Ozonolysis of β-(Alkoxycarbonyl)- and β-Acyl-Substituted Vinyl Ethers. Cycloaddition Chemistry of the Derived α-Keto Ester O-Oxides and α-Diketone O-Oxides

Tomohito Sugiyama, Hideyuki Yamakoshi, and Masatomo Nojima*

Chemical Process Engineering, Faculty of Engineering, Osaka University, Suita, Osaka 565, Japan

Ozonolyses of a series of vinyl ethers 1a–h having electron-withdrawing substituent(s) at the β-position were carried out in methanol and also in aprotic solvents in the presence of 1,3-dipolarophiles. Methanol-trapping experiments revealed that the cleavage of the primary ozonides from vinyl ethers 1a,b,d–f is regioselective, providing in each case the corresponding α-keto ester O-oxides 3a,b and α-diketone O-oxides 3d–f. These electron-deficient carbonyl oxides 3a,b,d–f could undergo cycloadditions with a variety of 1,3-dipolarophiles, particularly nitrones, and give in each case the corresponding cycloadducts.
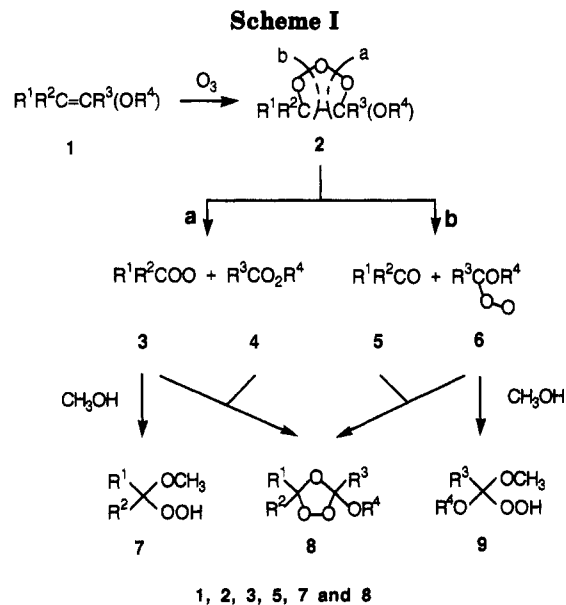
Extensive investigation of the mechanism of alkene ozonolysis has confirmed the essential features of the pathway originally proposed by Criegee.[1] For the cleavage of primary ozonides (PO), extensive studies by Fliszar[2] and Griesbaum[3] have led to a useful rule that cleavage of the PO tends to occur along the path which results in the placement of electron-donating substituents such as methyl on the carbonyl oxide fragment, while electron-withdrawing substituents such as acyl and halogen are incorporated in the carbonyl product. As fully understood by Kuczkowski, alkoxy groups also exhibit strong bias against incorporation in the carbonyl oxides.[4] Ozonolyses of alkenes, which incorporate both an electron-withdrawing substituent and the alkoxy group, must be therefore interesting, since for these alkenes the regioselectivity of PO cleavage would reflect the delicate competition between the opposing directive effects of these groups. Along this line, Bunnelle and co-workers have found that ozonolyses of 4-methoxy-3-methyl-3-buten-2-one and 4-methoxy-3-methyl-3-penten-2-one favor the formation of the corresponding α-diketone O-oxides,[5] whereas ozonolyses of 2-methyl-3-acetyl-5-phenyldihydrofuran and 2,3-dimethyl-6-phenyldihydropyran-4-one proceed by the alternative ester oxides.[6]

We report here our own results on the ozonolyses of a series of vinyl ethers 1a–h. We have considered that decomposition of the primary ozonides from the properly substituted vinyl ethers would give rise to selective generation of the corresponding α-keto ester O-oxides and α-diketone O-oxides. Because of the minimal interference from the byproduct ester,[4] the electron-deficient carbonyl oxides[7–11] would in turn undergo cycloadditions with the added 1,3-dipolarophiles.

Results and Discussion

Ozonolysis of Vinyl Ethers in Methanol. Following an initial attack of ozone to vinyl ether 1, it is expected that the resulting PO 2 should, a priori, undergo cleavage by either of the two possible modes (paths a and b in Scheme I) providing a diketone oxide 3/alkyl formate 4 pair and an ester oxide 6/ketone 5 pair, respectively. To determine the mode of fragmentation of the PO, ozonolysis

Scheme I

	R^1	R^2	R^3	R^4
a	CH_3OCO	H	H	CH_3
b	CH_3OCO	CH_3	H	CH_3
c	C_2H_5OCO	H	CH_3	C_2H_5
d	CH_3CO	H	H	CH_3
e	CH_3CO	CH_3	H	CH_3
f	CH_3	$-C(O)CH_2CH_2CH_2-$		C_2H_5
g	$-CO_2C(CH_3)_2OCO-$		H	CH_3
h	Ph	CF_3	H	CH_3
i	CH_3O	H	H	CH_3

(1) (a) Bunnelle, W. H. *Chem. Rev.* **1991**, *91*, 335. (b) Kuczkowski, R. L. In *Adv. Oxygenated Processes*; Baumstark, A. L., Ed.; JAI Press: Greenwich, 1991; Vol. 3. (c) McCullough, K. J.; Nojima, M. In *Organic Peroxides*; Ando, W., Ed.; Wiley: New York, 1992; Chapter 13.

(2) Fliszar, S.; Renard, J.; Simon, D. Z. *J. Am. Chem. Soc.* **1971**, *93*, 6953.

(3) (a) Griesbaum, K.; Greunig, H.-J.; Volpp, W.; Jung, I.-C. *Chem. Ber.* **1991**, *124*, 947. (b) Griesbaum, K.; Zwick, G. *Chem. Ber.* **1986**, *119*, 229. (c) Griesbaum, K.; Meister, M. *Chem. Ber.* **1987**, *120*, 1573. (d) Griesbaum, K.; Zwick, G.; Agarwal, S.; Keul, H.; Pfeffer, B.; Murray, R. W. *J. Org. Chem.* **1985**, *50*, 4194.

(4) (a) Wojciechowski, B. J.; Chiang, C.-Y.; Kuczkowski, R. L. *J. Org. Chem.* **1990**, *55*, 1120. (b) Nojima, M. *Rev. Heteroat. Chem.* **1991**, *5*, 23.

(5) Bunnelle, W. H. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, Vol. 3, in press.

(6) (a) Bunnelle, W. H.; Meyer, L. A.; Schlemper, E. O. *J. Am. Chem. Soc.* **1989**, *111*, 7612. (b) Bunnelle, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 7613. (c) Bunnelle, W. H.; Schlemper, E. O. *J. Am. Chem. Soc.* **1987**, *109*, 612.

Table I. Ozonolysis of Vinyl Ethers[a]

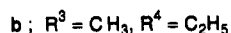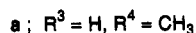| vinyl ether	solvent	products (% yield)
1a	CD$_3$OD	7a-d_4 (75), 4a (65)[b]
1a	CH$_3$OH	7a (52)
1b	CD$_3$OD	7b-d_4 (~100), 4a (80)[b]
1b	CH$_3$OH	7b (90)
1c	CD$_3$OD	8c (44)[b]
1c	ether	8c (57)
1d	CD$_3$OD	7d-d_4 (74), 4a (81)[b]
1e	CD$_3$OD	7e-d_4 (90), 4a (70)[b]
1f	CH$_3$OH	10 (76)
1f[c]	CH$_3$OH	11 (38)
1g	CH$_3$OH	8g (50)[d]
1g	CH$_2$Cl$_2$	8g (77)[e]
1h	CD$_3$OD	5h (~100), 6a (75)[b]
1h	ether	8h (37)

[a] Unless otherwise noted, vinyl ether 1 was treated with 1.5 equiv of ozone at –70 °C. [b] Determined by ^{1}H NMR analysis. [c] The reaction mixture was treated with triphenylphosphine. [d] Reaction with 5 equiv of ozone in MeOH/CH$_2$Cl$_2$ (1:1); 1h was recovered in 38%. [e] Reaction with 5 equiv of ozone.

