the initial short contact distances between such functional groups gave rise to an enzyme-like rate acceleration.²⁵

Acknowledgements

C.R. thanks Dr. S. Goldstein for helpful comments and the *Institut de Recherche Servier* (Suresnes, Fr 92150) for financial support. This work has been financially supported by the CNRS and the *Ministère de l'Enseignement Supérieur et de la Recherche*.

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- Ozone in oxygen was bubbled through a stirred solution of **1** (1 g, 3.65 mmol) in dichloromethane (130 mL) at -60°C for 7 h. The mixture was flushed with argon, and dimethylsulfide (5 mL) was slowly added. After stirring at room temperature overnight, the crude mixture was washed with water, dried over MgSO_4 and filtered. After concentration in vacuo, the colourless residue was purified by flash-chromatography on silica gel eluting with petroleum ether/diethyl ether 60:40 to give white crystals of **2**^{2a} (191 mg, 0.66 mmol, 18%), white crystals of **4** (134 mg, 0.44 mmol, 12%) and white crystals of **5** (262 mg, 0.77 mmol, 21%). Compound **4**, mp 196°C , $[\alpha]_{\text{D}}^{22} -18.4$ (c 1.0, CH_2Cl_2); ^1H (CDCl₃, 300 MHz) δ 5.37 (s, 1H), 3.00 (s, 1H), 2.99 (s, 1H), 1.99–1.88 (m, 4H), 1.80–1.69 (m, 3H), 1.14 (s, 3H), 1.02 (s, 3H), 0.96 (d, $J = 6.7$ Hz, 3H), 0.81 (s, 3H); ^{13}C NMR (CDCl₃, 75 MHz) δ 173.2 (s), 172.9 (s), 111.5 (s), 105.5 (d), 55.9 (s), 54.7 (s), 52.7 (d), 44.0 (s), 36.4 (t), 26.5 (t), 25.8 (t), 25.5 (d), 22.6 (q), 21.4 (q), 16.1 (q), 15.4 (q). Compound **5**, mp 226°C , $[\alpha]_{\text{D}}^{22} -11.8$ (c 2.1, CH_2Cl_2); ^1H (CDCl₃, 300 MHz) δ 5.54 (s, 1H), 4.06 (d, $J = 1.8$ Hz, 1H), 3.04 (m, 2H), 2.04–1.95 (m, 3H), 1.75 (m, 2H), 1.23 (s, 3H), 1.22 (s, 3H), 1.12 (d, $J = 7.2$ Hz, 3H), 0.88 (s, 3H); ^{13}C NMR (CDCl₃, 75 MHz) δ 173.3 (s), 171.5 (s), 109.9 (s), 105.6 (d), 60.2 (d), 56.4 (s), 54.8 (s), 52.9 (d), 50.4 (d), 43.7 (s), 39.1 (d), 25.8 (t), 24.4 (t), 22.6 (q), 22.3 (q), 18.9 (q), 15.4 (q).
- Compounds **2** and **3**, see Ref. 2a.
- Crystal data and structure refinement. CCDC 715199 contains the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk]. The two compounds **5** and **4** bearing either a Cl or an H atom on the same position on the cyclohexane co-crystallized together in the ratio 70:30. Crystallographic data: $\text{C}_{17}\text{H}_{21.3}\text{Cl}_{0.7}\text{O}_5$, $M_w = 330.46$, monoclinic, colourless, colourless crystal ($0.4 \times 0.3 \times 0.3$ mm³), $a = 7.8053(5)$ Å, $b = 11.6498(9)$ Å, $c = 8.6269(7)$ Å, $\beta = 91.048(3)^\circ$, $V = 784.31(1)$ Å³, space group $P2_1$, $Z = 2$, $\rho = 1.4$ g cm⁻³, $\mu(\text{MoK}\alpha) = 2.16$ cm⁻¹, 1987 unique reflections in the 1.75 – 28.13° θ range, 212 parameters refined on R^2 [Shelxl] to final indices $R[F^2 > 4\sigma F^2] = 0.059$ (1661 reflections), $wR[F^2] = 1/[\sigma^2(F_o^2) + (0.1132P)^2 + 10.36P]$, $P = (F_o^2 + 2F_c^2)/3 = 0.189$ (all reflections). The last residual Fourier positive and negative peaks were equal to 0.687 and -0.73 , respectively.
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