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Chemoselective Reactions of A Compound Containing Both Aldehyde and Ozonide Groups

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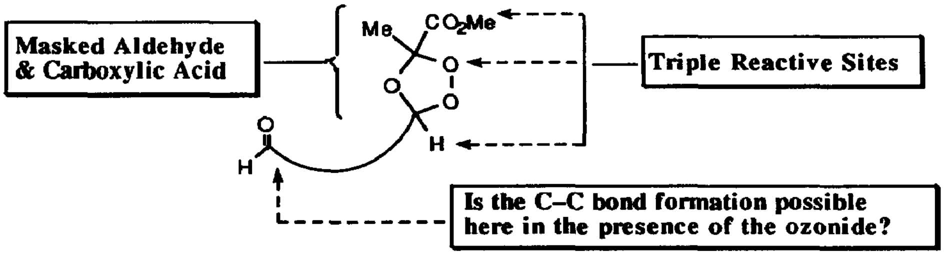
Abstract: The aldehyde of compound **2** is more reactive than the ozonide in the carbon-carbon bond formation reactions. The ozonide is stable under the Lewis acid, radical and organometallic conditions where aldehyde reacts efficiently. The ozonide moiety can be considered as a synthon or protecting group for the aldehyde and carboxylic acid.

Ozonides have long been considered as an unstable functional group in organic chemistry and are reduced or oxidized directly to the desired products right after the ozonolysis.[1] Although several ozonides have been isolated in the pure forms, studies on their stability and reactivity under different reaction conditions are rare.[2] In artemisinin (Qinghaosu) research area, the modification of the lactone ring without affecting the 1,2,4-trioxane moiety has been developed.[3-5] When artemisinin is reduced with $NaBH_4$ to give dihydroartemisinin, the lactone moiety of the molecule is converted into a lactol and the peroxide is preserved.[3] The (+)-deoxoartemisinin was successfully achieved in high yield from the reduction of artemisinin by $NaBH_4$ in the presence of $BF_3{\bullet}Et_2O$ in dry THF.[4] Recently, we reported that the ozonolytic cleavage of cycloalkenes in the presence of methyl pyruvate yielded the terminally differentiated compounds with an aldehyde at one end and the ozonide moiety at the other end.[6] We found that the aldedyde could be converted to the alcohol, carboxylic acid and dimethyl acetal without affecting the ozonide moiety. These observations prompted us to investigate the possibility of carrying out the carbon–carbon bond forming reactions in the presence of the ozonide. In compound **2**, the ozonide ring proton, peroxide, and CO_2Me were considered as triple reactive sites which could be converted to different

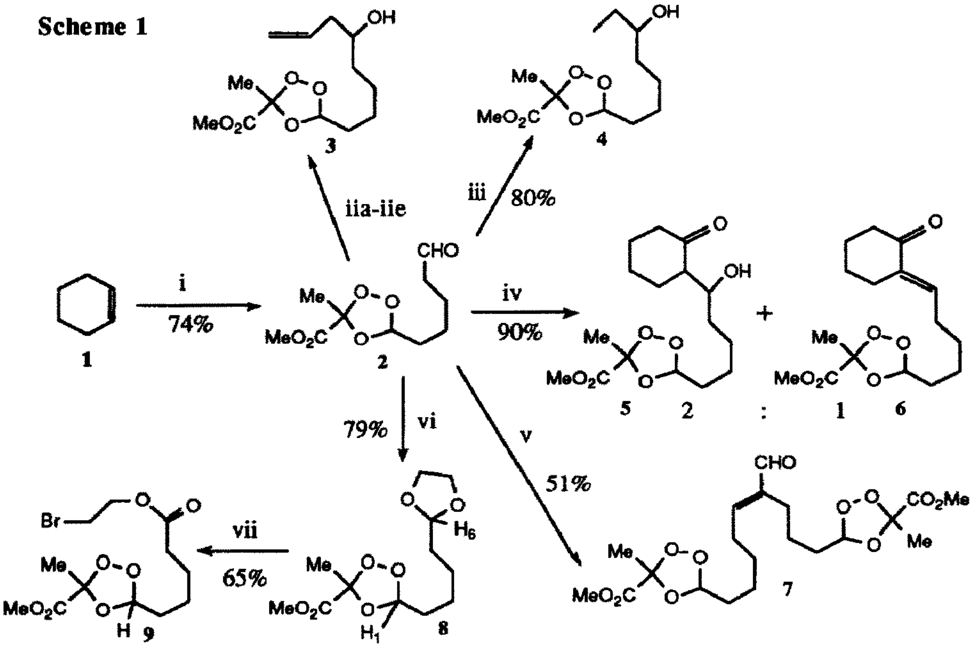
Figure 1 : The ozonide group contains triple reactive sites and is a synthon of the aldehyde or carboxylic acid



