# 1,3-Dipolar Cycloaddition Reactions of 2-Phenyl-4-arylidene-5(4*H*)-oxazolones with Nitrile Oxides



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Stable nitrile oxides are added stereospecifically and regioselectively to the carbon-carbon double bond of 2-phenyl-4-arylidene-5(4*H*)-oxazolones resulting spiro-derivatives **3, 5**. The spectral properties of the reaction products are discussed. The cycloadducts give several substituted isoxazolines *via* an opening of the oxazolone ring with nucleophilic reagents.

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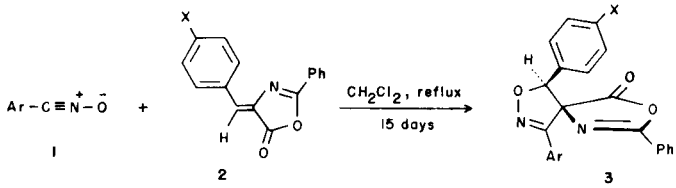
The chemistry of 5(4*H*)-oxazolones has been the subject of several reviews [1-3]. 5(4*H*)-Oxazolones furnish a convenient startng point for the synthesis of a variety of compounds and especially of α-amino acids and peptides [4, 5]. Many of their reactions are also of wide mechanistic interest. The carbon-carbon double bond of 4-arylidene-5(4*H*)-oxazolones consists a sterically rather hindered and electron deficient dipolarophile. Regarding the peculiarity of the regioselectivity behaviour of electron deficient dipolarophiles in 1,3-dipolar cycloadditions [6,7], reaction of 4-arylidene-5(4*H*)-oxazolones with 1,3-dipoles should be of some mechanistic interest. This kind of reactions may be also a route for the synthesis of various substituted heterocyclic rings. In this paper the reaction of nitrile oxides with 2-phenyl-4-arylidene-5(4*H*)-oxazolones is studied.

The used oxazolones are considered to be the *Z*-geometric isomers as it is accepted for the stable geometric isomers, which are prepared by the Perkin-Erlenmeyer reaction [8].

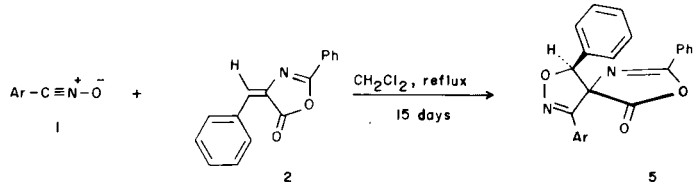
Stable nitrile oxides such as mesitonitrile oxice (**1a**) and 2,6-dichlorobenzonitrile oxide (**1b**) react with a series of *Z*-2-phenyl-4-arylidene-5(4*H*)-oxazolones **2a-e** to give the corresponding cycloaddition products **3a-j** in good yields (40-82%).




1 2 3

**1a**, Ar = 2,4,6-$(CH_3)_3C_6H_2$; **1b**, Ar = 2,6-$Cl_2C_6H_3$; **2a**, X = H; **2b**; X = $CH_3$; **2c**, X = Cl; **2d** X = $OCH_3$; **2e**, X = $NO_2$; **3a**, Ar = 2,4,6-$(CH_3)_3C_6H_2$, X = H; **3b**, Ar = 2,4,6-$(CH_3)_3C_6H_2$, X = $CH_3$; **3c**, Ar = 2,4,6-$(CH_3)_3C_6H_2$, X = Cl; **3d**, Ar = 2,4,6-$(CH_3)_3C_6H_2$, X = $OCH_3$; **3e**, Ar = 2,4,6-$(CH_3)_3C_6H_2$, X = $NO_2$; **3f**, Ar = 2,6-$Cl_2C_6H_3$, X = H; **3g**, Ar = 2,6-$Cl_2C_6H_3$, X = $CH_3$; **3h**, Ar = 2,6-$Cl_2C_6H_3$, X = Cl; **3i**, Ar = 2,6-$Cl_2C_6H_3$, X = $OCH_3$; **3j**, Ar = 2,6-$Cl_2C_6H_3$, X = $NO_2$

