Synthesis of 1,2,4-Dioxazolidines by the Ozonolysis of Vinyl Ethers in the Presence of Imines. The First [3 + 2] Cycloaddition of Carbonyl Oxide to the Carbon–Nitrogen Double Bond

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Carbonyl oxides, derived from the ozonolysis of vinyl ethers, readily undergo [3 + 2] cycloaddition reactions with imines affording 1,2,4-dioxazolidines in good yield.

Carbonyl oxides are well recognized as key intermediates in the ozonolysis of alkenes.[1] As a result of their 1,3-dipolar character, they undergo [3 + 2] cycloaddition (i) to carbonyl compounds, particularly simple aldehydes and ketones, and in certain circumstances, esters, acid chlorides, *etc.*[2] to give the corresponding ozonides (1,2,4-trioxolanes), and (ii) to electron rich alkenes to give 1,2-dioxolanes.[3] We report herein a new cycloaddition reaction between carbonyl oxides and imines which provides a convenient synthetic route to 1,2,4-dioxazolidines.[4] In competitive reactions, imines are often found to react significantly faster than carbonyl compounds with carbonyl oxides.

A solution of the appropriate vinyl ether (**1**) (2 mmol) and imine (**2**) (2 mmol) in methylene chloride (20 ml) was ozonized at −70 °C. The resulting products were isolated by trituration with methanol, or by rapid chromatography on silica gel. In general, the reactions were clean, only the unreacted imine (**2**) being recovered along with the adduct (**3**) (Table 1). Although the adducts (**3**) could be characterized by elemental analysis and ^{1}H n.m.r. and i.r. spectroscopy, it was important to establish unambiguously the nature of the ring system and consequently the mode of the cycloaddition. An

Table 1. Synthesis of 1,2,4-dioxazolidines.[a]

Vinyl ether	Imine	Dioxazolidine, % yield	Recovered imine, %
(**1a**)	(**2a**)	(**3a**) 78	—
(**1a**)	(**2b**)	(**3b**) 57	13
(**1a**)	(**2d**)	(**3c**) 68	23
(**1b**)	(**2a**)	(**3d**) 80	—
(**1b**)	(**2c**)	(**3e**) 69	—
(**1b**)	(**2d**)	(**3f**) 62	23
(**1b**)	(**2e**)	(**3g**) 81	—
(**1b**)	(**2f**)	(**3h**) 61	32
(**1b**)	(**2g**)	(**3i**) 54	30
(**1b**)	(**2h**)	(**3j**) 69	—
(**1c**)	(**2a**)	(**3k**) 51	30
(**1c**)	(**2c**)	(**3l**) 72	—
(**1c**)	(**2d**)	(**3m**) 59[b]	31
(**1c**)	(**2e**)	(**3n**) 97	—
(**1c**)	(**2f**)	(**3j**) 49	49

[a] The reaction of a 1 : 1 mixture of vinyl ether (**1**) and imine (**2**) with ozone (1 equiv.) in methylene chloride at −70 °C. [b] A mixture of two stereoisomers, the ratio being around 3 : 2.

(4) (2) (3)

(2)
- **a**: $R^3 = R^4 = R^5 = Ph$
- **b**: $R^3 = R^4 = Ph, R^5 = CMe_3$
- **c**: $R^3 = R^4 = Ph, R^5 = H$
- **d**: $R^3 = R^5 = Ph, R^4 = Me$
- **e**: $R^3, R^4 = -(CH_2)_5-, R^5 = Ph$
- **f**: $R^3 = R^5 = Ph, R^4 = H$
- **g**: $R^3 = 4\text{-}ClC_6H_4, R^4 = H, R^5 = Ph$
- **h**: $R^3 = (CH_2)_6Me, R^4 = H, R^5 = Ph$

