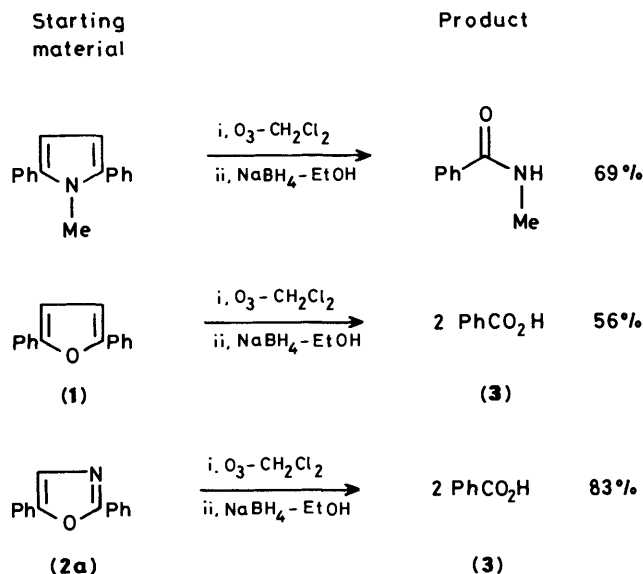# Convenient Synthesis of Mixed Anhydrides by the Ozonolysis of Oxazoles

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The ozonolysis of azoles was investigated, and the products formed *via* a 1,2-addition of ozone were the main ones obtained. In particular, 2,5-disubstituted oxazoles (2) were treated with an excess of an ozone–oxygen stream to give the corresponding acid anhydrides (6) quantitatively. This reaction should be useful for the preparation of the mixed anhydrides (6) in good yield at low temperature.

Recently, we have reported the relative reaction rates and the products of ozonolysis of five-membered heteroaromatics.[1] When five-membered heteroaromatics were treated with a stream of an excess of ozone–oxygen in dichloromethane at −78 °C, followed by treatment with sodium borohydride in ethanol, the main products were those formed *via* a 1,2-addition of ozone. In the case of five-membered heteroaromatics containing a nitrogen atom at the 1-position on the ring, the corresponding amides were obtained in high yields. In contrast, five-membered heteroaromatics having an oxygen atom instead of a nitrogen atom, such as 2,5-diphenylfuran (1) and 2,5-disubstituted oxazoles (2), yielded the corresponding carboxylic acids in the reaction with an excess of ozone–oxygen stream. Although carbon–nitrogen double bonds are generally inactive to the ozonolysis, the corresponding carboxylic acids were obtained from oxazoles (2) in higher yields than from the corresponding furans (1) (Scheme 1). In order to clarify these

Table 1. Ozonolysis[a] and various decompositions of the oxazole (2a)

Entry	Decomposition	Yield (%)	
		$PhCO_2H$ (3a)	$PhCO_2Et$ (4a)
1	On standing	8	
2	EtOH[b]	10	0
3	$NaBH_4$–EtOH[c]	83	0
4	NaOEt–EtOH[d]	116	80
5	5% aq. KOH–EtOH[e]	42	18
6	5% aq. NaOH–EtOH[f]	118	78

| | 88 | 50 |

[a] A stream of O_3–O_2 was bubbled into a solution of (2a) (1 mmol) in dry CH_2Cl_2 (25 ml) at −78 °C. When the reaction mixture became blue, bubbling of O_3 was stopped, and the excess of O_3 in the solution was released by a bubbling stream of N_2. [b] Ethanol (10 ml) was added. [c] Sodium borohydride (4 mmol) in ethanol (10 ml) was added. [d] Sodium ethoxide (2.6 mmol) in ethanol (10 ml) was added. [e] A mixture of potassium hydroxide (4 mmol) in water (4 ml) and ethanol (10 ml) was added. [f] A mixture of sodium hydroxide (4 mmol) in water (3.5 ml) and ethanol (10 ml) was added.

Scheme 1.
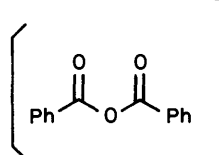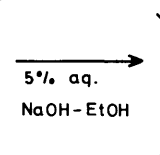
unexpected results, the ozonolysis of 2,5-disubstituted oxazoles (2) was investigated in detail.

