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MOLECULAR REARRANGEMENTS OF 1-OXA-2-AZOLES AS AN EXPEDIENT ROUTE TO FLUORINATED HETEROCYCLIC COMPOUNDS

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Abstract - Molecular rearrangements of O-N bond-containing azoles (1-oxa-2-azoles) represent a wide class of reactions by which various heterocycle-to-heterocycle transformations can be performed as alternative synthetic methodologies. The material presented in this review is an extensive survey of both thermal and photochemical methodologies that have been applied to fluorinated oxadiazoles, and shows how molecular rearrangements can be an alternative and in some cases the most convenient route for the synthesis of several fluorinated heterocycles.

CONTENTS

1. INTRODUCTION

Fluorinated heterocycles represent an interesting class of compounds which are applied as agrochemicals, pharmaceuticals, or in new material sciences, and their synthesis constitutes a rather intriguing and challenging research area.[1,2] Typically, two main strategies are used when synthesizing fluorinated

heterocyclic compounds: i) fluorination or perfluoroalkylation reactions, by which the fluorinated group is directly introduced into the heterocyclic structure; ii) the *building-block strategy*, by which the fluorinated heterocyclic structure is built-up from acyclic fluorinated precursors through conventional heterocyclization reactions such as cycloadditions or cyclocondensations.[2] Although the first methodology may appear the most appropriate, it is not applicable in cases where the low reactivity of the substrate or the regioselectivity of the reaction is a main concern. The presence of functional groups in the heterocycle could also, in some cases, prevent the use of the first approach in the synthesis of fluorinated or perfluoroalkylated systems. Therefore, the *building-block strategy* appears to be the more suitable approach, for the synthesis of fluorinated heterocyclic compounds, especially when such structures contain sensitive functional groups. [2]

Within the *building-block strategy* one can in principle apply all conventional procedures for heterocyclization reactions. The key step for this strategy consists of constructing the appropriate fluorinated acyclic precursor. However, conventional heterocyclization reactions are sometimes difficult due to the modification in reactivity induced by the fluorinated moiety.

Considering the several examples reported in recent literature, we summarize here a series of generally applicable methodologies which exploit heterocyclic rearrangements as a new strategy for the synthesis of fluorinated heterocycles. It is worthy to note that heterocyclic rearrangements (thermally or photochemically induced) represent a wide class of reactions largely studied from a mechanistic point of view and as an alternative methodology in synthesis.[3-5] This new strategy introduces the concept of using an easily accessible fluorinated heterocyclic system as a precursor itself, which can be transformed into a different fluorinated heterocyle by means of thermal or photochemical processes. Still belonging to the *building-block strategy* category, this approach takes the advantage from the *in situ* formation and subsequent heterocyclization (whenever not concerted) of fluorinated acyclic precursors (often non isolable as intermediates) originated from the reaction of the starting heterocyclic system.

This review collects the reported examples under thermal and photochemical methods, and primarily focuses on transformations of O-N bond-containing azoles such as fluorinated 1,2,4-oxadiazoles and 1,2,5-oxadiazoles (furazans).

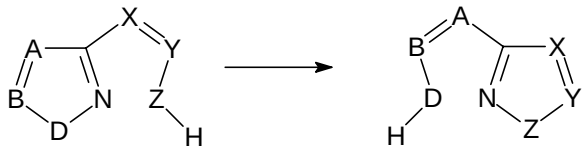
2. THERMAL METHODS

2.1. The Boulton-Katritzky Rearrangement

The most general pattern explaining the rearrangements of five-membered heterocycles is represented by the Boulton-Katritzky pattern (Scheme 1):[3b] a starting heterocycle containing a participating three atom

side-chain rearranges, in a thermal or base catalysed process, into the final ring through an internal nucleophilic substitution pattern.[3b-3f, 6]