functional groups (i.e. aldehyde, carboxylic acid or enal) specifically by employing different reagents (Fig. 1). The success in functionalizing the aldehyde group chemoselectively will broaden the synthetic applications of the ozonide chemistry. In this report, we summarize the results of our work in this direction.

Compound **2** was prepared from cyclohexene (**1**) in 74% yield as described in our previous report.[6] In the presence of $TiCl_4$ or $SnCl_4$, allylation of aldehyde group of compound **2** with allyl-silane[7] or -stannane[8] proceeded smoothly, and homoallylic alcohol **3** was obtained in high yields(Conditions iia-iid, Scheme 1). It is interesting to find that the ozonide moiety is stable in the presence of the stoichiometric amount of the Lewis acids at -78 ℃. With this information in hand, the Mukaiyama-type aldol condensation between compound **2** and 1-trimethylsiloxycyclohexene to form a mixture of compounds **5** and **6** is a logical

Scheme 1



Conditions : (i) O_3, -78 ℃, CH_2Cl_2, 1.5 eqiv. $MeCOCO_2Me$, 74% yield
(iia) 1.1 eqiv.$CH_2{=}CHCH_2SiMe_3$, 0.5 eqiv. $TiCl_4$, -78 ℃, CH_2Cl_2, 88% yield
(iib) 1.1 eqiv.$CH_2{=}CHCH_2SiMe_3$, 1.0 eqiv. $SnCl_4$, -78 ℃, CH_2Cl_2, 81% yield
(iic) 1.1 eqiv.$CH_2{=}CHCH_2SnBu_3$, 0.5 eqiv. $TiCl_4$, -78 ℃, CH_2Cl_2, 77% yield
(iid) 1.1 eqiv.$CH_2{=}CHCH_2SnBu_3$, 1.0 eqiv. $SnCl_4$, -78 ℃, CH_2Cl_2, 87% yield
(iie) 2.0 eqiv. $CH_2{=}CHCH_2ZnBr$, THF, RT 70% yield
(iii) 1.5 eqiv. Et_2Zn, 1.5 eq. $BF_3{\cdot}Et_2O$, CH_2Cl_2, -78 ℃, 80% yield
(iv) 1.5 eqiv. $TiCl_4$, 1-Trimethylsilyoxycyclohexene, -78 ℃, CH_2Cl_2, 90% yield
(v) 2.3 eqiv. $BF_3{\cdot}Et_2O$, CH_2Cl_2, RT, 1 hr, 51% yield
(vi) Ethylene Glycol, PPTS, Acetone, RT, 79% yield
(vii) NBS, THF, AIBN, 60 ℃, 65% yield