of methyl 3-methoxyacrylate ((E)-1a) was carried out in CD$_3$OD at –70 °C. The ^{1}H NMR spectrum of the reaction mixture indicated the exclusive formation of a 1:1 mixture of CH$_3$OC(O)CH(OCD$_3$)OOD (7a-d_4) and methyl formate (4a), suggesting the apparent dominance of the alkoxy directive effect in the PO cleavage (path a in Scheme I). By column chromatography on silica gel, methyl α-hydroperoxy-α-methoxyacetate (7a)[3c] was isolated in 52% yield (Table I).
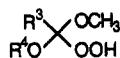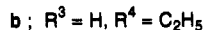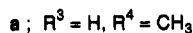
As Bunnelle has also found for the relevant β-acyl-substituted vinyl ethers,[5] the methyl substituent of vinyl ethers 1b,c at the α- or β-position seems to exert a remarkable influence on the direction of cleavage of the PO. Consistent with the reinforced directive effect of the methoxy group by the higher degree of methyl substitution at the β-position, the ozonolysis of (E)-1b in methanol gave exclusively a 1:1 mixture of methyl α-methoxy-α-hydroperoxypropionate (7b)[3c] and methyl formate (4a).

$$R^3CO_2R^4$$

4

a ; R^3 = H, R^4 = CH$_3$

b ; R^3 = CH$_3$, R^4 = C$_2$H$_5$

$$R^3COR^4$$
$$O\!-\!O$$

6

a ; R^3 = H, R^4 = CH$_3$

b ; R^3 = H, R^4 = C$_2$H$_5$

c ; R^3 = CH$_3$, R^4 = C$_2$H$_5$

$$R^3\!\!\diagdown\!\!\diagup OCH_3$$
$$R^4O\!\!\diagup\!\!\diagdown OOH$$

9

a ; R^3 = H, R^4 = CH$_3$

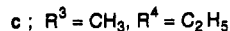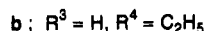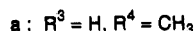b ; R^3 = H, R^4 = C$_2$H$_5$

c ; R^3 = CH$_3$, R^4 = C$_2$H$_5$

In contrast, ozonolysis of ethyl 3-ethoxycrotonate ((E)-1c) in CD$_3$OD provided the corresponding ozonide (1,2,4-trioxolane) 8c in 44% yield. From the ^{1}H NMR spectra of the reaction mixture, no evidence was obtained for the presence of ethyl α-hydroperoxy-α-methoxyacetate (7c) derived from capture of 3c by methanol.

For conversion of 1c to 8c, the ozonide could result from recombination of either pair of Criegee cleavage products (Scheme I; carbonyl oxide–ester from path a, ketone–ester

oxide from path b). Since carbonyl oxide–ester cycloadditions are generally not effective for the production of alkoxy ozonides,[4,6c] the formation of ozonide 8c would be the result of recombination of ethyl glyoxylate (5c) and ethyl acetate O-oxide (6c). It is well known that α-keto esters are an excellent dipolarophile toward carbonyl oxides,[12] and moreover, ester oxides 6 have been shown to exhibit normal reactivity toward aldehydes.[4a] Ozonolysis of 1c in ether gave ozonide 8c in a high yield of 79% (^{1}H NMR analysis; 57% isolated yield). This is in marked contrast to the fact that ozonolyses of 1a,b in the same solvent did not yield the corresponding ozonides 8a,b. Instead, after evaporation of the solvent in vacuo, only small amounts of unidentified products were obtained in each case. As will be seen later, the lability of the ozonides 8a,b is not the reason. These results imply that in the PO 2c the α-methyl group, as a weak electron donor, reinforces the directive effect of the ethoxycarbonyl group such that the sum of the directive effects of both groups would overcome that of the ethoxy group and, as a result, the scission pathway b would predominate.[6]

As may be expected from the substitution patterns, ozonolysis of a series of β-acyl-substituted vinyl ethers 1d–f seems to proceed predominantly by the scission pathway a (Scheme I). From the reaction of 4-methoxy-3-buten-2-one ((E)-1d) conducted in CD$_3$OD at –70 °C was obtained a 1:1 mixture of α-hydroperoxy-α-methoxyacetone-d_4 (7d-d_4)[3b] and methyl formate (4a). As Bunnelle[5] has also found, the reaction of 1e (a 4:1 mixture of two isomers) under similar conditions gave exclusively the corresponding hydroperoxide 7e,[3d] together with 4a. Upon standing at rt for 24 h, 7e decomposed into methyl acetate and acetic acid.[3d] In the case of the less stable methanol-derived product 7f from 1f (Scheme II), the decomposition seemed to occur even at –70 °C (a CIDNP signal at δ 9.77), and as a result, the reaction outcome was the production of glutaric acid monoethyl ester (10) and methyl acetate.[3d,8] Consistent with the formation of 7f, however, immediate treatment of the reaction mixture with triphenylphosphine dissolved in methylene chloride led to the production of diketone 11 (Scheme II and Table I).

A more electron-withdrawing substituent seems to exhibit a decisive bias against incorporation of the substituent in the carbonyl oxide.[2,3] The example is α-(trifluoromethyl)-β-methoxystyrene (1h; a 2:1 mixture of two stereoisomers). By measuring the ^{1}H NMR spectrum of the reaction mixture in CD$_3$OD, it was confirmed that ozonolysis of 1h in methanol does not yield a mixture of α-(trifluoromethyl)-α-methoxybenzyl hydroperoxide (7h) and methyl formate but instead gives a mixture of dimethoxymethyl hydroperoxide (9a) and trifluoroacetophenone (5h) (Table I), suggesting that by cleavage of the primary ozonide 2h methyl formate O-oxide (6a)[4a] is selectively produced (however, the labile 9a could

(7) For the chemistry of electron-deficient carbonyl oxides, trapping by methanol[8] and an oxygen-atom transfer to alkene,[9] sulfide, or sulfoxide[10] have been already reported. Also, spectroscopic and theoretical studies on these interesting intermediates have been conducted.[11] However, the 1,3-dipolar cycloaddition reaction has not been studied.
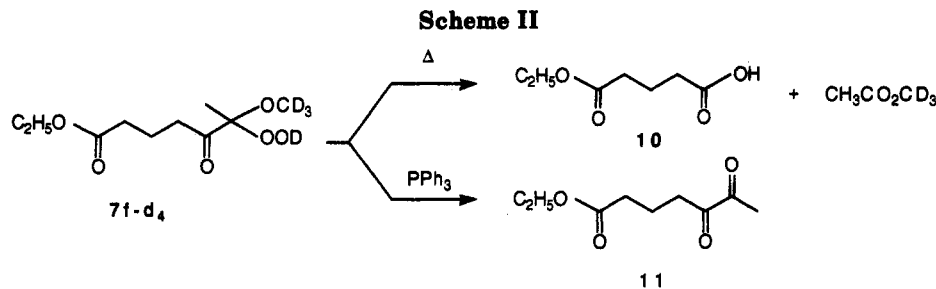
(8) (a) Bailey, P. S.; Bath, S. S. J. Am. Chem. Soc. 1957, 79, 3120. (b) Bailey, P. S.; Mainthia, S. B.; Abshire, C. J. J. Am. Chem. Soc. 1960, 82, 6136.

(9) Griesbaum, K.; Bruggemann, J. Chem. Ber. 1972, 105, 3638.

(10) (a) Ishiguro, K.; Hirano, Y.; Sawaki, Y. Tetrahedron Lett. 1987, 28, 6201. (b) Adam, W.; Hass, W.; Sieker, G. J. Am. Chem. Soc. 1984, 106, 5020.
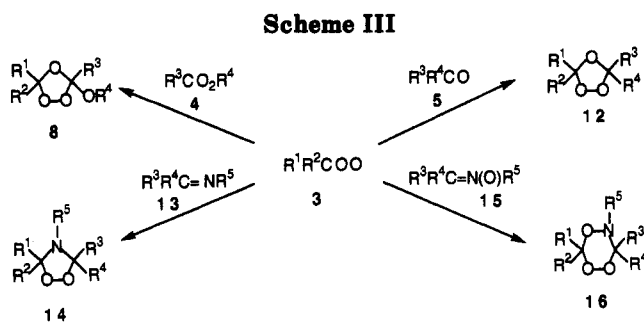
(11) Sander, W. Angew. Chem., Int. Ed. Engl. 1990, 29, 344.

(12) Tabuchi, T.; Nojima, M. J. Org. Chem. 1991, 56, 6591 and references cited therein.