Results and Discussion

2,5-Diphenyloxazole (2a) was treated with excess of ozone–oxygen (stream) in dichloromethane at −78 °C, followed by decomposition under the various conditions summarized in Table 1. Benzoic acid (3a) was the sole product, obtained in 83% yield [based on (2a) used], on treatment of the intermediate

with sodium borohydride in ethanol (entry 3), while 2,5-diphenyloxazole (2a), when treated with the excess of ozone–oxygen stream and kept overnight, gave only a trace of benzoic acid (entry 1). When potassium hydroxide or sodium hydroxide in aqueous ethanol was used instead of a reductant, benzoic acid and ethyl benzoate (4a) were obtained. Especially in the case of sodium hydroxide, a mixture of benzoic acid and ethyl benzoate was obtained quantitatively (entry 6). A similar result was obtained on treatment of (2a) with sodium ethoxide in ethanol (entry 4). The quantitative formation of ethyl benzoate and benzoic acid could be interpreted by postulating an attack of ethoxide anion on the ozonolysis intermediate. Benzoic anhydride was implied as this intermediate. Therefore, benzoic anhydride was treated with 5% ethanolic sodium hydroxide under the same conditions, and gave benzoic acid and ethyl benzoate in 88 and 50% yield as determined by gas chromatography. This result supported the assumption that ozonolysis of (2a) gave benzoic anhydride (6a), which was converted into benzoic acid and ethyl benzoate in good yields by the action of ethoxide ion. After compound (2a) was treated with an excess of ozone–oxygen stream, excess of methylamine

as nucleophile was bubbled into the solution, and *N*-methylbenzamide (5a) was obtained in 96% yield. Meanwhile, benzoic anhydride (6a) gave *N*-methylbenzamide in 115% yield on treatment with methylamine. This result also supported the assumption that ozonolysis proceeded *via* the corresponding anhydride (6) (Scheme 2).
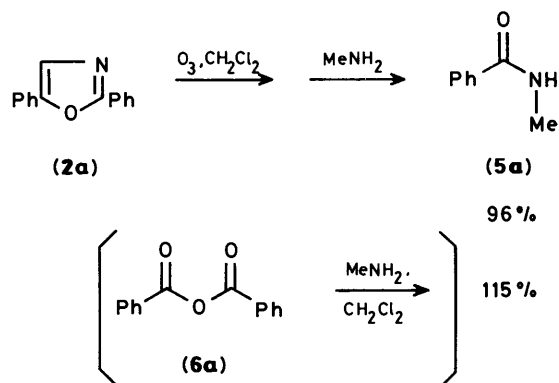

Scheme 2. Ozonolysis and aminolysis of compound (2a)

Similarly, when 2,5-diphenylfuran (1) was treated with ozone in dichloromethane at −78 °C, and decomposed by ethanolic sodium hydroxide, benzoic acid and ethyl benzoate were obtained in 168 and 20% yield, respectively. Previously, White had reported that ozonolysis of 2,5-diphenylfuran (1) in tetrachloro- or dichloro-methane gave benzoic anhydride and/or benzoic acid.[2] Therefore ozonolysis of oxazoles and furans gave the corresponding carboxylic anhydrides.

From these results it was expected that benzoic anhydride (6a) would be obtained quantitatively when 2,5-diphenyloxazole (2a) was treated with an ozone–oxygen stream in the absence of a nucleophile in dichloromethane at −78 °C. Although the mechanism of the ozonolysis of furan and pyrrole has been extensively investigated, ozonolysis of five-membered hetero-aromatics containing two heteroatoms on the ring such as oxazole has rarely been investigated.

The i.r. and [13]C n.m.r. spectra of ozonolysis products of 2,5-diphenyloxazole (2a) were measured in solution. The i.r. spectrum exhibited absorptions at 1 722 and 1 785 cm⁻¹, and the [13]C n.m.r. spectrum exhibited two singlets at δ 162.3 and 129.8 and three doublets at δ 128.8, 130.1, and 134.5, attributable to benzoic anhydride (6a). In addition, the i.r. spectrum exhibited an absorption at 2 266 cm⁻¹, which seemed to be assignable to isocyanic acid (or at any rate a heterocumulene structure). Moreover, from the structure of the substrate oxazole this absorption band could be assigned to isocyanic acid (7). Since (7) reacted with amine to afford the corresponding urea, compound (2a) was treated with ozone and then with *p*-anisidine, and *p*-methoxyphenylurea (8) was obtained quantitatively accompanied by a 45% yield of *N*-benzoyl-*p*-anisidine (5f) (Scheme 3).