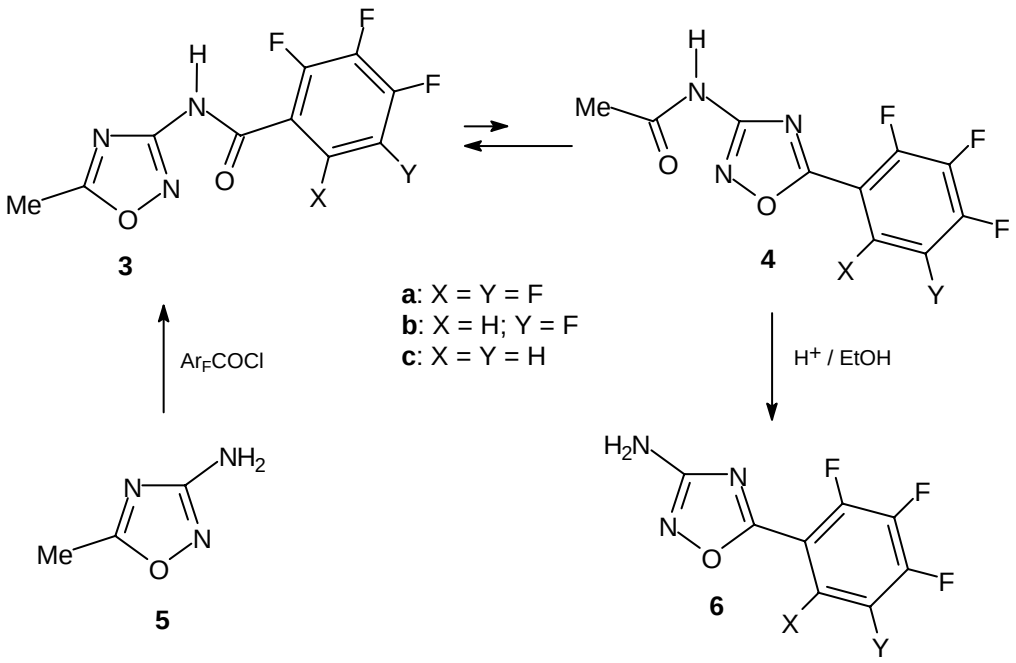
Scheme 1



1 **2**

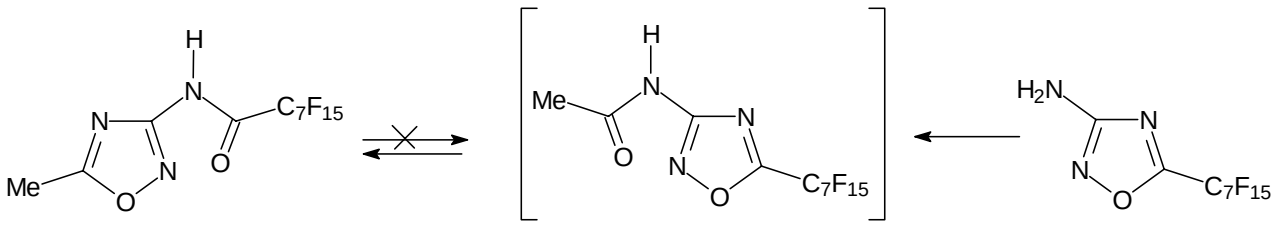
In most cases, these rearrangements have been used in synthetic protocols and examples of this approach for the obtainment of fluorinated heterocycles are rather recent: for instance, 3-amino-5-polyfluorophenyl-1,2,4-oxadiazoles (**6**) (Scheme 2) were synthesized through the ring-degenerate rearrangement of 3-acylamino-1,2,4-oxadiazoles.[7,8] Here, the thermal equilibration of 5-methyl-3-polyfluorobenzoylamino-1,2,4-oxadiazoles (**3**) [easily obtained by aroylation of the 3-amino-5-methyloxadiazole (**5**) with the appropriate polyfluorobenzoyl chloride in benzene/pyridine] produced a mixture of both the ring degenerate isomers (**3**) and (**4**) in an 80:20 ratio reflecting the balance between the electron withdrawing character of the polyfluorophenyl moiety (which stabilizes the carbamoyl group in **3**), and the poor diaryloid contribution to the stabilization of **4**.[8a,e,g] However, acid hydrolysis of this mixture induced a dynamic shift in the ring-degenerate equilibrium and produced the expected 3-aminocompounds (**6**)in about 75 % yields.[7]

Scheme 2



These results are noteworthy since attempts to obtain the same fluorinated oxadiazoles by conventional routes (e.g., through the acylcyanamide method[9]) were unsuccessful. Unfortunately, because of the structure dependant reactivity of 3-acylamino-1,2,4-oxadiazoles towards the ring-degenerate interconversions,[8] this approach was not applicable to the synthesis of 3-amino-5-perfluoroalkyl derivatives such as **9** (Scheme 3). In fact, the equilibration between the corresponding ring-degenerate components (**7**) and (**8**) can be considered irreversibly shifted towards the perfluoroalkanoylamino component (**7**).[7] As a confirmation of this hypothesis, it has been found that acetylation of the 3-amino-5-perfluoroheptyloxadiazole (**9**) directly produced compound (**7**) as a result of the ring-rearrangement of **8** as soon as it is formed.[7]