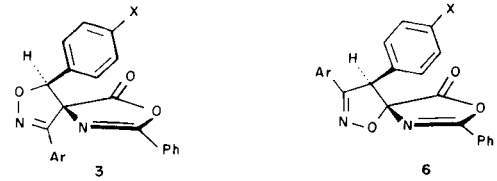
The carbon-carbon double bond of **2** seems to be a rather weak dipolarophile. Unstable nitrile oxides, such as benzonitrile oxide, were unreactive, whereas with the stable nitrile oxides **1a** and **1b** the reaction took place only after prolonged heating (reflux in methylene chloride for fifteen days). The cycloadducts **3** were isolated from the reaction mixture with successive crystallizations. Attempts to work out the reaction mixture with column chromatography (silica gel) were unsuccessful since only decomposition products were obtained from the column. In all cases only one regio-isomer was isolated, that is the reaction is regioselective. Reaction of **1a** and **1b** with the *E*-oxazolone **4**, the geometric isomer of **2a**, gave also one product the spiro-oxazolones **5a** and **5b** respectively, with lower melting points than their corresponding stereoisomers. Thus the reaction seems to be stereoselective as well as is the addition of diazomethane to 2-phenyl-4-arylidene-5(4*H*)-oxazolone [9].




1 2 5

5a, Ar = 2,4,6-$(CH_3)_3C_6H_2$; 5b, Ar = 2,6-$Cl_2C_6H_3$

The strucutral assignment of the isolated spiro-oxazolones **3** and **5** was made on the basis of their elemental analysis and spectroscopic data (ir, nmr, ms) which are summarised in Table I. Especially the isolated cycloadducts were considered as the regioisomers of type **3** instead of the possible regioisomer of type **6**.




3 6

This was based on the chemical shifts of isoxazoline ring protons in comparison with analogous cycloadducts. Thus the isoxazoline ring proton of **3a** resonates at δ 5.37 while the isoxazoline ring protons of analogous cycload-

