PHOTOCHEMICAL BEHAVIOUR OF 1,2,5-OXADIAZOLES - *IRRADIATION OF SOME 3-ACYLAMINO-1,2,5-OXADIAZOLES IN THE PRESENCE OF NUCLEOPHILES*[1]

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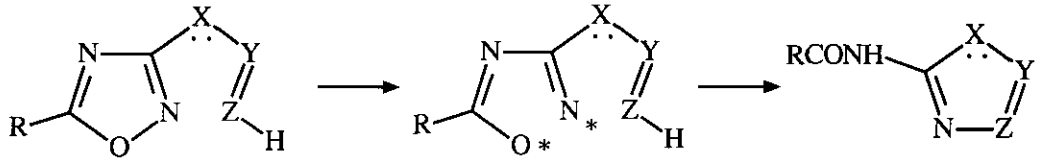
Abstract - The photochemical behaviour of some 3-acylamino-1,2,5-oxadiazoles (furazans) has been investigated. On irradiation at 254 nm in the presence of nucleophiles (ammonia, primary or secondary amines), the photoreaction produced 3-substituted 1,2,4-oxadiazoles in which the substituent at C(3) arises 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.[2] A similar behaviour is also reported for benzofurazans and benzofuroxans.[3] 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.[2,3]

Scheme 1

1

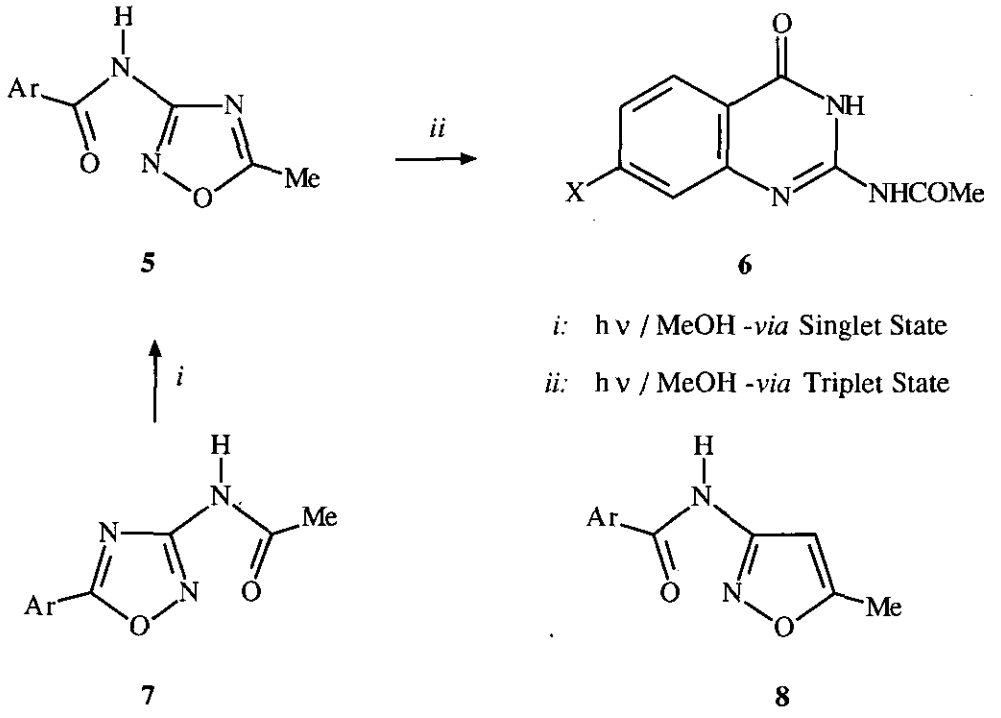


2 **3** **4**

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.[4,5] In this context we have reported[6,7] 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-aroylamino 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.[7] As a consequence, the 3-aroylamino derivatives (**5**)

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

Scheme 2



5 **6**

i: h ν / MeOH -*via* Singlet State

ii: h ν / MeOH -*via* Triplet State

7 **8**

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-acylaminofurazans (**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-acylaminofurazans (**10**) do not undergo the Boulton-Katritzky rearrangement[10-12] 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-acylaminofurazans (**10**).[12] On the other hand, attempts to rearrange photochemically some tetrahydrobenzofurazan arylhydrazones were unsuccessful.[13]

RESULTS AND DISCUSSION

Irradiation of the 3-acylaminofurazans (**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.

