PHOTOINDUCED MOLECULAR REARRANGEMENTS OF O-N BOND-CONTAINING FIVE-MEMBERED HETEROCYCLES. AN ASSAY FOR 1,2,4- AND 1,2,5-OXADIAZOLES

Nicolò Vivona* and Silvestre Buscemi

Dipartimento di Chimica Organica, Università di Palermo,
Via Archirafi 20, 90123 Palermo, Italy

Abstract - The photochemical behavior of 1,2,4- and 1,2,5-oxadiazoles is reviewed. Photoinduced molecular rearrangements of these five-membered rings are emphasized.

1 - Introduction: Scope and Organization

Molecular rearrangements of heterocycles constitute a widely investigated area in organic chemistry that appears of great importance both from a theoretical point of view and in a synthetic design of target compounds.[1-5] Among the enormous variety of molecular rearrangements, which depend both from the nature of substrates and from experimental conditions, a growing interest is gaining photoinduced rearrangements, that is processes which take place under irradiation at a wave-length, and are assumed to proceed from excited states of starting substrates. On the other hand, photochemistry of heterocycles, which has been reviewed in various publications,[6,7] is assuming great significance in biological and pharmaceutical field, as well as in synthesis of particular heterocycles which could be hardly accessible by conventional methods. Photoinduced ring isomerizations of five-membered heterocycles where interchange of annular atoms simply occurs, have been treated in various

Dedicated to Professor Alan R. Katritzky

contexts,[8,9] and to these papers we will refer for background and general informations. Moreover, ring transformations of five-membered heterocycles containing a participating side-chain group have been also reviewed.[5]

In connection with our researches both in the ring transformations and in the photochemical behavior of heterocycles, we became interested in an overview and an update of photoinduced rearrangements of five-membered heterocycles containing an O-N bond, that is 1-oxa-2-azoles (1) in which just a weak O-N bond can suffer photolytic breaking. In this context we have deliberately excluded isoxazoles (1; AB = CC), or benzisoxazoles, which appear the most investigated system in a photochemical approach.[9,10] Likewise, we have excluded mesoionic 1,2,3-oxadiazoles, whose photochemistry has been considered in different contexts.[9,11] On the other hand, the photochemistry of a stable naphtho[2,3-d]-1,2,3-oxadiazole has been related to the photoreactivity of the corresponding α-diazoketone.[12]
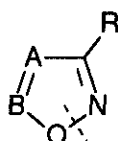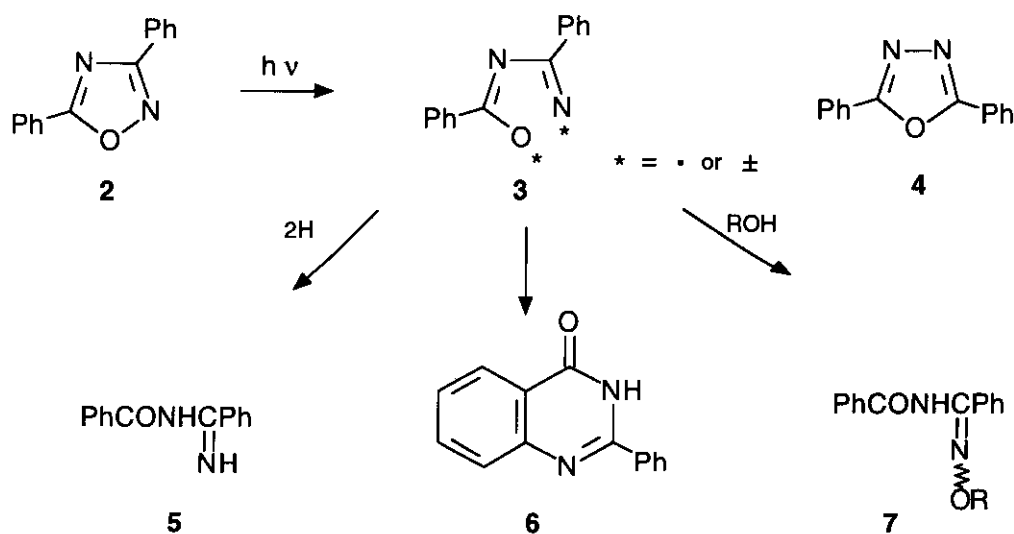

AB = NC: 1,2,4-Oxadiazoles
AB = CN: 1,2,5-Oxadiazoles (Furazans)

1

This survey is specifically devoted to 1,2,4-oxadiazoles (1; AB = NC) and 1,2,5-oxadiazoles (furazans) (1; AB = CN), for which the poor literature regarding their photochemistry appears fragmentarily documented. The material has been selected on the basis of interest rather than for an exaustive presentation, and it will essentially consider photoinduced rearrangements of heterocycles containing or not a participating side-chain group. Photoinduced strong fragmentations of starting substrates will be considered only when they represent behaviour of particular interest. Furthermore, since there is no homogeneity in experimental conditions used in photochemical studies, we will mention them only when of interest and/or expressely reported.

II - 1,2,4-Oxadiazoles

Newman[13,14] studied the photochemistry of the 1,2,4-oxadiazole aiming to point out a possible analogy with the isoxazole nucleus in the ring contraction-ring expansion pathway.[9]

Irradiation (Hanovia high-pressure mercury arc) of the 3,5-diphenyl derivative (2) in ether gave benzoylbenzamidine (5), whose formation is explained from an omolysis of the ring O-N bond into a diradical which will collaps by abstraction of hydrogens from the solvent. By contrast, on irradiating in hydroxylic solvent (methanol, isopropanol), heterolysis of the ring O-N bond is assumed: the resulting dipolar species will then stabilize by insertion of the solvent itself to give 7. Under both irradiation conditions, a heterocyclization reaction of the diradical or dipolar intermediate (3) explains the formation of the quinazolin-4-one system (6) The presumed ring contraction-ring expansion pathway to the 1,3,4-oxadiazole isomer (4) was not detected. [A subsequent reinvestigation[15] of this photochemistry in methanol at 254 nm confirmed the solvolytic compound (7; R = Me) as the main product; however, hplc analysis of the photoreaction revealed the presence of trace amounts of the oxadiazole (4). For some restrictions on this ring isomerization, see later].

Scheme 1

Photochemistry of 1,2,4-oxadiazoles (in methanol at 254 nm, low-pressure mercury lamps) was thoroughly investigated as a function of the nature and position of substituents, taking into account both the formation of open-chain compounds (10) and the ring isomerization into 8.[15,16] Significant and generalizable results are as follows:

