Site-and Regioselective $\pi^4S + \pi^2S$ Cycloaddition of Nitrileoxides to Pyridazin-3-ones: Formation of Novel 3a,7a-Dihydroisoxazolo[4,5-*d*]pyridazin-4-ones [1]

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A study of the cycloaddition behaviour of substituted pyridazin-3-ones with arylnitrile oxides has been carried out. Nitrile oxides udergo site and regioselective 1,3-dipolar cycloaddition to 4,5-double bond of pyridazinone to afford 3a,7a-dihydroisoxazolo[4,5-*d*]pyridazin-4-ones. The reactions follow frontier orbital predictions. Nitrile oxide HOMO-pyridazinone LUMO combination is dominant.

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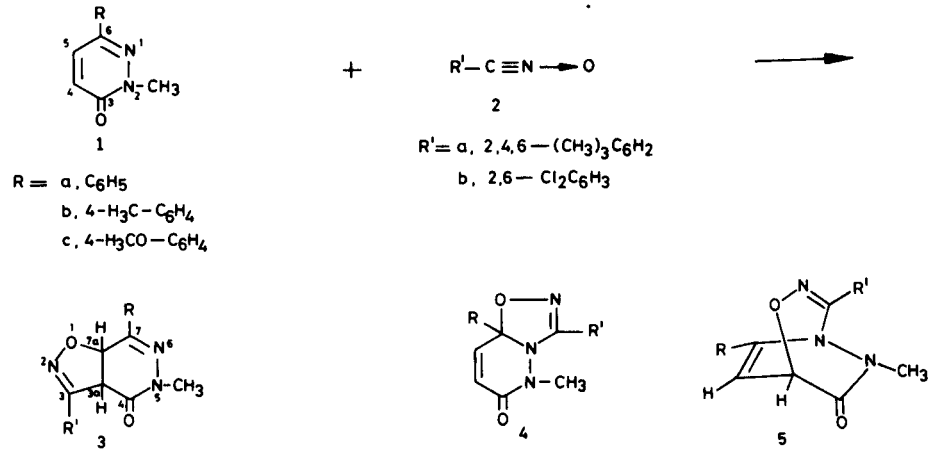
Attempts to involve the biologically important pyridazinone ring system **1** in 1,3-dipolar cycloaddition reactions for synthesizing novel fused heterocycles have not so far been successful except in the cycloaddition of diazoalkanes to pyridazinone giving an unstable cycloadduct [2]. Our interest in nitrile oxide cycloadditions [3] and in synthetic reactions involving pyridazinones [4,5] led to this study of cycloaddition of nitrile oxides with pyridazinones for the first time, to assess the dipolarophilicity of pyridazinones.

The cycloaddition of nitrile oxide **2** to pyridazinone **1** may involve either a $\pi^4S + \pi^2S$ reaction at 4,5 or 1,6 positions or a $\pi^4S + \pi^4S$ cycloaddition at 1,4 positions of the pyridazinone ring system leading to products **3**, **4** or **5** respectively (Scheme 1). The latter reaction, though forbidden, may be acceptable from the standpoint of ring strain [6]. There is also the theoretical possibility of the pyridazinone acting as a diene with nitrile oxide as a dienophile.

Two approaches are used in studying the problem. Since the reactions are expected to be pericyclic, a frontier orbital analysis is carried out first to see the various preferences for products **3**, **4** and **5** [7]. A parallel experimental study is carried out with derivatives of **1** and **2**.

Results and Discussion.

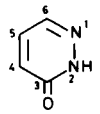
Scheme 1



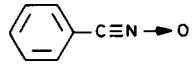
3 a, R = C_6H_5 ; R' = 2,4,6-$(CH_3)_3$ C_6H_2
b, R = C_6H_5 ; R'= 2,6-Cl_2 C_6H_3
c, R = 4-H_3C-C_6H_4 ; R'= 2,4,6-$(CH_3)_3$ C_6H_2
d, R = 4-H_3CO-C_6H_4 ; R'= 2,4,6-$(CH_3)_3$ C_6H_2
e, R = 4-H_3CO-C_6H_4 ; R'= 2,6-Cl_2 C_6H_3

a) Frontier Orbital Analysis.

The parent compounds **1** and **2** are optimised using the MNDO method keeping C_s and C_{2v} symmetry respectively [8].

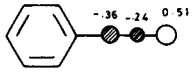


1



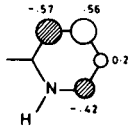
2

The HOMO-LUMO combination that seems to be dominant is HOMO **2** - LUMO **1** because their energy difference is only 8.60 eV while the reverse pair [HOMO **1** -LUMO **2**] is separated from each other by 8.98 eV. We have then looked for site selectivity and regioselectivity of the possible cycloadditions. To facilitate in this, the coefficients of the HOMO of **2** and the LUMO of **1** are given in **6** and **7**.



