Cycloaddition Reactions of Cumulenes. Part IV.[1] A Novel Mode of Reaction of Azomethine Oxides with 1,1-Dimethylallene; Formation of a Substituted Piperidin-4-one

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Reactions of *C*-aryl-*N*-alkyl azomethine oxides with 1,1-dimethylallene proceed through an initial 1,3-dipolar cycloaddition, followed by two competing processes: formation of a substituted piperidin-4-one by a further addition reaction of the intermediate with the azomethine oxide and intramolecular rearrangement of the alkylidene-isoxazolidine monoadduct leading to a pyrrolidin-3-one.

WHEN 1,3-dipoles react with allene and substituted allenes, an electrocyclic reaction takes place leading in the case of nitrile oxides to spirobi-isoxazolines.[2] Mono-adducts can also be isolated under similar reaction conditions;[3] the reaction with nitrile imides affords analogous adducts.[4]

A different reaction mode has been established with systems of the azomethine oxide type (1): they undergo an initial cycloaddition to the allene double bond followed by intramolecular rearrangement to yield pyrrolidin-3-ones (7) in the case with R = Ph.[5-8]

The available experimental evidence indicates that the mode of 1,3-dipolar cycloaddition of azomethine oxides (1) to carbon–carbon double bonds is little influenced by different *N*-substituents; however aliphatic, cyclic, and *C*-acyl azomethine oxides appear to be more reactive than other systems, *e.g.* heteroaromatic *N*-oxides and cyclic derivatives.[5] The exceptional behaviour of *N*-alkyl substituted derivatives has not hitherto been thoroughly investigated, and we now describe the reactions of some *N*-alkyl azomethine oxides (1) with 1,1-dimethylallene (2).

When the *C*-aryl-*N*-alkyl azomethine oxides (1a and b) reacted with 1,1-dimethylallene (2) an additional reaction pathway leading to the piperidinone (6) was observed, concurrent with formation of the expected pyrrolidin-3-one derivatives (7).[1,8] The latter was the only product isolated in the case of (1c). The novel reaction pathway provides clear evidence of the influence of the substituent groups of the dipole (1) in its reaction with allenes.

All the cycloaddition reactions were carried out in glass tubes at 85—95 °C, for 90—115 h, with various molar ratios of reactants (1) and (2). The products were separated either by spontaneous precipitation on cooling or by thick-layer chromatography. Compounds (7a and b) were purified by column chromatography or g.l.c. From the crude product of the reaction between (1a or b) and (2), 4-methyl-1-phenylpent-1-en-3-one was also isolated in small amounts by g.l.c., and was identical with material synthesized by literature methods.[9] The results of the various experiments are given in Table 1.

The products were identified from analytical and spectroscopic data. An independent synthesis[10] confirmed the structure of the piperidinone (6). The products (7a and b) were also identified by comparison with material synthesized by a different method.[11] In addition, compounds (6) and (7a) were separately heated