1) The ring isomerization into the 1,3,4-oxadiazole (reasonably *via* a ring contraction-ring expansion mechanism) occurs only when a tautomerizable group is present at the C(3) of the 1,2,4-oxadiazole (**9**; R' = NH$_2$, NHMe, NHPh, OH; R = Ar). This result suggests that this pathway should involve tautomeric forms in starting substrates and/or in three-membered intermediates arising from photolysis of the O-N bond in the ring contraction mechanism (Scheme 3). In line to this hypothesis, irradiation of the *N*-methyl-Δ^4-oxadiazolin-3-one (**18**), besides unidentified other photoproducts, revealed the occurrence of the ring isomerization into **19**, whereas attempts to isomerize 3-methoxyoxadiazole (**9**; R = Ph; R' = OMe) failed. In this connection it appeared worthy to note that differences in the fragmentation pattern of some 1,2,4-oxadiazoles under electronic impact [e.g., cleavage of the ring O-N bond in one hand, or a retro-cycloaddition involving the O(1)-C(5) bond in the other] were also explained on the basis of differences in position and structure of substituents.[17,18]
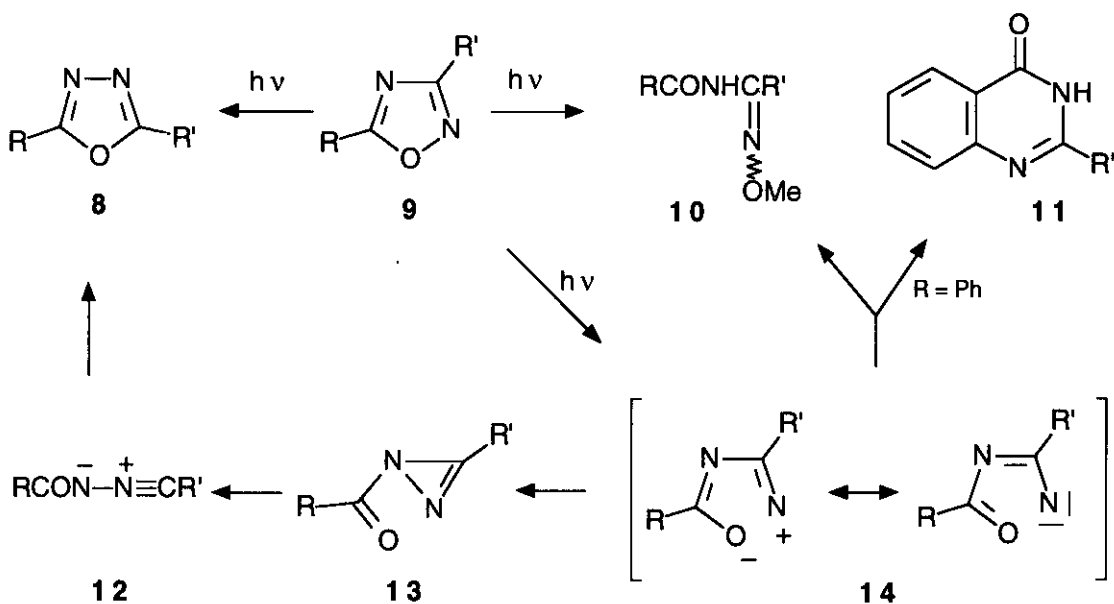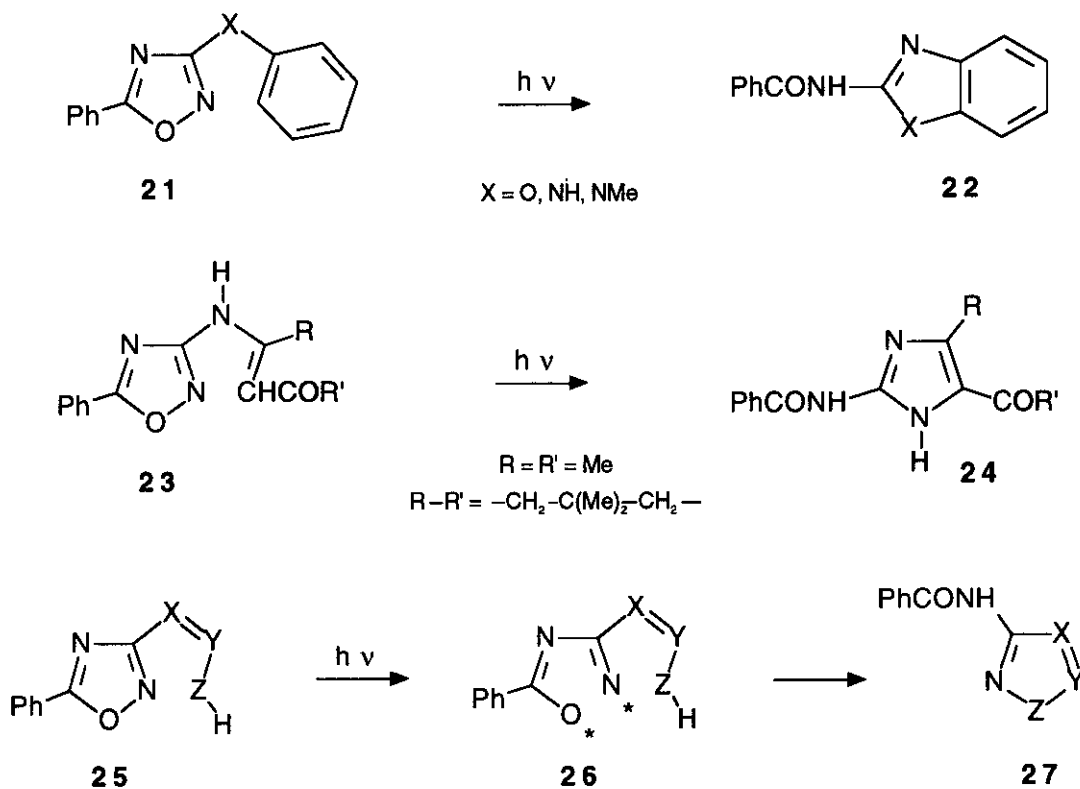

Scheme 2

2) When 1,2,4-oxadiazoles (**9**) do not contain these structural features, the photoreaction proceeds through cleavage of the ring O-N bond into an open-chain species (**14**) (zwitterionic

or nitrenic in nature) from which photoproducts will arise as a function of various parameters: e.g., the electrophilic nitrogen atom can react: i) with the nucleophilic solvent to give solvolytic products (**10**); ii) with a phenyl ring originally linked at C(5) of the oxadiazole to give quinazolinone system (**11**) (Scheme 2). Moreover, the nitrene species can isomerize into a carbodiimide which the solvent will capture.
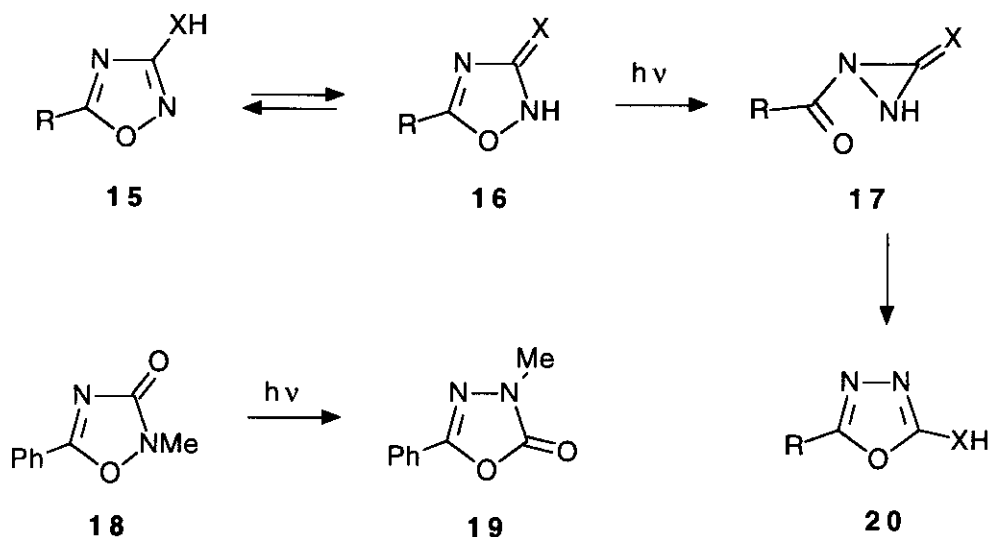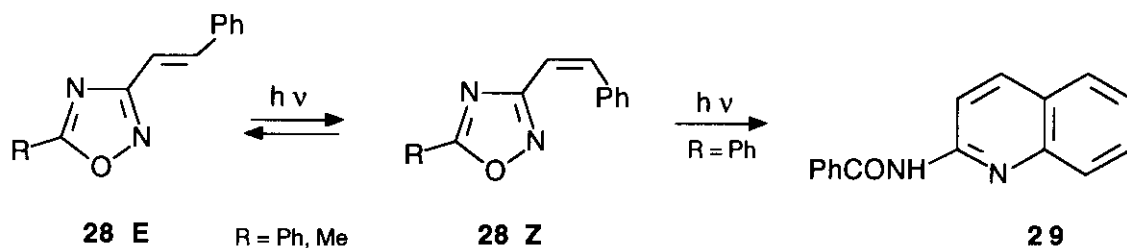