Scheme 3

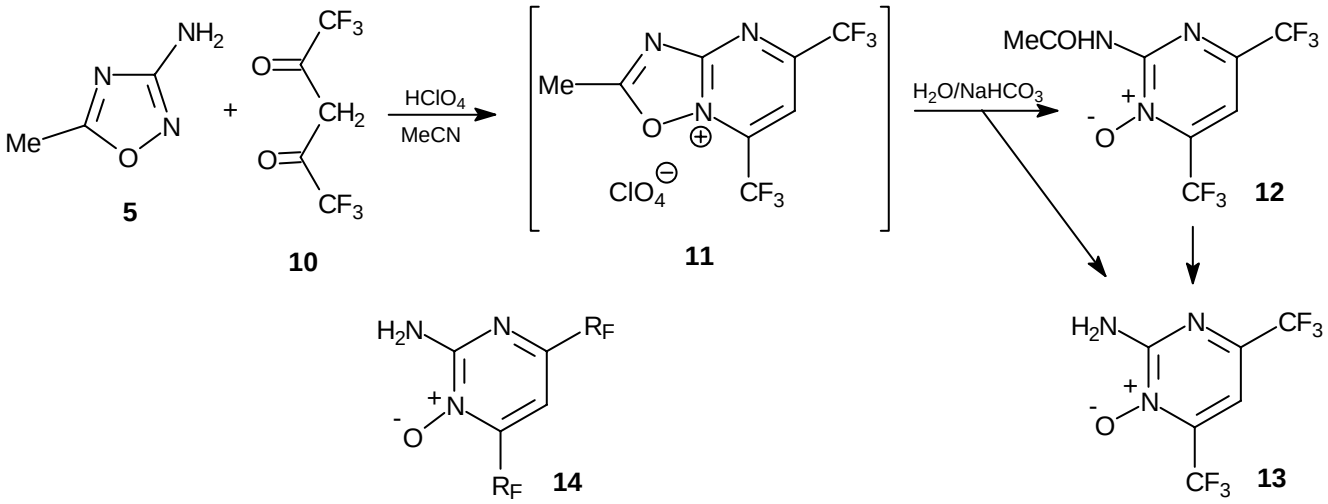


7 **8** **9**

2.2. The "Four Side-chain Atoms" Rearrangement

Within the class of heterocyclic rearrangements involving an internal nucleophilic attack from a side-chain, the involvement of a four-atom chain will result in a five- to six-membered ring conversion. In this context, the transformation of *N*-(1,2,4-oxadiazol-3-yl)-β-enamino ketones into the corresponding pyrimidine *N*-oxides through the initial formation of bicyclic pyrimidinium salts, followed by ring-opening of the oxadiazole moiety, has been previously documented.[10] In the example below, the reaction between the 3-amino-5-methyl-1,2,4-oxadiazole (**5**) with the fluorinated 1,3-diketone (**10**) in perchloric acid/acetonitrile medium did not allow the isolation of the pyridinium salt (**11**) (Scheme 4). A typical work-up of the reaction with water and sodium hydrogen carbonate directly produced the aminopyrimidine *N*-oxide (**13**) (in 40 % yields) together with some amounts of the corresponding acetylamino derivative (**12**).[11] These findings represent preliminary results on this topic, and, since one can vary the fluorinated diketone fragment, this synthesis could be considered a very simple and promising methodology to obtain fluorinated 2-aminopyrimidine-*N*-oxides of the general type (**14**). In fact, attempts to perfom an *N*-oxidation reaction of fluorinated 2-amino-pyrimidines by conventional methods (with hydrogen peroxide in acetic acid, or with *m*-chloro-perbenzoic acid) failed.