From these data, the ozonolysis intermediates were assigned to be benzoic anhydride (6a) and isocyanic acid (7). The spectral data indicated that benzoic anhydride was formed as an intermediate by ozonolysis of 2,5-diphenyloxazole (2a), and that two benzoyl moieties originated from the two phenyl groups at the 2- and 5-position of compound (2a).

In order to investigate the stoicheiometry of the reaction of compound (2a) with ozone, the oxazide was added to dichloromethane which contained a known amount of ozone, and the residual substrate was monitored by gas chromatography. Also, the resulting benzoic acid and ethyl benzoate were monitored after treatment of the reaction mixture with 5%
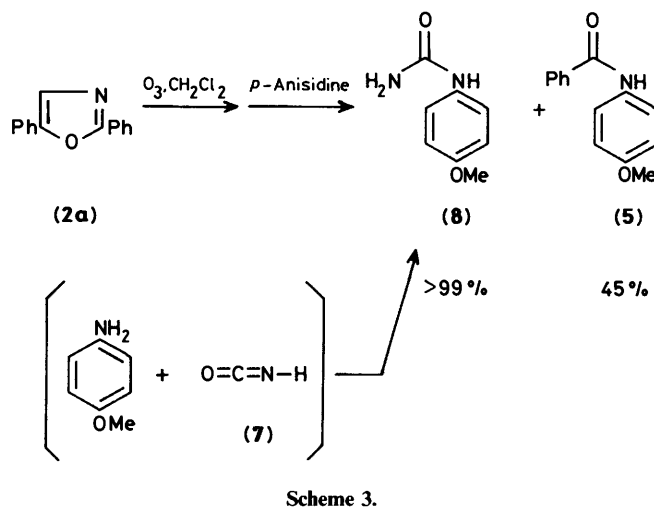
Scheme 3.

ethanolic sodium hydroxide. The molar ratio of ozone to (2a) *vs.* the amounts of residual (2a) and the two products was plotted (Figure 1). From Figure 1, it was apparent that benzoic acid and
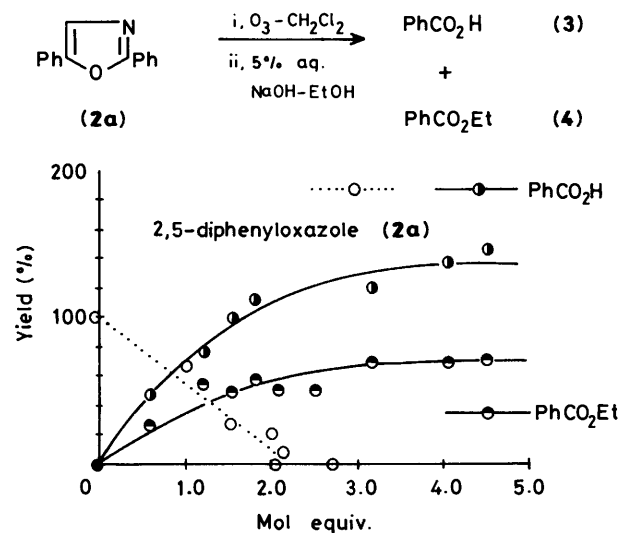

Figure 1. Stoicheiometry of reaction of (2a) with ozone, and yields of products

ethyl benzoate were generally obtained in the same ratio. The starting material consumed 2.0 mol equiv. of ozone, and the sum of yields of these products reached almost 200%. These results indicated that the oxazole (2a) required 2.0 mol equiv. of ozone for complete reaction and that the intermediate gave the products quantitatively by decomposition.