Scheme 3

3) Oxadiazoles containing a participating three-atoms side-chain at C(3) showed a peculiar reactivity (Scheme 4). Thus, compounds (**21**; X = O, NH, NMe), which does not give any thermally or base-induced rearrangement, in addition to the above-mentioned reaction paths, showed photoinduced transformation into benzimidazoles (**22**; X = NH, NMe) or benzoxazole (**22**; X = O).[19] Likewise, enamino ketones (**23**) rearrange into imidazoles (**24**). By contrast, irradiation of the 3-benzyl derivative (**21**; X = CH$_2$) gave the corresponding solvolytic compound (**10**; R = Ph; R' = CH$_2$Ph). These results are explained by assuming that photolytic intermediates (**26**) will collaps into the rearranged **27** through a ring-closure assisted by an aromatic transition state involving the side-chain XYZ (Scheme 4). Similar observations concerning the assisted new-ring-closure had been also made in the photochemistry of some 1,2,4-oxadiazolin-5-ones (see later).

21   h ν   **22**

X = O, ṄH, NMe

23   h ν   **24**

R = R' = Me

R–R' = –CH$_2$–C(Me)$_2$–CH$_2$–

25   h ν   **26**   **27**

Scheme 4

In the context of photoinduced transformations involving a participating side-chain, 3-styryl-oxadiazoles (**28**) have been also considered.[20] For these substrates, the primary photochemical process resulted in a fast **E** ⇌ **Z** equilibration at the styryl moiety. However, in the case of the 5-phenyl substituted oxadiazole (**28E**; R = Ph) [but not for the 5-methyl substituted compound (**28E**; R = Me)], a slow photorearrangement into the quinoline (**29**) took also place. This difference in photochemistry of these two styryloxadiazoles has been explained by assuming that two chromophores may be involved in the irradiation. That is, in one hand excitation of the styryl chromophore explains the **E** ⇌ **Z** equilibration; in the other, excitation of the 5-phenyloxadiazole chromophore would collaps into a photolytic intermediate by which a heterocyclization reaction at the styryl moiety in the suitable configuration will provide **29** (Scheme 5).
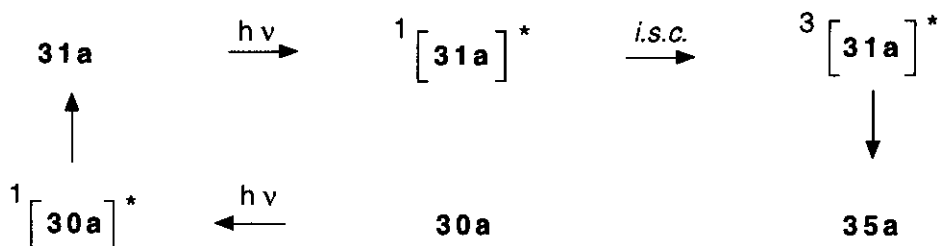
Scheme 5

3-Acetylamino-5-aryl-1,2,4-oxadiazoles (**30**) and their ring-degenerate counterpart 3-aroylamino-5-methyl derivatives (**31**) showed interesting photochemical results.[21-23] Irradiation (in methanol at 254 nm) of 3-aroylamino compounds (**31**) did not give the corresponding 3-acetylaminooxadiazoles (**30**) (which constitute the more stable component indeed in a thermally-induced ring-degenerate equilibration[5,24]), but it furnished the quinazolin-4-ones (**35**). In turn, irradiation of 3-acetylamino-5-aryloxadiazoles (**30**) gave compounds (**35**), too. However, in this latter case the photoinduced transformation of **30** into **35** proceeds through the previous formation of the aroylamino isomers (**31**), which can be even isolated or at least detected by hplc (Scheme 6).

a: Ar = Ph
b: Ar = p-CH₃C₆H₄
c: Ar = p-OMeC₆H₄

a: X = H
b: X = Me
c: X = MeO
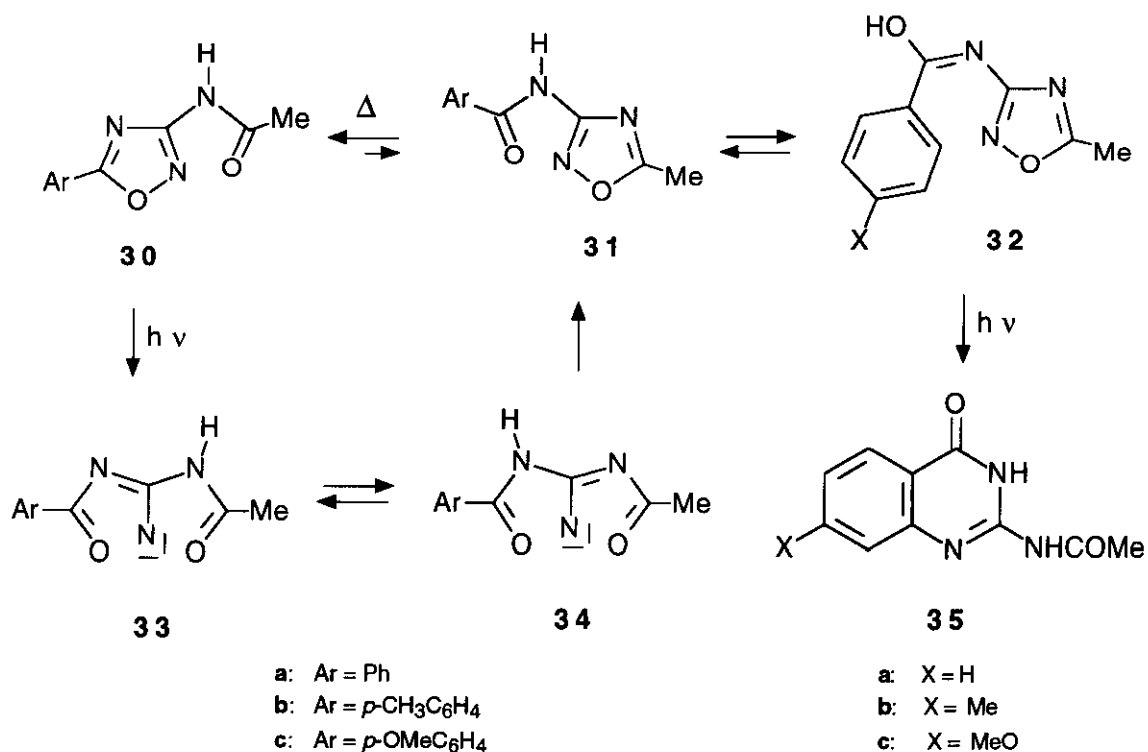
Scheme 6

Mechanistic investigations[23] suggest that irradiation of the 3-acetylamino compounds (**30**) may involve excitation of the 5-aryloxadiazole chromophore, developing into cleavage of the ring O-N bond. Open-chain species such as **33** will then undergo the new ring-closure by engaging the NCO sequence of the aroylamino group to give **31**. By contrast, irradiation of compounds (**31**) should involve excitation of the aroylamino chromophore, developing in a heterocyclization reaction between the oxadiazole moiety and the aryl ring. Subsequent ring-opening will then provide **35**. Some quenching experiments support this hypothesis which expects different photochemical pathways. In fact, formation of **35a** from the irradiation of **31a** involves triplet excited states; by contrast, formation of the 3-benzoylaminooxadiazole (**31a**) from the irradiation of **30a** involves singlet excited states (Scheme 7). In line to this, emission spectra of 3-aroylamino compounds (**31**) showed significant phosphorescence emission, whereas 3-acetylamino derivatives (**30**) mainly decays through fluorescence emission.