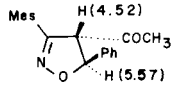
Table I

Analytical and Spectral Data of **3** and **5**

| Compound | Mp °C | Yield % | Molecular Formula MW | Analysis % Calcd/Found C | H | N | Spectral Data |
|---|---|---|---|---|---|---|---|
| **3a** | 180-182 | 76 | $C_{26}H_{22}N_2O_3$ 410.5 | 76.07 76.12 | 5.41 5.50 | 6.83 6.90 | ir: (nujol, $cm^{-1}$): 1830 (C=O), 1650 (C=N); nmr (δ, $CDCl_3$): 2.18 (s, 3H), 2.4 (s, 6H), 5.37 (s, 1H), 6.77 (s, 2H), 7.07-7.63 (m, 8H), 7.75-7.98 (m, 2H); ms: m/z 410 (14) $M^{+\cdot}$ 249 (57), 235 (100), 191 (32), 145 (19), 105 (90) |
| **3b** | 184-187 | 47 | $C_{27}H_{24}N_2O_3$ 424.53 | 76.38 76.68 | 5.71 5.73 | 6.60 6.37 | ir (nujol, $cm^{-1}$): 1825 (C=O), 1655 (C=N); nmr ($\delta CDCl_3$): 2.12 (s, 3H), 2.17 (s, 3H), 2.38 (s, 6H), 5.33 (s, 1H), 6.67-7.55 (m, 9H), 7.75-8.03 (m, 2H); ms: m/z 424 (1) $M^{+\cdot}$ 263 (5), 161 (9), 145 (6), 105 (100) |
| **3c** | 215-217 | 62 | $C_{26}H_{21}ClN_2O_3$ 444.94 | 70.18 70.25 | 4.78 4.69 | 6.30 6.29 | ir (nujol, $cm^{-1}$): 1830 (C=O), 1655 (C=N); nmr ($\delta CDCl_3$): 2.18 (s, 3H), 2.37 (s, 6H), 5.32 (s, 1H), 6.77 (s, 2H), 6.97-7.58 (m, 7H), 7.72-8.00 (m, 2H); ms: m/z 444 (3) $M^{+\cdot}$ 283 (12), 161 (19), 145 (11), 105 (100) |
| **3d** | 186-188 | 42 | $C_{27}H_{24}N_2O_4$ 440.53 | 73.61 73.48 | 5.50 5.54 | 6.36 6.29 | ir (nujol, $cm^{-1}$): 1825 (C=O), 1655 (C=N); nmr ($\delta CDCl_3$): 2.18 (s, 3H), 2.40 (s, 6H), 3.60 (s, 3H), 5.33 (s, 1H), 6.60 (d, 2H, J = 8 Hz), 6.75 (s, 2H), 7.07 (d, 2H, J = 8 Hz), 7.23-7.57 (m, 3H), 7.72-8.02 (m, 2H); ms: m/z 440 (6) $M^{+\cdot}$ 279 (29), 161 (13), 145 (19), 105 (100) |
| **3e** | 199-203 | 74 | $C_{26}H_{21}N_3O_5$ 455.50 | 68.55 68.62 | 4.66 4.76 | 9.23 9.05 | ir (nujol, $cm^{-1}$): 1825 (C=O), 1655 (C=N); nmr ($\delta CDCl_3$): 2.20 (s, 3H), 2.38 (s, 6H), 5.40 (s, 1H), 6.77 (s, 2H), 7.12-7.65 (m, 5H), 7.75-7.98 (m, 2H), 8.17 (d, 2H, J = 13 Hz); ms: m/z 455 (20) $M^{+\cdot}$ 161 (46), 145 (15), 105 (100) |
| **3f** | 211-213 | 82 | $C_{23}H_{14}Cl_2N_2O_3$ 437.29 | 63.17 62.99 | 3.23 3.15 | 6.41 6.30 | ir (nujol, $cm^{-1}$): 1835 (C=O), 1640 (C=N); nmr ($\delta CDCl_3$): 5.75 (s, 1H), 7.00-7.60 (m, 11H), 7.73-8.02 (m, 2H); ms: m/z 436 (n) [a], $M^+$ 249 (70), 187 (8), 171 (24), 105 (100) |
| **3g** | 201-203 | 80 | $C_{24}H_{16}Cl_2N_2O_3$ 451.32 | 63.87 63.87 | 3.58 3.56 | 6.21 5.92 | ir (nujol, $cm^{-1}$): 1830 (C=O), 1645 (C=N); nmr ($\delta CDCl_3$): 2.17 (s, 3H), 5.73 (s, 1H), 6.93 (d, 2H, J = 8 Hz), 7.10-7.60 (m, 8H), 7.78-8.03 (m, 2H); ms: m/z 450 (n) [a], $M^+$ 263 (11), 187 (7), 171 (33), 105 (100) |
| **3h** | 218-220 | 40 | $C_{23}H_{13}Cl_3N_2O_3$ 471.73 | 58.56 58.23 | 2.78 2.66 | 5.94 5.69 | ir (nujol, $cm^{-1}$): 1830 (C=O), 1640 (C=N); nmr ($\delta CDCl_3$): 5.73 (s, 1H), 7.02-7.63 (m, 10H), 7.78-8.08 (m, 2H); ms: m/z 470 (n) [a], $M^+$ 283 (24), 187 (6), 171 (18), 105 (100) |
| **3i** | 205-207 | 59 | $C_{24}H_{16}Cl_2N_2O_4$ 467.32 | 61.68 61.53 | 3.46 3.42 | 6.00 5.97 | ir (nujol, $cm^{-1}$): 1830 (C=O), 1640 (C=N); nmr ($\delta CDCl_3$): 3.63 (s, 3H), 5.72 (s, 1H), 6.65 (d, 2H, J = 8 Hz), 7.05-7.58 (m, 8H), 7.67-8.10 (m, 2H); ms: m/z 466 (2) $M^+$, 279 (6), 187 (100), 171 (45), 105 (100) |
| **3j** | 228-230 | 79 | $C_{23}H_{13}Cl_2N_3O_5$ 482.29 | 57.27 57.22 | 2.72 2.67 | 8.72 8.69 | ir (nujol, $cm^{-1}$): 1830 (C=O), 1645 (C=N); nmr ($\delta CDCl_3$ + $CF_3COOH$): 5.92 (s, 1H), 7.13-8.22 (m, 12H); ms: m/z [b] 166 (n)-[a], 187 (4), 171 (20), 105 (100) |
| **5a** | 174-176 | 80 | $C_{26}H_{22}N_2O_3$ 410.5 | 76.07 75.96 | 5.41 5.25 | 6.83 6.69 | ir (nujol, $cm^{-1}$): 1830 (C=O), 1655 (C=N); nmr ($\delta CDCl_3$): 2.20 (s, 3H), 2.37 (s, 6H), 5.12 (s, 1H), 6.77 (s, 2H), 6.93-7.65 (m, 8H), 7.82-8.13 (m, 2H); ms: m/z 410 (1) $M^+$, 249 (7), 161 (14), 145 (11), 105 (100) |
| **5b** | 186-188 | 82 | $C_{23}H_{14}Cl_2N_2O_3$ 437.29 | 63.17 63.11 | 3.23 3.22 | 6.41 6.36 | ir (nujol, $cm^{-1}$): 1825 (C=O), 1640 (C=N); nmr ($\delta CDCl_3$): 5.72 (s, 1H), 6.90-7.63 (m, 11H), 7.88-8.12 (m, 2H); ms: m/z 436 (n) [a], $M^+$ 249 (60), 187 (7), 171 (20), 105 (100) |

[a] Negligible intensity. [b] No peak for the molecular ion.

ducts such as **7** and **8** are shifted (ppm, δ) as indicated below [10,7].