Wibaut and Boon have proposed that in the case of the ozonolysis of compounds containing a carbon–nitrogen double bond, attack on nitrogen by the central atom of ozone is followed by formation of a four-membered ring and breaking of the nitrogen–oxygen single bond.[3] Here, one molecule of ozone attacked the carbon–carbon double bond to afford the ozonide. Then, the central oxygen atom of another molecule of ozone attacked the nitrogen atom at the 3-position of oxazole ring to afford a four-membered ring. This breaking of the N–O bond accelerated the cleavage of ozonide to give benzoic anhydride and isocyanic acid (Scheme 4). This mechanism required two mol equiv. of ozone, but only one mole of ozone in the net reaction. This suggested that the remaining mole of ozone catalysed the ozonolysis of (2a).

Scheme 4.
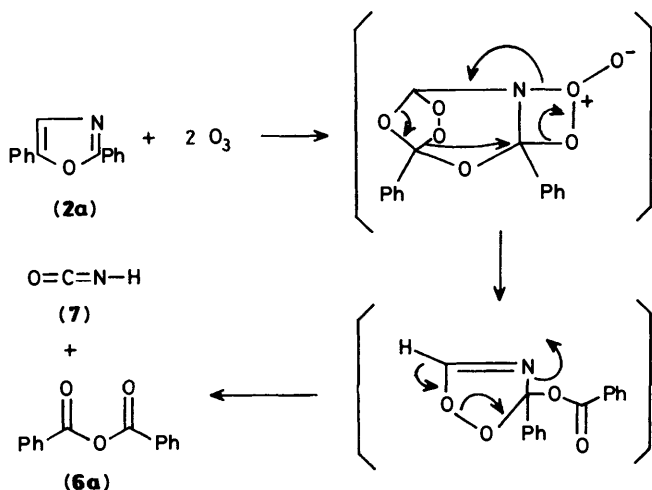
The intermediate, benzoic anhydride (6a), was isolated quantitatively by evaporation of the ozonolysis solution of the oxazole (2a). Hence, the ozonolysis of oxazoles (2) in dichloromethane at $-78\ ^\circ$C would be useful for the preparation of acid anhydrides.

Since the preparation of mixed anhydrides requires complicated reaction conditions, the development of a convenient preparative method for mixed anhydrides seemed to be very significant from the synthetic viewpoint. By introducing different substituents at the 2- and 5-position on the oxazole ring, these oxazoles were expected to give the corresponding mixed anhydrides in good yield. Thus, such oxazoles (2b—f) were synthesized. These compounds were treated with ozone followed by treatment with 5% ethanolic sodium hydroxide or amines. Ozonolysis and decomposition (by 5% ethanolic sodium hydroxide) of these compounds gave the corresponding carboxylic acid and ethyl ester (Table 2). In the case of the ozonolysis of 2-(p-substituted phenyl)-5-phenyloxazoles (2d—f) and treatment with methylamine, the more electron-withdrawing the group bonded at the para position the better was the yield of the corresponding amide (5) (Table 3). When either 2-methyl-5-phenyloxazole (2b) or 5-methyl-2-phenyloxazole (2c) was treated with ozone in dichloromethane and treated with p-anisidine, N-acetyl-p-anisidine (5g) and p-anisylurea (8) were obtained quantitatively. These results suggested the presence of a mixed anhydride in the system.

In order to estimate the reactivity of various oxazoles with ozone at $-78\ ^\circ$C, the relative rates of ozonolysis were determined by measurement of the decrease of the starting material under competitive conditions at $-78\ ^\circ$C in dichloromethane, where the relative reaction rates of these oxazoles were compared with that of (2a). These compounds possessed different substituent groups on the para position of the phenyl group at C-2 of the oxazole ring, and it is well known that compounds having a high value of the Hammett constant σ have higher electron density in the ring. While the Hammett constant should be the most suitable parameter to estimate the double-bond character, a Hammett plot of the ozonolysis of oxazoles (2d—f) gave a straight line with $\rho = -0.33$ (Figure 2).