$$ \mathbf{31a} \quad \xrightarrow{\;h\nu\;} \quad {}^{1}\!\left[\,\mathbf{31a}\,\right]^{*} \quad \xrightarrow{\;i.s.c.\;} \quad {}^{3}\!\left[\,\mathbf{31a}\,\right]^{*} $$

$$ \Big\uparrow \qquad\qquad\qquad\qquad\qquad\qquad\qquad \Big\downarrow $$

$$ {}^{1}\!\left[\,\mathbf{30a}\,\right]^{*} \quad \xleftarrow{\;h\nu\;} \quad \mathbf{30a} \qquad\qquad\qquad \mathbf{35a} $$
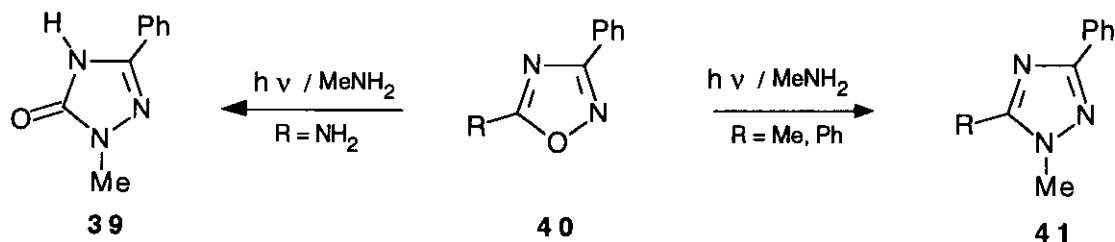
Scheme 7

On the basis of these findings, an interesting photochemical behavior was recognised in the irradiation of 5-aryl-substituted oxadiazoles (**36**) at 310 nm in the presence of triplet sensitizers (^{3}S). Under these conditions, compounds (**36**) gave quinazolinones (**38**) directly. Here, the photolytic intermediate arising from cleavage of the ring O-N bond (likely a nitrene in a triplet state) develops into a ring-closure at the aryl originally linked at the C(5) of the oxadiazole (Scheme 8). Interestingly, this photochemical behavior has been claimed[23] as a useful tool in synthesis of target quinazolinones, although further investigations in the scope and restrictions appear necessary.

X = H; R = Me, Ph, NH$_2$, NHCOMe

X = Me, MeO; R = NHCOMe
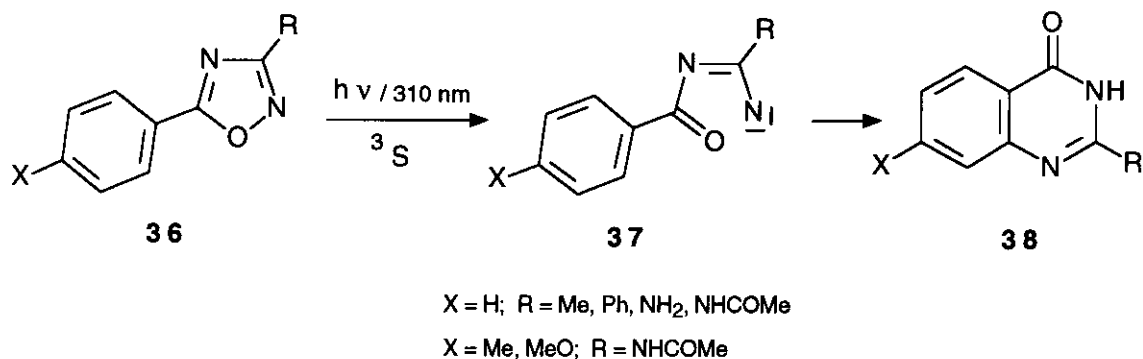
Scheme 8

Photoinduced aminolysis of the 1,2,4-oxadiazole has been recently considered.[25] Preliminary results from our laboratories show that irradiation of compounds (**40**; R = Me, Ph) at 254 nm in the presence of an excess of methanolic methylamine gives triazoles (**41**). On the other hand, irradiation of the oxadiazole (**40**; R = NH$_2$) in the presence of methylamine produces the triazolin-5-one (**39**) (Scheme 9).
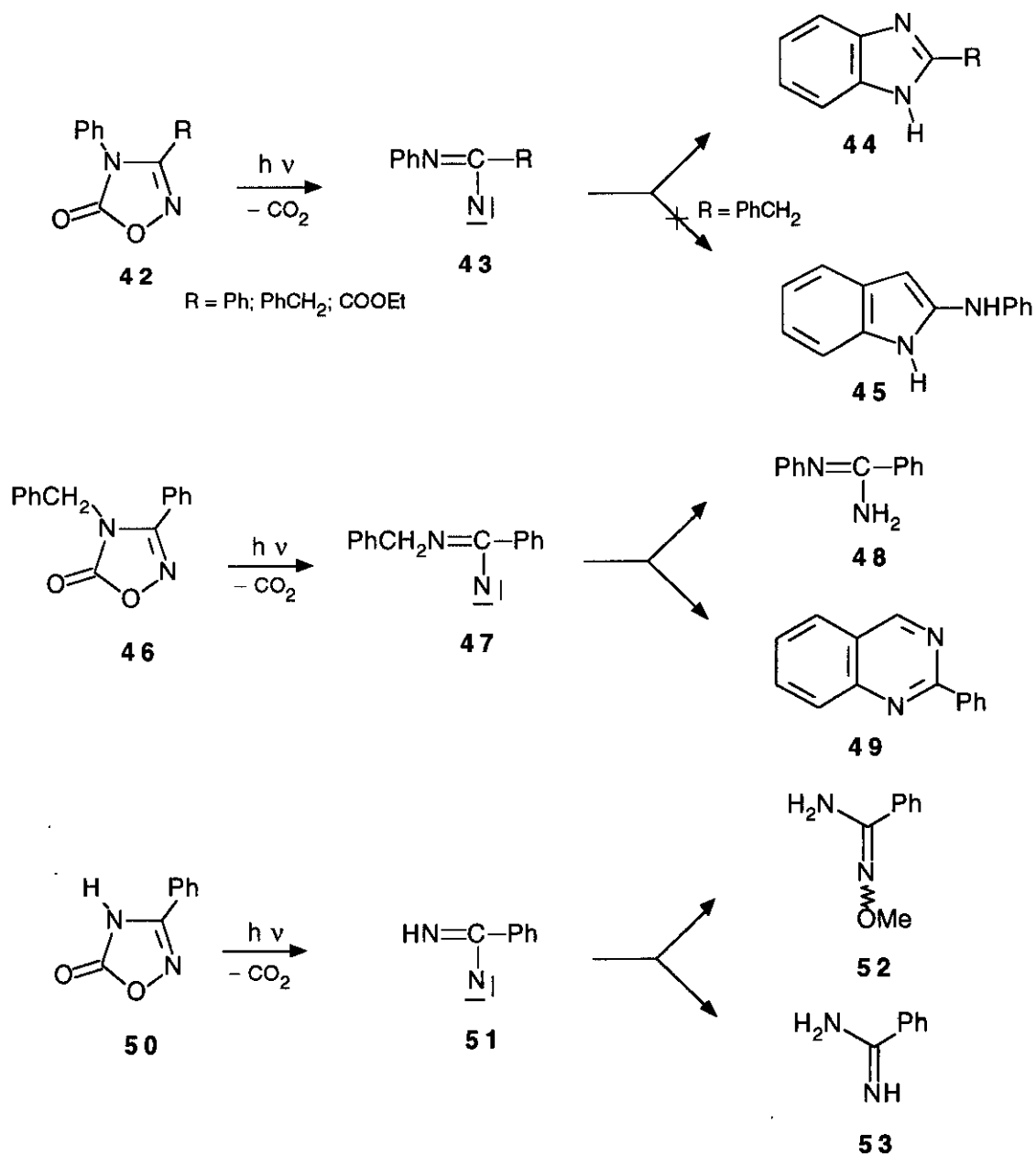