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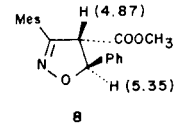


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On the other hand the chemical shifts of the isoxazoline ring proton for the isolated cycloadducts **3**, in deuteriochloroform solution, are varied between δ 5.32 and 5.75. Thus this proton should be at the 5-position.

Frontier molecular orbital consideration of the reacting systems leads also to the conclusion that the formation of regioisomer **3** is favored. According to Houk's approxima-

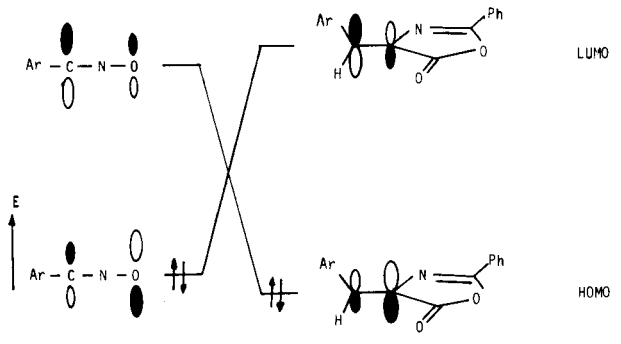
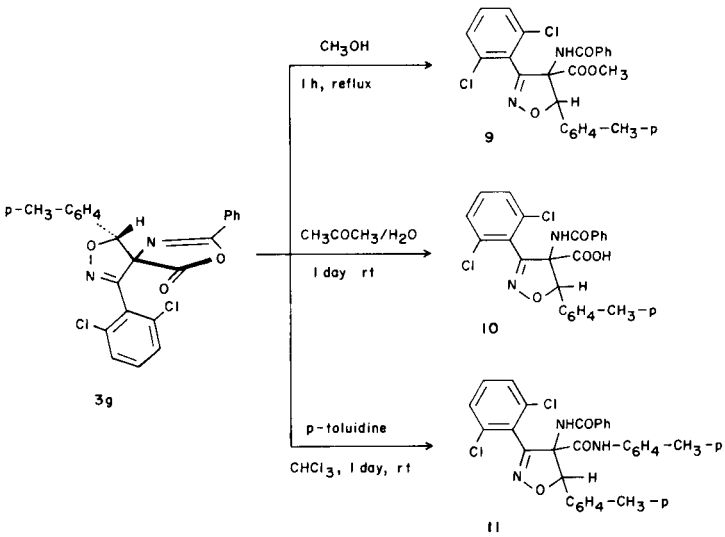



Figure 1. FMO interaction diagram of **1** and **2**.

tions [11,12] for the energy levels and the magnitudes of the atomic orbital coefficients the diagram of frontier molecular orbital interaction for **1** and **2** is as in Figure 1. From Figure 1 the reaction is probably HOMO, LUMO dipole controlled because both interactions correspond to almost equal energy differences. However, irrespective of which interaction is the dominant one, the formation of regioisomer **3** is favored, since in both interactions bond formation between the atoms with the larger atomic orbital cofficients leads to the same regioisomer **3**.

The ir spectra of compounds **3** and **5** have the carbonyl absorption at about 1830 $cm^{-1}$, which is characteristic of saturated oxazolones [2] and the carbon-nitrogen double bond absorption at about 1650 $cm^{-1}$. In the mass spectra they gave, besides the molecular ion and other fragments, peaks corresponding to a retro-1,3-dipolar cycloaddition which is characteristic for cycloaddition products [13,14, 15]. The base peak corresponds in most cases to the fragment $PhCO^+$ (m/z 105).

Spiro-oxazolones **3** give also the characteristic reactions of oxazolones. Thus the compound **3g** reacts readily with methanol, water and *p*-toluidine and gives the corresponding isoxazolines **9**, **10**, **11** in very good yields (75-85%).




From the above reactions it seems that spiro-oxazolones **3** may be used as precursors for the synthesis of various substituted isoxazolines.

## EXPERIMENTAL

All melting points were uncorrected and they were obtained with a Kofler hot-stage apparatus. The ir spectra were obtained with a Perkin-Elmer Model 297 spectrophotometer. The nmr spectra, reported in δ units, were obtained with a Varian A60A spectrometer with tetramethylsilane as internal standard. The mass spectra were measured with a Hitachi-Perkin-Elmer Model RMU-6L spectrometer, with an ionization energy of 70 eV. Elemental analyses were performed with a Perkin-Elmer analyzer Model 240-B.