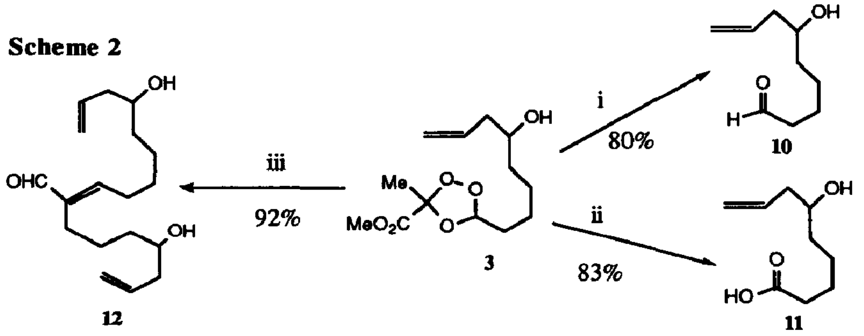
extension.[9] Before workup, β-hydroxyketone 5 was the predominant product. However, the dehydration occurred rapidly during the aqueous workup. The double bond configuration of compound 6 was assumed to be the one shown in the Scheme 1 but was not assigned unambiguously. Interestingly, even the reaction temperature was raised to 25 °C, the $BF_3 \cdot Et_2O$-catalyzed aldol condensation of compound 2 occurred chemoselectively to form the conjugated enal 7 in 51% yield. The double bond configuration of enal 7 was determined by 2D-NOSY NMR technique.

It is known in the literature that the ozonides could react with the organomagnesium reagent to give carbinols.[10] We found that the aldehyde group of compound 2 could react with excess amount of the allylzinc bromide at room temperature to give the homoallylic alcohol 3 in 70% yield. Presumably, organometallic reagent such as the organozinc halide is compatible with the ozonide moiety. However, when diethylzinc was used, the Lewis acid[11] such as $BF_3 \cdot Et_2O$ was required to catalyze the formation of the secondary alcohol 4 in 80% yield. The procedure involved the addition of a solution of diethylzinc in hexane to a solution containing compound 2 and an equivalent amount of $BF_3 \cdot Et_2O$ in CH_2Cl_2 at -78 °C.

We reported that the ozonide ring proton was quite labile to the phosphorus ylide and bases.[6, 12] It is interesting to see its stability under the free radical conditions. For this purpose, the 1,3-dioxolane 8 was made in high yield by treatment of compound 2 with ethylene glycol in acetone in the presence of catalytic amount of the pyridinium *p*-toluenesulfonate (PPTS). When a solution of 1,3-dioxolane 8 in THF was treated with N-bromosuccinimide (NBS) in the presence of AIBN at 60 °C for 1 hr,[13] the bromoethyl ester 9 was formed in 65% yield. To our surprise, the H-6 on the 1,3-dioxolane was much more labile than H-1 on the 1,2,4-trioxolane of compound 8. In other words, it is possible to functionalize the cyclic acetal via the free radical process without breaking the ozonide ring.[14]

We have demonstrated that the ozonide group is stable under the Lewis acid, free radical, and organometallic conditions. Therefore, the functionalization of the aldehyde followed by decomposition of the ozonide moiety represents an extremely convenient and versatile methodology to prepare terminally differentiated compounds from simple cycloalkenes. For example, compound 3 can be converted into compounds **10**-**12** in high yields under the different conditions (Scheme 2). Since the ozonide moiety of compound 2 is a synthon of the carboxylic acid or aldehyde[6], it means that this moiety is also a protecting group of the aldehyde and carboxylic acid based on the present results (Fig. 1). To the best of our

Scheme 2



Conditions : *(i)* Ph_3P, CH_2Cl_2, *RT (ii)* Et_3N, CH_2Cl_2, *RT (iii) 1N* $NaOH$, H_2O-*THF* knowledge, this is the first report to describe the possibility to form the carbon-carbon bond in the presence of the ozonide group. Further studies on the utility of ozonides as both the protecting group and masked group in organic synthesis are underway in our laboratory.

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14. All new compounds have been fully characterized by ^{1}H-, ^{13}C-NMR, IR. Satisfactory CI-MS and HRMS results were obtained for ozonides **3-9** and compounds **10-12**, respectively.

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