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The Ozonolytic Cleavage of Cycloalkenes in the Presence of Methyl Pyruvate to Yield the Terminally Differentiated Compounds

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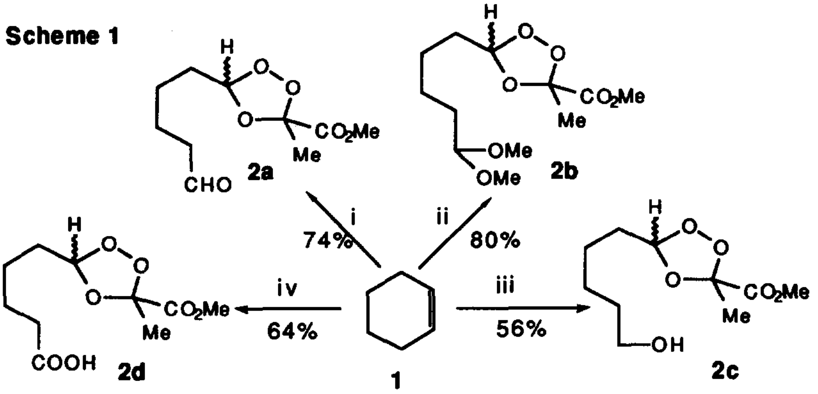
Abstract: The ozonolytic cleavage of cycloalkenes in the presence of methyl pyruvate affords the tri-substituted ozonides. These ozonides possess triple reactive sites which could be converted to several terminally differentiated products via reduction or base treatment.

Ozonation of cycloalkenes in anhydrous nonparticipating aprotic solvents results in formation of polymeric ozonides because of the intramolecular cycloaddition of carbonyl oxide with aldehyde is much slower than that of intermolecular process[1-2]. The terminal bifunctional aliphatic compounds are very important intermediates in organic synthesis. In order to prepare the terminal differentiated aliphatic compounds from cycloalkenes, Schreiber *et al.* used methanol to trap the carbonyl oxide intermediate to give an aliphatic chain with an aldehyde and α-alkoxy hydroperoxide at both ends[3-4]. Recently, we have reported that the decomposition of ozonides by base is a facile and convenient process to workup the ozonolysis reaction[5]. This procedure works well only if the mono-ozonide was formed in good yield. In order to avoid the polymeric ozonides formation, a good 1,3-dipolarophile is needed to trap the carbonyl oxide intermediate[6-9]. The methyl pyruvate was used to trap the carbonyl oxide to form the tri-substituted ozonides in our laboratory. In this report, we want to describe both the efficiency of methyl pyruvate in trapping the carbonyl oxides generated in the ozonolysis of cycloalkenes and the applications of these tri-substituted ozonides in organic synthesis.

