

**PHOTOCHEMICAL BEHAVIOUR OF 1,2,5-OXADIAZOLES -  
IRRADIATION OF SOME 3-ACYLAMINO-1,2,5-  
OXADIAZOLES IN THE PRESENCE OF NUCLEOPHILES<sup>1</sup>**

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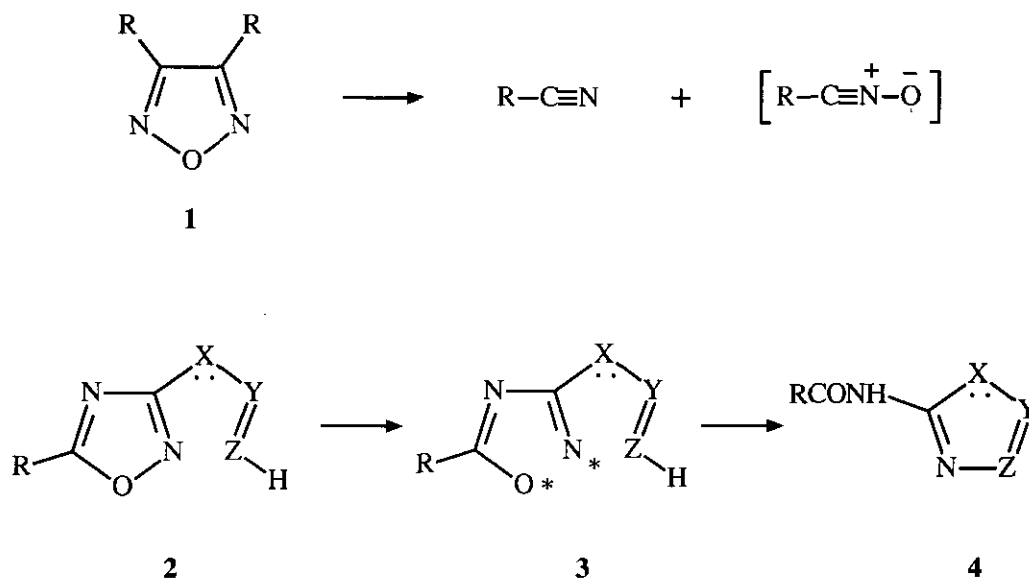
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**Abstract** - The photochemical behaviour of some 3-acylamino-1,2,5-oxadiazoles (furazans) has been investigated. On irradiation at 254 nm in the presence of nucleophiles (ammonia, primary or secondary amines), the photoreaction produced 3-substituted 1,2,4-oxadiazoles in which the substituent at C(3) arises from the used reagent. Some mechanistic considerations are reported.

The photochemistry of 1,2,5-oxadiazoles (furazans) is little represented in the literature; some reports concern irradiation of 3,4-dimethyl- (1; R = Me) or 3,4-diphenylfurazan (1; R = Ph), by which a fragmentative retro-cycloaddition into nitriles and nitrile oxides takes place.<sup>2</sup> A similar behaviour is also reported for benzofurazans and benzofuroxans.<sup>3</sup> In turn, the nitrile oxide species will collapse into the final product depending on the photoreaction

medium; that is, it can react with a dipolarophile in a cycloaddition pathway, or can rearrange into an isocyanate or nitrene which then will react.<sup>2,3</sup>

