

Cycloaddition Reactions of 2,4-Diphenyl-3-methyl-1,3-oxazolium 5-Oxide with 4-Methylene-4,5-dihydroisoxazoles: ^1H and ^{13}C Nuclear Magnetic Resonance Stereochemical Assignments of the Products

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Some 3-aryl-4-methylene-5-morpholino-4,5-dihydroisoxazoles (**2**) were treated with 2,4-diphenyl-3-methyl-1,3-oxazolium 5-oxide (**1**) to give corresponding cycloaddition products, namely spiro[isoxazolo-4,3'-pyrroles] (**3**) and (**4**). The steric configuration of the spiro-derivatives has been assigned on the basis of ^1H and ^{13}C n.m.r. evidence.

One of our research programs deals with the behaviour of 5-amino-4-methylene-4,5-dihydroisoxazoles, which offer good reactivity of the exocyclic double bond towards both nucleophiles¹ and 1,3-dipoles.² Recently we investigated the reaction of 3-aryl-4-methylene-5-morpholino-4,5-dihydroisoxazoles (**2a—d**) with 2,4-diphenyl-3-methyl-1,3-oxazolium 5-oxide (**1**). This mesoionic derivative, which behaves as a 1,3-dipole,³ gave as expected a $[3 + 2]\pi$ cycloaddition on the exocyclic double bond of (**2a—d**), affording the spiro heterocyclic derivatives (**3a—d**) and (**4a—d**) (see Scheme 1). This paper describes the steric configuration of these final products as assessed by exhaustive ^1H and ^{13}C n.m.r. analysis.

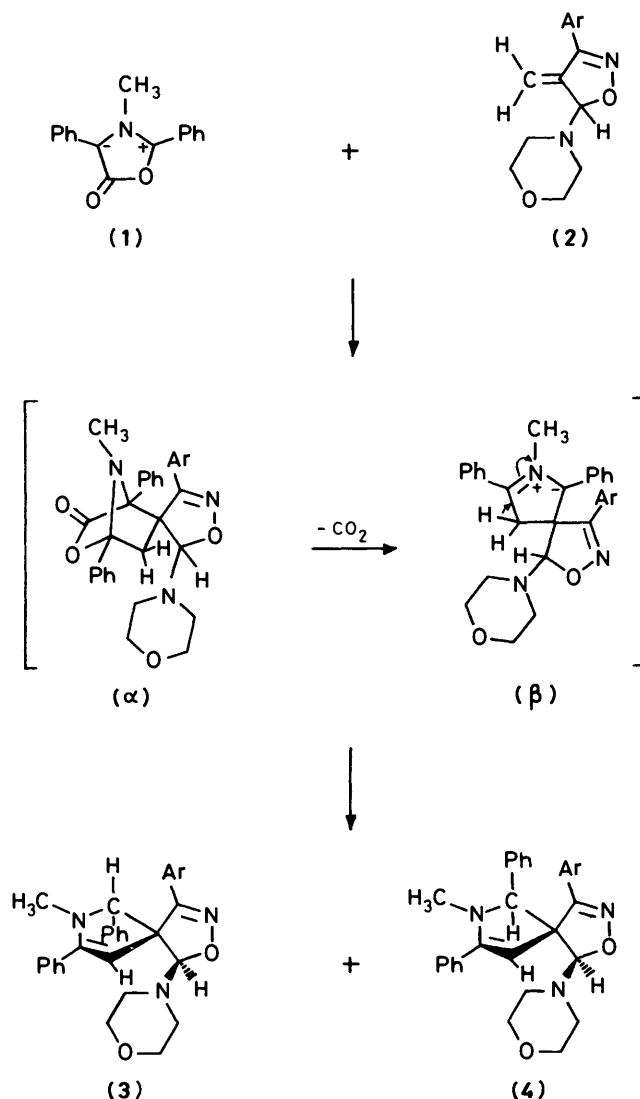
Results and Discussion

Reaction of (**1**) with (**2**) in toluene at 60 °C for 12 h afforded, in all cases, a 1:4 mixture of two isomeric products, (**3**) and (**4**), which were separated by column chromatography and further purified by crystallization. Physical and spectroscopic data for compounds (**3**) and (**4**) are summarized in Table 1. The use of the 2,4-symmetrically disubstituted mesoionic compound (**1**) ruled out the possibility of formation of two regioisomers and consequently the final products (**3**) and (**4**) must be considered to be a pair of diastereoisomers. Since the substrates (**2**) are racemic mixtures at C-5, and the products contain two additional chiral centres, it is necessary, in order to assign their relative configuration, to choose among eight possible stereoisomers. For the sake of simplicity only the four diastereoisomeric structures depicted in Scheme 2 are considered in the discussion, namely (I)—(IV), disregarding their relative mirror images. It is implied of course that the final products are enantiomeric mixtures.

