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Stable nitrile oxides add regioselectively to the carbon-carbon double bond of 4-arylidene-2-phenyl-1,4-dihydroimidazol-5-ones to afford spiro isoxazolines **3**. Compounds **3** are further hydrolysed to isoxazole derivatives.

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Although unsaturated 2,4-disubstituted 5-oxazolones (azlactones) consist an early and well studied class of synthons [1-4], their nitrogen analogs unsaturated 2,4-disubstituted imidazol-5-ones have been studied only to a small extent [5,6]. Previously we have studied the 1,3-dipolar cycloaddition reactions of nitrile oxides and nitrile imines with 4-arylidene-5(4*H*)-oxazolones affording spiro isoxazoline and pyrazoline derivatives which are easily transformed to heterocyclic amino acid derivatives by nucleophilic ring opening of the oxazolone ring [7,8]. In connection with these studies and in order to examine the reactivity of unsaturated imidazolones in 1,3-dipolar cycloaddition reactions and the possible use of these reactions as a route for the synthesis of several substituted heterocycles in this paper the reaction of nitrile oxides with 2-phenyl-4-arylidene-1,4-dihydroimidazol-5-ones is studied.

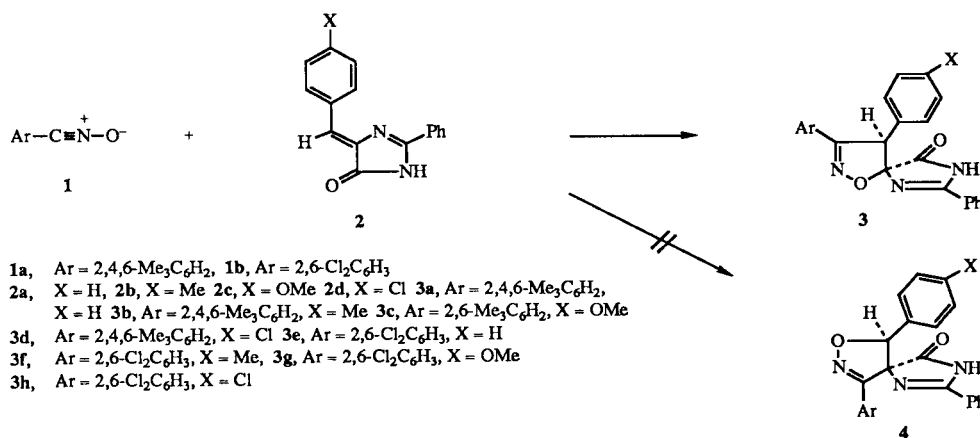
The reaction of the stable mesitonitrile oxide **1a** and 2,6-dichlorobenzonitrile oxide **1b** with the imidazolones **2a-d** took place after reflux of a chloroform solution of the reactants for 40-60 hours using nitrile oxide in excess (2:1) and gave 3,4-diaryl-7-phenyl-1-oxa-2,6,8-triazaspiro[4,4]nona-2,6-diene-9-ones **3** in good yields (60-80%) (Scheme 1).

The imidazolones used, prepared from the corresponding *Z*-4-arylidene-2-phenyl-5(4*H*)-oxazolones, are considered to be the *Z*-isomers according to their nmr data [9].

The reaction of imidazolones with nitrile oxides show a close similarity to the analogous reaction of oxazolones. Thus, the carbon-carbon double bond of **2** is a rather weak dipolarophile. No product was isolated from attempted reactions with the unstable benzonitrile oxide, whereas with the stable nitrile oxides **1a** and **1b** the reaction took place only after prolonged heating. In all cases only one regioisomer was isolated. The formation of only one regioisomer was also evidenced from tlc and ¹H nmr of the crude reaction mixtures.

The structural assignments of the isolated spiro-imidazolones **3** was made on the basis of their elemental analysis and spectroscopic data (ir, ¹H nmr, ms) which are summarized in Table I. In the ir spectra they have the N-H absorption at 3150-3200, the C=O at 1735-1745 and the C=N at 1615-1630 cm⁻¹. In the mass spectra, almost in all cases, they give molecular ion of negligible intensity or not at all and characteristic high intensity peaks corresponding to a retro-1,3-dipolar cycloaddition fragments. In the ¹H nmr the isoxazoline ring protons resonate at δ 5.22-5.31 for the 3-mesityl derivatives **3a-d** and 5.67-5.73 for

