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Diozonides from Coozonolyses of Suitable O-Methyl Oximes and Ketones

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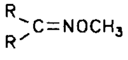
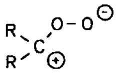
Abstract: Ozonolyses of the O-methyl oximes of cyclic ketones **5a** - **c** in the presence of 1,4-cyclohexanedione (**6**) and ozonolyses of the O-methylated dioxime **8** of 1,4-cyclohexanedione in the presence of cycloketones **7a** - **c** afforded the corresponding diozonides **11**. Ozonolysis of the O-methyl oxime of acetone gave diozonide **18** in the presence of **6** and diozonide **21** in the presence of butanedione. Ozonolysis of the O-methyl oxime of cyclohexanone in the presence of butanedione gave diozonide **22**. In addition, representatives of the hitherto unknown types of dispiro ozonides **12** having a lactam ring system have been obtained from the ozonolyses of **8** and **7**. © 1997 Elsevier Science Ltd.

INTRODUCTION

Ozonolyses of O-methyl oximes of ketones **1** have been reported to generate the corresponding carbonyl oxides **2** and amides **4**, the latter probably *via* intermediates **3**.[1] Recently, we have been able to make use of this mode of generation of carbonyl oxides for the preparation of ozonides by coozonolyses of some O-methyl oximes in the presence of acid derivatives.[2] We have now tried whether this mode of reaction can be extended to the syntheses of diozonides.


$R_2C=NOCH_3$

1


$R_2C^{\oplus}-O-O^{\ominus}$

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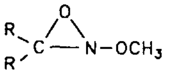

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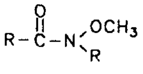
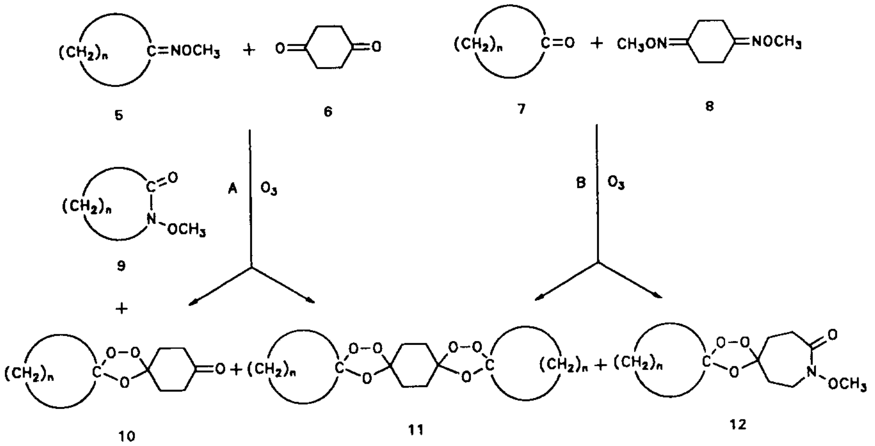

$R-C(=O)-N(R)OCH_3$

4

RESULTS AND DISCUSSION

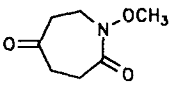
In our work we tried a two-way approach, *viz.* ozonolysis of the O-methyl oxime of a monoketone in the presence of a diketone on one hand, and ozonolysis of a O-methylated dioxime in the presence of a monoketone on the other hand. The ozonolysis reactions were carried out in aprotic solvents and the ozonides obtained have been isolated in the yields reported below, and characterized by positive peroxide tests, correct elemental analyses and by their ^{1}H and ^{13}C NMR spectra.

Ozonolyses of **5a** - **c** in the presence of **6** *via* route A gave the crystalline, stable diozonides **11a** - **c** in yields of 29%, 32% and 15%, respectively. By-products of these reactions were the known[3] lactams **9a** - **c** in yields of 22 - 26% and the known[3] γ-oxo ozonides **10a** - **c** in yields of ca. 16%, each. Ozonolyses of **8** in the presence of **7a** - **c** *via* route B produced diozonides **11a** - **c** in 39%, 44% and 39%, respectively, *i.e.* in higher yields than *via* route A. Additional products in these reactions were ozonides **12a** - **c** in yields of 40%, 36% and 26%, respectively.