Considering the structures in Scheme 2, (I) and (II), which correspond as shown later to products (**3**) and (**4**), respectively, derive from the attack of the dipole on the side of the double bond opposite to the morpholino group and differ only in the stereochemistry at C-2'.

Structures (III) and (IV) (not formed) conversely derive from the attack on the more crowded side of the double bond, differ in the stereochemistry at C-2', and have, with respect to the first pair considered, the opposite stereochemistry at the spirocentre C-4.

Considering molecular models of the pairs (I)—(II) and (III)—(IV) and the differences in spatial relationships of the carbon and hydrogen atoms among them, it is apparent that C-4' must have a long-range coupling $^3J_{\text{C-H}^4}$ with H-5 in (III) and (IV) (dihedral angle *ca.* 0°) but none in (I) or (II) (dihedral angle *ca.* 90°) (neither with H-5 nor -2'). This fact

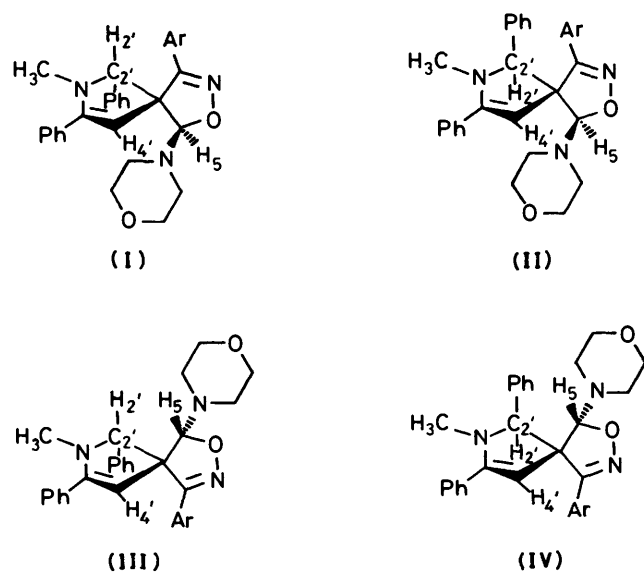


- a; Ar = C₆H₅
 b; Ar = C₆H₄-4-Cl
 c; Ar = C₆H₄-4-OCH₃
 d; Ar = C₆H₄-4-NO₂

Scheme 1.

Table 1. Physical, analytical, and ^1H n.m.r. data of products (3) and (4)