Scheme 9

Although the intimate mechanism of this transformation is not fully-established, the results can be accomodated on the basis of the usual photolysis of the oxadiazole ring into a reactive species which the amine will capture to form open-chain intermediates. Subsequent base-induced ring-closures which would imply elimination of water or ammonia will provide **41** or **39**, respectively.

III - 1,2,4-Oxadiazolin-5-ones

The photochemistry of 1,2,4-oxadiazolin-5-ones is characterized by extrusion of carbon dioxide and formation of transient nitrenes from which final products will arise as depending

from the nature of substituents as well as from the work-up procedure. Irradiation (in dioxan at 254 nm, low-pressure mercury lamps) of compounds (**42**), characterized by the presence of a phenyl ring at the N(4), mainly provides high yields of benzimidazoles (**44**) as a result of a heterocyclization reaction involving the aromatic ring at the N(4)[26-30] (Scheme 10).

Scheme 10

Carbodiimides and/or their subsequent rearrangement/fragmentation products, as well as some amidines were also detected. As expected, irradiation of (42; R = CH$_2$Ph) does not give the indole (45): of course, the hypothesized heterocyclization at the benzyl moiety appears unlikely.[29] Differently, irradiation of the 4-benzyl derivative (46), gave a complex photoreaction from which some amounts of N-phenylbenzamidine (48) and phenylquinazoline (49), arising from development of a firstly-formed nitrene (47), were detected.[30] A nitrene species is also assumed in the photolysis (low-pressure mercury lamps) of the 3-phenyl derivative (50) in either dioxan or methanol.[31] Here, besides the fragmentative benzonitrile or the rearranged phenylcyanamide, formation of 53 as the reduction product (from triplet nitrene), and insertion of methanol to give 52 (from singlet nitrene), respectively, are observed (Scheme 10).
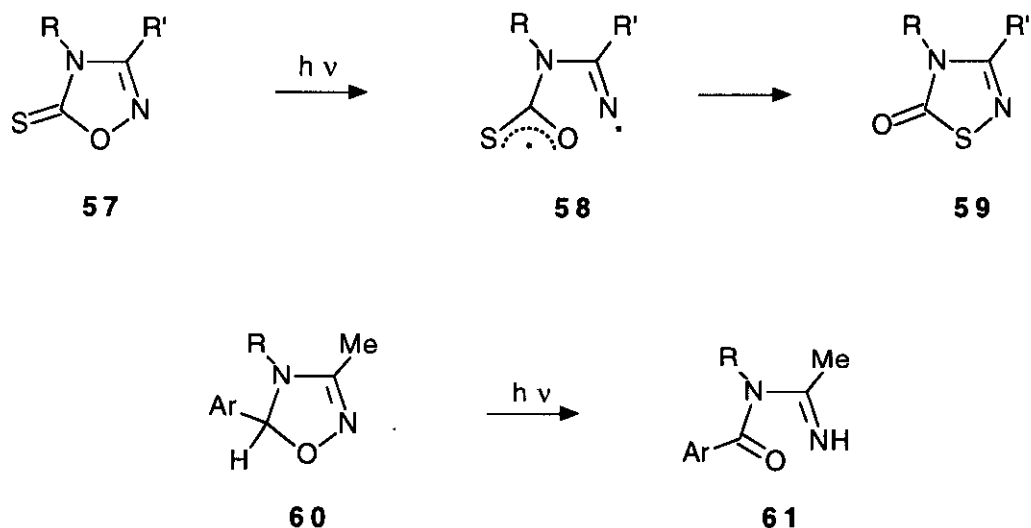
Nitrenes as intermediates are also assumed in the photochemistry of Δ^3-1,2,4-oxadiazolin-5-ones (54) and (55), which produce the expected benzimidazoles (44; R = Ph) and 56, respectively.[30,32] Irradiation of 54 also furnishes some amounts of the diphenylcarbodiimide and traces of the unexplained ring-isomer 2,4-diphenyl-Δ^2-1,3,4-oxadiazolin-5-one (presumably through a nitrilimine which carbon dioxide will capture). Furthermore, in the irradiation of 55 (Ar = 3-MeC$_6$H$_4$), ring-closure gives both the expected benzimidazoles (56b)[32] (Scheme 11).
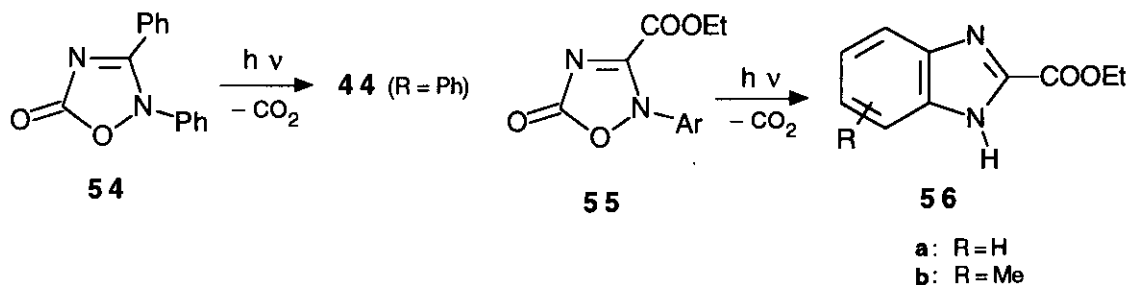
Scheme 11

The photoinduced (as well as copper-catalyzed) rearrangement of oxadiazoline-5-thiones (57) into 59 (in methanol, low-pressure mercury lamps) is reported as proceeding from diradical (58), which develops into the new-ring closure at the N-S bond level.[33,34] In the

photochemistry of Δ^2-1,2,4-oxadiazolines (**60**) (in ether at 254 nm), intermediates arising from omolysis of the ring O-N bond develop into *N*-aroylacetamidines (**61**) as final products[35,36] (Scheme 12).

