OZONOLYSIS OF SUBSTITUTED ISOXAZOLES†

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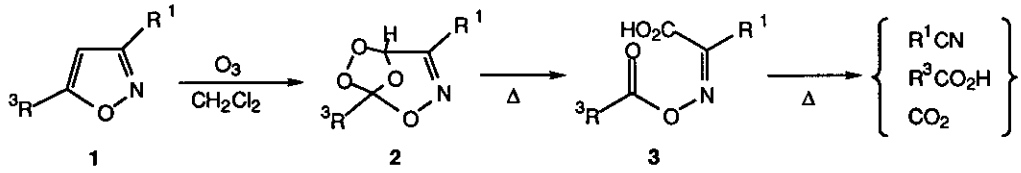
Abstract - The ozonolysis of substituted isoxazoles was investigated. The ozonolysis rates and the products were dependent on the site of the substituent group on isoxazole ring. The reaction mechanism of the ozonolysis of isoxazoles was also proposed.

We have reported the products and the reaction mechanism of the ozonolysis of five-membered heterocycles such as pyrroles, furans, pyrazoles, and oxazoles.[1] We also achieved the new peptide synthesis using the ozonolysis of oxazole derivatives which acted as both protection and activation of the carboxylic groups of an amino acid.[2]

Among various kinds of heterocycles, few papers concerning to the ozonolysis of isoxazoles have appeared in the literature.[3] As one of the typical heterocycles, the ozonolysis of isoxazoles should be of much interest as the useful functionalization reaction.

When 3,5-diphenylisoxazole (**1a**) was treated with ozone in CH_2Cl_2 at -78°C, ozone attacked at C4-C5 bond of isoxazole ring to give the corresponding ozonide (2,5-diphenyl-3-aza-4,6,7,8-tetraoxa-bicyclo[3,2,1]-2-octene, **2a**). Isolated **2a** was characterized by iodometric titration, ^{13}C-nmr peak at δ 117.2 ppm of C5, no carbonyl absorption in ir spectrum, and elemental analysis. Under the thermal conditions, ozonide (**2a**) was decomposed to give benzonitrile, benzoic acid and carbon dioxide (eq. 1) *via* intermediate (**3a**), which was identified by comparison with the authentic

† This paper is dedicated to Prof. Alan R. Katritzky on the occasion of his 65th birthday for his brilliant achievement in the field of heterocyclic chemistry.



1 2 3

$1a \rightarrow 2a$ $k_{-78} = 5.1 \times 10^{-3}\ M^{-1}s^{-1}$

$2a \rightarrow 3a$ $k_{66} = 8.0 \times 10^{-4}\ s^{-1}$

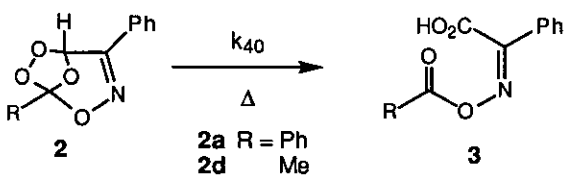
dec.of **3a** $k_{66} = 7.9 \times 10^{-5}\ s^{-1}$

Table 1. Ozonolysis of **1**

	R^1	R^3	yield (%)	
			R^1CN	R^3CO_2H
1a	Ph	Ph	96	80
1b	Me	Ph	–	50
1c	Me	Tol	–	64
1d	Ph	Me	71	–
1e	Tol	Me	79	–
1f	Tol	Ph	82	100
1g	*t*-Bu	Ph	–	87
1i	Ph	H	76	–
1j	Tol	H	78	–
1l	H	Ph	–	81
1m	H	Tol	–	59

sample.[4] Evolution of carbon dioxide was detected by aqueous $Ba(OH)_2$. Similarly various 4-unsubstituted isoxazoles gave nitriles and carboxylic acids in good yields (Table 1). In some cases, the isolation of ozonides (**2**) was succeeded even at room temperature. Reaction rate constants at each step of this reaction are evaluated with the kinetic parameters of **2a** to **3a**; E_a = 20 kcal mol^{-1}, $\Delta S^{\ddagger}_{27}$ = -15 cal $mol^{-1}K^{-1}$, $\Delta G^{\ddagger}_{27}$ = 24 kcal mol^{-1}.