Scheme II

12

	R¹	R²	R³	R⁴
a	CH₃OCO	H	Ph	CF₃
b	CH₃OCO	H	Ph	H
c	CH₃OCO	H	2-CF₃C₆H₄	H
d	CH₃OCO	H	(adamantylidene)	
e	CH₃OCO	CH₃	Ph	CF₃

14

	R¹	R²	R³	R⁴	R⁵
a	CH₃OCO	H	Ph	Ph	Ph
b	CH₃OCO	H	Ph	Ph	p-tolyl
c	CH₃OCO	CH₃	Ph	Ph	CH₃

Scheme III

16

	R¹	R²	R³	R⁴	R⁵
a	CH₃OCO	H	Ph	H	Ph
b	CH₃OCO	H	Ph	H	CH₂Ph
c	CH₃OCO	H	heptyl	H	CH₂Ph
d	CH₃OCO	H	Ph	Ph	Ph
e	CH₃OCO	H	Ph	Ph	CH₃
f	CH₃OCO	CH₃	Ph	H	CH₂Ph
g	CH₃OCO	CH₃	heptyl	H	CH₂Ph
h	CH₃OCO	CH₃	Ph	Ph	CH₃
i	CH₃CO	H	Ph	H	CH₂Ph
j	CH₃CO	H	heptyl	H	CH₂Ph
k	CH₃CO	H	Ph	Ph	CH₃
l	CH₃CO	CH₃	Ph	H	CH₂Ph
m	CH₃CO	CH₃	heptyl	H	CH₂Ph
n	EtOCO(CH₂)₃CO	CH₃	heptyl	H	CH₂Ph
o	CH₃O	H		heptyl	H	CH₂Ph

not be isolated). Ozonolysis of **1h** in ether gave the corresponding ozonide **8h** in 70% yield (¹H NMR analysis; 37% isolated yield), as did the reaction of 1,2-dimethoxyethene (**1i**) with ozone in ether in the presence of **5h** (35% isolated yield).

In the case of 2,2-dimethyl-5-(methoxymethylene)-1,3-dioxane-4,6-dione (**1g**), ozonolysis in methanol led to the formation of the corresponding ozonide **8g**[13] in 81% yield. No evidence was obtained for capture of the carbonyl oxide intermediate(s) by the solvent. Because of the strong directing effect of the two electron-withdrawing ester substituents at the β-position, ozonide **8g** is most likely to be produced by recombination of methyl formate O-oxide (**6a**) and trione **5g** (path b in Scheme I). In accordance with this, ozonolysis of 1,2-dimethoxyethylene (**1i**) in ether

in the presence of the trione **5g** resulted in the formation of **8g** (70% yield).

In summary, in the case of β-(alkoxycarbonyl)- and β-acyl-substituted vinyl ethers **1a,b,d–f**, the directive effect of the alkoxy group (σ_I^{14} 0.27) is stronger than that of the electron-withdrawing ROCO (σ_I 0.20) and of RCO (σ_I 0.20), providing in each case the corresponding (methoxycarbonyl)- and acyl-substituted ketone oxides **3a,b,d–f**, respectively. This dominance of directive effect of the alkoxy group would be easily altered by the placement of a weakly electron-donating methyl group (σ_I –0.04) on the α-position of vinyl ether.[5,6] Thus, ozonolysis of **1c** seems to proceed mainly by the alternative pathway b (Scheme I) via the ester oxide **6c**. If the β-substituent is the more electron-withdrawing one such as CF₃ (σ_I 0.42), the scission pathway is highly regioselective providing exclusively the corresponding ester oxide **6**.

Ozonolysis of Vinyl Ethers in the Presence of 1,3-Dipolarophiles. Since the ozonolyses of vinyl ethers **1a,b,d–f** were found to proceed in each case via the corresponding α-keto ester and α-diketone O-oxides **3a,b,d–f**, we next conducted the ozonolysis of these vinyl ethers in ether or CH₂Cl₂ in the presence of a 1,3-dipolarophile such as ketone, imine,[15] and nitrone.[16]

(a) Carbonyl Compounds. Ozonolysis of **1a** in the presence of trifluoroacetophenone (**5h**) gave methyl 3-phenyl-3-(trifluoromethyl)-1,2,4-trioxolane-5-carboxylate (**12a**) in 58% yield (Scheme III and Table II). Similarly, methyl glyoxylate O-oxide (**3a**) could undergo cycloaddition to the added benzaldehyde (**5j**), 2-(trifluoromethyl)benzaldehyde (**5k**), and adamantanone (**5l**). However, cycloadducts were not obtained from benzophenone, acetophenone, and acetone (even when it was used as the solvent).

Treatment of a 2:1:1 mixture of **1a, 5j**, and **5k** with ozone resulted in the formation of 53% of **12b** and 34% of **12c**,

(13) Schank, K.; Schuhknecht, C. *Chem. Ber.* **1982**, *115*, 2000.

(14) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 2nd ed.; Plenum Press: New York, 1984; p 183.

(15) Mori, M.; Nojima, M.; Kusabayashi, S.; McCullough, K. J. *J. Chem. Soc., Chem. Commun.* **1988**, 1550.

(16) Mori, M.; Sugiyama, T.; Nojima, M.; Kusabayashi, S.; McCullough, K. J. *J. Am. Chem. Soc.* **1989**, *111*, 6884; *J. Org. Chem.* **1992**, *57*, 2285.

Table II. Ozonolysis of Vinyl Ethers in the Presence of 1,3-Dipolarophiles[a]

vinyl ether	dipolarophile	products (% yield)[b]
1a[c]	4a; R¹ = H, R² = CH₃	8a (21) [52]
1a	5h; R¹ = Ph, R² = CF₃	12a (58) [82][d,e]
1a	5j; R¹ = Ph, R² = H	12b (69) [83][d,e]
1a	5k; R¹ = 2-CF₃C₆H₄; R² = H	12c (66) [81][d,e]
1a	5l; 2-adamantanone	12d (20) [32][d]
1b[c]	4a	8b (10) [50][d]
1b	5h	12e (73)
1a	13a; R³ = R⁴ = R⁵ = Ph	14a (49)
1a	13b; R³ = R⁴ = Ph, R⁵ = p-tolyl	14b (57)
1b	13c; R³ = R⁴ = Ph, R⁵ = CH₃	14c (21)
1a	15a; R³ = R⁵ = Ph, R⁴ = H	16a (30) [69][d]
1a	15b; R³ = Ph, R⁴ = H, R⁵ = CH₂Ph	16b (38) [70][d]
1a	15c; R³ = heptyl, R⁴ = H, R⁵ = CH₂Ph	16c (26) [35][d,f]
1a	15d; R³ = R⁴ = R⁵ = Ph	16d (47) [75][d]
1a	15e; R³ = R⁴ = Ph, R⁵ = Me	16e (65) [86][d]
1b	15b	16f (93)
1b	15c	16g (75)
1b	15e	16h (80)
1d	15b	16i (60) [91][d]
1d	15c	16j (33)[f]
1d	15e	16k (65)
1e	15b	16l (56)
1e	15c	16m[f] (60)
1f	15c	16n (55)
1j	15c	16o (40)

[a] Ozonolysis of a 2:1 mixture of 1 and an appropriate 1,3-dipolarophile at -70 °C. For carbonyl compounds the solvent was ether, and for imine and nitrone the solvent was CH₂Cl₂. [b] Isolated yield. [c] Ozonolysis in methyl formate. [d] The yield estimated from the ¹H NMR spectra of the mixture of the crude products. [e] A mixture of two isomers; the ratio = ca. 4:1. [f] 5-Benzyl-3,6-diheptyl-5,6-dihydro-1,2,4,5-trioxazine was also isolated in ca. 15% yield.

suggesting that the reactivity of 5j toward 3a is much the same as that of electron-deficient 5k. This is in marked contrast to the fact that benzaldehyde *O*-oxide reacts with 5k eight times faster than with 5j.[17] It is also noteworthy that the ozonolysis of 1a in methyl formate (4a) led to the formation of methyl 3-methoxy-1,2,4-trioxolane-5-carboxylate (8a) in a high yield of 52% (¹H NMR; 21% isolated yield) (Table II). Although formaldehyde *O*-oxide certainly undergoes cycloaddition to methyl formate (ozonolysis of ethyl vinyl ether in methyl formate gives 3-ethoxy-1,2,4-trioxolane in 29% yield[18]), alkyl-, and aryl-substituted carbonyl oxides exhibit a negligible reactivity to methyl formate (4a).[17] Consistent with the high reactivity of 3a toward 4a, ozonolysis of a mixture of 1a and benzaldehyde (5j) in methyl formate resulted in the formation of both 12b and 8a in yields of 21% and 29%, respectively. However, ozonolyses of 1a in methyl acetate or in methyl trifluoroacetate/CH₂Cl₂[19] did not yield the expected cycloadducts. Instead, small amounts of unidentified polymeric products were produced.