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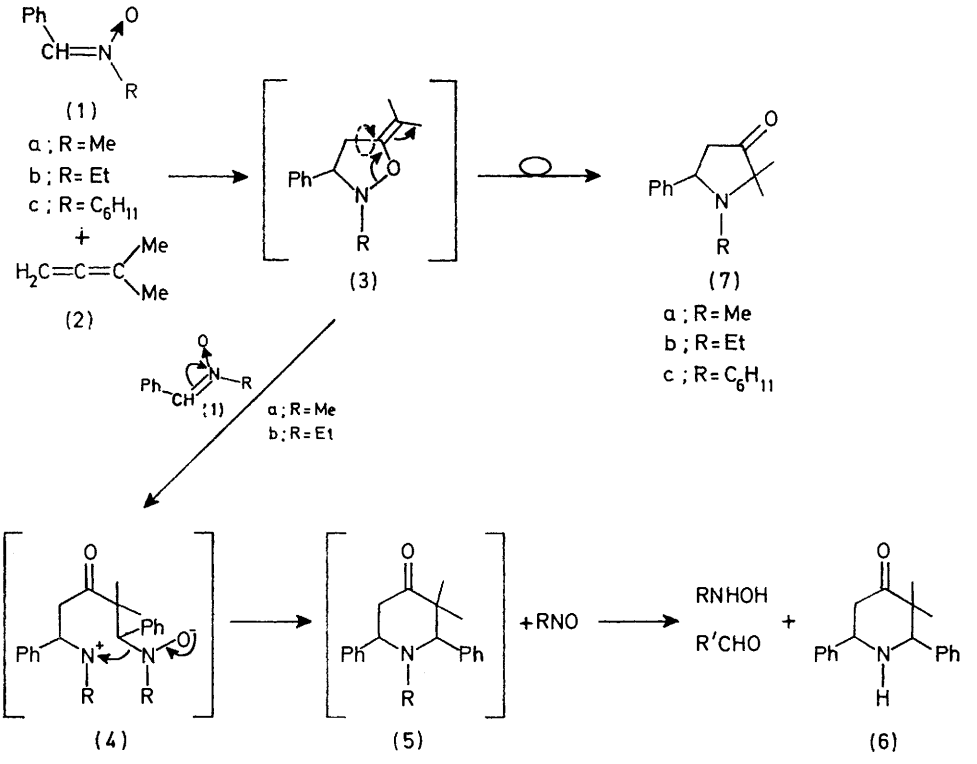
in a glass tube at 110 and 80 °C, respectively for 100 h and were essentially unaltered; in both cases, no 4-methyl-1-phenylpent-1-en-3-one was detected by t.l.c. of the crude material.

In order to evaluate the role of the *N*-alkyl substituent in the azomethine oxide, the reaction between compounds (1c) and (2) was carried out (see Table 1); the only product isolated was the pyrrolidinone (7c), less hindered double bond of the 1,1-dimethylallene (2). The addition is regioselective, giving the intermediate (3) as a consequence of direction of the oxygen atom of the dipole (1) to the more hindered end of the dipolarophile (2). The isoxazolidine (3) appears, however, to be highly unstable under the general reaction conditions. This type of product has been found to undergo internal rearrangement to a pyrrolidin-3-one (7) (see Scheme) *via*



SCHEME

identified on the basis of i.r., n.m.r., and mass spectral data.

Formation of the six-membered heterocycle (6) can be satisfactorily interpreted in terms of the reaction

TABLE 1

Reaction of azomethine oxides (1) with 1,1-dimethylallene (2) [a]

Azomethine oxide	Ratio of (1) to (2)	Temp. (°C)	Time (h)	Products (%) (6)	(7)
(1a)	2 : 1	85	90	35	20
(1a)	1 : 1	85	90	24	23
(1b)	2 : 1	90	115	20	20
(1c)	2 : 1	95	110	—	60

[a] A mixture of (1a, b, or c) (20 or 10 mmol) with (2) (10 mmol) was heated, in an SVL Sovirel glass tube, at 85—95 °C for several hours.

sequence shown in the Scheme. The process leading to the piperidin-4-one (6) involves an initial $[{}_{\pi}4_s + {}_{\pi}2_s]$ cycloaddition of the azomethine oxide (1a or b) on to the heterolysis of the N–O bond, ring opening, rotation around the 4,5-bond, and C–N bond formation.[1,8] An intramolecular rearrangement of this type seems to be favoured when a five-membered ring containing adjacent oxygen and nitrogen atoms possesses a trigonal (sp^2) carbon atom at position 5, as in the case of some Δ^4-isoxazolines;[12] exceptions may occur when delocalisation stabilizes the intermediate [2] or rotation around the 4,5-bond is prevented.[13]