a: n=4; **b**: n=5; **c**: n=6

Reductions of diozonides **11a** - **c** with triphenylphosphine (TPP) gave the expected fragments **6** and **7a** - **c** in a ratio of 1:2 and reductions of ozonides **12a** - **c** gave **13** and **7a** - **c** in ratios of ca. 1:1. The formation of ozonides **12** *via* route B can be rationalized by ozone cleavage of one of the C=N bonds of **8** to give a carbonyl oxide moiety and epoxidation of the other C=N bond to give an oxaziridine moiety. This can happen simultaneously to give **14** or, more likely, consecutively to give **15** and/or **16** in the first step.



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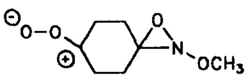

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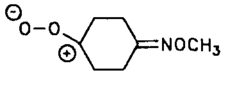

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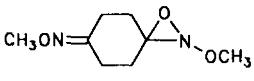

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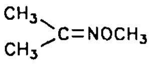
Ozonolysis of **17** in the presence of **6** provided the crystalline, stable diozonide **18** in 9% yield. Additional products were the known monoozonide **19** (4%)[3] and amide **4** (R=CH_3; 23%).[3] Ozonolysis of **8** in the presence of acetone gave 30% of **18** and 28% of ozonide **20**. Reduction of **18** gave acetone and **6** in a ratio of 2:1, and reduction of **20** gave acetone and **13** in a ratio of 1:1.



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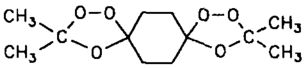

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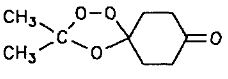

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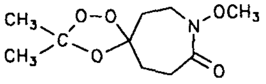

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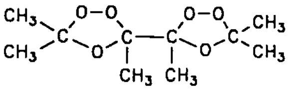
The above described method can be also applied for the synthesis of α-diozonides: Ozonolysis of **17** in the presence of butanedione gave a 1:2-mixture of the known[4] meso- and racem.-isomers of structure **21** in 18% yield. Similarly, ozonolysis of **5b** in the presence of butanedione gave a mixture of two diastereomers of diozonide **22** in 67% yield. The latter isomers have been individually isolated by HPLC separation and tentatively assigned based on the assumption that, as in the case of ozonides **21**, the meso-isomer exhibits the shorter retention time.[4] Reduction of **22** with TPP gave cyclohexanone, butanedione and acetic anhydride (**25**) in a molar ratio of 1:0.2:0.5. The a priori unexpected formation of **25** is rationalized by a stepwise reduction of **22** to give cyclohexanone and **23**, followed by decomposition of **23** to give cyclohexanone and **25** *via* an intermediate of type **24** by analogy with the decomposition of other α-oxo ozonides.[5] In a similar manner, diozonide **21** had been shown previously[4] to give acetone, butanedione and **25** *via* the corresponding α-oxo ozonide which, in that case had been detected by ^1H NMR spectroscopy.



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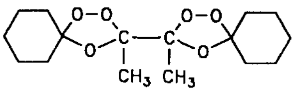

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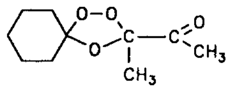

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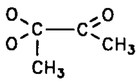

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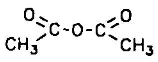

25

The ozonolysis reactions described above open a new access to diozonides, a class of compounds, of which hitherto only a limited amount of representatives have been known. This short-path synthesis has the advantage over the conventional procedure that it obviates the preparation of the parent diolefins and that the synthesis can be performed by a two-way approach, as represented by routes A and B, in which the optimum combination of substrates can be preselected.

Support of this work by the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

EXPERIMENTAL

All reagents used were of commercial grade. NMR spectra were obtained in $CDCl_3$ with TMS as internal reference on a Bruker AC 250 instrument. HPLC separation was carried out on a Merck-Hitachi chromatograph 655 A11.

General procedure for ozonolysis reactions: Coozonolyses of **5a** - **5c** or of **17** with **6** were carried out in a mixture of 40 mL of pentane and 20 mL of dichloromethane at 0 °C. The solution was decanted from a solid precipitate, the precipitate was dissolved in 50 mL of dichloromethane, the two solutions were combined and the solvents were distilled off at room temperature and reduced pressure. The viscous liquid residue was separated by flash chromatography using silica gel and petroleum ether/ether 97:3 (700 mL), 1:1 (500 mL) and 2:3 (500 mL), followed by acetone (500 mL).