### Preparation of Sarting Materials.

Oxazolones **2** were prepared by a Perkin-Erlenmeyer reaction, according to an Organic syntheses procedure [16], from the appropriate substituted benzaldehyde, hippuric acid, sodium acetate and acetic anhydride. Mesitonitrile oxide **1a** as well as 2,6-dichlorobenzonitrile oxide **1b** were prepared according to known procedures [17] from the corresponding aldoximes with *N*-bromosuccinimide and triethylamine. *E*-2-Phenyl-4-benzylidene-5(4*H*)-oxazolone (**4**) was prepared by isomerization of the *Z*-isomer **2a** in saturated hydrobromic acid [8]. The melting points of all the prepared starting materials, which were known compounds, were in accordance with those given in the literature.

### General Procedure for the Reactions of 2-Phenyl-4-arylidene-5(4*H*)-oxazolones **3**a nd **4** with Nitrile Oxides.

A solution of oxazolone **2a-e**, **4** (1 mmole) and nitrile oxide **1a,b** (2 mmoles) in methylene chloride (25 ml) was refluxed for fifteen days. Then the methylene chloride was removed *in vacuo* and the residue was crystallized by a mixture of equal volume of methylene chloride and ethyl ether. A second crop of spiro-oxazolones **3a-j** and **5a,b** was collected by evaporation of the filtrates and treatment of residues with ethyl ether-hexane mixtures. For analytical purposes **3a-j** and **5a,b** were recrystallized from a mixture of methylene chloride-hexane. Analytical and spectral data are summarized in Table I.

### Reaction of **3g** with Methanol.

A solution of **3g** (0.2 mmole) in methanol (3 ml) was refluxed for one hour. After the removal of methanol *in vacuo*, recrystallization of the residue from methylene chloride-hexane gave **9** in 85% yield, mp 220-220°; ir (Nujol, $cm^{-1}$): 3330 (NH), 1740 (C=O), 1645 (C=N and/or C=O); nmr (deuteriochloroform): δ 2.28 (s, 3H), 3.92 (s, 3H), 5.7 (s, 1H), 6.57 (broad singlet, 1H), 6.95-7.50 (m, 12H).

*Anal.* Calcd. for $C_{25}H_{20}Cl_2N_2O_4$ (MW 483.37): C, 62.12; H, 4.18; N, 5.80. Found: C, 62.31; H, 4.13; N, 5.94.

### Reaction of **3g** with Water.

A solution of **3g** (0.2 mmole) in acetone (2 ml) and water (0.5 ml) was allowed to stay at room temperature for two days. Then the solvents were evaporated *in vacuo* and benzene (2 × 5 ml) was added and evaporated in order to remove traces of water. Recrystallization of the residue from methylene chloride/hexane gave **10** in 80% yield, mp 158-165°; ir (Nujol): $cm^{-1}$ 3320 (NH), 1750 (C=O), 1635 (C=N and/or C=O); nmr (deuteriochloroform): δ 2.28 (s, 3H), 5.98 (s, 1H), 6.78 (s, 1H), 6.97-7.62 (m, 12H), 1.03 (broad singlet, 1H).

*Anal.* Calcd. for $C_{24}H_{18}Cl_2N_2O_4$ (MW 469.34): C, 61.41; H, 3.87; N, 5.97. Found: C, 61.22; H, 3.91. N, 5.70.

### Reaction of **3g** with *p*-Toluidine.

A solution of **3g** (0.2 mmole) and *p*-toluidine (0.6 mmole) in chloroform (5 ml) was allowed to stay at room temperature for 24 hours. Then by addition of hexane compound **11** was crystallized. Recrystallization from methylene chloride-hexane gave **11** in 77% yield, mp 233-234°; ir (Nujol): $cm^{-1}$ 3390 (NH), 3320 (NH), 1690 (C=O), 1675 (C=O); nmr (deuterio-

chloroform + trifluoroacetic acid): δ 2.33 (s, 3H), 2.37 (s, 3H), 5.68 (s, 1H), 6.83-7.53 (m, 17H), 9.45 (broad singlet, 1H).

*Anal.* Calcd. for $C_{31}H_{25}Cl_2N_3O_3$ (MW 558.49): C, 66.66; H, 4.52; N, 7.53. Found; C, 66.60; H, 4.56; N, 7.39.

Acknowledgement.

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