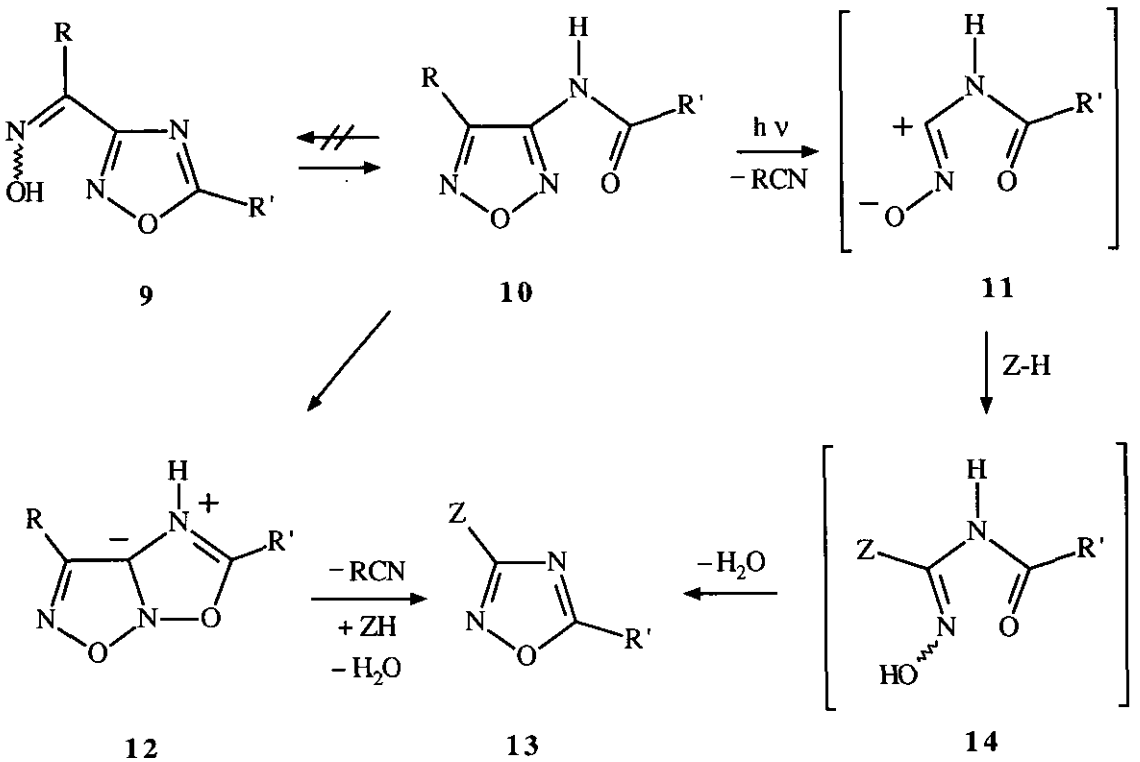
When irradiated, the acylamino compounds (**10**) gave the corresponding nitrile (verified by hplc analysis in the case of benzonitrile) and the 3-substituted 1,2,4-oxadiazoles (**13**), in which the substituent at C(3) arises from the used nucleophile (see Scheme 3). As expected, the formation of 1,2,4-oxadiazole 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



9 10 11 12 13 14

10

	R	R'
a	Me	Ph
b	Ph	Ph
c	Me	*p*-$MeOC_6H_4$
d	Ph	Me

13

	R'	Z
a	Ph	NH_2
b	Ph	NHMe
c	Ph	$N(Me)_2$
d	Ph	NC_4H_8
e	Ph	NC_5H_{10}
f	Ph	NHC_4H_9(n)
g	*p*-$MeOC_6H_4$	NH_2
h	Me	NH_2

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus; ir spectra (nujol mulls) were determined with a Perkin-Elmer 257 instrument, ^{1}H nmr (250 MHz) and ^{13}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**),[14] (**10b**),[14] and (**10d**)[15] 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 cm^{-1} (NH), 1660 cm^{-1} (CO); ^{1}H nmr (DMSO-d_6) δ: 2.33 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 7.00-8.00 (m, 4H, aromatic), 11.10 (s, 1H, NH). Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.72; N, 18.03. Found C, 56.60; H, 4.70; N, 18.00.