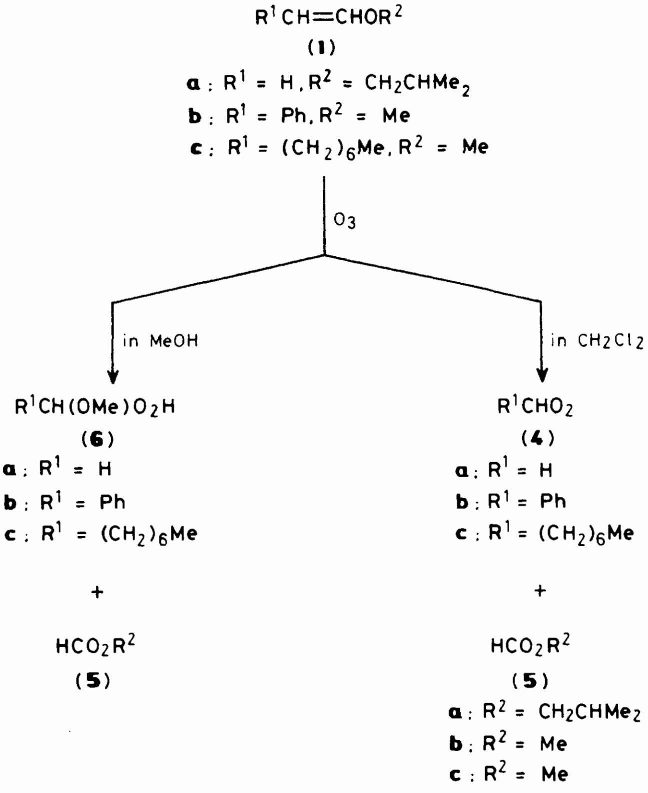
(3)
- **a**: $R^1 = H, R^3 = R^4 = R^5 = Ph$
- **b**: $R^1 = H, R^3 = R^4 = Ph, R^5 = CMe_3$
- **c**: $R^1 = H, R^3 = R^5 = Ph, R^4 = Me$
- **d**: $R^1 = R^3 = R^4 = R^5 = Ph$
- **e**: $R^1 = R^3 = R^4 = Ph, R^5 = H$
- **f**: $R^1 = R^3 = R^5 = Ph, R^4 = Me$
- **g**: $R^1 = R^5 = Ph, R^3, R^4 = -(CH_2)_5-$
- **h**: $R^1 = R^3 = R^5 = Ph, R^4 = H$
- **i**: $R^1 = R^5 = Ph, R^3 = 4\text{-}ClC_6H_4, R^4 = H$
- **j**: $R^1 = R^5 = Ph, R^3 = (CH_2)_6Me, R^4 = H$
- **k**: $R^1 = (CH_2)_6Me, R^3 = R^4 = R^5 = Ph$
- **l**: $R^1 = (CH_2)_6Me, R^3 = R^4 = Ph, R^5 = H$
- **m**: $R^1 = (CH_2)_6Me, R^3 = R^5 = Ph, R^4 = Me$
- **n**: $R^1 = (CH_2)_6Me, R^3, R^4 = -(CH_2)_5-, R^5 = Ph$

X-ray crystallographic study of the moderately stable crystalline compound (**3a**) reveals that it is indeed a 1,2,4-dioxazolidine derivative (Figure 1).†

In a non-participating solvent like methylene chloride, the carbonyl oxide (**4**), generated *in situ* by selective ozonolysis of the vinyl ether (**1**),‡ reacts preferentially with the imine (**2**) to yield the corresponding 1,2,4-dioxazolidine (**3**). There is little apparent competition for capture of the carbonyl oxide (**4**) from the alkyl formate (**5**), which is also produced from (**1**), because it is a compartively poor 1,3-dipolarophile[3] (Scheme 1). To gain further insight into the mechanism of formation of the 1,2,4-dioxazolidines, a series of reactions were carried out under varying conditions.

If the ozonolysis reactions were repeated with methanol as the reaction solvent, it would be expected that the α-methoxy hydroperoxides (**6**), arising from efficient solvent capture of the carbonyl oxide (**4**), would become the major products with the yields of the adduct (**3**) being substantially depressed. This was certainly observed in the ozonolysis of a mixture of isobutyl vinyl ether (**1a**) and *N*,*N*-diphenylmethyleneaniline (**2a**) in methanol; the unreacted imine (**2a**) was recovered quantitatively.