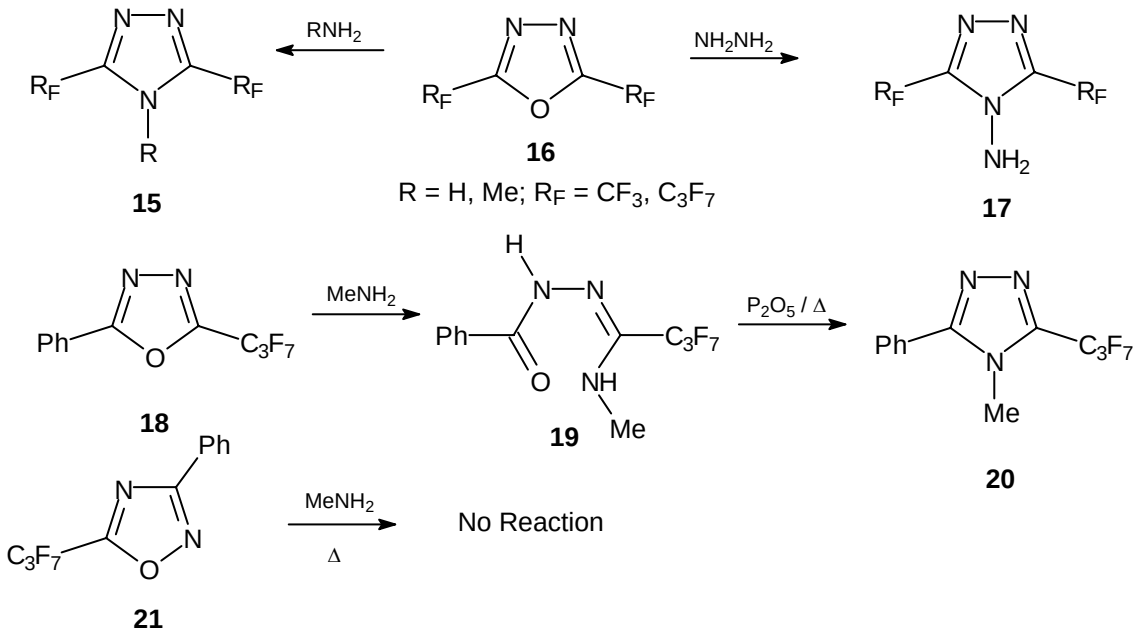
Scheme 4



2.3. The ANRORC-type Rearrangement

Among ring-interconversion reactions is the ANRORC rearrangement which consists of the ***A***ddition of a ***N***ucleophile to a π-deficient heterocycle, followed by ***R***ing-***O***pening and ***R***ing-***C***losure steps;[4] this pattern, which is largely documented in the azine series,[4,12] is observed also for five-membered heterocycles with particular substituents.[4,13] With this approach, an easily accessible fluorinated heterocycle can be transformed into a different one containing the heteroatoms originally belonging to the nucleophilic reagent.

Scheme 5



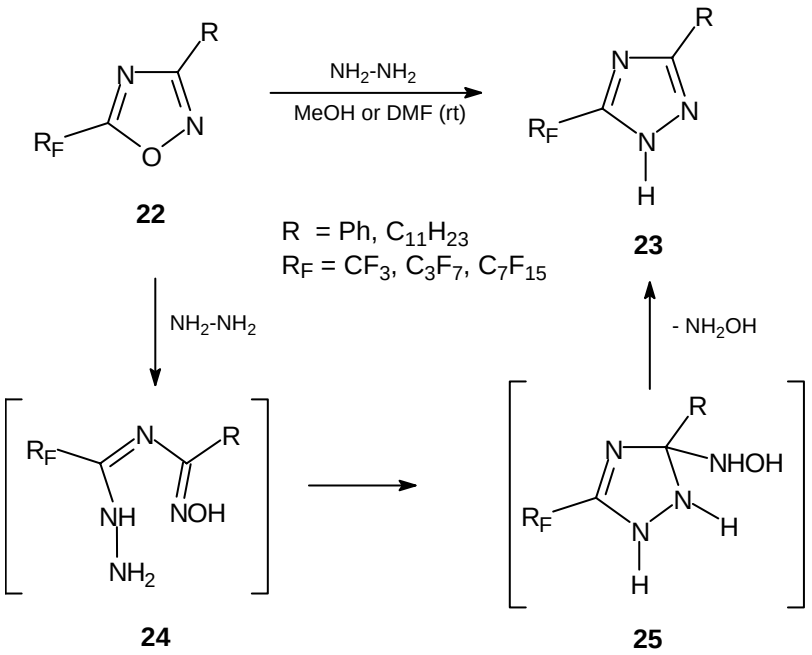
ANRORC-like reactions involving fluorinated heterocycles different from 1-oxa-2-azoles have been conducted by aminolysis or hydrazinolysis of 2,5-diperfluoroalkyl-1,3,4-oxadiazoles (**16**) (Scheme 5).[14] Following the expected mechanism, the reaction leads to diperfluoroalkyl-1,3,4-triazoles (**15**) or (**17**)

either directly or through subsequent heterocyclization of the intermediates. A similar reaction is reported for the 2-perfluoropropyl-5-phenyl-1,3,4-oxadiazole (**18**): aminolysis of **18** produces open-chain compound (**19**) which undergoes cyclodehydration into **20** by treatment with phosphorus pentoxide. However, the aminolysis of the 1,2,4-oxadiazole analogue (**21**) failed (Scheme 5).[15]