Compd.	M.p. ($^{\circ}\text{C}$)	Solvent	Yield (%)	δ_{H}	Analysis (%)						
					Found			Formula	Required		
					C	H	N		C	H	N
(3a)	78—80	MeOH	9	7.7—7.0 (m, 15 H, aromatic), 4.9 (s, 1 H, H-4'), 4.7 (s, 1 H, H-5), 4.4 (s, 1 H, H-2'), 3.5 (t, 4 H, CH_2OCH_2), 2.7—2.6 (m, 4 H, CH_2NCH_2), 2.5 (s, 3 H, NCH_3)	77.3	6.4	9.05	$\text{C}_{29}\text{H}_{29}\text{N}_3\text{O}_2$	77.1	6.5	9.3
(4a)	220—221	Pr ⁱ OH	45	7.5—7.0 (m, 15 H, aromatic), 5.1 (s, 1 H, H-5), 4.8 (s, 1 H, H-4'), 4.5 (s, 1 H, H-2'), 3.8 (t, 4 H, CH_2OCH_2), 2.8—2.6 (m, 4 H, CH_2NCH_2), 2.5 (s, 3 H, NCH_3)	76.9	6.4	9.1	$\text{C}_{29}\text{H}_{29}\text{N}_3\text{O}_2$	77.1	6.5	9.3
(3b)	135—136	MeOH	11	8.3—7.6 (m, 14 H, aromatic), 5.2 (s, 1 H, H-4'), 5.1 (s, 1 H, H-5), 4.7 (s, 1 H, H-2'), 3.8 (t, 4 H, CH_2OCH_2), 2.8—2.5 (m, 7 H, $\text{CH}_2\text{NCH}_2 + \text{NCH}_3$)	71.35	5.9	8.4	$\text{C}_{29}\text{H}_{28}\text{ClN}_3\text{O}_2$	71.65	5.8	8.65
(4b)	206—207	Pr ⁱ OH	58	8.2—7.6 (m, 14 H, aromatic), 5.5 (s, 1 H, H-5), 5.1 (s, 1 H, H-4'), 4.8 (s, 1 H, H-2'), 4.0 (t, 4 H, CH_2OCH_2), 3.0 (t, 4 H, CH_2NCH_2), 2.7 (s, 3 H, NCH_3)	71.25	6.0	8.3	$\text{C}_{29}\text{H}_{28}\text{ClN}_3\text{O}_2$	71.65	5.8	8.65
(3c)	179—180	MeOH	14	8.3—7.2 (m, 14 H, aromatic), 5.5 (s, 1 H, H-4'), 5.1 (s, 1 H, H-5), 4.8 (s, 1 H, H-2'), 4.1—3.9 (m, 7 H, $\text{OCH}_3 + \text{CH}_2\text{OCH}_2$), 3.0 (t, 4 H, CH_2NCH_2), 2.7 (s, 3 H, NCH_3)	74.7	6.4	8.6	$\text{C}_{30}\text{H}_{31}\text{N}_3\text{O}_3$	74.8	6.5	8.7
(4c)	208—209	Pr ⁱ OH	65	8.9—7.5 (m, 14 H, aromatic), 5.2 (s, 1 H, H-5), 5.0 (s, 1 H, H-4'), 4.7 (s, 1 H, H-2'), 4.2 (s, 3 H, OCH_3), 3.8 (t, 4 H, CH_2OCH_2), 2.8—2.6 (m, 7 H, $\text{CH}_2\text{NCH}_2 + \text{NCH}_3$)	74.5	6.4	8.5	$\text{C}_{30}\text{H}_{31}\text{N}_3\text{O}_3$	74.8	6.5	8.7
(3d)	173—174	MeOH	17	8.3—7.2 (m, 14 H, aromatic), 4.86 (s, 1 H, H-4'), 4.70 (s, 1 H, H-5), 4.36 (s, 1 H, H-2'), 3.5 (t, 4 H, CH_2OCH_2), 2.6—2.4 (m, 7 H, $\text{CH}_2\text{NCH}_2 + \text{NCH}_3$)	69.9	5.7	10.9	$\text{C}_{29}\text{H}_{28}\text{N}_4\text{O}_4$	70.1	5.7	11.3
(4d)	199—200	Pr ⁱ OH	70	7.8—7.2 (m, 14 H, aromatic), 5.10 (s, 1 H, H-5), 4.76 (s, 1 H, H-4'), 4.50 (s, 1 H, H-2'), 3.8 (t, 4 H, CH_2OCH_2), 2.8 (m, 4 H, CH_2NCH_2), 2.6 (s, 3 H, NCH_3)	69.9	5.3	10.9	$\text{C}_{29}\text{H}_{28}\text{N}_4\text{O}_4$	70.1	5.7	11.3

**Scheme 2.**

suggested that analysis of the coupling pattern of C-4', -2', and -5 would be a good way to distinguish among the four structures and assign two of them to the products obtained.

Only the two diastereoisomers derived from the reaction of

(1) with (2d) were considered for the exhaustive n.m.r. analysis, because they were obtained in greater yield. In the ^1H n.m.r. spectrum of both reaction products, H-5, -2', and -4' appeared as sharp singlets and were heterocorrelated by a classical 2D experiment to the corresponding carbon signals. A total coupling ^{13}C n.m.r. experiment then provided the coupling patterns of these signals. As a further aid to the task of signal assignment, 2D n.o.e. experiments were run for both products.

The relevant data from ^1H and ^{13}C n.m.r. and n.o.e. experiments are collected in Table 2.

Considering first the experimental data collected for compound (4d), the signal at δ_{H} 4.50 shows a clear n.o.e. effect with the *N*-methyl group in position 1'. The carbon corresponding to that hydrogen atom is associated with the signal at δ_{C} 84.69 which shows a high degree of multiplicity and a characteristic $^1J_{\text{CH}}$ coupling value (135.0 Hz).

The centre with a hydrogen close enough to *N*- CH_3 and whose carbon could couple with the *N*-methyl hydrogens ($^3J_{\text{CH}}$ 5.0 Hz) is C-2' in every possible structure of Scheme 2.

Of the two remaining unassigned carbons, one (δ_{C} 98.36) has no long-range coupling. This carbon is not C-2' in (III) and (IV) (long-range coupling with H-4'), C-5 in (III) (long range with H-2' and -4') and in (IV) (long range with H-4'), C-4' in (III) (long range with H-5) and in (IV) (long range with H-2' and -5), C-2' in (I) and (II) (long range with H-4', -5), and C-5 in (II) (long range with H-2' and -4') and in (I) (long range with H-4'), because all these carbons can exhibit long-range couplings different from zero.