R   R'   R   R'   R   R'
 N   N   N   N   N   N
  \   / /   hv   \   / /   \   / /
   S-O   S...O   O-S
        N   N   N

   57   58   59

        R   Me   R   Me
         N   N
    Ar   /   \   hv   \
      \ N   N   Ar   \
       H   O   O   NH

        60   61

Scheme 12

IV - 1,2,5-Oxadiazoles

There are no systematic studies on the photochemistry of 1,2,5-oxadiazoles (furazans). The first report concerns irradiation (Hanovia medium-pressure mercury arc) of 3,4-diphenyl- (**62**; R = Ph) and 3,4-dimethylfurazan (**62**; R = Me).[37] Essentially, results show a retro-cycloaddition involving a double fragmentation of O-N and C-C bonds to form nitriles and nitrile oxides. These latter species will give final products as a function of the medium[37,38] (Scheme 13). Thus, irradiation of the diphenylfurazan (**62**; R = Ph) gave phenyl isocyanate (irradiation in ether) or methyl *N*-phenyl carbamate (irradiation in methanol). Moreover, irradiation of **62** (R = Ph) in the presence of phenylacetylene gave the 3,5-diphenylisoxazole (**65**). On the other hand, in the irradiation of the dimethylfurazan (**62**; R = Me), the resulting nitrile oxide was trapped with cyclopentene in a cycloaddition reaction to give **66**. Furthermore, in the irradiation of **62** (R = Ph), some amounts of the isomeric 3,5-diphenyl-1,2,4-oxadiazole and of the diphenylfuroxan were also recovered, as a result of a

cycloaddition between benzonitrile and benzonitrile oxide in one hand, and of dimerization of the nitrile oxide in the other. Some sensitizing experiments (carried out for the diphenylfurazan) suggested that the ring fragmentation occurs from excited singlets.[37]
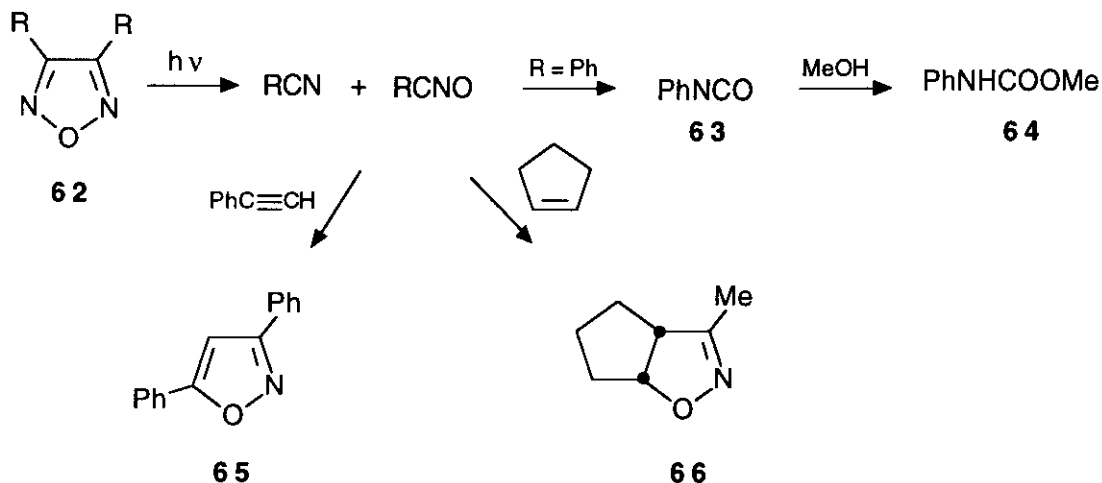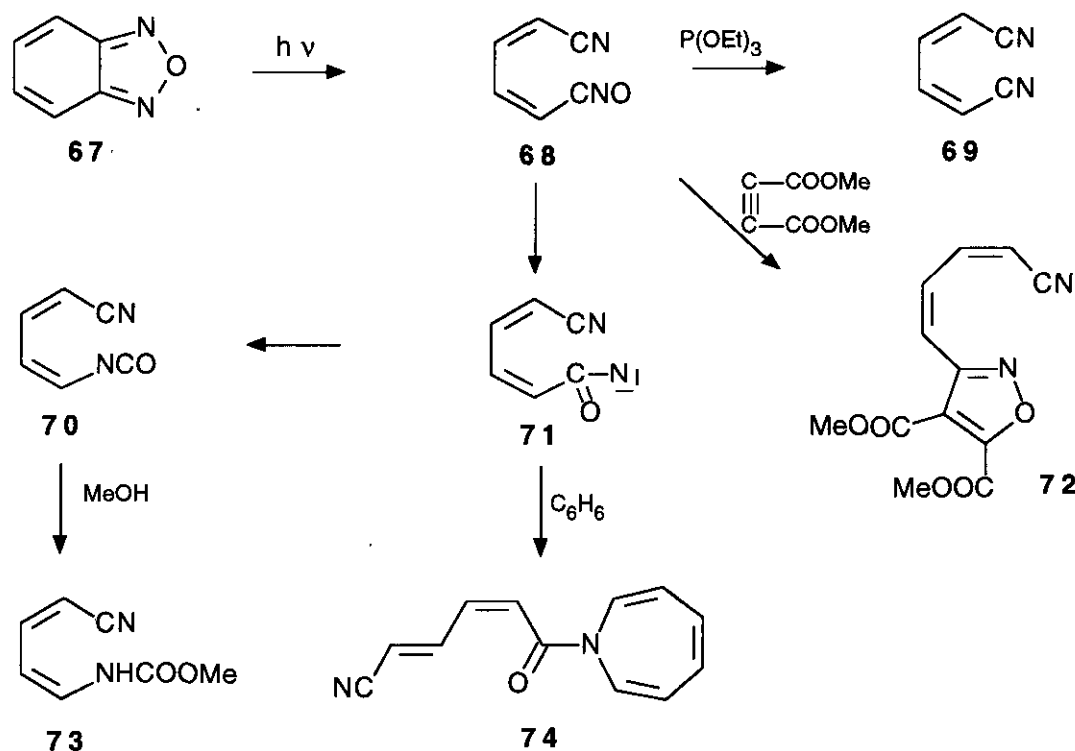

Scheme 13

Benzofurazans or naphtho- and phenanthrofurazans behaved similarly.[39-43] Irradiation of compound (**67**) in benzene (Pyrex, high-pressure mercury lamps) in the presence of triethyl phosphite as reducing reagent, gave the 1,4-dinitrile (**69**) (Scheme 14): among the possible different geometrical isomers, the *cis-cis*-isomer was the predominant component.

Also in this case, quenching and sensitizing experiments suggested the involvement of singlet excited states.[39] In the absence of reducing reagent, irradiation of benzofurazan in benzene produced the azepine (**74**), implying insertion of the solvent into the nitrene (**71**), whereas irradiation in methanol gave methyl cyano carbamate (**73**) (mixture of isomers).[42,43]

Mechanistic studies have been also performed and intermediates (**68**) and (**70**) have been detected and characterized by means of uv and ir spectroscopy.[43] Furthermore, irradiadion (at 300 nm) of compound (**67**) in the presence of dimethyl acethylenedicarboxylate gave the expected various geometrical isomers of dimethyl 3-(4-cyanobuta-1,3-dienyl)isoxazole-4,5-dicarboxylate (**72**)[44] (Scheme 14). In the irradiation of the naphtho[1,2-*c*]furazan, where a

styryl chromophore can be recognised, photodimerization reactions (through triplet excited
states of the furazan substrate) were also observed.[45]