Recent ANRORC examples involve the reaction of 5-perfluoroalkyl-1,2,4-oxadiazoles with bifunctional nucleophiles such as hydrazines[16] or hydroxylamine,[17] by which 5-perfluoroalkyl-1,2,4-triazoles or the regioisomers 3-perfluoroalkyl-1,2,4-oxadiazoles, respectively, are formed (Schemes 6, 7, and 8).

2.3.1. ANRORC Reactions with Hydrazines: In the reaction of 5-perfluoroalkyl-oxadiazoles (**22**) with hydrazine,[16] the formation of 5-perfluoroalkyl-1,2,4-triazoles (**23**) goes through the following steps: i) the addition of the nucleophilic reagent at the C(5) of the oxadiazole ring (whose electrophilic character is markedly enhanced by the perfluoroalkyl group); ii) the ring-opening (into **24**) followed by a ring-closure (into **25**) involving the β-nitrogen atom of the hydrazine and the C(3) of the original oxadiazole **22**; iii) the re-aromatization reaction by elimination of a molecule of hydroxylamine. In this final step, the higher thermodynamic stability of the formed 1,2,4-triazole ring with respect to the 1,2,4-oxadiazole, plays a determining role.[18] A significant solvent effect has been reported for this reaction, where the use of DMF enhanced the nucleophilic character of the reagent in the first step of the reaction and minimized the unproductive hydrolysis of open-chain intermediates.[16]

Scheme 6

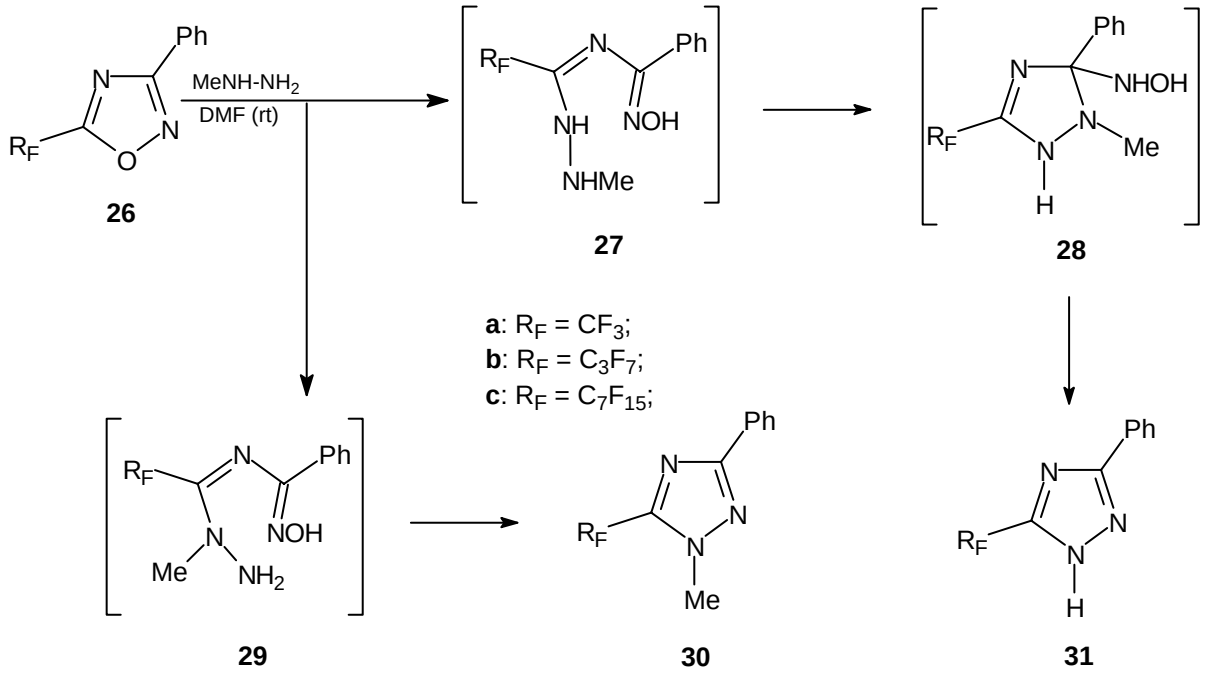


22 **23** **24** **25**

Overall, this ANRORC-like reaction is dependant upon the marked electrophilic character of the C(5) which is determined by the presence and position of the fluorinated group [in fact, neither 5-methyl-3-phenyl- nor 5-phenyl-3-perfluoroheptyl-1,2,4-oxadiazoles reacted with hydrazine under the same