By conducting the ozonolysis of 1b in the presence of 5h, ozonide 12e was obtained in 73% yield. Also, the reaction of 1b in methyl formate with ozone afforded methyl 3-methoxy-5-methyl-1,2,4-trioxolane-5-carboxylate (8b) (10% isolated yield). In contrast, ozonolysis of 1c in the presence of 5h did not yield the cross ozonide derived from recombination of ester oxide 6c and 5h but instead gave the normal ozonide 8c (38% yield), suggesting

(17) Griesbaum, K.; Kim, W.-S.; Nakamura, N.; Mori, M.; Nojima, M.; Kusabayashi, S. *J. Org. Chem.* **1990**, *55*, 6153.

(18) Keul, H.; Choi, H.-S.; Kuczkowski, R. L. *J. Org. Chem.* **1985**, *50*, 3365.

(19) Sugiyama, T.; Nojima, M.; Krieger-Beck, P.; Kim, W.-S.; Griesbaum, K. *J. Org. Chem.* **1992**, *57*, 3487.

that recombination of 6c and ethyl glyoxylate in the cage is a very efficient process. Also, 8c was the sole product from the ozonolysis of 1c in methyl formate. In the case of vinyl ethers 1d,e, we failed to isolate the expected trioxolanes derived from cycloaddition of carbonyl oxides 3d,e with carbonyl compounds, 5h and 4a. Probably, the lability of the acyl-substituted 1,2,4-trioxolanes is the reason.[3a]

(b) Imine. Carbonyl oxide 3a underwent cycloaddition to imines 13a,b. The corresponding 1,2,4-dioxazolidines 14a,b were isolated in moderate yields (Scheme III and Table II). Also, the reaction of a mixture of 1b and imine 13c with ozone in CH₂Cl₂ gave rise to the formation of 14c. In the case of vinyl ethers 1d–f, we failed to isolate the expected cycloadducts derived from cycloaddition of 3d–f with imine 14. During the evaporation of the solvent in vacuo, the products decomposed with fuming.

(c) Nitrone. Nitrone 15a–e were found to be excellent dipolarophiles toward carbonyl oxide 3a. The corresponding 5,6-dihydro-1,2,4,5-trioxazines 16a–e were isolated in 26–65% yields (Scheme III and Table II). The ¹H NMR spectrum of the mixture of the crude products showed the formation of the trioxazine 16 in much higher yield, but during column chromatography on silica gel significant decomposition was observed. Ozonolysis of 1a in the presence of α,N-diphenylnitrone (15a) is illustrative. Trioxazine 16a seemed to be formed in 69% yield as a mixture of two isomers (the ratio 57:43). By column chromatography, however, only the major isomer of 16a was isolated in 30% yield. A similar trend was observed for adducts 16b,c. Ozonolyses of 1b in the presence of 15b,c,e gave in each case the corresponding adducts 16f–h.

Among the 1,3-dipolarophiles examined, nitrone was the most reactive toward carbonyl oxide 3a. Ozonolysis of a 2:1:1 mixture of 1a, 15b, and 5j revealed that only nitrone 15b participates in the cycloaddition affording the adduct 16b in 38% yield. A similar trend was observed between 15c and 4a; the reaction of 1a with ozone in the presence of 15c in methyl formate lead to the formation of only 16c (24% yield).

Although we failed to isolate acyl-substituted 1,2,4-trioxolanes and 1,2,4-dioxazolidines, acyl-substituted trioxazines 16h–n could be isolated in 33–93% yield from the ozonolyses of β-acyl-substituted vinyl ethers 1d–f in the presence of nitrones 15b,c,e (Table II). This provides additional evidence to suggest that reaction of 1d–f and ozone proceeds mainly by diketone *O*-oxide 3d–f. Ozonolysis of 1,2-dimethoxyethene (1i) in the presence of 15c did produce the methoxy-substituted trioxazine 16o (40% yield), suggesting that methyl formate *O*-oxide (6a) also can undergo cycloaddition to nitrone. Ozonolysis of 1h in the presence of 15c, however, resulted in the exclusive formation of the normal ozonide 8h (40% yield).

Conclusion. We have discovered that ozonolyses of the properly substituted vinyl ethers 1a,b,d–f produce selectively the (alkoxycarbonyl)- and acyl-substituted carbonyl oxides 3a,b,d–f, which in turn undergo cycloadditions with the added 1,3-dipolarophiles 5, 13, and 15 to give in each case the corresponding cycloadducts 12, 14, and 16. The simplicity and easiness of the procedure and the efficiency of the cycloaddition must substantiate the usefulness of this method for the synthesis of a variety of labile (alkoxycarbonyl)- and acyl-substituted 1,2,4-trioxolanes, 1,2,4-dioxazolidines, and 1,2,4,5-trioxazines.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were obtained with a JNM-PS-100 spectrometer and a JEOL JNM-GSX-400 spectrometer, respectively; unless otherwise noted, the solvent was $CDCl_3$. Infrared spectra were obtained with a Hitachi 215 spectrometer. Vinyl ethers **1b**,[20] **1e**,[21] **1g**,[22] **1h**,[17] and **1i**[23] were prepared by the reported methods. **1c,d,f** were purchased from Aldrich, and **1a** was donated from Ube Kosan Co. Ltd. Ozonolyses were carried out with a Nippon Ozone Model 0-1-2 ozonator; dry oxygen containing about 2% of ozone was introduced at a speed of 50 L/h in the solution of a substrate.

Caution. The peroxides prepared in this work are potentially explosive compounds, and therefore, appropriate precautions should be taken. The product mixtures containing acyl-substituted 1,2,4-trioxolanes and 1,2,4-dioxazolidines were particularly dangerous, and they sometimes decomposed with fuming.

Ozonolysis of Methyl 3-Methoxyacrylate (1a) in Methanol. Over a CD_3OD solution (0.5 mL) of **1a** (35 mg, 0.3 mmol) was passed a slow stream of ozone (0.45 mmol) at −70 °C. The ^{1}H NMR spectrum showed the formation of $CH_3OC(O)CH(OCD_3)OOD$ (**7a**-d_4) and methyl formate (**4a**): ^{1}H NMR δ 3.73 (s, 3 H, **4a**), 3.79 (s, 3 H, **7a**), 5.16 (s, 1 H, **7a**), 8.08 (s, 1 H, **4a**). The quantitative analysis was based on the comparison of the intensities of the signals of the individual components with that of 1,1,2,2-tetrachloroethane at δ 5.90. The same reaction of **1a** (233 mg, 2 mmol) was repeated in methanol (15 mL). The reaction mixture was poured into water, extracted with ether, and dried over anhydrous magnesium sulfate. Then, the products were separated by column chromatography on silica gel. Elution with ether–hexane (1:1) gave methyl α-hydroperoxy-α-methoxyacetate (**7a**)[3c] (141 mg, 52% yield): an oil; ^{1}H NMR δ 3.58 (s, 3H), 3.84 (s, 3 H), 5.16 (s, 1 H), 9.83 (br s, 1 H); IR (neat) 3400, 2960, 1745, 1625, 1440, 1320, 1210, 1155, 1105, 1010, 770 cm⁻¹. The hydroperoxide **7a** was reduced by dimethyl sulfide very easily. In a NMR tube **7a** (50 mg) dissolved in $CDCl_3$ was treated with 1 drop of dimethyl sulfide; after 10 min, the ^{1}H NMR spectrum showed the formation of methyl hydroxymethoxyacetate [δ 3.44 (s, 3 H), 3.78 (s, 3 H), 4.88 (s, 1 H), 5.13 (br s, 1 H)],[3b] together with dimethyl sulfoxide [δ 2.64 (s, 6 H)].

Ozonolysis of Methyl 3-Methoxymethacrylate (1b) in Methanol. Ozonolysis of **1b** (27 mg, 0.2 mmol) with ozone in CD_3OD (1 mL) gave **7b**-d_4 [δ 1.45 (s, 3 H), 3.80 (s, 3 H)], together with methyl formate (**4a**). The same reaction of **1b** (268 mg, 2 mmol) was conducted in methanol. By the conventional workup, **7b** was isolated in 90% yield.

Methyl α-hydroperoxy-α-methoxypropionate (7b): mp 30-32 °C (lit.[3c] mp 32-33 °C); ^{1}H NMR δ (CCl_4) 1.45 (s, 3 H), 3.38 (s, 3 H), 3.80 (s, 3 H), 9.73 (br s, 1 H); ^{13}C NMR δ 18.39, 50.07, 52.91, 104.11, 169.20; IR (KBr) 3700-3100, 1750, 1440, 1300, 1140, 1040, 970, 550 cm⁻¹.