Scheme 1



Scheme 2

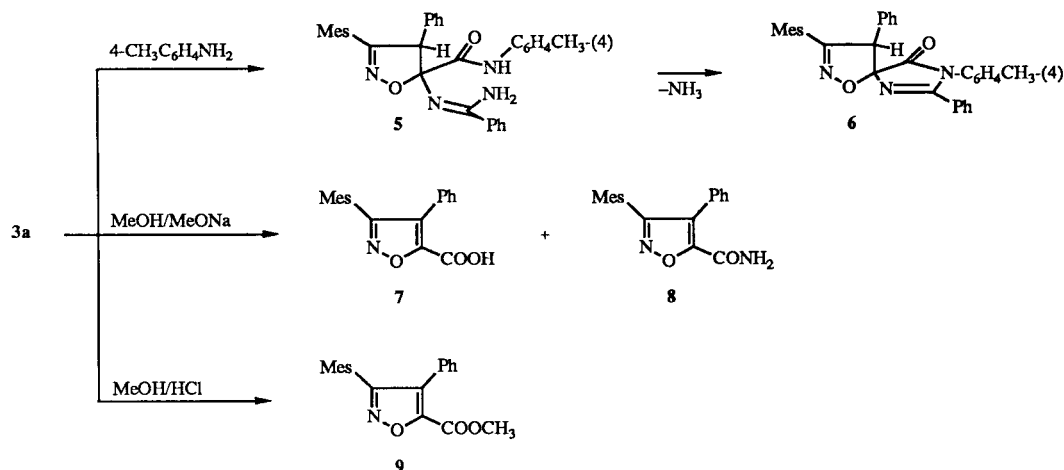


Table I
Analytical and Spectral Data of Spiro-compounds 3

Compound	MP °C	Yield %	Molecular Formula (MW)	Analyses %			Spectral Data
				Calcd./	Found	N	
			C	H			
3a	216-218	75	C ₂₆ H ₂₃ N ₃ O ₂ (409.47)	76.26 76.36	5.66 5.74	10.26 10.23	ir (nujol, cm ⁻¹), 3150 (NH), 1735 (C=O), 1615 (C=N), ¹ H nmr (deuteriochloroform) : δ 2.28 (s, 3H), 2.38 (s, 6H), 5.31 (s, 1H), 6.80 (s, 2H), 7.0-8.23 (m, 10H); ms : m/z (%) 409 (M ⁺ , 5), 248 (100), 161 (90), 145 (45), 130 (49), 117 (99), 104 (81), 103 (55)
3b	198-200	70	C ₂₇ H ₂₅ N ₃ O ₂ (423.5)	76.57 76.65	5.95 6.12	9.92 9.74	ir (nujol, cm ⁻¹), 3180 (NH), 1740 (C=O), 1630 (C=N), ¹ H nmr (deuteriochloroform) : δ 2.12 (s, 3H), 2.17 (s, 3H), 2.38 (s, 6H), 5.25 (s, 1H), 6.72 (s, 2H), 6.83-7.95 (m, 9H), ms : m/z (%) 423 (M ⁺ , 1), 262 (92), 161 (74), 145 (26), 130 (100), 129 (56), 117 (18), 104 (93), 103 (68)
3c	223-226	60	C ₂₇ H ₂₅ N ₃ O ₃ (439.49)	73.78 73.58	5.73 5.76	9.56 9.32	ir (nujol, cm ⁻¹), 3180 (NH), 1745 (C=O), 1620 (C=N); ¹ H nmr (deuteriochloroform) : δ 2.14 (s, 3H), 2.33 (s, 6H), 3.53 (s, 3H), 5.22 (s, 1H), 6.57 (d, 2H, J = 9 Hz), 6.73 (s, 2H), 7.09 (d, 2H, J = 9 Hz), 7.18-8.0 (m, 5H); ms : m/z (%) [a] 278 (16), 161 (20), 145 (20), 130 (30), 104 103 (100)
(50), 3d	217-220	62	C ₂₆ H ₂₂ N ₃ O ₂ Cl (443.92)	70.34 70.48	4.96 4.93	9.47 9.52	ir (nujol, cm ⁻¹), 3180 (NH), 1740 (C=O), 1620 (C=N), ¹ H nmr (deuteriochloroform) : δ 2.20 (s, 3H), 2.36 (s, 6H), 5.27 (s, 1H), 6.8 (s, 2H), 7.01-8.0 (m, 9H); ms : m/z (%) 443 (M ⁺ , 1), 282 (60), 161 (74), 151 (41), 145 (27), 130 (41), 117 (20), 104 (100), 103 (61)
3e	242-245	80	C ₂₃ H ₁₅ N ₃ O ₂ Cl ₂ (436.29)	63.31 63.04	3.46 3.35	9.63 9.60	ir (nujol, cm ⁻¹), 3200 (NH), 1740 (C=O), 1620 (C=N); ¹ H nmr (deuteriochloroform) : δ 5.73 (s, 1H), 7.03-7.88 (m, 13H); ms : m/z (%) 435 (M ⁺ , 1), 248 (80), 187 (30), 171 (27), 126 (20), 124 (64), 117 (84), 104 (100), 103 (37)
3f	198-203	78	C ₂₄ H ₁₇ N ₃ O ₂ Cl ₂ (450.31)	64.01 63.98	3.81 4.10	9.33 9.21	ir (nujol, cm ⁻¹), 3200 (NH), 1745 (C=O), 1630 (C=N) ¹ H nmr (deuteriochloroform) : δ 2.12 (s, 3H), 5.68 (s, 1H), 6.81-8.16 (m, 12H); ms : m/z (%) [a] 262 (90), 187 (25), 171 (65), 131 (75), 124 (24), 116 (17), 104 (70), 103 (100)
3g	218-222	80	C ₂₄ H ₁₇ N ₃ O ₃ Cl ₂ (466.31)	61.81 61.81	3.67 3.48	9.01 8.98	ir (nujol, cm ⁻¹), 3180 (NH), 1740 (C=O), 1630 (C=N), ¹ H nmr (deuteriochloroform) : δ 3.65 (s, 3H), 5.67 (s, 1H), 6.66 (d, 2H, J = 7 Hz), 7.25-7.5 (m, 10H); ms : m/z (%) 465 (M ⁺ , 1), 278 (92), 187 (45), 171 (45), 148 (20), 147 (80), 132 (35), 124 (64), 104 (100), 103 (89)
3h	237-240	60	C ₂₃ H ₁₄ N ₃ O ₂ Cl ₃ (470.74)	58.68 58.64	2.99 2.85	8.92 8.75	ir (nujol, cm ⁻¹), 3180 (NH), 1740 (C=O), 1615 (C=N), ¹ H nmr (deuteriochloroform) : δ 5.70 (s, 1H), 6.53-7.88 (m, 12H), ms : m/z (%) [a] 282 (50), 187 (50), 171 (70), 124 (60), 116 (15), 104 (70), 103 (100)