HOMO OF 2

6



LUMO OF 1

7

The site selectivity can be immediately judged from the size of the coefficients of C_4,C_5 and N_1,C_6 of **1**. Since the coefficients at the C_4-C_5 double bond is larger, the C_4,C_5 site will be preferred. The 4 + 2 cycloaddition involving **1** as diene and C=N in **2** as dienophile (2π system) is also not favourable. The HOMO-LUMO matching also confirms that a 4 + 4 cycloaddition between **1** and **2** is symmetry forbidden [9]. There are two products expected from the 4 + 2 addition of **1** and **2** depending on the orientation of **2** with respect to the C_4-C_5 double bond of **1**. This regiospecificity cannot be predicted by the LUMO coefficients as these are almost the same **7**. It is likely that charge control decides the regiospecificity of the addition [10]. Since oxygen is the negative end in the nitrile oxide **2**, it may prefer to attach itself to C_5 of **1** which has more positive character. This has been ascertained from the resonance structures possible for **1** and from a Mulliken overlap population analysis. Similar studies are also carried out using extended Hückel calculations with the actual compounds employed in the experimental study. These give the same conclusions for the site and regiochemistry of the 4 + 2 addition products.

b) Experimental Results.

We have carried out the following reactions to verify these expectations. Pyridazinone **1** and nitrile oxide **2** are heated at 60° in chloroform for 170 hours and the product obtained is purified by column chromatography. The reaction gives exclusively a single stable product.

The accurate mass measurement of the products indicated that a 1:1 cycloaddition took place betwen nitrile oxide **2** and pyridazinone **1**. The structural assignment is based mainly upon ^1H and ^{13}C nmr studies. In the 500 MHz ^1H nmr spectrum, two doublets centered around δ 4.6 and δ 5.9 clearly rule out structure **4**. In this structure **4**, C_4-H and C_5-H protons of the starting pyridazinone **1** are intact and should be seen around δ 6.9 to δ 7.9 along with aromatic protons as observed in **1**. The proton resonance at these positions may be favourably assigned to C_{3a}-H and C_{7a}-H respectively in structure **3**. This does not, however, completely preclude structure **5**. The final proof of the structure in favour of **3** has come from ^{13}C nmr investigation. The proton decoupled ^{13}C nmr spectrum with two peaks at 37.7 ppm and 76.5 ppm confirms the structure **3** and can be assigned respectively to C_{3a} and C_{7a} carbons. Structure **5**, however, would not have any resonance at 37.7 ppm and instead additional olefinic carbons should appear in the spectrum.

All the products obtained are characterized by nmr, ms, accurate mass measurement and elemental analysis.

In conclusion, the work described in this paper reveals that arylsubstituted nitrileoxides undergo a site and regioselective 1,3-dipolar cycloaddition to 4,5-double bond of pyridazinones as predicted by frontier orbital analysis to give rise to novel 3a,7a-dihydroisoxazolo[4,5-*d*]pyridazin-4-ones in fairly good yields.

EXPERIMENTAL

Infrared spectra were recorded on a Perkin-Elmer model 283B. The ^1H and ^{13}C nmr spectra of **3a** were recorded respectively at 500 and 125.7 MHz on a Bruker AM-500 spectrometer. The nmr spectra of compounds **3b-e** were recorded on a Bruker AM-300 spectrometer with TMS as internal standard. Accurate mass measurements were carried out with VG Micromass 70 70H mass spectrometer at a resolution of 5000 with PFK as reference using a VG data system. Melting points were recorded on a Büchi 510 melting point apparatus and are uncorrected. Commercial reagents and solvents were purified to match reported physical and spectral data.

2-Methyl-3-oxo-6-arylpyridazines **1a-c** were synthesized from β-aroylpropionic acids as reported earlier [11,12,13,14]. Aryl nitrile oxides were prepared from the corresponding oximes by sodium hypobromite oxidation as described by Grundmann and Dean [15].

The MNDO calculations were carried out using the programme QCPE, 353 (1980) at the computer centre of National Informatic Centre, Hyderabad. MNDO geometries of **1** and **2** are available from the authors.

General Procedure.

Preparation of 3a,7a-Dihydro-3-(2,4,6-trimethylphenyl)-4-oxo-5-methyl-7-phenylisoxazolo[4,5-*d*]pyridazine **3a**.

To 2-methyl-3-oxo-6-phenylpyridazine **1a** (1.86 g, 10 mmoles) dissolved in dry chloroform (20 ml) was added 2,4,6-trimethylbenzonitrile oxide **2a** (1.61 g, 10 mmoles) in chloroform (20 ml) at ambient temperature and heated at 60° for 170 hours. The solvent was removed under reduced pressure. The cycloadduct formed was purified by column chromatography on silicagel using chloroform as eluent. The product obtained was recrystallized from chloroform-ether, 2.43 g (70%) mp 145-147°; 0.45 g of **1a** was recovered; ir (potassium bromide): 1660 cm^{-1} (CO); ^1H nmr (deuteriochloroform): 300 MHz, δ 6.90-7.92 (m, 7H), 5.90 (d, 1H, J = 12.2 Hz), 4.62 (d, 1H, J = 12.2 Hz), 3.44 (s, 3H), 2.29 (s, 6H), 2.21 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 37.72 (C-3a), 76.50 (C-7a); accurate mass Calcd. for $C_{21}H_{21}N_3O_2$: 347.1631. Found: 347.1639; ms: m/z 347 (M^+), 186, 161.