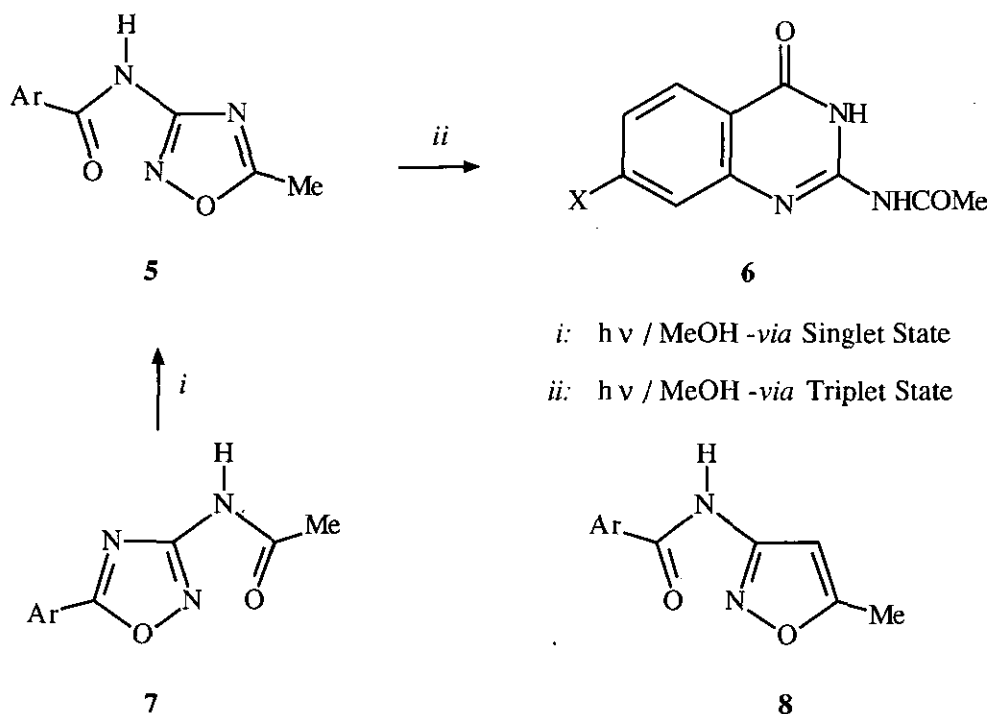
Scheme 1



During the last few years we became interested in the photochemical behaviour of five-membered heterocycles, with special attention to photoinduced rearrangements of suitably substituted azoles.<sup>4,5</sup> In this context we have reported<sup>6,7</sup> the photorearrangements of 1,2,4-oxadiazoles containing various side-chain groups (2) into compounds (4), according to the generalized pattern of the Scheme 1. Here, the photolysis of the ring O-N bond represents the key-step of the reaction, whereas the new ring-closure occurs only when assisted by an aromatic transition state. Interestingly, 3-acetylamino-5-aryl-1,2,4-oxadiazoles (7) and their ring-degenerated counterparts 3-arylamino derivatives (5) gave photochemical results (see Scheme 2) which have been rationalized on the basis of different chromophores (the oxadiazole ring and the aroylamino group in the side-chain, respectively) and different multiplicity of the involved excited state.<sup>7</sup> As a consequence, the 3-arylamino derivatives (5)

rearranged into compounds (**6**) through a six-membered photoinduced heterocyclization involving the aroylamino moiety. Differently, irradiation of 3-arylamino-5-methylisoxazoles (**8**) did not produce<sup>8</sup> rearrangements involving the aroylamino group, but low yields of the corresponding 2-arylamino-oxazoles, following the typical ring contraction - ring expansion route.<sup>9</sup>

Scheme 2



In the framework of our studies in this area, and pursuing our interest in photoinduced transformations of five-membered heterocycles as a versatile tool in the synthesis of target structures, we have now planned to explore the photochemistry of substituted furazans. Particularly, in order to generalize the photochemical behaviour of 3-acylamino-1,2-oxazoles, we have looked at possible photorearrangements of 3-acylamino-furazans (**10**). Taking into account the photolytic fragmentation of the furazan ring, here we have considered irradiations of the 3-acylamino compounds in the presence of some nucleophiles which could

have interacted with the species arising from the photolysis of the starting ring to give recyclizations involving the acylamino side-chain. It seems worth to remind that 3-acylamino-furazans (**10**) do not undergo the Boulton-Katritzky rearrangement<sup>10-12</sup> into the corresponding 1,2,4-oxadiazole oximes (**9**), as a consequence of the low reactivity of the furazan ring towards this reactions type. By contrast, the reverse reaction occurred; that is, the oxadiazole oximes (**9**) thermally rearranged into the 3-acylamino-furazans (**10**).<sup>12</sup> On the other hand, attempts to rearrange photochemically some tetrahydrobenzofurazan arylhydrazones were unsuccessful.<sup>13</sup>

## RESULTS AND DISCUSSION

Irradiation of the 3-acylamino-furazans (**10a-d**) was carried out at 254 nm by using low-pressure Hg lamps (17 W) in an immersion apparatus equipped with water circulation at 0-5°C. In the case of the 3-benzoylamino-4-methylfurazan (**10a**), various nucleophiles were tested (using aqueous ammonia, ethanolic methylamine or dimethylamine as solvents in one hand, or an excess of pyrrolidine, piperidine and n-butylamine in methanol in the other); in the case of other substrates, irradiation was carried out only in aqueous ammonia.