conditions]. Furthermore, the use of a bifunctional nucleophile is fundamental in allowing the subsequent closure to form a new heterocyclic structure [in fact, 5-perfluoropropyl-3-phenyl-1,2,4-oxadiazole (**21**) (Scheme 5) did not react with a monofunctional nucleophile such as methylamine]. Finally, the driving-force of the reaction is found in the heterocyclization of open-chain intermediates into the more stable 1,2,4-triazole heterocycle.[16]

Scheme 7

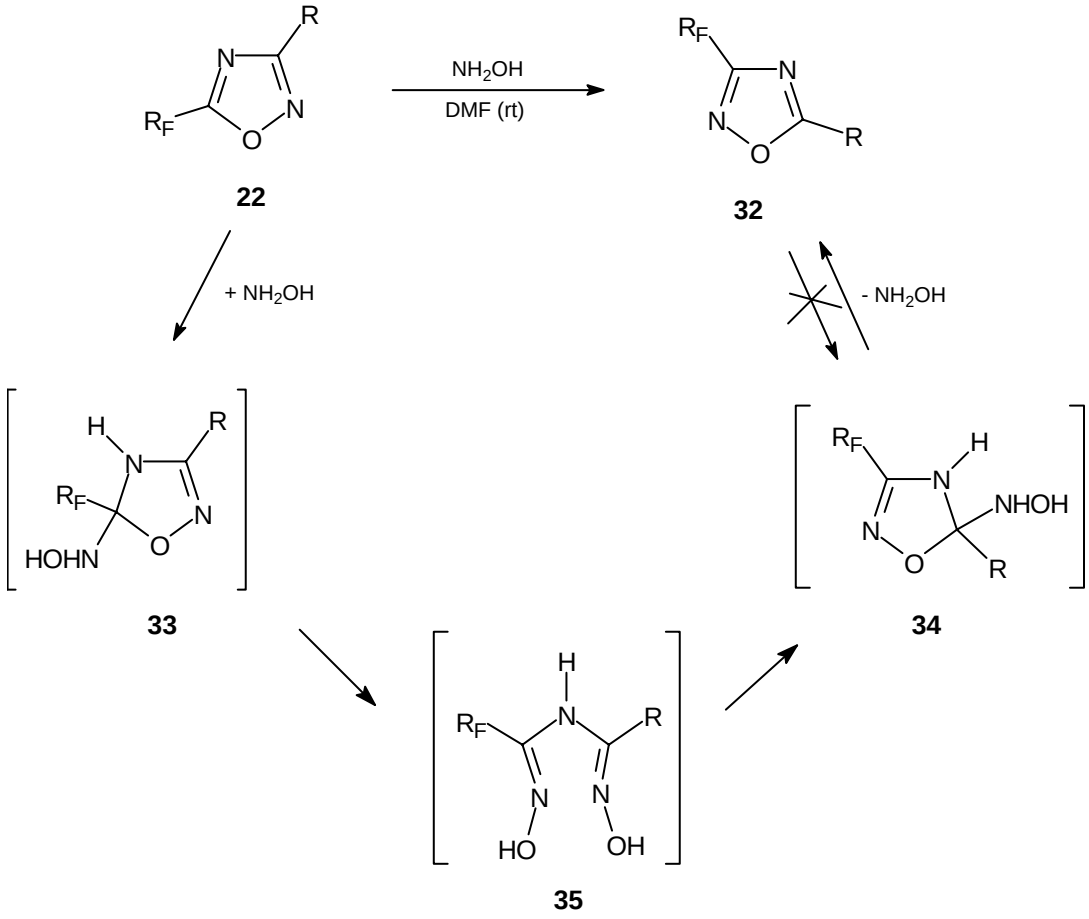


When methylhydrazine was used, the reaction, performed in DMF, produced the expected 1-methyl substituted triazoles (**30**) and, interestingly, the non-methylated triazoles (**31**), which is explained by assuming a demethylation process in the final aromatization step (Scheme 7). In the case of the 5-trifluoromethyl derivative (**26a**), the reaction produced the 1-methyltriazole (**30a**) in 70% yields and a small percent of the corresponding unsubstituted compound (**31a**)**.** In contrast, in the case of the 5-perfluoroheptyl derivative (**26c**), compounds (**30c**) and (**31c**) were obtained in 49 and 22% yields, respectively. This clearly showed that the regioselectivity of the nucleophilic attack of the unsymmetrical reagent depends on steric effects exercised by the perfluoroalkyl group.[16]