The oxadiazoles (**13a**),[16] (**13b**),[4] (**13c**),[17] (**13g**),[4,18] and (**13h**)[19] 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[20] 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}H nmr ($CDCl_3$) δ: 1.90-2.10 (m, 4H, 2 CH_2), 3.48-3.53 (m, 4H, 2 CH_2), 7.27-8.10 (m, 5H, aromatic); ^{13}C nmr ($CDCl_3$) δ: 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 (M^+). Anal. Calcd for $C_{12}H_{13}N_3O$: 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}H nmr ($CDCl_3$) δ: 1.65-1.68 (m, 6H, 3 CH_2), 3.48-3.51 (m, 4H, 2 CH_2), 7.43-8.00 (m, 5H, aromatic);.^{13}C nmr ($CDCl_3$) δ: 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.(M^+). Anal. Calcd for $C_{13}H_{15}N_3O$: 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 cm^{-1} (NH); ^{1}H nmr (DMSO-d_6) δ: 0.90 (t, J = 7.5Hz, 3H, CH_3), 1.30-1.43 (m, 2H, CH_2), 1.50-1.61 (m, 2H, CH_2), 3.10-3.16 (m, 2H, CH_2), 7.00 (t, J = 5.5Hz, 1H, NH), 7.57-8.00 (m, 5H, aromatic); ^{13}C nmr (DMSO-d_6) δ: 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 (M^+). Anal. Calcd for $C_{12}H_{15}N_3O$: 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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REFERENCES AND NOTES

1 Presented in part at the "III Joint Meeting on Heterocyclic Chemistry", Sciacca (Italy), 6-9 May 1992

2 T. S. Cantrell and W. S. Haller, *Chem. Comm.*, 1968, 977; T. Mukai, T. Oine, and A. Matsubara, *Bull. Chem. Soc. Japan*, 1969, **42**, 581.

3 T. Mukai and M. Nitta, *J. Chem. Soc., Chem. Comm.*, 1970, 1192; M. Georgarakis, H. I. Rosenkranz, and H. Schmid, *Helv. Chim. Acta*, 1971, **54**, 819; I. Yavari, S. Esfandiari, A. J. Mostashari, and P. W. Hunter, *J. Org. Chem.*, 1975, **40**, 2880; W. Heinzelmann and P. Gilgen, *Helv. Chim. Acta*, 1976, **59**, 2727; M. Hasegawa and T. Takabatake, *J. Heterocycl. Chem.*, 1991, **28**, 1079.

4 S. Buscemi, M. G. Cicero, N. Vivona, and T. Caronna, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1313.

5 S. Buscemi, M. G. Cicero, N. Vivona, and T. Caronna, *J. Heterocycl. Chem.*, 1988, **25**, 931.

6 S. Buscemi and N. Vivona, *J. Heterocycl. Chem.*, 1988, **25**, 1551; S. Buscemi, G. Cusmano, and M. Gruttadauria, *J. Heterocycl. Chem.*, 1990, **27**, 861.

7 S. Buscemi and N. Vivona, *Heterocycles*, 1989, **29**, 737; S. Buscemi, G. Macaluso, and N. Vivona, *Heterocycles*, 1989, **29**, 1301; S. Buscemi and N. Vivona, *J. Chem. Soc., Perkin Trans. 2*, 1991, 187.

8 S. Buscemi, V. Frenna, and N. Vivona, *Heterocycles*, 1991, **32**, 1765.

9 A. Padwa, "Rearrangements in Ground and Excited States", ed. P. de Mayo, Academic Press, 1980, Vol. III, p. 501.

10 The Boulton-Katritzky rearrangement designates a generalized pattern of ring-transformations of five-membered heterocycles.[11,12]

11 A. J. Boulton, A. R. Katritzky, and A. M. Hamid, *J. Chem. Soc. C*, 1967, 2005.

12 M. Ruccia, N. Vivona, and D. Spinelli, *Adv. Heterocycl. Chem.*, 1981, **29**, 141.

13 S. Lefkopolou, J. Stephanidou-Stephanatou, C. Tsoleridis, and N. E. Alexandron, *Helv. Chim. Acta*, 1985, **68**, 1748.

14 V. G. Andrianov and V. Eremeev, *Chem. Heterocycl. Compnd. (Engl. Transl.)*, 1984, **20**, 937.

15 F. Angelico and S. Cusmano, *Gazz. Chim. Ital.*, 1936, **66**, 3.

16 G. Westphal and R. Schmidt, *Z. Chem.*, 1974, **14**, 94 [*Chem. Abstr.*, 1974, **81**, 13443];W. K. Warburton, *J. Chem. Soc. C*, 1966, 1522.

17 P. Choi, C. W. Rees, and E. H. Smith, *Tetrahedron Lett.*, 1982, **23**, 125.

18 F. Eloy and A. Deryckere, *Bull. Soc. Chim. Belg.*, 1969, **78**, 41 [*Chem. Abstr.*, 1969, **71**, 49862].

19 G. W. Anderson, H. E. Faith, H. W. Marson, P. S. Winner, and R. O. Roblin, *J. Am. Chem. Soc.*, 1942, **64**, 2902.

20 F. Eloy, A. Deryckere, and A. Van Overstracen, *Bull. Soc. Chim. Belg.*, 1969, **78**, 47 [*Chem. Abstr.*, 1969, **71**, 49863].

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