Criegee *et al.* previously reported the solvent effect of the thermal decomposition of the ozonides which had at least one hydrogen atom on the trioxirane ring.[5] The thermal decomposition of **2a** and **2d** was examined in various solvents. Table 2 represents the remarkable solvent effect which gives good agreement with Criegee's suggestion.



2 **3**

2a R = Ph
2d Me

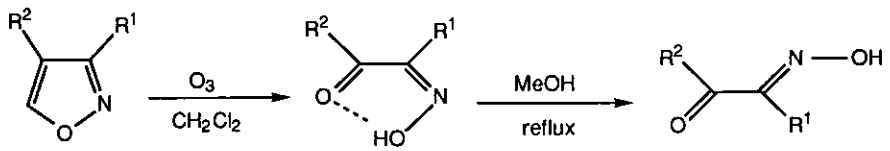
Table 2. Solvent Effect of Decomposition of Ozonides (**2a** and **2d**)

$k_{40} \times 10^4 (s^{-1})$	**2a**	**2d**	E_T*
Benzene	0.02	~0	34.5
THF	0.72	0.12	37.4
MeCN	2.1	1.2	46.0
MeOH	>8	6.1	55.5

* ref 6

On the contrary, 4-substituted isoxazoles reacted with ozone in a different manner. 3,4-Disubstituted isoxazoles (**4**) were ozonolyzed to give α-diketone monoxime (*s-cis*) (**5**) which isomerized to stable *s-trans* isomer (**6**) at reflux in MeOH (Table 3). The shift of the ir carbonyl absorption from 1771-1763 cm^{-1} to 1677-1660 cm^{-1} supported the formation of **6** in good agreement with the Kohler's results.[6]

When 4,5-diphenylisoxazole (**7a**) was treated with ozone followed by Me_2S, benzoyl cyanide and benzoic acid were formed *via* unstable intermediate **8a** (Table 4). Similarly **7b** and **7c** gave the corresponding acyl cyanides and carboxylic acids.

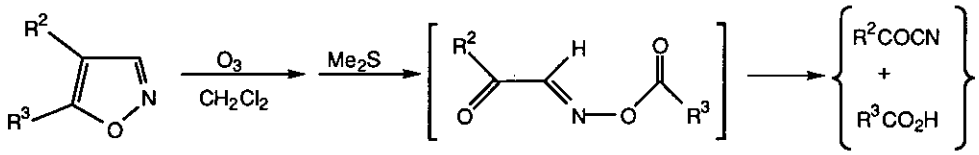


4 **5** **6**

Ir 1771 - 1763 cm^{-1} Ir 1677 - 1660 cm^{-1}

Table 3. Ozonolysis of 4

	R^1	R^2	yield of **6**(%)
4a	Ph	Ph	48
4b	Ph	Me	31
4c	Me	Ph	31
4d	H	Ph	24



7 **8**

Table 4. Ozonolysis of 7

			yield (%)	
	R^2	R^3	R^2COCN	R^3CO_2H
7a	Ph	Ph	51	87
7b	Ph	Tol	69	61
7c	Me	Ph	—	46

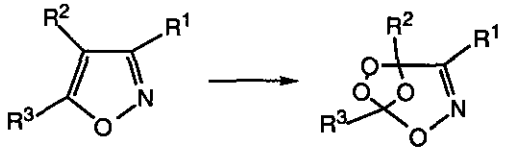
Finally the reactivity of various isoxazoles toward ozone was compared by the competitive reactions summarized in Table 5. The ozonolysis was retarded by the introduction of substituent on C5, while it was accelerated by C3 substituent. The electron-donating effect of substituent on C5 was observed in the case of tolyl and methyl substituent. On the contrary, the obvious electronic effect of the substituent on C3 was not observed.