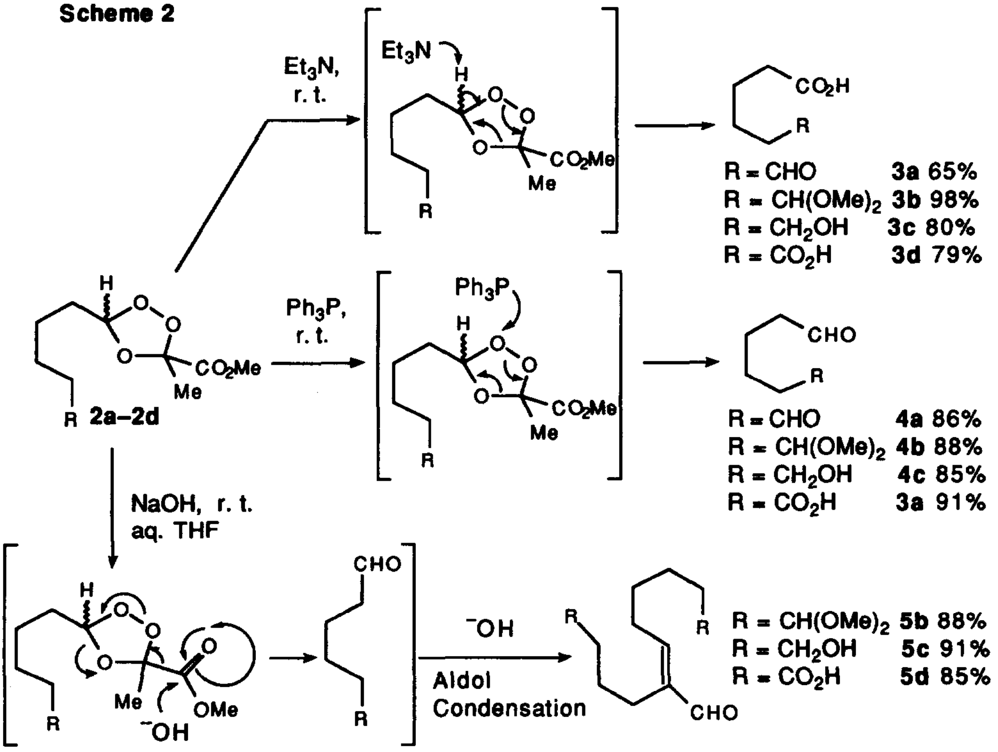
A two-necked flask is fitted with a glass tube to admit ozone, a $CaCl_2$ drying tube and a magnetic stirring bar and is charged with cyclohexene (3.0 g, 1 mol. equiv.), methyl pyruvate (5.6 g, 1.5 mol. equiv.) in 100 mL of CH_2Cl_2. The flask is cooled to -78 °C and ozone is bubbled through the solution. When the solution turns blue, ozone addition is stopped. Nitrogen is passed through the solution until the blue color is discharged. Removal of solvent afforded the crude product. After silica gel column chromatography, the aldehyde-ozonide **2a** could be obtained in 74% yield as a mixture of two diastereomers in a ratio of 1:1. Their ^{1}H-NMR chemical shift corresponding to the proton on the trioxolane ring appeared at δ 5.45 (t, J = 5.1 Hz) and 5.24 (t, J = 4.8 Hz), respectively. If MeOH was added right after the ozonolysis at -78 °C and the solution was then warmed up to room temperature, the acetal-ozonide **2b** was isolated in 80% yield without any catalyst. Reacting the aldehyde-ozonide **2a** with a solution of lithium borohydride in THF produced the alcohol–ozonide **2c** in 56% yield. If the ozonolysis was carried out at 0 °C, the acid–ozonide **2d** was formed in 64% yield (Scheme 1). Apparently, the methyl pyruvate (1.5 equivalents) is good enough to trap the the carbonyl oxide intermediate[8]. In addition, the reaction conditions for the transformation of the aldehyde to the acid, acetal and alcohol can be tolerated by the ozonide moiety. Conceptionally, the ozonide moiety can also be considered as a protecting group during the functional group transformations of the other end of the molecule.

Scheme 1



Reagents: (i) 1.5 eq. methyl pyruvate, O_3, CH_2Cl_2, –78 °C (ii) 1.5 eq. methyl pyruvate, O_3, CH_2Cl_2, –78 °C; MeOH, r.t. (iii) 1.5 eq. methyl pyruvate, O_3, CH_2Cl_2, –78 °C; 0.75 eq. $LiBH_4$, THF, 0 °C (iv) 1.5 eq. methyl pyruvate, O_3, CH_2Cl_2, 0 °C