Scheme 14

Photochemistry of furoxans and benzofuroxans is also reported.[46] Photolysis (high-pressure
mercury lamps) of the 4-azido-3-phenylfurazan-2-oxide (**75**) in dichloromethane/ethanol is
claimed[47] as a tool for the synthesis of the (*E*)-oxime (**76**) (Scheme 15), through an
inadequately supported reaction path; as the reaction is improved by the presence of
alcohols, this component is assumed to promote elimination of the "NO segment by forming a
nitrite ester" from a photolytic open-chain species.[47] Irradiation (high-pressure mercury lamps)
of the benzofuroxan (**77**) in acetonitrile containing little amounts of water furnished the
azepinedione (**80**), resulting from the initially-formed **79** having two nitrile oxide groups.[48]
However, different photoreactions are observed in the irradiation of the pyrido[2,3-*c*]furoxan at
254 nm (low-pressure mercury lamps).[49]
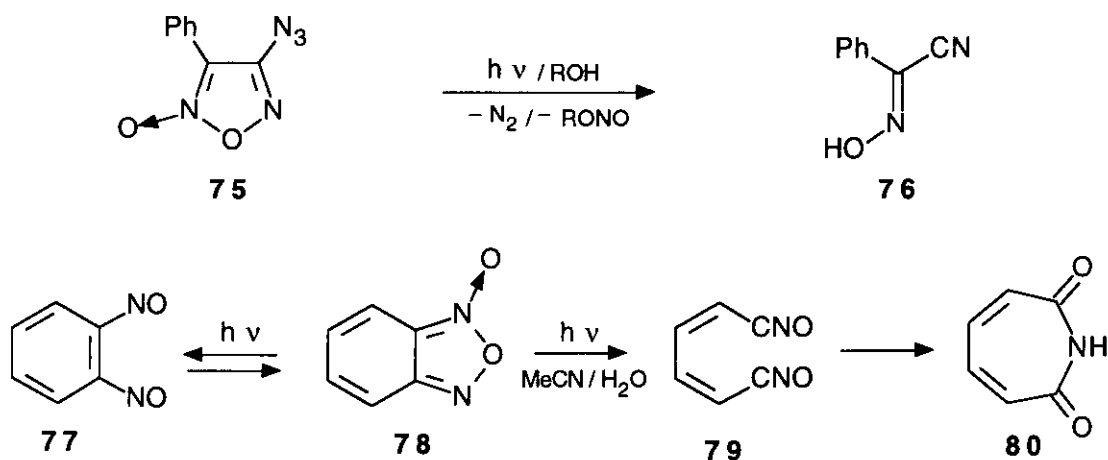
Scheme 15

Photoinduced ring isomerizations of 4-substituted benzofuroxans are also reported.[46,50] Moreover, in the photochemistry of the benzofuroxan in inert matrices, formation of 1,2-dinitrosobenzene (**77**) as the key intermediate in the ring isomerizations has been pointed out.[51]

In a study of the photochemistry of 3-acylamino-1-oxa-2-azoles, 3-acylaminofurazans (**81**) have been considered.[52-54] The photochemical reactivity has been studied by irradiating them in the presence of nucleophiles, such as ammonia or primary or secondary aliphatic amines, in a synthetic design.[52] Under these conditions final products were 3-amino-(or *N*-substitutd amino-)1,2,4-oxadiazoles (**84**) where the substituent at C(3) arises from the reagent used (Scheme 16). Yields were not excellent because of subsequent photoreactivity of the resulting oxadiazoles.


Z = NH$_2$, NHMe, N(Me)$_2$, N(CH$_2$)$_4$, N(CH$_2$)$_5$, NHC$_4$H$_9$(n)
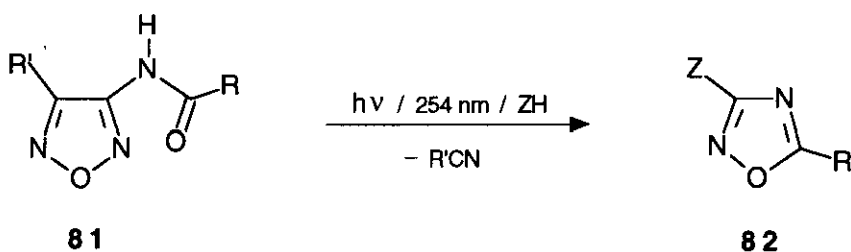
Scheme 16

Photoreactivity of 3-acylaminofurazans has been thoroughly investigated as a function of different parameters in a mechanistic approach.[53] To this aim, structurally different substrates such as 3-aroylamino-4-methylfurazans (**83**) and 3-acetylamino-4-phenylfurazan (**90**) have been considered. These substrates differ in that compounds (**83**) contain an aroylamino side-chain and a methyl-substituted furazan ring, whereas compound (**90**) shows an acetylamino group and a phenyl-substituted furazan ring. Moreover, and this appeared of some significance, 3-aroylaminofurazans showed phosphorescence emission more intense than that observed for the acetylamino substrate. Of course, these different features should have affected the nature of actual chromophore and then photochemical pathways.