Anal. Calcd. for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.09. Found: C, 72.81; H, 6.08; N, 12.06.

Compounds **3b-e** were prepared from **1** (10 mmoles) and **2** (10 mmoles) under essentially the same conditions.

3a,7a-Dihydro-3-(2,6-dichlorophenyl)-4-oxo-5-methyl-7-phenylisoxazolo-[4,5-*d*]pyridazine **3b**.

This compound was obtained in 58% yield (2.17 g) mp 235-237°; 0.72 g of **1a** was recovered; ir (potassium bromide): 1660 cm^{-1} (CO); ^1H nmr (deuteriochloroform): 300 MHz, δ 6.92-7.81 (m, 8H), 5.91 (d, 1H, J = 12.1 Hz), 4.54 (d, 1H, J = 12.1 Hz), 3.46 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 37.54 (C-3a), 76.72 (C-7a); accurate mass Calcd. for $C_{18}H_{13}Cl_2N_3O_2$: 373.0383. Found: 373.0399; ms: m/z 373 (M^+), 187, 186.

Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_2$: C, 57.77; H, 3.50; N, 11.23. Found: C, 57.87; H, 3.48; N, 11.21.

3a,7a-Dihydro-3-(2,4,6-trimethylphenyl)-4-oxo-5-methyl-7-(4-methylphenyl)isoxazolo[4,5-*d*]pyridazine **3c**.

This compound was obtained in a yield of 68% (2.45 g) mp 188-189°; 0.60 g of **1b** was recovered; ir (potassium bromide): 1665 cm^{-1} (CO); ^1H nmr (deuteriochloroform): 300 MHz, δ 6.90-7.92 (m, 6H), 5.85 (d, 1H, J = 12.2 Hz), 4.52 (d, 1H, J = 12.2 Hz), 3.44 (s, 3H), 2.32 (s, 9H), 2.14 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 37.82 (C-3a), 76.84 (C-7a); accurate mass Calcd. for $C_{22}H_{23}N_3O_2$: C, 361.1787. Found: 361.1781; ms: m/z 361 (M^+), 200, 161.

Anal. Calcd. for $C_{22}H_{23}N_3O_2$: C, 73.11; H, 6.41; N, 11.63. Found: C, 73.30; H, 6.40; N, 11.58.

3a,7a-Dihydro-3-(2,4,6-trimethylphenyl)-4-oxo-5-methyl-7-(4-methoxyphenyl)isoxazolo[4,5-*d*]pyridazine **3d**.

This compound was obtained in a yield of 61% (2.30 g) mp 168-170°; 0.78 g of **1c** was recovered; ir (potassium bromide): 1660 cm^{-1} (CO); ^1H nmr (deuteriochloroform): 300 MHz, δ 6.93-7.84 (m, 6H), 5.90 (d, 1H, J = 12 Hz), 4.62 (d, 1H, J = 12 Hz), 3.91 (s, 3H), 3.42 (s, 3H), 2.34 (s, 6H), 2.26 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 37.84 (C-3a), 76.52 (C-7a); accurate mass Calcd. for $C_{22}H_{23}N_3O_3$: 377.1737. Found: 377.1744; ms: m/z 377 (M^+), 216, 161.

Anal. Calcd. for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 70.20; H, 6.13; N, 11.02.

3a,7a-Dihydro-3-(2,6-dichlorophenyl)-4-oxo-5-methyl-7-(4-methoxyphenyl)-isoxazolo[4,5-*d*]pyridazine **3e**.

This compound was obtained in a yield of 64% (2.60 g) mp 125-126°; 0.70 g of **1c** was recovered; ir (potassium bromide): 1660 cm^{-1} (CO); ^1H nmr (deuteriochloroform): 300 MHz, δ 6.92-7.93 (m, 7H), 5.82 (d, 1H, J = 12 Hz), 4.64 (d, 1H, J = 12 Hz), 3.92 (s, 3H), 3.44 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 37.56 (C-3a), 76.06 (C-7a); accurate mass Calcd. for $C_{19}H_{15}Cl_2N_3O_3$: 403.0489. Found: 403.0499; ms: m/z 403 (M^+), 216, 187.

Anal. Calcd. for $C_{19}H_{15}Cl_2N_3O_3$: C, 56.45; H, 3.74; N, 10.39. Found: C, 56.56; H, 3.73; N, 10.28.

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