This leaves only C-4' in (I) and in (II); in these structures C-4'

Table 2. Relevant n.m.r. data for compounds (3d) and (4d) (CDCl₃)^a

Centre	(3d) [structure (I)]				(4d) [structure (II)]			
	C-5	C-2'	C-4'	C-4	C-5	C-2'	C-4'	C-4
¹ H Chemical shifts	4.70	4.36	4.86		5.10	4.50	4.76	
Observed n.O.e. effects between protons	<i>b</i>	<i>b</i>			with H-2'	with H-5 with N-CH ₃		
¹³ C Chemical shifts, C-H coupling constants (Hz), and multiplicity	99.48 ¹ J 164.1 (d) ³ J 5.9	76.77 ¹ J 135 (d) Δ <i>v</i> _± 20 ^c	98.87 ¹ J 175.3 (d)	66.42	108.72 ¹ J 162.1 (d) ³ J 7.4	84.69 ¹ J 135.0 (d) ³ J 10.1 (d) ³ J 5.0 (q) Δ <i>v</i> _± 20	98.36 ¹ J 175.3 (d)	69.04

^a Only the data necessary to discussion are reported. ^b N.O.e. effects were observed corresponding to overlapping peaks of NCH₃ and NCH₂ (morpholine), but no attempt to distinguish the different contributions was made. ^c The values of ³J_{C-2'/H-4'} and ³J_{C-2'/N-CH₃} were not detectable owing to partial overlap with the CDCl₃ signal.

has a dihedral angle of 90° with H-2' and -5 with no long-range coupling.

The carbon signal at δ 108.72 is for C-5, whose hydrogen shows a large n.O.e. effects with H-2'. This allows us to choose, for product (4d), structure (II), where H-2' is on the same side as H-5'.

For the set of data reported for product (3d) in Table 2, the same kind of reasoning assigns the signal at δ 76.77 to C-2' because of its multiplicity in the total coupling experiment; the corresponding atom H-2' does not show any n.O.e. effect with H-5 in this case, and so structure (I) is assigned to this product.

The signal at δ 98.87 is assigned to C-4' and that at δ 99.48 to C-5 because of the same values for their respective one-bond C-H coupling constants when compared with the corresponding signals in product (4d).

These considerations for products (4d) and (3d) can be extended to the products derived from (2a-c), as the mechanism shown in Scheme 1 is independent of the aryl substituent at C-3.

These assignments agree with our previous results² for the addition of 1,3-dipoles to 4-methyleneisoxazolines, where the approach of the dipole occurs only from the less hindered diastereotopic side of the dipolarophile. The steric configurations of both the spiro carbon and the carbon bearing the morpholino substituent are thus selected [structures (I), (II) instead of (III), (IV)]. The configuration at C-2' arises during the last step of the cycloaddition reaction (Scheme 1). The unstable primary tricyclic adduct α loses carbon dioxide to give the dipolar intermediate β, which can rearrange to (3) and (4) through deprotonation of the CH₂ group and reprotonation at C-2' or possibly through a [1,4]sigmatropic hydrogen shift. In both cases the formation of two diastereoisomeric products is expected.

The ratio observed (1:4) can be explained on the basis of different steric hindrance in the transition state or a preferred proton transfer from position 4' to 2' assisted by the sterically well located morpholino group.

Experimental

M.p.s were measured with a Büchi apparatus and are uncorrected. ¹H N.m.r. spectra were recorded on a Varian EM-390 (90 MHz) or XL-200 (200 MHz) instrument. Total coupling ¹³C n.m.r. spectra were obtained on a CFT-20 Varian instrument (20 MHz) with retention of n.O.e. to improve the signal to noise ratio. 2D Experiments (¹³C/¹H correlation, n.O.e. effect)

were run on the XL-200 instrument, using standard pulse sequences.^{5,6} A mixing time of 0.5 s was used for the NOESY sequence. All chemical shifts are expressed in δ values from tetramethylsilane as reference.

Compounds (1),⁷ (2a),² (2b),¹ and (2d)¹ were synthesized according to methods reported in the literature.

3-(4-Methoxyphenyl)-4-methylene-5-morpholino-4,5-dihydroisoxazole (2c).—This new compound was prepared according to the procedure described for (2a),² yield 61%, crystal (diisopropyl ether), m.p. 98–100 °C (Found: C, 65.6; H, 6.6; N, 10.1. C₁₅H₁₈N₂O₃ requires C, 65.7; H, 6.6; N, 10.2%); δ_H (90 MHz) 7.50 (2 H, d, aromatic), 6.90 (2 H, d, aromatic), 5.80–5.65 (2 H, m, α- and 5-H), 5.50 (1 H, d, α-H), 3.80 (3 H, s, OCH₃), 3.70 (4 H, t, CH₂OCH₂), and 3.10–2.70 (4 H, m, CH₂NCH₂).

Cycloaddition Reactions. General Procedure.—A mixture of (1) (13 mmol) and (2) (10 mmol) in toluene (40 ml) was heated at 60 °C for 12 h under nitrogen. The solvent was evaporated and the residue was column chromatographed on silica gel. Elution with toluene-ethyl acetate (9:1) gave the products (3) and (4) listed in Table 1.

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