[a] No peak for the molecular ion.

2,6-dichlorophenyl derivatives **3e-h**. These values are very close to the isoxazoline hydrogens chemical shift of the analogous oxazolone derivatives [7], supporting the same regiochemistry for both cycloadducts. Although these, rather low field chemical shifts, are more consistent with structure **4**, structure **3** has been proved for the cycloadducts, through their decomposition products as in the case of spiro oxazolones [8].

Unlike the close similarity observed in the reaction of imidazolones with nitrile oxides to that of oxazolones, the resulted spiro-cycloadducts **3** show different chemical behaviour. Cycloadducts **3** are stable enough to be separated without decomposition by column chromatography. As it is expected they are not readily ring opened by nucleophiles. No reaction of **3a** was observed with methanol (2 hours reflux of a methanolic solution of **3a**) and with *p*-toluidine (allowing at room temperature for 24 hours a chloroform solution of **3a** with toluidine in excess, molar ratio 1:3). Reaction with toluidine under harsher conditions (50 hours reflux) resulted in spiro-derivative **6** along with unreacted **3a**. Compound **6** is probably formed through initial aminolysis of **3a** to the amidine **5** and subsequent recyclization with abstraction of ammonia, in resemblance to the reaction scheme accepted for the conversion of oxazolones to imidazolones [10]. Reaction of **3a** with methanol in the presence of sodium methoxide gave isoxazole carboxylic acid **7** and amide **8** along with benzonitrile. Also acid hydrolysis of **3a** gave the ester **9**. (Scheme 2).

The formation of the isoxazole-5-carboxylic acid derivatives proves structure **3** for the isolated cycloadducts, since regioisomer **4** should result the corresponding isoxazole-4-carboxylic acid derivatives. In summary, although the easy transformation of cycloadduct **3** to isoxazole derivatives may be useful for synthetic purposes, it seems that they cannot serve as a source for heterocyclic amino acid derivatives since the relatively harsh reaction conditions used for their nucleophilic ring opening cause simultaneously aromatization of the isoxazoline ring through abstraction of the amino moiety.