Mixed anhydrides of aliphatic and aromatic carboxylic acids are known to undergo disproportionation (Scheme 3).[4] Since acid anhydrides are a very important class of reagents, and are usually the preferable reactive acid derivative used for the preparation of amides, esters, and a wide variety of other acid derivatives, the ozonolysis of 2,5-substituted oxazoles (2) in

Table 2. Ozonolysis and decomposition of oxazoles (2)

Starting material			Yield (%)			
	R^1	R^2	(3)	(3′)	(4)	(4′)
(2d)	p-ClC$_6$H$_4$	Ph	23	59	44	20
(2a)	Ph	Ph		59		39
(2e)	p-MeC$_6$H$_4$	Ph	27	26	0	23
(2f)	p-(MeOC$_6$H$_4$	Ph	0	24	0	33

Table 3. Ozonolysis and reaction of oxazoles (2) with methylamine

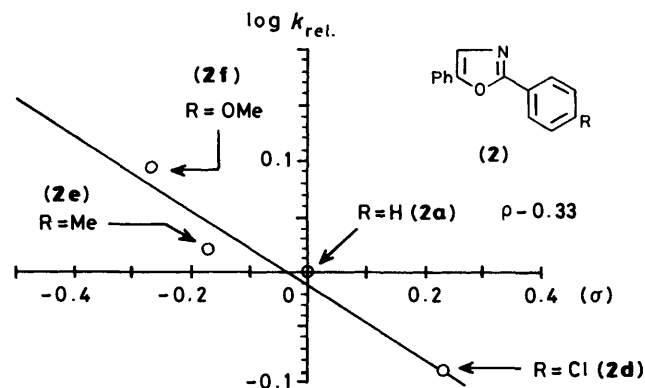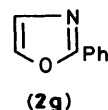| Starting material			Yield (%)	
	R^1	R^2	(5)	(5′)
(2d)	p-ClC$_6$H$_4$	Ph	39	34
(2a)	Ph	Ph		96
(2e)	p-MeC$_6$H$_4$	Ph	19	25
(2f)	p-MeOC$_6$H$_4$	Ph	0	89
(2b)	Me	Ph	MeCONHC$_6$H$_4$OMe-p ($\sim$100%) (g)	
(2c)	Ph	Me	(8) ($\sim$100%)	

Figure 2. Hammett plot of relative reaction rates

dichloromethane was concluded to be an extremely convenient procedure for the preparation of a wide variety of acid anhydrides at lower temperatures (Scheme 5).

For the purpose of formylation of the nucleophile, 2-phenyloxazole (2g) was synthesized and treated according to the above
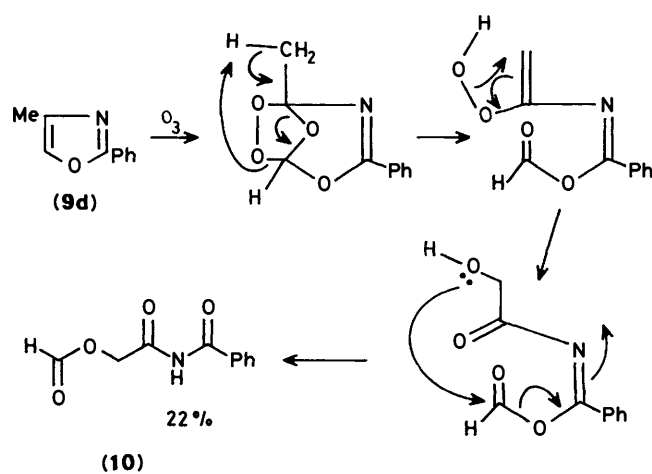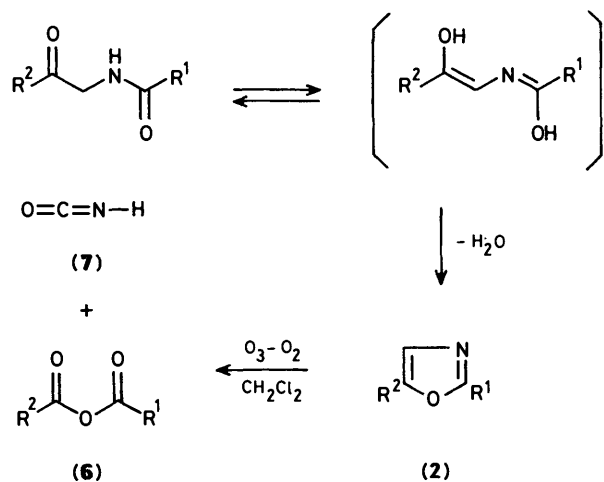

(2g)

Scheme 5.

Scheme 6.