Ozonolysis of Ethyl 3-Ethoxycrotonate (1c) in CD_3OD. Ozonolysis of **1c** (32 mg, 0.2 mmol) with 1.5 equiv of ozone was carried out in 1.0 mL of CD_3OD at −70 °C. The ^{1}H NMR spectrum of the product mixture suggested the presence of ethyl acetate (**4b**) (and/or $CH_3CO_2CD_3$) (ca. 30%; δ 2.03 (s)) and ethyl α-methoxy-α-hydroxyacetate-d_4[24] (ca. 30%; δ 4.84, s, CH), together with **8c** (44%, δ 5.60, 5.97). Because of the complexity of the methyl and methylene signals in the ^{1}H NMR spectrum and the lability of **8c** (GC and HPLC), the exact yields of products could not be determined. Ozonide **8c** was isolated in 20% yield from the ozonolysis of **1c** (2 mmol) in methanol (15 mL) at −70 °C, followed by column chromatography on silica gel.

Ozonolysis of 1c in Ether. Ozonolysis of **1c** (316 mg, 2 mmol) with 1.5 equiv of ozone was conducted in ether (15 mL) at −70 °C. After evaporation of the solvent, the products were separated by column chromatography on silica gel. Elution with ether–hexane (1:10-1:7) gave ozonide **8c** (a 3:2 mixture of two isomers;

(20) Shaw, G.; Warrener, R. N. *J. Chem. Soc.* **1958**, 153.
(21) Clive, D. L. J.; Bergstra, R. J. *J. Org. Chem.* **1991**, *57*, 4976.
(22) Bihlmayer, G. A.; Derflinger, G.; Derkosch, J.; Polansky, O. E. *Monatsh. Chem.* **1967**, *98*, 564.
(23) Iwatsuki, S.; Iguchi, S.; Yamashita, Y. *Kogyokagaku Kaishi* **1965**, *68*, 2463.
(24) Perez, D. G.; Nudelman, N. S. *J. Org. Chem.* **1988**, *53*, 408.

237 mg, 57%). The repeated column chromatography gave first the major isomer and then the minor one.

Ethyl 3-ethoxy-3-methyl-1,2,4-trioxolane-5-carboxylate (8c) (major): an oil; ^{1}H NMR δ 1.22 (t, *J* = 7 Hz, 3 H), 1.35 (t, *J* = 7 Hz, 3 H), 1.70 (s, 3 H), 3.91 (q × d, *J* = 7 and 2 Hz, 2 H), 4.37 (q, *J* = 7 Hz, 2 H), 5.52 (s, 1 H); IR (neat) 2990, 1760, 1380, 1185, 1090, 1055 cm⁻¹. Anal. Calcd for $C_8H_{14}O_6$: C, 46.60; H, 6.80. Found: C, 46.90; H, 6.75.

8c (minor): an oil; ^{1}H NMR δ 1.22 (t, *J* = 7 Hz, 3 H), 1.33 (t, *J* = 7 Hz, 3 H), 1.78 (s, 3 H), 3.78 (q, *J* = 7 Hz, 2 H), 4.32 (q, *J* = 7 Hz, 2 H), 5.80 (s, 1 H). Anal. $C_8H_{14}O_6$: C, 46.60; H, 6.80. Found: C, 46.85; H, 6.74.

Ozonolysis of 4-Methoxy-3-buten-2-one (1d) in CD_3OD. The reaction of vinyl ether **1d** (30 mg, 0.3 mmol) and ozone (0.4 mmol) in CD_3OD (0.5 mL) was carried out in a NMR tube. The ^{1}H NMR spectrum of the reaction mixture showed the formation of a 1:1 mixture of $CH_3C(O)CH(OCD_3)OOD$ (**7d**-d_4)[3b] and **4a**: ^{1}H NMR δ 2.22 (s, 3 H, **7d**-d_4), 3.71 (s, 3 H, **4a**), 4.94 (s, 1 H, **7d**-d_4), 8.05 (s, 1 H, **4a**).

Ozonolysis of 3-Methyl-4-methoxy-3-buten-2-one (1e) in CD_3OD. Ozonolysis of **1e** (29 mg, 0.2 mmol) with 1.5 equiv of ozone was conducted at −70 °C. The ^{1}H NMR spectrum of the reaction mixture showed the presence of 3-hydroperoxy-3-methoxy-2-butanone-d_4 (**7e**-d_4) [90%, δ 1.33 (s, 3 H), 2.27 (s, 3 H)][3d] and methyl formate (**4a**) [70%, δ 3.73 (s, 3 H), 8.10 (s, 1 H)]. Then, the reaction mixture was slowly warmed to rt (1 h) and was kept at this temperature for 24 h. The ^{1}H NMR spectrum of this mixture showed the presence of methyl acetate-d_3 (90%, δ 2.03) and acetic acid (90%, δ 2.03) together with **4a** (70%).

Ozonolysis of 3-Ethoxy-2-methyl-2-cyclohexen-1-one (1f) in MeOH. Ozonolysis of **1f** (31 mg, 0.2 mmol) with 1.5 equiv of ozone was conducted in CD_3OD (1 mL) at −70 °C. The ^{1}H NMR spectrum of the reaction mixture showed the presence of glutaric acid monoethyl ester[25] (**10**) (90%) and $CH_3CO_2CD_3$ (85%, δ 2.00). The same reaction of **1f** (308 mg, 2 mmol) was conducted in methanol (15 mL). After evaporation of the solvent in vacuo, the products were separated by column chromatography on silica gel. Elution with ether gave **10** (122 mg, 76%): an oil; ^{1}H NMR δ 1.26 (t, *J* = 7 Hz, 3 H), 1.8-2.9 (m, 6 H), 4.16 (q, *J* = 7 Hz, 2 H), 9.02 (br s, 1 H). Hydrolysis (KOH/aqueous ethanol, reflux, 2 h) gave glutaric acid: mp 94-97 °C (from benzene/hexane); IR (neat) 3500-2200, 1700, 1430, 1300, 1210, 920 cm⁻¹.

To the reaction mixture (from 1 mmol of **1f**) was added 1 equiv of triphenylphosphine in CH_2Cl_2 (15 mL) at −70 °C, and the mixture was allowed to warm to rt (30 min) and continued at this temperature for 2 h. After evaporation of the solvent, the products were separated by column chromatography on silica gel. Elution with ether–benzene (1:20) gave diketone **11** (69 mg, 38%): an oil; ^{1}H NMR (CCl_4) δ 1.25 (t, *J* = 7 Hz, 3 H), 1.7-2.6 (m, 4 H), 2.29 (s, 3 H), 2.77 (t, *J* = 7 Hz, 2 H), 4.10 (q, *J* = 7 Hz, 2 H). Anal. Calcd for $C_9H_{14}O_4$: C, 58.06; H, 7.53. Found: C, 57.89; H, 7.45.

Ozonolysis of 2,2-Dimethyl-5-(methoxymethylene)-1,3-dioxane-4,6-dione (1g) in Methanol. A solution of **1g** (186 mg, 1 mmol) in methanol–methylene chloride (15 mL; 1:2 v/v) was treated with ozone (5 mmol) at −70 °C. The products were extracted with ether. After evaporation of the solvent, the products were separated by column chromatography on silica gel. Elution with ether-benzene (1:25) gave 3-methoxy-6,10-dioxo-8,8-dimethyl-1,2,4,7,9-pentaoxaspiro[4.5]decane (**8g**) (117 mg, 50% yield): an oil (lit.[13] mp 10 °C); ^{1}H NMR δ 1.85 (s, 3 H), 1.96 (s, 3 H), 3.70 (s, 3 H), 6.51 (s, 1 H).

Ozonolysis of α-(Trifluoromethyl)-β-methoxystyrene (1h) in Methanol. To a CD_3OD solution (0.5 mL) of **1h** (43 mg, 0.21 mmol) in a NMR tube was passed a slow stream of ozone (0.47 mmol) at −70 °C. The ^{1}H NMR spectrum showed the formation of a 1:1 mixture of $CH_3O(CD_3O)CHOOD$ (**9a**-d_4)[4a] and trifluoroacetophenone (**5h**): ^{1}H NMR δ 3.48 (s, 3 H, **9a**), 5.29 (s, 1 H, **9a**), 7.5-8.2 (m, 5 H, **5h**).