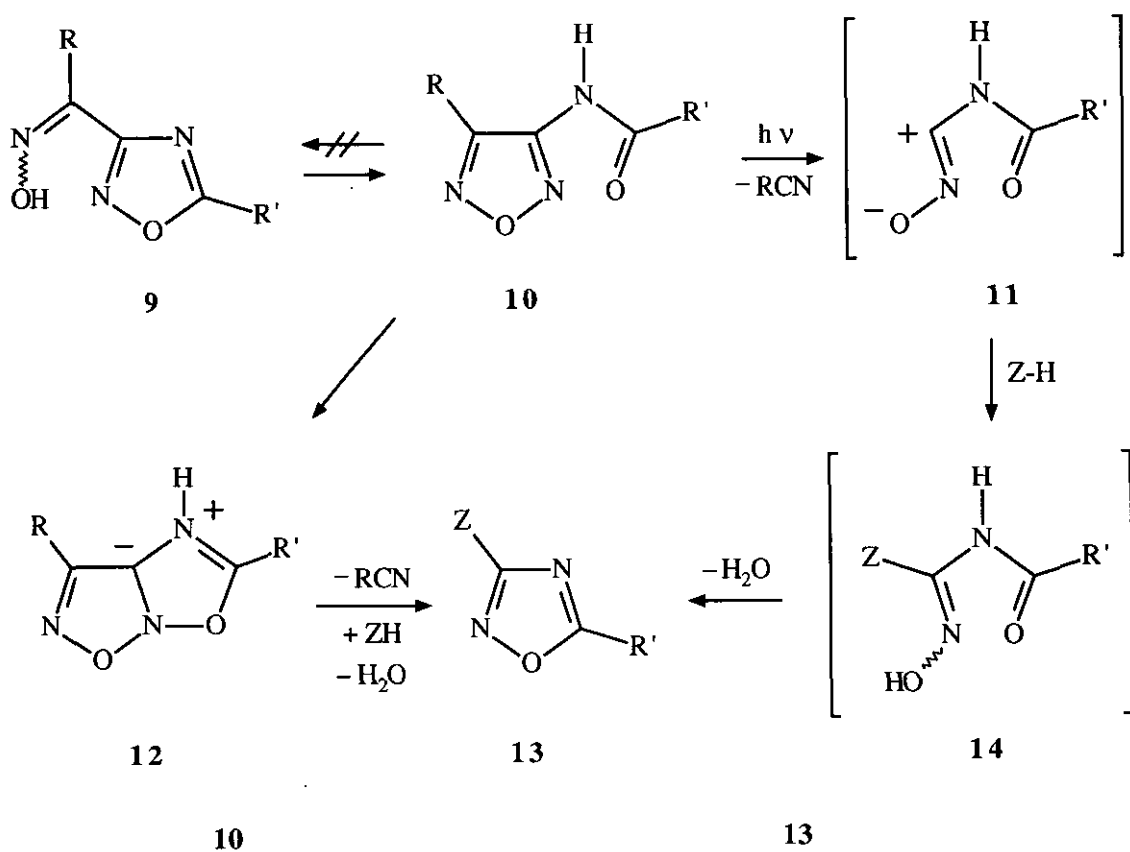
When irradiated, the acylamino compounds (**10**) gave the corresponding nitrile (verified by hplc analysis in the case of benzonitrile) and the 3-substituted 1,2,4-oxadiazoles (**13**), in which the substituent at C(3) arises from the used nucleophile (see Scheme 3). As expected, the formation of 1,2,4-oxadiazole oximes (**9**) was not observed; moreover, none of the products resulting from a six-membered ring-closure involving the aroylamino side-chain were isolated. The yields of the isolated oxadiazoles (**13**) (45-50%) could not be improved since the formation of secondary products from subsequent photoreactions. In a test experiment, irradiation of compound (**10a**) with pyrrolidine in methanol was carried out in a Rayonet apparatus; hplc analyses of the photoreaction showed that the yield of the corresponding oxadiazole (**13d**) reached the maximum value (50%) within 3 h of irradiation. However, the photoreaction is characterized by its simplicity and it seems of a general

applicability in the synthesis of 3-amino-, 3-(*N*-monosubstituted amino-), or 3-(*N,N*-disubstituted amino)-1,2,4-oxadiazoles.