2.3.2. ANRORC Reactions with Hydroxylamine: In the case of the reaction with hydroxylamine as a bifunctional nucleophile, the entering atoms (N-O, from the reagent) and the leaving ones (O-N, from the oxadiazole ring) are the same, therefore a ring-degenerate rearrangement is expected. In fact, the reaction of a series of 5-perfluoroalkyl-1,2,4-oxadiazoles (**22**) with hydroxylamine in DMF at room temperature produced excellent yields of regioisomers 3-perfluoroalkyl-1,2,4-oxadiazoles (**32**), resulting in a virtual C(5)-C(3) annular switch.[17] The reaction follows the ANRORC pattern, where the heterocyclization of

the dioxime-like intermediate (**35**) followed by the displacement of hydroxylamine is driven by the formation of the more stabilized 3-perfluoroalkyloxadiazoles (**32**) in an irreversible ring-degenerate rearrangement. A theoretical study on representative substrates substantiated the higher stability of the 3-perfluoroalkyl substituted 1,2,4-oxadiazoles with respect to the corresponding 5-perfluoroalkyl derivatives (Table 1) and explains the irreversible process shifted towards the 3-perfluoroalkyl-oxadiazoles.

Scheme 8



a: R = Ph; R_F = CF_3; **b**: R = Ph; R_F= C_3F_7; **c**: R = Ph; R_F = C_7F_{15}
d: R = *p*-$NO_2C_6H_4$; R_F = CF_3; **e**: R = *p*-$MeOC_6H_4$; R_F= CF_3
f: R = $C_{11}H_{23}$; R_F = CF_3; **g**: R = *p*-$MeOC_6H_4$; R_F= C_7F_{15}

Table 1. Yields and Calculated ΔE for the Ring-Degenerate Rearrangement of Representative **22**

R	R_F	Substrate	Product	Yield	Calcd ΔE
Ph	CF_3	**22a**	**32a**	74	-17.8
p-$NO_2C_6H_4$	CF_3	**22d**	**32d**	94	-13.3
p-$MeOC_6H_4$	CF_3	**22e**	**32e**	82	-19.8

In summary for this reaction it was observed that: i) the hydroxylamine acts as a reagent in the first step and as a leaving group in the final one, therefore, the reaction develops even by using low molar ratios of the reagent; ii) steric effects of the C(5)-perfluoroalkyl group affect nucleophilic attack in the first step; iii) electron withdrawing substituents that increase the electrophilic character of the C(3) of the oxadiazole ring, where the ring closure takes place, speed-up the reaction; iv) the ring-degenerate rearrangement is a thermodynamically irreversible process.

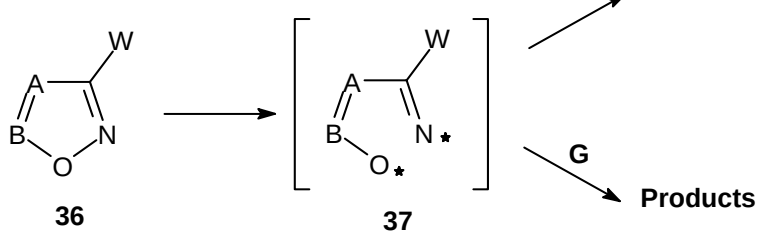
Since the preparation of 5-perfluoroalkyloxadiazoles is an efficient reaction using the perfluoroacylation/cyclodehydration of amidoximes,[15,19] the above rearrangement represents an elegant approach for the synthesis of 3-perfluoroalkyl substituted 1,2,4-oxadiazoles, whereas conventional methods[18,20] through an acylation/cyclodehydration reaction of fluorinated amidoximes sometimes require drastic conditions or produce low yields.

In the above ANRORC-type rearrangements, different bifunctional nucleophiles able to attack the C(5) and to allow subsequent heterocyclization could be used for the synthesis of various five-membered as well as six-membered fluorinated heterocycles.