When the ozonolysis of vinyl ether (**1a**) was carried out in the presence of a 1 : 1 mixture of benzophenone and imine (**2b**) in methylene chloride at −70 °C, 1,1-diphenylethylene ozonide and the dioxazolidine (**3b**) were obtained in yields of 3 and 46%, respectively. Imine (**2b**), therefore, captures the carbonyl oxide more efficiently than benzophenone. A similar trend was noted in the analogous competitive reaction between cyclohexanone and *N*-cyclohexylideneaniline (**2e**). Moreover, the presence of tetracyanoethylene (1 equiv.), a good oxygen acceptor for carbonyl oxides,[6] did not adversely affect the formation of the cycloadduct (**3a**) from formaldehyde oxide (**4a**) and imine (**2a**) to any significant extent.



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† *Crystal data* for compound (**3a**): $C_{20}H_{17}NO_2$, $M = 303.4$, monoclinic, space group $P2_1/n$ (non-stand. No. 14), $a = 10.384$ (6), $b = 9.590$ (3), $c = 15.403$ (9) Å, $\beta = 91.00$ (8)°, $U = 1533.6$ Å^3, $Z = 4$, $D_c = 1.314$ g cm^{-3}, μ(Mo-K_α) = 0.79 cm^{-1}. The intensity data were collected on a CAD4 diffractometer [Mo-K_α radiation; ω-2θ scanning; $1<\theta<23°$]. The structure was solved by direct methods (SHELXS86) and refined by full-matrix least-squares techniques (SHELX76) with anisotropic temperature factors for the non-hydrogen atoms. At convergence, the conventional and weighted *R*-factors were 0.049 and 0.079, respectively for 1587 intensity data with $I > 3\sigma(I)$.

‡ The reaction between imines and ozone is very slow; the rate constant for the ozonation of *N*-benzylideneaniline is 10^4 times smaller than that of styrene.[5]

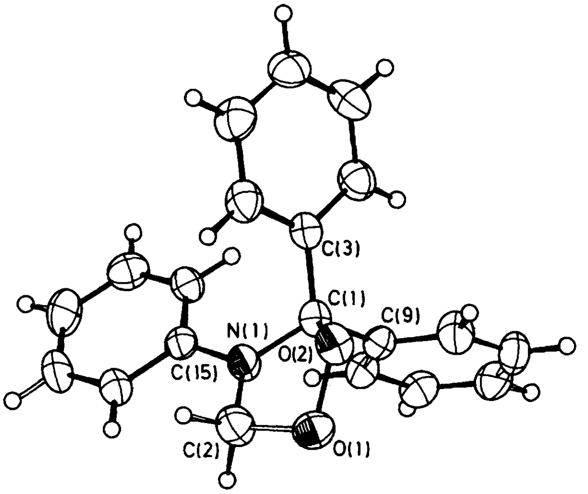

Figure 1. *X*-Ray crystal structure of 1,2,4-dioxazolidine (**3a**). Important bond lengths (Å) and angles (°): O(1)–O(2) 1.472 (3), O(1)–C(2) 1.420 (4), O(2)–C(1) 1.450 (3), N(1)–C(1) 1.464 (3), N(1)–C(2) 1.447 (4); O(2)–O(1)–C(2) 100.8 (2), O(1)–O(2)–C(1) 101.9 (2), C(1)–N(1)–C(2) 108.4 (2), O(2)–C(1)–N(1) 100.9 (2), O(1)–C(2)–N(1) 103.5 (2).

The substituents R^3 and R^4 were found to exert an influence on the reactivity of the imines (**2**). When the ozonolysis of the vinyl ether (**1b**) was performed in the presence of a 1 : 1 mixture of *N*,*N*-diphenylmethyleneaniline (**2a**) and *N*-cyclohexylideneaniline (**2e**), only the dioxazolidine (**3g**), derived from the selective cycloaddition of benzaldehyde oxide (**4b**) to the latter imine (**2e**) was isolated (79% yield) indicating a greater reactivity of imine (**2e**) over (**2a**). This is contrary to the situation for carbonyl compounds where the ozonolysis of vinyl ether (**1a**) in the presence of benzophenone (1 equiv.) afforded the 1,1-diphenylethylene ozonide in 20% yield, whereas the analogous experiment with cyclohexanone resulted in quantitative recovery of the ketone.

Our results to date indicate that the imines examined thus far exhibited a greater reactivity towards carbonyl oxide intermediates than either esters (**5**) which are generated in the ozonolysis process, or ketones which are added to the reaction mixture. As a consequence, the ozonolysis of vinyl ethers in the presence of imines appears to offer a convenient synthetic route to 1,2,4-dioxazolidines.

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