Irradiation of compounds (**83**) in methanol produced 3-methoxyoxadiazoles (**87**; Z = OMe) and O-aroylamidoximes (**89**) as primary photochemical products; in turn, irradiation of **83** in the presence of pyrrolidine gave the expected 3-pyrrolidinyloxadiazoles [**87**, Z = N(CH$_2$)$_4$]. Assuming the nitrile oxide fragment (**85**) as key intermediate, a fast reaction between **85** and the nucleophile will give **86**, precursors of the 1,2,4-oxadiazoles. In the absence of the base, the nitrile oxide will isomerize into a carbodiimide (**88**) which methanol will then capture to provide **89**. Some quenching experiments suggested that: i) formation of **89a-c** should arise from singlet excited states, presumably involving the furazan ring chromophore; ii) formation of 3-methoxy-oxadiazoles (**87**; Z = OMe) should arise both from a thermal ring-closure of the corresponding N-aroylamidoximes (**86**; Z = OMe), and from an additional photochemical route which may involve triplet excited states. For this additional pathway, excitation at the aroylamino chromophore was suggested, presumably developing through a bicyclic species such as **84**. Regarding this point, a substituent effect was observed in the irradiation of **83d**. In this case, quenching experiments suggested the involvement of triplet excited states in the formation of both **89d** and **87d** (Z = OMe). This result is accomodated by assuming that the cyano group could affect both the energy and the nature of excited states in such a way to direct the photochemical route via triplet states involving the aroylamino group. In line to this hypothesis was the observation that the aroylaminofurazan (**83d**) showed the most intense phosphorescence emission.
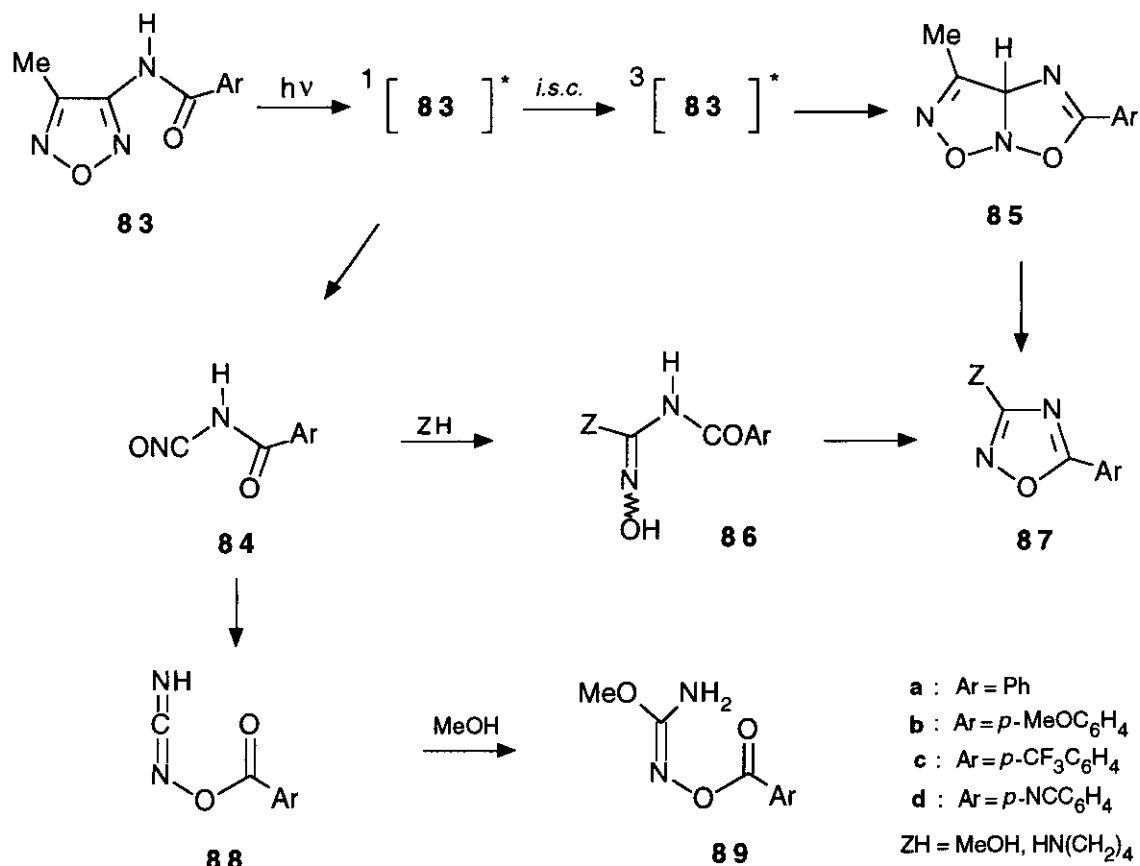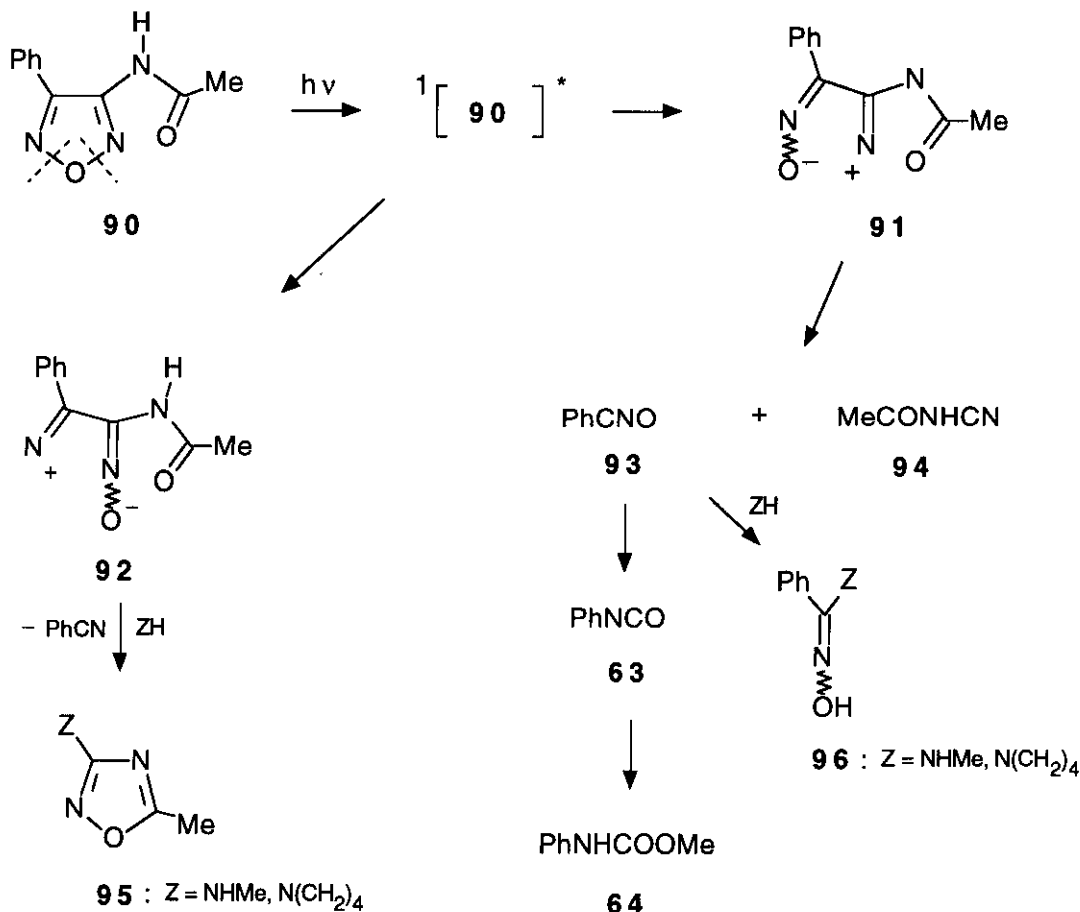
Scheme 17

In the irradiation of 3-acetylamino-4-phenylfurazan (**90**) only singlet excited states, presumably involving the phenyl-substituted furazan chromophore, were operative. Interestingly, at variance with what observed for compounds (**83**), in the photochemistry of **90** the cleavage of both O(1)-N(5) and O(1)-N(2) bonds of the heterocycle was pointed out. In this regard, it appeared noteworthy that literature on the photochemistry of furazans reported cleavage of an unspecified O-N bond of the ring; of course, symmetrical substrates had been considered. Differently, mass spectra of the 3-amino-4-phenylfurazan suggested the occurrence of the cleavage of both the O-N bonds of the ring under electronic impact.[18] On irradiating compound (**90**) in methanol, benzonitrile in one hand and acetylcyanamide (**94**) and phenylcarbamate (**64**) in the other, were isolated; on the other hand, irradiation in the presence of pyrrolidine or methylamine, toghether with the expected benzonitrile and

acetylcyanamide, gave oxadiazoles (**95**) and oximes (**96**). Photochemical routes are shown in the Scheme 18.

Scheme 18

Exploitation of photoinduced rearrangements of 3-alkanoylaminofurazans in the synthesis of 3-amino- or 3-*N*-substituted amino-5-alkyl-1,2,4-oxadiazoles has been pointed out.[54] To this aim, to minimize subsequent photoreactivity of the firstly-formed oxadiazoles, irradiations at 310 nm in Pyrex vessels were considered. Under these conditions, irradiation of **97** (R = alkyl) in the presence of an excess of some aliphatic primary or secondary amines (or ammonia) gave excellent yields (70-90%) of oxadiazoles (**82**; R = alkyl), with almost complete conversion of starting meterial (Scheme 19). Significantly, fragmentation again involves only

the O(1)-N(5) bond of the furazan ring. Although the intimate mechanism does not appear fully-established, it is suggested that the amine should play an important role in determining both photoreactivity and direction of the ring-fragmentation; to this, a complex between the acylamino compound and the base was tentatively hypothesized as actual photoreactive species.
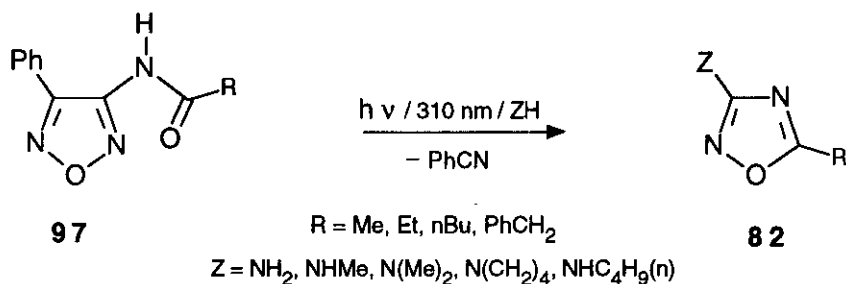
Scheme 19

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