Ozonolysis of various types of isoxazoles is reasonably explained by Scheme 1. The reaction profile of ozonolysis is dependent on the nature of substituents on the isoxazole ring. In conclusion, isoxazoles easily react with ozone to form ozonides, which are thermally decomposed in polar solvent without the aid of oxidative/reductive post-treatment.

Table 5. Relative Reaction Rate of Ozonolysis of Various Types of Isoxazoles

	R^1	R^2	R^3	$k_{-78} \times 10^2$ $M^{-1} s^{-1}$
1a	Ph	H	Ph	0.51
1b	Me	H	Ph	0.96
1c	Me	H	Tol	1.3
1d	Ph	H	Me	3.2
1e	Tol	H	Me	0.98
1f	Tol	H	Ph	0.43
1g	*t*-Bu	H	Ph	0.52
1h	*t*-Bu	H	*t*-Bu	0.88
1i	Ph	H	H	2.4
1j	Tol	H	H	1.5
1k	*t*-Bu	H	H	3.1
1l	H	H	Ph	0.32
1m	H	H	Tol	0.53
1n	H	H	Me	1.7

	R^1	R^2	R^3	$k_{-78} \times 10^2$ $M^{-1} s^{-1}$
4a	Ph	Ph	H	7.2
4b	Ph	Me	H	9.3
4c	Me	Ph	H	14
4d	H	Ph	H	18
7a	H	Ph	Ph	0.30
7b	H	Ph	Tol	0.70
7c	H	Me	Ph	1.0

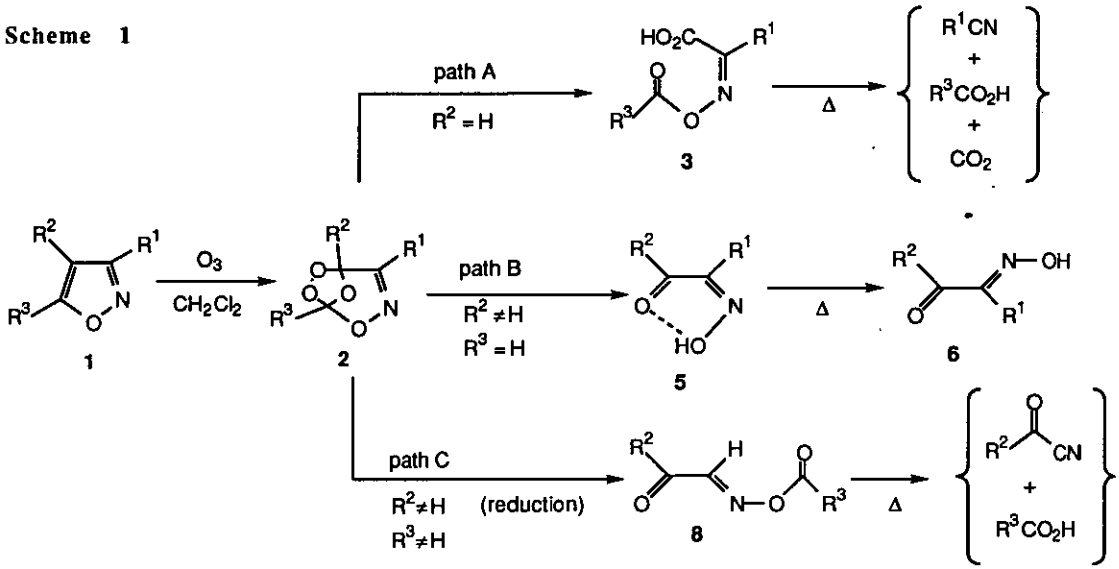


EXPERIMENTAL

Melting points were measured on a Yanagimoto Melting Point Apparatus, and uncorrected. Ir spectra were measured on a Shimadzu IR-460 spectrophotometer. ^{1}H-Nmr and ^{13}C-nmr spectra were recorded using JEOL JNM-EX270 (270 MHz) spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a Shimadzu QP-2000 spectrometer. Preperative

hplc was performed using JAI-LC20. Elemental analyses were performed by Perkin-Elmer Model 240 elemental analyzer.