However, if the nitrogen atom of the intermediate (3) is bound to an alkyl group, as in the Scheme, the rearrangement to pyrrolidin-3-ones is subjected to electronic influences which affect the energy requirements of the transition state. Thus, in comparison with an aryl substituent, an alkyl group destabilizes the zwitterionic intermediate (the nitrenium ion) and allows another path to become competitive. In this situation a further addition reaction on to the exocyclic double bond of the intermediate (3) takes place, involving an

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additional molecule of the azomethine oxide (1). The conversion (3) ⟶ (5) can be intepreted on the basis of the susceptibility of azomethine oxides to electrophilic addition reactions with reactive nucleophiles,[14] proceeding through the species (4). Nevertheless substrates known to undergo electrophilic addition reactions with (1) are usually carbonyl reagents.[14]

In order to elucidate more thoroughly the source of the foregoing novel behaviour of *N*-alkyl azomethine oxides (1), detailed quantum-mechanical calculations on a model system of type (8) have been performed by the CNDO/2 method to evaluate the electronic distribution in the potential intermediate.[15] Even though the system studied is only an approximation, *i.e.* (8) rather than (3), introducing a quantitative inaccuracy, we expected the results to be qualitatively meaningful. The results (Table 2) indicate the polarisation of the nucleophilic substrate in the reaction step (3) ⟶ (4) from the differences in formal charge amongst N-2, C-5, and C-5′, thus supporting the postulated trend towards addition with azomethine oxides as electrophiles, and the orientation of the reaction indicated in the Scheme.

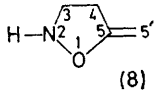
The reaction of the adduct (4) proceeds *via* elimination of a nitroso-derivative and ring closure to the substituted piperidin-4-one (5). Under the reaction conditions the tertiary amine group of (5) undergoes dealkylation to (6), brought about by the nitroso-derivative present.[16]

When a 1 : 1 molar ratio is used in the reaction between compounds (1a) and (2), compound (6) is produced in approximately the same yield, *i.e.* 24%, thus, showing that the electrophilic addition reaction of (1a) with (3) competes effectively with the internal rearrangement (3) ⟶ (7). Since previous results indicate that, when *CN*-diaryl azomethine oxides react with allene or allene-like systems, substituted pyrrolidin-3-ones are the only products,[1,8] it appears that the amount of compound (6) obtained can be influenced by electronic as well as by steric factors. The occurrence of the overall process leading to (6) is therefore strictly related to the nature of the *N*-substituent in the dipole used. In fact, in the case of the reaction between (1c) and (2) no trace of (6) was detected by t.l.c., and compound (7c) was the only product isolated. Furthermore, 4-methyl-1-phenylpent-1-en-3-one is also absent in the crude material from the reaction between (1c) with (2), as demonstrated by g.l.c. analysis. These observations imply that a steric effect (of the *N*-substituent) is operating in the reaction step (3) ⟶ (5), thus discriminating against the formation of (6). There is thus good evidence that the presence of a bulky group (*e.g.* cyclohexyl) makes the transition state for the formation of a piperidin-4-one less favoured. Thus, the steric hindrance and the electronic effect, respectively, of the aryl group in destabilising the dipolar intermediate (4) and in stabilising the intermediate leading to (7), provide a general explanation of the substantial difference between *N*-alkyl and *N*-aryl azomethine oxides.

Finally, the formation of 4-methyl-1-phenylpent-1-en-3-one as a product [found only when compounds (a and b) react with (2)] remains to be rationalised. Since this compound is not formed by thermal decomposition of (6) or of (7a and b) and is not produced from *N*-aryl or *N*-cyclohexyl azomethine oxides, its formation may compete with that of the piperidinone (5), and probably involves the common intermediate (4).

TABLE 2

Formal charge distribution on the 5-methyleneisoxazolidine molecule (8)



(8)

O	N	C-3	C-4	C-5	C-5′
−0.192	−0.113	0.211	−0.364	0.215	−0.140

EXPERIMENTAL

The Experimental section is available as Supplementary Publication No. SUP 21630 (4 pp.).*

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* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1974, Index issue.

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