Ozonolysis of 1h in Ether. To an ether solution (15 mL) of **1h** (203 mg, 1 mmol) was passed a slow stream of ozone (2 mmol) at −70 °C. The ^{1}H NMR spectrum of the crude products showed the presence of only 3-methoxy-5-phenyl-5-(trifluoromethyl)-

(25) Sakuragi, H.; Tokumaru, K.; Itoh, H.; Terakawa, K.; Kikuchi, K.; Caldwell, R. A.; Hsu, C.-C. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1049.

1,2,4-trioxolane (8h). By column chromatography on silica gel (elution with ether–hexane 3:97) was isolated pure 8h (93 mg, 37%): an oil (a 1:1 mixture of two isomers); ¹H NMR (CCl₄) δ 3.36 (s) + 3.60 (s) (3 H), 6.11 (s) + 6.35 (s) (1 H), 7.4–7.7 (m, 5 H); ¹³C NMR δ 52.12, 52.26, 114.43, 114.59, 120.92, 121.62, 126.76, 128.44, 128.61, 128.79, 130.69, 130.84, 131.95; IR (neat) 2955, 1455, 1303, 1190, 1080, 960, 915, 760, 728, 712, 698, 658 cm⁻¹. Anal. Calcd for C₁₀H₉F₃O₄: C, 48.01; H, 3.60. Found: C, 47.73; H, 3.58.

Ozonolysis of Methyl 3-Methoxyacrylate (1a) in the Presence of a Carbonyl Compound. The reaction in the presence of trifluoroacetophenone (5h) is representative. A mixture of 1a (233 mg, 2 mmol) and 5h (188 mg, 1 mmol) in ether (15 mL) was treated with 2.6 mmol of ozone at –70 °C. After evaporation of the solvent, the products were separated by column chromatography on silica gel. Elution with benzene gave methyl 3-phenyl-3-(trifluoromethyl)-1,2,4-trioxolane-5-carboxylate (12a) (161 mg, 58% yield): an oil (a mixture of two isomers; the ratio = 64:36); IR (neat) 1765, 1450, 1185, 1085, 950, 760, 705 cm⁻¹; ¹H NMR (CCl₄) (major) δ 3.65 (s, 3 H), 5.91 (s, 1 H), 7.3–8.2 (m, 5 H); (minor) δ 3.85 (s, 3 H), 5.61 (s, 1 H), 7.3–8.2 (m, 5 H); ¹³C NMR δ (major) 52.98, 98.01, 104.73 (q, J = 33 Hz), 121.30 (q, J = 288 Hz), 126.65, 128.34, 129.06, 130.81, 164.97; (minor) 53.34, 98.33, 104.77 (q, J = 33 Hz), 120.88 (q, J = 288 Hz), 126.65, 128.50, 130.32, 130.85, 163.21. Anal. Calcd for C₁₁H₉F₃O₅: C, 50.38; H, 3.44. Found: C, 48.94; H, 3.53.

Methyl 3-phenyl-1,2,4-trioxolane-5-carboxylate (12b): an oil (a mixture of two isomers; the ratio = 80:20); ¹H NMR (CCl₄) δ 3.75 (s, 3 H), 5.66 (s, 1 H), 5.88 (s, major) + 6.23 (s, minor) (1 H), 7.3–7.7 (m, 5 H); IR (neat) 3030, 2950, 1760, 1460, 1440, 1380, 1310, 1220, 1090, 995, 750, 690 cm⁻¹. Anal. Calcd for C₁₀H₁₀O₅: C, 57.14; H, 4.80. Found: C, 57.21; H, 4.88.

Methyl 3-[2-(trifluoromethyl)phenyl]-1,2,4-trioxolane-5-carboxylate (12c): an oil (a mixture of two isomers; the ratio = 78:22); ¹H NMR (CCl₄) δ 3.81 (s, 3 H), 5.72 (s, 1 H), 6.29 (s, minor) + 6.66 (s, major) (1 H), 7.2–8.4 (m, 4 H); IR (neat) 2955, 1760, 1440, 1311, 1222, 1165, 1110, 765 cm⁻¹. Anal. Calcd for C₁₁H₉F₃O₅: C, 47.12; H, 3.24. Found: C, 47.21; H, 3.33.

Methyl spiro[tricyclo[3.3.1.1³,⁷]decane-2,3′-[1,2,4]trioxolane]-5′-carboxylate (12d): an oil; ¹H NMR (CCl₄) δ 1.6–2.2 (m, 14 H), 3.85 (s, 3 H), 5.59 (s, 1 H); ¹³C NMR δ 26.31, 26.63, 34.16, 34.66, 34.81, 35.00, 35.38, 35.53, 36.52, 52.70, 96.54, 113.75, 167.06; IR (neat) 2920, 2860, 1762, 1450, 1380, 1215, 1120, 1080, 1000 cm⁻¹.

Ozonolysis of 1a in Methyl Formate (4a). The ozonolysis of 1a (350 mg, 3 mmol) in methyl formate (20 mL) was carried out at –70 °C. After evaporation of 4a, the products were separated by column chromatography on silica gel. Elution with ether–benzene (3:97) gave methyl 3-methoxy-1,2,4-trioxolane-5-carboxylate (8a) (103 mg, 21% yield): an oil (a mixture of two isomers; the ratio = 3:2); IR (neat) 2970, 1760, 1450, 1230, 1100, 830, 728 cm⁻¹; ¹H NMR (major) (CCl₄) δ 3.48 (s, 3 H), 3.87 (s, 3 H), 5.75 (s, 1 H), 6.17 (s, 1 H); ¹³C NMR (major) δ 51.80, 53.07, 96.49, 112.76, 166.06; ¹H NMR (minor) δ 3.56 (s, 3 H), 3.95 (s, 3 H), 5.35 (s, 1 H), 6.10 (s, 1 H); ¹³C NMR (minor) δ 52.00, 53.38, 97.45, 113.79, 163.85. Anal. Calcd for C₅H₈O₆: C, 36.59; H, 4.88. Found: C, 36.95; H, 4.60.

Ozonolysis of 1a in the Presence of Benzaldehyde (5j) and 2-(Trifluoromethyl)benzaldehyde (5k). A mixture of 1a (233 mg, 2 mmol), 5j (106 mg, 1 mmol), and 5k (174 mg, 1 mmol) in ether (15 mL) was treated with ozone (2 mmol) at –70 °C. After evaporation of the solvent, the products were separated by column chromatography on silica gel (elution with benzene–hexane (7:3)). The first fraction contained 12c (95 mg, 34% yield). From the second fraction was obtained 12b (74 mg, 53% yield).

Ozonolysis of 1a in the Presence of 5j in Methyl Formate. A mixture of 1a (237 mg, 2 mmol) and 5j (110 mg, 1 mmol) in methyl formate (15 mL) was treated with ozone (2 mmol) at –70 °C. After evaporation of the solvent, the products were separated by column chromatography on silica gel. The first fraction (elution with ether–benzene (1:99)) contained 12b (45 mg, 21% based on 5j). From the second fraction (elution with ether–benzene (3:97)) was obtained 8a (48 mg, 15%).

Ozonolysis of 1b in Methyl Formate (4a). A methyl formate solution of 1b (144 mg, 1 mmol) was treated with ozone (1.5 equiv) at –70 °C. After evaporation of 4a, the products were

separated by column chromatography on silica gel. Elution with ether–benzene (1:50) gave the ozonide 8b (18 mg, 10%).

Methyl 3-Methyl-5-methoxy-1,2,4-trioxolane-3-carboxylate (8b): a mixture of two isomers (5:1); an oil; IR (neat) 1750, 1440, 1370, 1280, 1120, 1040, 820, 710 cm⁻¹; ¹H NMR (major) (CCl₄) 1.70 (s, 3 H), 3.38 (s, 3 H), 3.77 (s, 3 H), 6.10 (s, 1 H); ¹³C NMR (major) δ 16.98, 51.48, 53.08, 104.78, 113.59, 168.37; ¹H NMR (minor) δ 1.60 (s, 3 H), 3.38 (s, 3 H), 3.77 (s, 3 H), 6.03 (s, 1 H); ¹³C NMR (minor) δ 17.98, 52.17, 53.13, 105.25, 114.65, 167.50.