Scheme 1



Isoxazoles (**1a-e**) were prepared by the method of Claisen[7] and the isomerization reaction through isoxazolium salts.[8] Isoxazoles (**1l-n** and **7a-c**) were synthesized from hydroxylamine and α-formylketones,[9] and **4c-d** were made according to Adembri's[10] and Arnold's[11] method. Compounds (**1f-g, 1i-k, 4a** and **4b**) were prepared by 1,3-dipolar cycloaddition of nitrile oxide with the corresponding alkynes and enamines.[12]

Ozonolysis of 1

Isoxazole (**1**) (1.0 mmol) was dissolved in CH_2Cl_2 (20 ml) and ozone-oxygen stream was bubbled through the solution at -78 °C (at -15 ° C in the cases of **1a-b, 1l-m**, and **7a-c**). The disappearance of isoxazole was monitored by hplc, and the solution was allowed to warm to room temperature with bubbling nitrogen gas to remove excess ozone. The solvent was removed under reduced pressure in cold water bath. All ozonides (**2**) were purified by preparative hplc, and were solidified after removal of solvent ($CHCl_3$). For the isolation of **3**, the crude ozonolysate from **1** was refluxed in THF (10 ml). The reaction was monitored by hplc. After removal of the solvent, the product was recrystallized from benzene - hexane - ethyl acetate mixture. **3a** (yield 22%) and **3i**

(yield 22%) were identified with authentic samples[4] by comparison of ir, ^{1}H and ^{13}C spectra, and retention time in hplc.

3,5-Diphenylisoxazole-ozonide (2a) : mp 135-140 °C; ir (KBr) 3080 (w), 3040 (w), 1750-1690 (broad, w), 1600 (w), 1450 (w) cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 6.46 (s, 1H), 7.35-8.13 (m, 10H); ^{13}C-nmr ($CDCl_3$) δ 92.9 (CH), 117.2 (C), 125.8 (CH), 126.8 (CH), 128.5 (C), 128.5 (C), 128.6 (CH), 129.2 (CH), 131.2 (CH), 131.4 (CH), 154.5 (C). Anal. Calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.86; H, 3.97; N, 4.93.

5-Methyl-3-phenylisoxazole-ozonide (2d) : mp 59 °C; ir (KBr) 3450 (broad, w), 3040 (m), 1780-1590 (broad, w) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 1.94 (s, 3H), 6.24 (s, 1H), 7.41-7.62 (m, 5H); ^{13}C-nmr ($CDCl_3$) δ 17.8, 92.4, 118.5, 126.4, 129.5, 130.8, 131.4, 154.5. Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.84; H, 4.40; N, 6.70.

5-Methyl-3-*p*-methylphenylisoxazole-ozonide (2e) : mp 75-80 °C; ^{1}H-nmr ($CDCl_3$) δ 1.89 (s, 3H), 2.32 (s, 3H), 6.26 (s, 1H), 7.16-7.47 (m, 4H); ^{13}C-nmr ($CDCl_3$) δ 17.3, 21.3, 92.0, 118.1, 125.6, 127.5, 129.8, 141.5, 154.1; Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 60.50; H, 5.13; N, 6.20.

3-*p*-Methylphenyl-5-phenylisoxazole-ozonide (2f) : mp 152-153 °C; ir (KBr) 3430 (broad, w), 3000 (w), 1600 (w), 1440(w), 1328(m), 1100(m), 974(m); ^{1}H-nmr ($CDCl_3$) δ 2.40 (s, 3H), 6.44 (s, 1H), 7.25-7.81 (m, 9H); ^{13}C-nmr ($CDCl_3$) δ 21.5, 92.9, 117.2, 125.7, 126.8, 127.6, 128.6, 129.9, 131.3, 141.7, 154.4; Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.53; H, 4.66; N, 4.88.

3-*tert*-Butyl-5-phenylisoxazole-ozonide (2g) : mp 86-92 °C; ir (KBr) 3430 (broad, m), 2980 (s), 1728 (broad, w), 1440 (s), 1370 (s), 1330 (s); ^{1}H-nmr ($CDCl_3$) δ 1.25 (s, 9H), 6.06 (s, 1H), 7.42-7.75 (m, 5H); ^{13}C-nmr ($CDCl_3$) δ 27.7 (CH_3), 36.1 (C), 91.1 (CH), 116.7 (C), 126.7 (CH), 128.6 (CH), 128.8 (C), 131.2 (CH), 162.7 (C); Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.13; H, 6.03; N, 5.40.