Table 4. Ozonolysis and decomposition of oxazoles (9)

		R^1CO_2H	+	R^1CO_2Et	
		(3)		(4)	
		R^2CO_2H	+	R^2CO_2Et	
		(3')		(4')	

Starting material		Yield (%)			
	R^1	R^2	(3)	(3')	(4)	(4')
(9a)	Ph	Ph	13		27	
(9b)	p-MeC$_6$H$_4$	Ph	24	19	23	34
(9c)	p-MeOC$_6$H$_4$	Ph	0	24	0	33
(9d)	Ph	Me	10	0	17	0

Table 5. Stoicheiometry of reaction of oxazoles with ozone

Compound		Stoicheiometry
	(2g)	0.938
	(9a)	1.565
	(9d)	1.012

method. In the case of p-anisidine as nucleophile, N-benzoyl-p-anisidine (5f) was obtained from (2g) in 59% yield without co-production of formylated products.

Similarly, 2,4-disubstituted oxazoles (9), which were also expected to form formylating reagents by ozonolysis, were synthesized, and the ozonolysis and decomposition of these compounds was attempted in order to produce the corresponding mixed anhydride. Although this type of oxazole was expected to give formylated products, the acid derivatives

originating from the 2- and 4-positional substituent groups were detected without any formylated product as summarized in Table 4.

Ozonolysis and decomposition of oxazoles (9) afforded the corresponding acids and acid esters, and these yields did not indicate any remarkable effect of the para substituent on the phenyl group at C-2 of the oxazole ring. The i.r. and ^{13}C n.m.r. spectra of the intermediate from ozonolysis of 2,4-diphenyloxazole (9a) were measured, but no trace of the corresponding acid anhydride and isocyanic acid was obtained. The stoicheiometry of the ozonolysis was measured and is summarized in Table 5.

In the case of 4-methyl-2-phenyloxazole (9d), no products originating from the methyl group at C-4 of the oxazole ring were detected, and benzoic acid and ethyl benzoate were obtained in low yields. The ^{1}H n.m.r. spectrum of the reaction mixture of (9d) with ozone gave a singlet attributable to the C-4 methyl group, which shifted from δ 2.2 to δ 2.6, and the i.r. spectrum exhibited absorptions at 2 260 and 1 700 cm^{-1}. Here, the intermediate product was isolated without post-treatment. The ^{1}H n.m.r. spectrum of the product exhibited a singlet at δ 8.2, and the ^{13}C n.m.r. spectrum exhibited a doublet at δ 160.0 attributable to the O-formyl group. The methylene group was observed in the ^{1}H n.m.r. spectrum as a singlet at δ 5.3 and in the ^{13}C n.m.r. spectrum as a triplet peak at δ 63.9. Also, peaks characteristic of the benzoyl group appeared at δ 7.4—7.9 in the ^{1}H n.m.r. spectrum. Further, one more carbonyl carbon was assigned in the ^{13}C n.m.r. spectrum and the secondary amide peak was assignable in the i.r. absorption. From these spectral data, the structure of this product was deduced to be (10), which was supported by elemental analysis and mass spectroscopy. Since complete ozonolysis of 4-methyl-2-phenyloxazole (9d) required an equimolar amount of ozone and the intermediate (10) could be isolated, the reaction mechanism could be as shown in Scheme 6.

Although the stoicheiometry of the reaction of 2,5-diphenyloxazole (2a) with ozone was postulated to be 2.0 mol equiv., 2-phenyloxazole (2g) and 2,4-diphenyloxazole (9a) required almost 1.0 and 1.5 mol equiv. of ozone, respectively. This result suggested that the mechanism of ozonolysis of oxazoles (2g) and (9a) was different from that of (2a). Unfortunately, in the case of (2g) and (9a), the reaction mechanism of ozonolysis is still unclear.

Experimental

M.p.s were measured on a Yanagimoto micro melting point apparatus, and are uncorrected. ^{1}H N.m.r. and ^{13}C n.m.r.

spectra were measured on a Hitachi R-24 (60 MHz) spectrometer and JEOL FX-100 (100 MHz) spectrometer for solutions in CDCl₃ with internal SiMe₄ as standard. I.r. spectra were measured on a Jasco IRA-1 infrared spectrophotometer for solutions in chloroform. Gas chromatography was carried out on a Shimadzu GC-4CM gas chromatograph, using a SE-30 (2 m) column. Flash column chromatography was carried out on a column of silica gel (230—400 mesh, Merck). Mass spectra were obtained on a Hitachi M-80 gas chromatograph–mass spectrometer. Elemental analysis was performed on a Perkin-Elmer Model 240 elemental analyser.