Methyl 3-Methyl-5-phenyl-5-(trifluoromethyl)-1,2,4-trioxolane-3-carboxylate (12e): an oil (a mixture of two isomers; 3:2), IR (neat) 1760, 1440, 1330, 1080, 950, 710 cm⁻¹; ¹H NMR (major) δ (CCl₄) 1.77 (s, 3 H), 3.50 (s, 3 H), 7.2–7.8 (m, 5 H); ¹³C NMR (major) δ 17.34, 52.80, 104.68 (q, J = 33 Hz), 106.59, 121.42 (q, J = 288 Hz), 126.71–130.58 (6 C), 166.78; ¹H (minor) NMR δ 1.57 (s, 3 H), 3.77 (s, 3 H), 7.2–7.8 (m, 5 H); ¹³C NMR (minor) δ 19.37, 53.07, 104.71 (q, J = 33 Hz), 107.26, 120.75 (q, J = 288 Hz), 126.71–130.58 (6 C), 167.42. Anal. Calcd for C₁₂H₁₁F₃O₅: C, 49.32; H, 3.80. Found: C, 49.16; H, 3.74.

Ozonolysis of 1a,b in the Presence of an Imine. Ozonolysis of 1a in the presence of diphenylmethyleneaniline (13a) is representative. A mixture of 1a (232 mg, 2 mmol) and 13a (mg, 1 mmol) in CH₂Cl₂ (15 mL) was treated with 2 mmol of ozone at –70 °C. After evaporation of the solvent, the crude products were triturated with methanol to give methyl 3,3,4-triphenyl-dioxazolidine-5-carboxylate (14a): mp 125–129 °C (from ethyl acetate–hexane); ¹H NMR δ 3.87 (s, 3 H), 5.88 (s, 1 H), 7.2–7.8 (m, 15 H); IR (KBr) 3060, 1755, 1602, 1502, 1450, 1358, 1205, 1175, 1042, 955, 748, 692 cm⁻¹. Anal. Calcd for C₂₂H₁₉NO₄: C, 73.12; H, 5.30; N, 3.88. Found: C, 72.77; H, 5.38; N, 3.89.

Methyl 3,3-diphenyl-4-(p-tolyl)-1,2,4-dioxazolidine-5-carboxylate (14b): mp 108–111 °C (from ethyl acetate–hexane); ¹H NMR (CDCl₃) δ 2.19 (s, 3 H), 3.83 (s, 3 H), 5.86 (s, 1 H), 6.42 (d, J = 8 Hz, 2 H), 6.86 (d, J = 8 Hz, 2 H), 7.2–7.8 (m, 10 H); ¹³C NMR (CDCl₃) δ 20.36, 52.85, 89.81, 101.64, 116.65, 127.85, 128.25, 128.63, 128.74, 129.47, 129.54, 129.73, 129.93, 136.63, 138.12, 139.96, 167.99; IR (KBr) 1758, 1520, 1445, 1358, 1205, 755, 698 cm⁻¹. Anal. Calcd for C₂₃H₂₁NO₄: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.61; H, 5.64; N, 3.74.

Methyl 3,3-diphenyl-4,5-dimethyl-1,2,4-dioxazolidine-5-carboxylate (14c): an oil; ¹H NMR δ 1.48 (s, 3 H), 2.38 (s, 3 H), 3.73 (s, 3 H), 7.3–7.7 (m, 10 H); ¹³C NMR δ 18.62, 32.53, 52.13, 96.02, 101.40, 127.61–140.48 (12 C), 170.88; IR (neat) 1740, 1440, 1150, 750, 700 cm⁻¹. Anal. Calcd for C₁₈H₁₉NO₄: C, 68.99; H, 6.12; N, 4.47. Found: C, 68.99; H, 6.07; N, 4.29.

Ozonolysis of 1a,b in the Presence of a Nitrone. Ozonolysis of 1a in the presence of N-methyl-α,α-diphenylnitrone (15e) is representative. The reaction of a mixture of 1a (232 mg, 2 mmol) and 15e (283 mg, 1 mmol) with 2 mmol of ozone was conducted in CH₂Cl₂ at –70 °C. After evaporation of the solvent, the crude products were triturated with methanol to give methyl 5-methyl-6,6-diphenyl-5,6-dihydro-1,2,4,5-trioxazine-3-carboxylate (16e): mp 84–86 °C (from methanol); ¹H NMR (CDCl₃) δ 2.84 (s, 3 H), 3.73 (s, 3 H), 6.31 (s, 1 H), 7.2–7.7 (m, 10 H); IR (KBr) 2960, 1759, 1495, 1452, 1434, 1362, 1241, 1210, 1178, 1098, 1055, 1025, 988, 961, 920, 909, 855, 781, 751, 699, 635, 579 cm⁻¹. Anal. Calcd for C₁₇H₁₇NO₅: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.38; H, 5.38; N, 4.43.

Methyl 5,6-Diphenyl-5,6-dihydro-1,2,4,5-trioxazine-3-carboxylate (16a). The ¹H NMR spectrum of the crude products showed the formation of two isomeric forms of 16a (the ratio = 57:43): δ (minor) 3.91 (s, 3 H), 6.08 (s, 1 H), 6.47 (s, 1 H), 7.13 (s, 5 H), 7.26 (s, 5 H). However, column chromatography on silica gel resulted in the isolation of only the major isomer of 16a: mp 72–73 °C (from ethanol–hexane); ¹H NMR (CCl₄) δ 3.80 (s, 3 H), 5.94 (s, 1 H), 6.33 (s, 1 H), 7.09 (s, 5 H), 7.26 (s, 5 H); IR (KBr) 3040, 2955, 1762, 1492, 1440, 1216, 1078, 1052, 1000, 751, 732, 698 cm⁻¹. Anal. Calcd for C₁₆H₁₅NO₅: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.81; H, 5.04; N, 4.61.

Methyl 5-Benzyl-6-phenyl-5,6-dihydro-1,2,4,5-trioxazine-3-carboxylate (16b). The ¹H NMR spectrum of the crude products showed the presence of two isomeric forms of 16b (the ratio = 2:1; δ 6.24 and 6.10). By column chromatography on silica gel, however, only the major isomer was isolated in a pure state: mp 90–92 °C (from ethanol–hexane); ¹H NMR δ 3.76 (s, 3 H), 3.82 (s, 2 H), 5.79 (s, 1 H), 6.24 (s, 1 H), 7.2–7.6 (m, 10 H);

IR (KBr) 3040, 2955, 2892, 1761, 1494, 1453, 1442, 1338, 1310, 1280, 1078, 1020, 998, 842, 759, 734, 718, 696 cm⁻¹. Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.74; H, 5.43; N, 4.43.

In the ¹H NMR spectrum the methylene hydrogens in the benzyl-substituted trioxazine 16b was expected to appear as AB multiplets. Inconsistent with this expectation, they were observed as a singlet. The same trend was observed for 16f, 16i, and the major isomer of 16l.

Methyl 5-benzyl-6-heptyl-5,6-dihydro-1,2,4,5-trioxazine-3-carboxylate (16c): an oil; ¹H NMR (CCl₄) δ 0.7–2.4 (m, 15 H), 3.62 (s, 3 H), 3.76 (d, J = 14.2 Hz, 1 H), 4.08 d, J = 14.2 Hz, 1 H), 4..7–4.9 (m, 1 H), 5.79 (s, 1 H), 7.0–7.4 (m, 5 H); IR (neat) 2940, 2860, 1768, 1442, 1385, 1332, 1279, 1220, 1078, 1025, 838, 776, 732, 699 cm⁻¹. Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 64.00; H, 8.08; N, 4.31.

Methyl 5,6,6-triphenyl-5,6-dihydro-1,2,4,5-trioxazine-3-carboxylate (16d): mp 76–78 °C (from ethyl acetate–hexane); ¹H NMR δ 3.80 (s, 3 H), 6.13 (br s, 1 H), 7.0–7.9 (m, 15 H); ¹³C NMR δ 52.79, 88.10, 93.07, 127.95–137.38 (18 C), 165.64; IR (KBr) 3050, 2950, 1592, 1493, 1442, 1222, 1055, 748, 692 cm⁻¹. Anal. Calcd for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.07; N, 3.71. Found: C, 68.79; H, 5.05; N, 3.73.

Methyl 3-methyl-5-benzyl-6-phenyl-5,6-dihydro-1,2,4,5-trioxazine-3-carboxylate (16f): mp 126–127 °C; ¹H NMR δ (CCl₄) 1.40 (3 H, s), 3.68 (s, 2 H), 3.72 (s, 3 H), 5.57 (s, 1 H), 7.2–7.7 (m, 10 H); ¹³C NMR δ 19.83, 53.25, 56.62, 100.16, 104.80, 127.43–136.24 (12 C), 166.22; IR (KBr) 1750, 1440, 1290, 1140, 740, 690 cm⁻¹. Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.63; H, 5.83; N, 4.25. Found: C, 65.91; H, 5.80; N, 4.16.