Coozonolyses of **8** with **7a** - **7c** or acetone were carried out in 60 mL of pentane at 0 °C. The solvent was distilled off at room temperature and reduced pressure and the viscous liquid residue was separated by flash chromatography on silica gel using petroleum ether/ether 97:3 (1000 mL) and 3:2 (400 mL), followed by ether/acetone 7:3 (500 mL).

Coozonolysis of 5a and 6: Ozonolysis of 1.00 g (8.9 mmol) of **5a** and 0.33 g (3.0 mmol) of **6** gave 1.35 g of a residue, from which 0.30 g (26%) of **9a**, 0.30 g (16%) of **10a** and 0.40 g (29%) of **11a** were isolated. Compounds **9a** and **10a** have been assigned based on the identity of their ^{1}H and ^{13}C NMR data with those of authentic samples.[3]

6,11,17,18,21,22-Hexaoxatetraspiro[4.1.2.1.4.2.2.2]docosane (11a): Colorless solid, m.p. 80 °C; ^{1}H NMR δ 1.68 (m, 8H), 1.90 (m, 8H), 1.93 (s, 8H); ^{13}C NMR δ 23.72, 31.11, 35.20, 107.51, 107.55, 118.62. Anal. calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 8.08. Found: C, 61.37; H, 8.27.

Coozonolysis of 5b and 6: Ozonolysis of 1.10 g (8.7 mmol) of **5b** and 0.32 g (2.9 mmol) of **6** gave 1.45 g of a residue, from which 0.27 g (22%) of **9b**, 0.31 g (16%) of **10b** and 0.47 g (32%) of **11b** were isolated. Compounds **9b** and **10b** have been assigned based on the identity of their ^{1}H and ^{13}C NMR data with those of authentic samples.[3]

7,12,19,20,23,24-Hexaoxatetraspiro[5.1.2.1.5.2.2.2]tetracosane(11b): Colorless solid, m.p. 83.5 °C; ^{1}H NMR δ 1.40 (m, 4H), 1.59 (m, 8H), 1.71 (m, 8H), 1.92 (s, 8H); ^{13}C NMR δ 23.79, 24.88, 24.91, 31.42, 34.52, 107.52, 107.60, 109.33. Anal. calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.41; H, 8.43.

Coozonolysis of 5c and 6: Ozonolysis of 1.30 g (9.2 mmol) of **5c** and 0.34 g (3.1 mmol) of **6** gave 1.65 g of a residue, from which 0.33 g (23%) of **9c**, 0.37 g (17%) of **10c** and 0.25 g (15%) of **11c** were isolated. Compounds **9c** and **10c** have been assigned based on the identity of their ^{1}H and ^{13}C NMR data with those of authentic samples.[3]

8,13,21,22,25,26-Hexaoxatetraspiro[6.1.2.1.6.2.2.2]hexacosane (11c): Colorless solid, m.p. 90 °C; ^{1}H NMR δ 1.56 (broad s, 16H), 1.90 (m, 16H); ^{13}C NMR δ 22.68, 29.36, 29.46, 31.32, 37.46, 107.76, 107.83, 113.55, 113.60. Anal. calcd for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75. Found: C, 65.14; H, 8.88.

Reductions of diozonides 11a - c: Solutions of 0.04 g of an ozonide of structure **11** in 1 mL of $CDCl_3$ were admixed with excess triphenyl phosphine and kept in sealed NMR tubes at 50 °C for 48 h. Subsequent ^{1}H NMR analysis showed that **11a** gave **6** and **7a**, **11b** gave **6** and **7b**, and **11c** gave **6** and **7c** in a ratio of ca. 1:2, each. The assignments of these products were confirmed by ^{13}C NMR analyses.

Coozonolysis of 8 and 7a: Ozonolysis of 0.77 g (4.5 mmol) of **8** and 1.51 g (18.0 mmol) of **7a** gave 2.10 g of a residue, from which 0.55 g (39%) of **11a** and 0.46 g (40%) of **12a** were isolated.