As regards the mechanistic aspects, the formation of the 1,2,4-oxadiazole could be explained by assuming a photochemical conversion of the furazan ring into nitriles and a dipolar species (**11**), which will stabilize into the unisolated *N*-acylamidoximes (**14**) by a reaction with the nucleophile. The photolysis at the ring O(1)-N(2) bond level seems to be excluded; on the other hand, the double cleavage of the O(1)-N(5) and C(3)-C(4) bonds of the furazan ring in a retro-cycloaddition pattern could also result from a stepwise mechanism. In turn, the subsequent cyclization of the *N*-acylamidoximes into 1,2,4-oxadiazoles would represent a base-induced ring-closure via nucleophilic attack of the oxime oxygen atom at the carbonyl carbon of the acylamino group. In a different mechanism the 1,2,4-oxadiazole ring-closure could precede the furazan ring-fragmentation; that is, the photoreaction could proceed through a bicyclic species, represented by **12**, arising from a preliminary electrocyclic ring-closure involving the NCO sequence of the acylamino side-chain. From this species, extrusion of RCN and subsequent addition of the nucleophile and elimination of water would explain the formation of the compounds (**13**).

Further mechanistic investigations in this area are being carried out both on the photophysical properties of the molecules under study and on the mechanism of the observed photochemical processes.

Scheme 3



	R	R'
a	Me	Ph
b	Ph	Ph
c	Me	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>
d	Ph	Me

	R'	Z
a	Ph	NH <sub>2</sub>
b	Ph	NHMe
c	Ph	N(Me) <sub>2</sub>
d	Ph	NC <sub>4</sub> H <sub>8</sub>
e	Ph	NC <sub>5</sub> H <sub>10</sub>
f	Ph	NHC <sub>4</sub> H <sub>9</sub> (n)
g	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	NH <sub>2</sub>
h	Me	NH <sub>2</sub>

## EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus; ir spectra (nujol mulls) were determined with a Perkin-Elmer 257 instrument,  $^1\text{H}$  nmr (250 MHz) and  $^{13}\text{C}$  nmr (62 MHz) spectra with a Bruker 250/52 spectrometer (tetramethylsilane as internal standard; multiplicities by DEPT pulse sequence.), and mass spectra with a Finnigan INCOS XL spectrometer. Flash chromatography was performed on Merck silica gel (0.040-0.063 mm). Light petroleum refers to that fraction boiling in the range 40-60°C. Photochemical reactions at 254 nm were carried out with low-pressure Hg lamps (Helios Italquartz 17 W) in an immersion apparatus equipped with water circulation at 0-5°C and in a Rayonet RPR-100 photoreactor for test experiments. Hplc analyses were performed with a Perkin-Elmer Series 10 instrument, by using a C-18 SIL-X-10 Perkin-Elmer column (25 cm x 4.6 mm diameter) eluting with water/acetonitrile (7:3 v/v) at flow rate of 1.5 ml/min, monitoring the optical density at 254 nm. Ethanolic (33%) methylamine and dimethylamine were Fluka reagents.

The acylaminofurazans (**10a**),<sup>14</sup> (**10b**),<sup>14</sup> and (**10d**)<sup>15</sup> were prepared as reported. Similarly, on reacting 3-amino-4-methylfurazan with *p*-methoxybenzoyl chloride in benzene containing equimolar amount of pyridine and then working as usual gave compound **10c**, mp 123°C (benzene); ir: 3270, 3230, 3180  $\text{cm}^{-1}$  (NH), 1660  $\text{cm}^{-1}$  (CO);  $^1\text{H}$  nmr (DMSO- $d_6$ )  $\delta$ : 2.33 (s, 3H,  $\text{CH}_3$ ), 3.86 (s, 3H,  $\text{OCH}_3$ ), 7.00-8.00 (m, 4H, aromatic), 11.10 (s, 1H, NH). Anal. Calcd for  $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_3$ : C, 56.65; H, 4.72; N, 18.03. Found C, 56.60; H, 4.70; N, 18.00.