Methyl 3-methyl-5-benzyl-6-heptyl-5,6-dihydro-1,2,4,5-trioxazine-3-carboxylate (16g): mp 66.5–68 °C; ¹H NMR δ (CCl₄) 0.7–1.9 (m, 18 H), 3.73 (s, 3 H), 3.74 (d, J = 14 Hz, 1 H), 4.08 (d, J = 14 Hz, 1 H), 4.5–4.9 (m, 1 H), 7.3–7.8 (m, 5 H); ¹³C NMR δ 14.05, 20.64, 22.58, 23.67, 24.66, 29.10, 29.20, 31.70, 52.42, 56.66, 95.23, 104.87, 127.63, 128.21, 129.02, 135.07, 168.94; IR (KBr) 1760, 1440, 1290 cm⁻¹. Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.92; H, 8.33; N, 3.99. Found: C, 64.71; H, 8.30; N, 3.94.

Methyl 3,5-dimethyl-6,6-diphenyl-5,6-dihydro-1,2,4,5-trioxazine-3-carboxylate (16h): an oil; ¹H NMR δ 1.33 (s, 3 H), 2.77 (s, 3 H), 3.86 (s, 3 H), 7.2–7.6 (m, 10 H); ¹³C NMR δ 20.48, 39.59, 52.50, 100.31, 104.24, 127.45–137.45 (12 C), 169.74; IR (neat) 1760, 1450, 1280, 1130, 760, 700 cm⁻¹.

Ozonolysis of Methyl 3-Methoxyacrylate in the Presence of Benzaldehyde (5j) and N-Benzyl-α-phenylnitrone (15b). A mixture of 1a (233 mg, 2 mmol), 5j (106 mg, 1 mmol), and 15b (211 mg, 1 mmol) in CH₂Cl₂ (15 mL) was treated with 2 mmol of ozone at –70 °C. After evaporation of the solvent, the crude products were separated by column chromatography on silica gel. The first fraction (elution with benzene) gave 5j (50 mg). From the second fraction (elution with ether–benzene (2:98)) was obtained 16b (120 mg, 38%).

Ozonolysis of 1d–i in the Presence of a Nitrone. The reaction of 4-methoxy-3-buten-2-one (1d) in the presence of α,α,N-triphenylnitrone (15d) is representative. A mixture of 1d (200 mg, 2 mmol) and 15d (273 mg, 1 mmol) in CH₂Cl₂ (15 mL) was treated with 2 mmol of ozone at –70 °C. After evaporation of the solvent, the crude products were triturated with methanol to give 3-acetyl-5,6,6-triphenyl-5,6-dihydro-1,2,4,5-trioxazine (16k) (235 mg, 65%): mp 73–75 °C (from ethyl acetate–hexane); IR (KBr) 3065, 1743, 1495, 1455, 1193, 1072, 965, 695 cm⁻¹. Anal. Calcd for $C_{22}H_{19}NO_4$: C, 73.11; H, 5.30; N, 3.88. Found: C, 72.95; H, 5.21; N, 3.76.

3-Acetyl-5-benzyl-6-phenyl-5,6-dihydro-1,2,4,5-trioxazine (16i). Two isomers (the ratio = 3:2) were separated by column chromatography on silica gel (elution with ether–benzene (1:50)). The first fraction contained the minor isomer 16i: an oil; ¹H NMR (CCl₄) δ 2.07 (s, 3 H), 3.73 (s, 2 H), 5.63 (s, 1 H), 5.69 (s, 1 H), 7.2–7.6 (m, 10 H); IR (neat) 3050, 2900, 1745, 1090, 1015, 948, 760, 700 cm⁻¹. Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.05; H, 5.85; N, 4.79. From the second fraction was obtained the major isomer 16i: mp 84–85 °C (from ethanol–hexane); ¹H NMR δ 2.06 (s, 3 H), 3.72 (s, 2 H), 5.44 (s, 1 H), 5.83 (s, 1 H), 7.2–7.5 (m, 10 H); IR (KBr) 3050, 2920, 1735, 1081, 1070, 1032, 1018, 966, 763, 755, 702 cm⁻¹. Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.27; H, 5.79; N, 4.70.

3-Acetyl-5-benzyl-6-heptyl-5,6-dihydro-1,2,4,5-trioxazine (16j): an oil; ¹H NMR (CCl₄) δ 0.8–2.4 (m, 15 H), 2.03 (s, 3 H), 3.84 (d, J = 14.1 Hz, 1 H), 4.15 (d, J = 14.1 Hz, 1 H), 4.8–4.9 (m, 1 H), 5.65 (s, 1 H), 7.2–7.4 (m, 5 H); IR (neat) 2935, 2855, 1743, 1457, 1360, 1083, 955, 733, 698 cm⁻¹.

3-Acetyl-3-methyl-5-benzyl-6-phenyl-5,6-dihydro-1,2,4,5-trioxazine (16l). Ozonolysis of 1e in the presence of 15b, followed by column chromatography on silica gel, gave two isomeric forms of 16l. The isomer of 16l which eluted first (27% yield) (ether–benzene (1:99)) had the following properties: mp 59–61 °C; ¹H NMR δ 1.87 (s, 3 H), 2.15 (s, 3 H), 3.52 (d, J = 14 Hz, 1 H), 3.84 (d, J = 14 Hz, 1 H), 5.55 (s, 1 H), 7.2–7.7 (m, 10 H); IR (KBr) 1730, 1350, 1160, 1100, 1010, 755, 735, 690 cm⁻¹. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.12; N, 4.47. Found: C, 68.89; H, 6.14; N, 4.58. From the second fraction (ether–benzene (3:97)) was obtained the isomeric 16l (29% yield): mp 90–92 °C; ¹H NMR δ 1.28 (s, 3 H), 2.07 (s, 3 H), 3.67 (s, 2 H), 5.57 (s, 1 H), 7.2–8.0 (m, 10 H); IR (KBr) 1740, 1460, 1380, 1160, 1120, 1050, 940, 750, 700 cm⁻¹. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.12; N, 4.47. Found: C, 68.52; H, 6.15; N, 4.55.

3-Acetyl-3-methyl-5-benzyl-6-heptyl-5,6-dihydro-1,2,4,5--trioxazine (16m): an oil; ¹H NMR δ 0.9–1.7 (m, 18 H), 1.93 (s, 3 H), 3.76 (d, J = 14 Hz, 1 H), 4.06 (d, J = 14 Hz, 1 H), 4.8–4.9 (m, 1 H), 7.2–7.4 (m, 5 H); ¹³C NMR δ 13.99, 19.69, 22.50, 23.54, 24.75, 28.87, 29.32, 29.51, 31.60, 50.89, 98.35, 107.57, 127.60, 128.12, 128.35, 129.70, 204.39; IR (neat) 1730, 1450, 1350, 1150, 1110, 730, 690 cm⁻¹.

Ethyl (3-methyl-5-benzyl-6-heptyl-5,6-dihydro-1,2,4,5-trioxazin-3-yl)-5'-oxo-5'-pentanoate (16n): an oil; ¹H NMR δ 0.6–2.5 (m, 27 H), 3.73 (d, J = 14 Hz, 1 H), 4.07 (d, J = 14 Hz, 1 H), 4.12 (q, J = 7 Hz, 2 H), 4.6–4.9 (m, 1 H), 7.3–7.5 (m, 5 H); ¹³C NMR δ 13.95, 14.14, 18.55, 19.92, 22.47, 23.54, 28.83, 29.30, 29.47, 31.58, 33.19, 35.63, 56.82, 60.13, 98.21, 107.48, 127.59–129.76 (6 C), 172.98, 205.56.

3-Heptyl-5-benzyl-6-methoxy-5,6-dihydro-1,2,4,5-trioxazine (16o): To a solution of vinyl ether 1i (1.5 mmol) and nitrone 15c (1 mmol) in CH₂Cl₂ was passed a slow stream of ozone at 0 °C. After evaporation of the solvent, the products were separated by column chromatography on silica gel. Elution with ether–hexane (2:98) gave 16o: an oil; ¹H NMR (CCl₄) δ 0.7–1.9 (m, 15 H), 3.41 (s, 3 H), 3.81 (d, J = 14 Hz, 1 H), 4.15 (d, J = 14 Hz, 1 H), 4.3–4.7 (m, 1 H), 5.77 (s, 1 H), 7.2–7.6 (m, 5 H). Anal. Calcd for $C_{17}H_{27}NO_4$: C, 66.02; H, 8.74; N, 4.53. Found: C, 66.15; H, 8.75; N, 4.48.