***N-Methoxy-6,14,15-trioxa-10-azadispiro[4.1.6.2]pentadecan-11-one (12a)*:** Colorless liquid; ^{1}H NMR δ 1.65 - 1.75 (m, 4H), 1.85 - 1.95 (m, 4H), 1.95 - 2.10 (m, 4H), 2.50 - 2.60 (m, 2H), 3.72 - 3.80 (m, 2H), 3.77 (s, 3H); ^{13}C NMR δ 23.63, 23.72, 30.88, 31.76, 34.81, 35.27, 36.38, 46.89, 62.08, 108.27, 119.30, 170.78. Anal. calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 56.10; H, 7.67; N, 5.60.

Coozonolysis of 8 and 7b: Ozonolysis of 0.77 g (4.5 mmol) of **8** and 1.76 g (18.0 mmol) of **7b** gave 2.30 g of a residue, from which 0.68 g (44%) of **11b** and 0.44 g (36%) of **12b** were isolated.

***N-Methoxy-7,15,16-trioxa-11-azadispiro[5.1.6.2]hexadecan-12-one (12b)*:** Colorless liquid; ^{1}H NMR δ 1.30 - 1.80 (m, 10H), 1.90 - 2.10 (m, 4H), 2.50 - 2.60 (m, 2H), 3.70 - 3.80 (m, 2H), 3.77 (s, 3H); ^{13}C NMR δ 23.51, 23.59, 24.59, 30.69, 31.97, 34.18, 34.33, 36.55, 46.67, 61.89, 108.10, 110.06, 170.66. Anal. calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.70; H, 7.77; N, 5.30.

Coozonolysis of 8 and 7c: Ozonolysis of 0.77 g (4.5 mmol) of **8** and 2.02 g (18.0 mmol) of **7c** gave 0.65 g (39%) of **11c** and 0.34 g (26%) of **12c**.

***N-Methoxy-8,16,17-trioxa-3-azadispiro[6.1.6.2]heptadecan-4-one (12c)*:** Colorless liquid; ^{1}H NMR δ 1.57 (m, 8H), 1.85 - 2.05 (m, 8H), 2.50 - 2.60 (m, 2H), 3.72 - 3.80 (m, 2H), 3.76 (s, 3H); ^{13}C NMR δ 22.36, 22.42, 29.12, 30.67, 31.82, 36.39, 37.10, 37.19, 46.68, 61.83, 108.31, 114.22, 170.64. Anal. calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 59.00; H, 8.00; N, 5.00.

Reductions of ozonides 12a - c: Solutions of 1 drop of an ozonide of structure **12** in 1 mL of $CDCl_3$ were admixed with excess triphenylphosphine and kept in sealed NMR tubes at 50 °C for 24 h. Subsequent ^{1}H NMR analyses showed the presence of equimolar amounts of **7a** and **13**, **7b** and **13** as well as **7c** and **13**.

***N-Methoxy-azepan-2.5-dione (13)*:** Colorless liquid; ^{1}H NMR δ 2.61 (s, 4H), 2.69 (m, 2H), 3.79 (s, 3H), 3.83 (m, 2H); ^{13}C NMR δ 30.90, 38.72, 42.50, 46.59, 61.95, 169.79, 206.14.

Coozonolysis of 17 and 6: Ozonolysis of 1.29 g (14.8 mmol) of **17** and 0.55 g (5.0 mmol) of **6** gave 1.65 g of a viscous residue, from which 0.37 g (23%) of **4** (R=CH_3), 0.17 g (9%) of **18** and 0.70 g (24%)

of **19** were isolated. The structures of **4** (R=CH_3) and of **19** were assigned based on the identity of their ^{1}H and ^{13}C NMR data with those of authentic samples.[3]

3,3,11,11-Tetramethyl-1,2,4,9,10,12-hexaoxadispiro[4.2.4.2]tetradecane (18): Colorless solid, m.p. 68 °C; ^{1}H NMR δ 1.47 (s, 12H), 1.92 (s, 8H); ^{13}C NMR δ 24.74, 31.20, 107.93, 107.98, 108.75. Anal. calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.49; H, 7.87.