3-Phenylisoxazole-ozonide (2i) : ^{1}H-Nmr ($CDCl_3$) δ 6.28 (d, J = 1 Hz, 1H), 6.80 (d, J = 1 Hz, 1H), 7.40-7.62 (m, 5H); ^{13}C-nmr ($CDCl_3$) δ 89.7, 108.9, 125.6, 129.2, 130.3, 131.3, 155.2; Anal. Calcd for $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25. Found: C, 56.18; H, 3.86; N, 7.34.

Benzoyloximino-*p*-methylphenylacetic acid (3f) : yield 51%; ir (KBr) 3105 (broad, s), 1744 (s), 1715 (s), 1597 (m), 1446 (m), 1321 (m), 1268 (s), 1204 (s), 1085 (s), 1010 (m) cm^{-1} ; ^{1}H-nmr

(DMSO-d_6) δ 2.49 (s, 3H), 7.61-8.13 (m, 9H); ^{13}C-nmr (DMSO-d_6) δ 125.5, 128.0, 128.5, 128.8, 129.1, 129.4, 129.4, 130.1, 130.3, 143.0, 160.0, 162.6, 163.6; Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.87; H, 4.64; N, 4.97.

Ozonolysis of 4

Isoxazole (**4a**) (1.0 mmol) was ozonolyzed by the method described above and the unstable intermediate (**5a**) was purified by the preparative hplc; yield 36 %; ir (CH_2Cl_2) 3060 (w), 1766 (s), 1446 (w), 1127 (m), 908 (s); ^{1}H-nmr ($CDCl_3$) δ 7.17-7.62 (m), 8.44-8.60 (m); ^{13}C-nmr ($CDCl_3$) δ 127.9 (CH), 128.1 (CH), 128.3 (C), 128.4 (CH), 128.6 (CH), 129.1 (C), 129.2 (CH), 130.4 (CH), 132.3 (CH), 161.9 (C); and isomerized to **6a** by refluxing in methanol (10 ml) for 12 h. The product was identified by the comparison with the authentic sample.[6,13]

Ozonolysis of 7

Isoxazole (**7a**) (1.0 mmol) was ozonolyzed and excess ozone was removed by nitrogen bubbling. Dimethyl sulfide (7 mmol) was added, and the solution was allowed to warm to room temperature with stirring for 12 h. The solvent was removed to give crude **8a**; yield 30 %; ir (CH_2Cl_2) 3055 (w), 1756 (s), 1663 (m), 1596 (m), 1448 (m), 1234 (s) cm^{-1} ; ^{1}H-nmr ($CDCl_3$) δ 7.46-8.29 (m); ^{13}C-nmr ($CDCl_3$) δ 127.6 (C), 128.5 (CH), 128.8 (CH), 129.7 (CH), 130.6 (CH), 134.1 (CH), 134.4 (CH), 134.7 (C), 153.5 (CH), 163.2 (C), 187.5 (C). The crude **8a** was decomposed by refluxing in THF for 12 h. Yields of the products were measured by hplc.

Reactivity of Isoxazoles with Ozone

The reaction rate was determined by the reaction of **1a** (10 mg) with the saturated solution of ozone in CH_2Cl_2 (10 ml) at -78°C ($[O_3] = 4.22 \times 10^{-2}$ mol/l) in the presence of nitrobenzene (15 mg) as an internal standard, and the reaction products were monitored by hplc. The relative ozonolysis rates were given by the action of the different isoxazole mixture (0.40 mmol each in CH_2Cl_2). After the blue color of ozone was disappeared, unreacted isoxazoles were measured by gc. Kinetic parameters and solvent effects of ozonide (**2a**, **2d** and **3a**) were evaluated by hplc of the solution of **2a** (15-30 mg) at 66°C using diphenyl ether as an internal standard.

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