The oxadiazoles (**13a**),<sup>16</sup> (**13b**),<sup>4</sup> (**13c**),<sup>17</sup> (**13g**),<sup>4,18</sup> and (**13h**)<sup>19</sup> which were used as pure samples for comparison were prepared as reported. Similarly to the preparation of **13b,c**, the oxadiazoles (**13d**), (**13e**), and (**13f**) were prepared by reacting 3-chloro-5-phenyl-1,2,4-oxadiazole<sup>20</sup> with an excess of pyrrolidine, piperidine, or *n*-butylamine, respectively, in methanol. After work up by standard procedures, the products were purified by chromatography.

Compound (**13d**) had mp 65°C (light petroleum);  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$ : 1.90-2.10 (m, 4H, 2  $\text{CH}_2$ ), 3.48-3.53 (m, 4H, 2  $\text{CH}_2$ ), 7.27-8.10 (m, 5H, aromatic);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ )  $\delta$ : 26.61 (t), 47.52 (t), 124.93 (s), 127.70 (d), 128.64 (d), 132.19 (d), 168.62 (s), 174.03 (s); ms m/z: 215 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}$ : C, 66.94; H, 6.09; N, 19.53. Found C, 67.00; H, 6.00; N, 19.50.

Compound (**13e**) had mp 32°C (light petroleum, by freezing);  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$ : 1.65-1.68 (m, 6H, 3  $\text{CH}_2$ ), 3.48-3.51 (m, 4H, 2  $\text{CH}_2$ ), 7.43-8.00 (m, 5H, aromatic);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ )  $\delta$ : 24.13 (t), 24.96 (t), 46.96 (t), 124.80 (s), 127.78 (d), 128.77 (d), 132.16 (d), 170.80 (s), 174.04 (s); ms m/z: 229 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}$ : C, 68.10; H, 6.59; N, 18.33. Found C, 68.00; H, 6.60; N, 18.30.

Compound (**13f**) had mp 35°C (light petroleum, by freezing); ir: 3365, 3340  $\text{cm}^{-1}$  (NH);  $^1\text{H}$  nmr ( $\text{DMSO-d}_6$ )  $\delta$ : 0.90 (t,  $J = 7.5\text{Hz}$ , 3H,  $\text{CH}_3$ ), 1.30-1.43 (m, 2H,  $\text{CH}_2$ ), 1.50-1.61 (m, 2H,  $\text{CH}_2$ ), 3.10-3.16 (m, 2H,  $\text{CH}_2$ ), 7.00 (t,  $J = 5.5\text{Hz}$ , 1H, NH), 7.57-8.00 (m, 5H, aromatic);  $^{13}\text{C}$  nmr ( $\text{DMSO-d}_6$ )  $\delta$ : 13.88 (q), 19.74 (t), 30.95 (t), 42.43 (t), 124.29 (s), 127.56 (d), 129.56 (d), 132.86 (d), 169.20 (s), 173.08 (s); ms m/z: 217 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}$ : C, 66.32; H, 6.96; N, 19.35. Found C, 66.30; H, 7.00; N, 19.30.

#### Irradiation of Compounds (**10a-d**) in Aqueous Ammonia

The acylaminofurazan (**10**) (2.5 mmol) was dissolved in aqueous ammonia (30%; 100 ml) and then irradiated for 5 h. The solvent was removed under vacuum and the residue was subjected to chromatography by using light petroleum ethyl-acetate in varying ratios to give 3-amino-1,2,4-oxadiazoles (**13a**), (**13g**), and (**13h**), respectively (45-50%). In the case of compounds (**10a-c**), starting material (40%) was also recovered.

#### Irradiations of Compound (**10a**) in the Presence of Amines

Compound (**10a**) (0.5g; 2.5 mmol) was dissolved in ethanolic (33%) methylamine or dimethylamine (100 ml), or in methanol (100 ml) containing an excess (25 mmol) of freshly



distilled pyrrolidine, piperidine, or n-butylamine, and then irradiated for 5 h. The solvent was removed under vacuum and the residue was chromatographed by using light petroleum-ethyl acetate in varying ratios, affording starting material (40%) and the corresponding 3-*N*-substituted amino-5-phenyl-1,2,4-oxadiazoles (**13b-f**), respectively (45-50%). In a test experiment, irradiation of compound (**10a**) with pyrrolidine in methanol was carried out in the Rayonet apparatus; monitoring the photoreaction by hplc analysis showed that the yield of the corresponding oxadiazole (**13d**) reached the maximum value (50%) within 3 h of irradiation.

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