Materials.—2,5-Diphenylfuran (**1**) was prepared by Lutz's method.[5] 2-Methyl-5-phenyloxazole (**2b**) and 5-methyl-2-phenyloxazole (**2c**) were prepared by Gabriel's method.[6] 2-(4-Chlorophenyl)-5-phenyloxazole (**2d**), 5-phenyl-2-(*p*-tolyl)-oxazole (**2e**), and 2-(4-methoxyphenyl)-5-phenyloxazole (**2f**) were prepared by Fischer's method.[7] 2,4-Diphenyloxazole (**9a**), 4-phenyl-2-(*p*-tolyl)oxazole (**9b**), and 2-(4-methoxyphenyl)-4-phenyloxazole (**9c**) were prepared by Lewy's method.[8] Methyl-2-phenyloxazole (**9d**) was prepared by Friedman's method.[9] These compounds had physical constants and spectra identical with literature values. 2,5-Diphenyloxazole (**2a**) and benzoic anhydride (**6a**) were commercially available.

Ozonolysis of Oxazoles.—A stream of ozone–oxygen was bubbled into a solution of an oxazole (1 mmol) in dry dichloromethane (25 ml) at −78 °C. When the reaction mixture became blue, ozone flow was stopped, and the excess of ozone in the solution was released by bubbling through nitrogen gas. Post-treatment of the reaction mixture was carried out as indicated in the footnotes in Table 1.

The solution was kept overnight at room temperature, and the products were extracted with dichloromethane under acidic conditions. The organic layer was dried over anhydrous magnesium sulphate, and the solvent was removed under reduced pressure. The residue was dissolved in diethyl ether, and the solution was treated with diazomethane. The products were determined by gas chromatography.

Measurement of the Amount of Ozone in a Saturated Solution.—According to Rubin,[10] a saturated solution of ozone in dichloromethane at −78 °C contains 0.04 mol l⁻¹. This value was checked by iodometric titration, and a saturated solution of ozone was found to contain 4.22 × 10⁻² mol l⁻¹ at 78 °C.

A certain amount of dichloromethane was treated with a stream of ozone–oxygen (bubbled) and was saturated with ozone. Then a solution of the oxazole in dry dichloromethane (5 ml) (with an unreactive standard compound such as ethyl hydrogen carbonate) was added to the dark blue solution which contained a known amount of ozone. The decrease of the starting material was monitored by gas chromatography. Decomposition of the reaction mixture by 5% ethanolic sodium hydroxide gave the corresponding acid and acid ethyl ether, which were determined by gas chromatography.

Measurement of the Spectrum of Ozonolysis Products.—Ozonolysis of oxazoles (**2a**), (**9a**), and (**9d**) was carried out by the above method at −78 °C, then the dichloromethane solution was withdrawn and used for measurements of i.r., ¹H n.m.r., and ¹³C n.m.r. spectra.

Benzoylcarbamoylmethyl Formate (**10**).—A solution of 4-methyl-2-oxazole (**9d**) (2 mmol) in dichloromethane (30 ml) was treated with an excess of ozone–oxygen stream, and the solution was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel with chloroform–acetone–ethanol (100:5:1) as eluant. The white residue was recrystallized from benzene–hexane to yield the title compound (22%), m.p. 148—149 °C (Found: C, 57.8; H, 4.3; N, 6.8. C₁₀H₉NO₄ requires C, 57.97; H, 4.37; N, 6.76%); ν_{max.}(KBr) 3 240 (NH), 1 720 (C=O), and 1 700 cm⁻¹ (C=O); δ_H 5.37 (2 H, s, CH₂), 7.4—7.9 (5 H, m, PhCO), 8.20 (1 H, s, OCHO), and 9.40 (1 H, br s, NH); δ_C 63.9 (t, CH₂), 128.01 (d, ArC), 129.10 (d, ArC), 133.76 (s, ArC), 160.03 (d, OCHO), 165.94 (s, CO), and 170.05 (s, CO); *m/z* 105 (PhCO), 207 (*M*⁺), and 208 (*M* + 1).

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