Reduction of 18: A solution of 0.02 g of **18** in 1 mL of $CDCl_3$ was admixed with excess triphenylphosphine and kept in a sealed NMR tube at 50 °C for 24 h. ^{1}H NMR analysis showed the presence of acetone and of **6** in a ratio of 2:1.

Coozonolysis of 8 and acetone: Ozonolysis of 0.77 g (4.5 mmol) of **8** and 1.05 g (18.0 mmol) of acetone gave 0.80 g of a viscous residue, from which 0.35 g (30%) of **18** and 0.29 g (28%) of **20** were isolated.

N-Methoxy-3,3-dimethyl-1,2,4-trioxa-8-azaspiro[4.6]undecan-9-one (20): Colorless liquid; ^{1}H NMR δ 1.48(s, 6H), 1.90 - 2.10 (m, 4H), 2.50 - 2.60 (m, 2H), 3.70 - 3.80 (m, 2H), 3.77 (s, 3H); ^{13}C NMR δ 24.51, 24.77, 30.80, 31.91, 36.48, 46.77, 62.07, 108.68, 109.50, 170.81. Anal. calcd for $C_{10}H_{17}NO_5$: C, 55.37; H, 7.74; N, 6.06. Found: C, 55.60; H, 7.67; N, 6.00.

Reduction of 20: A solution of 1 drop of **20** in 1 mL of $CDCl_3$ in a sealed NMR tube was kept at 50 °C for 24 h. ^{1}H NMR analysis showed the presence of acetone and **13** in a ratio of 1:1.

Coozonolysis of 17 and butanedione: A solution of 0.56 g (6.4 mmol) of **17** and 0.10 g (1.2 mmol) of butanedione in 40 mL of pentane was ozonized at -20 °C. The crude product was poured into a mixture of 20 mL of pentane and 20 mL of water, the pentane phase was washed with an aqueous solution of $NaHCO_3$ and dried with $MgSO_4$. Distillation of the solvent at room temperature and reduced pressure left 0.45 g of a liquid residue, from which 0.05 g (18%) of **21** was isolated (solvent: pentane/ether, 10:1). Diozonide **21** was a 1:2 mixture of meso-**21** (^{1}H NMR δ 1.52, s) and racem.-**21** (^{1}H NMR δ 1.53, s), based on the identity of their ^{1}H NMR data with those of authentic samples.[4]

Coozonolysis of 5b and butanedione: A solution of 1.15 g (9.1 mmol) of **5b** and 0.23 g (2.7 mmol) of butanedione in 70 mL of pentane was ozonized at -20 °C. The product was worked up as described above for the coozonolysis of **17** and butanedione to give 1.27 g of a liquid residue, from which

0.56 g (67%) of a mixture of meso-**22** and racem.-**22** was isolated. HPLC separation (column: 3.2 x 25 cm, LiChrosorb Si 60; pentane/ether, 98:2) gave 0.12 g (14%) of meso-**22** and 0.29 g (34%) of racem.-**22**.

3-Methyl-3-(3-methyl-1,2,4-trioxaspiro[4.5]decan-3-yl)-1,2,4-trioxaspiro[4.5]decane (22)

a) Mixture of meso- and racem.-22: Colorless liquid; Anal. calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 61.20; H, 8.65.

b) meso-22: Colorless liquid; ^1H NMR δ 1.53 (s, 6H), 1.30 - 2.00 (m, 20H); ^{13}C NMR δ 20.44, 23.80, 23.83, 24.99, 32.86, 34.54, 108.55, 110.32.

c) racem.-22: Colorless liquid; ^1H NMR δ 1.53 (s, 6H), 1.30 - 2.00 (m, 20H); ^{13}C NMR δ 20.48, 23.76, 23.87, 24.93, 33.10, 34.63, 108.51, 110.46.

Reduction of 22: A solution of one drop of **22** in 0.8 mL of $CDCl_3$ was admixed with excess triphenylphosphine and kept at room temperature for 2 d. ^1H NMR analysis showed the presence of cyclohexanone (δ 1.80 - 2.20), butanedione (δ 2.33) and acetic anhydride **(25)** (δ 2.22) in a ratio of 1:0.2:0.5.

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