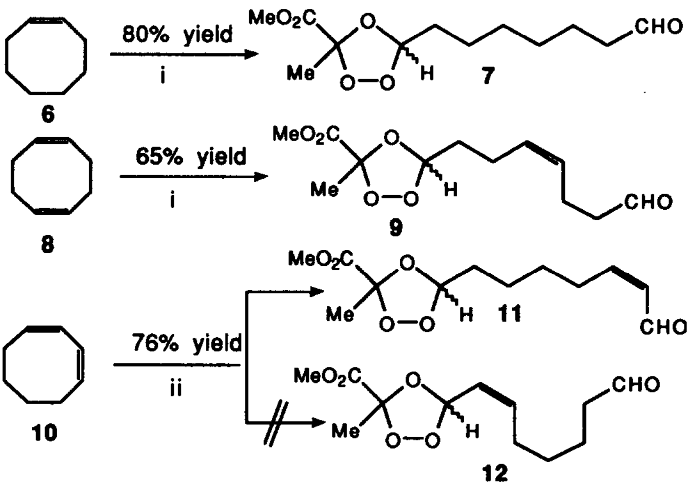
Scheme 2



In order to prepare the bifunctional compound, the acetal–ozonide **2b** was treated with triethylamine to give 6,6'-dimethoxyhexanoic acid (**3b**) in 98% yield. The 6,6-dimethoxyhexanal (**4b**) was formed in 88% yield when the same starting material reacted with triphenylphosphine (Scheme 2). Interestingly, reacting the acetal–ozonide **2b** with aqueous sodium hydroxide in THF produced the α,β-unsaturated aldehyde **5b** in 88% yield. This is consistent with that hydrolysis of the ester group occurred in the first place to give compound **4c** which was then underwent the aldol condensation (Scheme 2). The E configuration of the double bond of compound (**5b**) was confirmed by the 2D-NOESY technique[10]. The tri-substituted ozonide shown here serves as the masked functionalities of aldehyde and carboxylic acid. In addition, the carbomethoxy substituent of the trioxolane also serves as another reactive site to trigger the fragmentation of the ozonide. The triple reactive sites in compound (**2b**) could be converted to different functional groups selectively by applying the different reaction conditions. To the best of our knowledge, this is the first example to illustrate the broad synthetic applicability of the ozonide moiety.

For compounds **2a**, **2c** and **2d**, they could also be applied to synthesize the terminal differentiated compounds in high yield[11–13] (Scheme 2). The methyl pyruvate is also effective to the carbonyl oxide intermediate generated from the ozonolysis of cyclooctene (**6**) and 1,5-cyclooctadiene (**8**) (Scheme 3). To ensure that only one of the conjugated olefin was ozonized, the ozonolysis of 1,3-cyclooctadiene (**10**) was carried out in methylene chloride at -78 °C in the presence of Sudan red 7B[14], which turned from red to colorless when the first olefin has been consumed. The *cis*-enal–ozonide **11** was isolated in 85% yield . Spectral analyses revealed that the structural isomer **12** was not present[15](Scheme 3).

Scheme 3



Reagents: (i) 1.5 eq. methyl pyruvate, CH_2Cl_2, -78 °C;
(ii) 1.5 eq. methyl pyruvate, CH_2Cl_2, cat. Sudan red 7B, -78 °C

Starting with cycloalkene, via two simple experimental operations, 10 types of terminal differentiated compounds could be synthesized in high yields (Scheme 1 and 2). Our method demonstrated the versatile potential of the ozonide moiety in organic synthesis. Further studies of the utility of ozonides as both the protecting group and masked group in organic synthesis are underway[16] and will be reported in the future.

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10. Compound (**5b**) ^{1}H-NMR ($CDCl_3$) δ 1.30–1.65 (m, 10 H), 2.26 (t, J = 7.6 Hz, 2H, $-\underline{CH_2}-(CH_2)_2-CH(OMe)_2$), 2.37 (q, J = 7.4 Hz, 2H, $\underline{CH_2}-CH=CCHO$), 3.31 (s, 6H, OMe), 3.34 (s, 6H, OMe), 4.32–4.39 (m, 2H, $C\underline{H}(OMe)_2$), 6.46 (t, J = 7.4 Hz, 1H, $C\underline{H}=C$), 9.36 (s, 1H, $C\underline{H}O$); ^{13}C-NMR ($CDCl_3$) δ 23.66, 24.35, 28.50, 28.85, 32.32, 52.74 ($O\underline{C}H_3$), 104.34 ($\underline{C}H(OMe)_2$), 143.43 ($CH=\underline{C}$), 155.05 ($\underline{C}H=C$), 195.05 ($\underline{C}HO$).
11. Compounds (**3a**) and (**4c**) were isolated as their methyl esters in 65% and 85% yields, respectively.
12. The adipic dialdehyde (**4a**) could be isolated in 85% yield after silica gel column chromatography. This compound is not stable in the air at room temperature.
13. The yield of the reaction between compound (**2d**) and sodium hydroxide is dependent on the solvent used. In aqueous THF or methanol, significant amount of adipic acid was obtained. In pure water, compound (**5d**) was obtained in 90% yield.
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15. The structure of compound (**11**) could be unambiguously determined by ^{1}H NMR spectrum. The diagonostic absorptions appeared as following: 10.07 (d, J = 10.1 Hz, 1H, RCHO), 6.63 (dt, J = 11.2 and 8.1 Hz, 1H), 5.97 (ddt, J = 11.2, 8.0 and 1.5 Hz, 1H), 5.45 (t, J = 5.1 Hz, 0.5 H, trioxolane proton of one diastereomer), 5.25 (t, J = 4.9 Hz, 0.5 H, trioxolane proton of the other diastereomer).
16. The ozonolysis of mono-substituted olefin (i.e. 4-phenyl-1-butene) in the presence of 3 eq. of methyl pyruvate gave both the tri-substituted ozonide in 55% yield and mono-substituted ozonide in 30% yield. Apparently, a better dipolarophile than methyl pyruvate is needed to give the trapped product in high yield. We are trying to work out this problem now.

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