EXPERIMENTAL

All melting points were uncorrected and 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 Bruker AW-80 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 Model 240-B analyzer. Column chromatography was performed over Merck Kieselgel 60.

Preparation of Starting materials.

Nitrile oxides **1** were prepared according to known procedures [11] from the corresponding aldoximes with *N*-bromosuccinimide and triethylamine. Imidazolones **2** were prepared from the corresponding oxazolones with ammonium hydroxide and potassium carbonate [12].

General Procedure for the Reactions of Imidazolones **2** with Nitrile Oxides.

A suspension of Imidazolone **2a-d** (1 mmole) and nitrile oxide **1a,b** (2 mmoles) in chloroform (25 ml), was refluxed with stirring for 40-60 hours. The initially partly insoluble imidazolone was dissolved after 20-30 hours and the reaction was monitored by tlc until the consumption of all the imidazolone. After the removal of the solvent the residue was chromatographed on a silica gel column using hexane-ethyl acetate mixture (2:1) as eluant. The isolated cycloadducts **3** were further recrystallized from methylene chloride-hexane mixtures. Analytical and spectral data are summarized in Table I.

Reaction of **3a** with *p*-Toluidine.

A solution of spiro-compound **3a** (0.5 mmole) and *p*-toluidine (1.5 mmoles) in chloroform (5 ml) was refluxed for 50 hours. After evaporation of the solvent the residue was chromatographed on a silica gel column with a mixture of hexane-ethyl acetate 2:1 as eluant to give along with unreacted starting materials compound **6** in 70% yield, mp 192-195° (from hexane-diethyl ether); ir (nujol): cm^{-1} 1755 (C=O), 1620 (C=N); nmr (deuteriochloroform): δ 2.21 (s, 3H), 2.31 (s, 3H), 2.42 (s, 6H), 5.46 (s, 1H), 6.68-6.79 (m, 4H), 6.95-7.36 (m, 12H); ms: m/z (%) 499 (M^+ , 1), 338 (100), 235 (72), 194 (96), 161 (98), 103 (98).

Anal. Calcd. for $C_{33}H_{29}N_3O_2$ (MW, 499.61): C, 79.33; H, 5.85; N, 8.41. Found: C, 79.47; H, 5.72; N, 8.51.

Reaction of **3a** with Methanol/Sodium Methoxide.

A solution of spiro-compound **3a** (0.5 mmole) in absolute methanol (5 ml) containing a catalytic amount (5%) of sodium methoxide was refluxed for 2 hours. After evaporation of the methanol, water and diethyl ether were added. The water layer was acidified with hydrochloric acid and extracted with diethyl ether to give 3-mesityl-4-phenylisoxazole-5-carboxylic acid **7** in 32% yield, identified by comparison of its spectral data with those previously reported [8]. The organic layer was dried and chromatographed on a silica gel column with a mixture of hexane-ethyl acetate 10:1 as eluant to give benzonitrile in 40% yield and 3-mesityl-4-phenylisoxazole-5-carboxamide **8** in 50% yield, mp 143-145° (from hexane-dichloromethane); ir (nujol): cm^{-1} 3440, 3170 (NH_2), 1665 (C=O), 1615 (C=N); ^1H nmr (deuteriochloroform): δ 1.98 (s, 6H), 2.25 (s, 3H), 6.40 (bs, 2H), 6.84 (s, 2H), 7.23 (s, 5H); ms: m/z (%) 306 (M^+ , 13), 262 (21), 234 (9), 77 (100).

Anal. Calcd. for $C_{15}H_{18}N_2O_2$ (MW, 306.36): C, 74.49; H, 5.97; N, 9.14. Found: C, 74.11; H, 6.01; N, 8.99.

Reaction of **3a** with Methanol/Hydrochloric Acid.

A solution of the spiro-compound **3a** (0.5 mmole) in methanol (5 ml) containing 10% hydrochloric acid was refluxed for 4 hours. An insoluble solid was obtained and identified as methyl 3-mesityl-4-phenylisoxazole-5-carboxylate **9**, by comparison of its spectral data with those previously reported [8]. The filtrate after evaporation of the methanol was taken up with water-diethyl ether. The organic layer was dried and after evaporation of the

solvent was chromatographed on a silica gel column with a mixture of hexane-ethyl acetate 2:1 as eluant to give a second crop of **9** along with some unreactive **3a**. The total yield of **9** was 72%.

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