3. THE PHOTOCHEMICAL APPROACH

The synthetic application of photoinduced rearrangements of O-N bond containing azoles follows the general pattern reported in Scheme 9. In accordance with this scheme, photolytic intermediates (or their fragments) resulting from the cleavage of the ring O-N bond can develop into different heterocyclic structures with or without the involvement of a reacting species G present in the photoreaction medium. Several examples for non-fluorinated substrates are reported from our laboratories and regard the photochemistry of 1,2,5-oxadiazoles (furazans)[21-23] and 1,2,4-oxadiazoles.[21, 24-26] In this section we will emphasize some applications of photoinduced rearrangements of the above oxadiazoles in the synthesis of fluorinated compounds.

Scheme 9

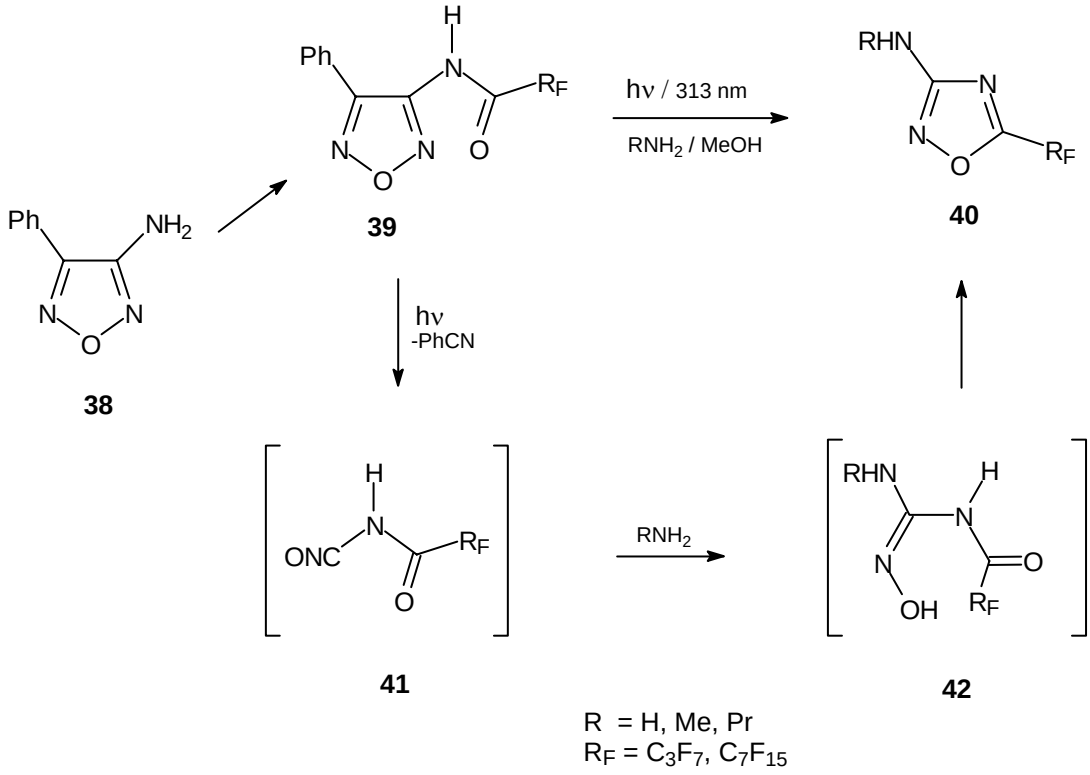


W = Substituent or a Side-chain
G = Interacting reagent

3.1. The Photochemistry of 1,2,5-Oxadiazoles (Furazans)

This approach exploits the photofragmentation pattern of the furazan heterocycle into a nitrile and a nitrile oxide species and follows previous results described for non-fluorinated substrates.[21-23] Irradiation of 3-perfluoroalkanoylamino compounds (**39**) (easily accessible in almost quantitative yields from the 3-aminofurazan (**38**) and perfluoroacylating reagents by conventional procedures) at λ = 313 nm in methanol and in the presence of ammonia or primary aliphatic amines produces the corresponding 3-amino- or 3-*N*-alkylamino-5-perfluoroalkyl-1,2,4-oxadiazoles (**40**) in 30-50 % yields (Scheme 10).[27] Although yields of isolated products were not excellent [because of the photoreactivity of the first-formed oxadiazoles (**40**) under irradiation conditions, see later], this methodology appears significant because conventional procedures for the synthesis of these targeted fluorinated oxadiazoles produced very poor results.

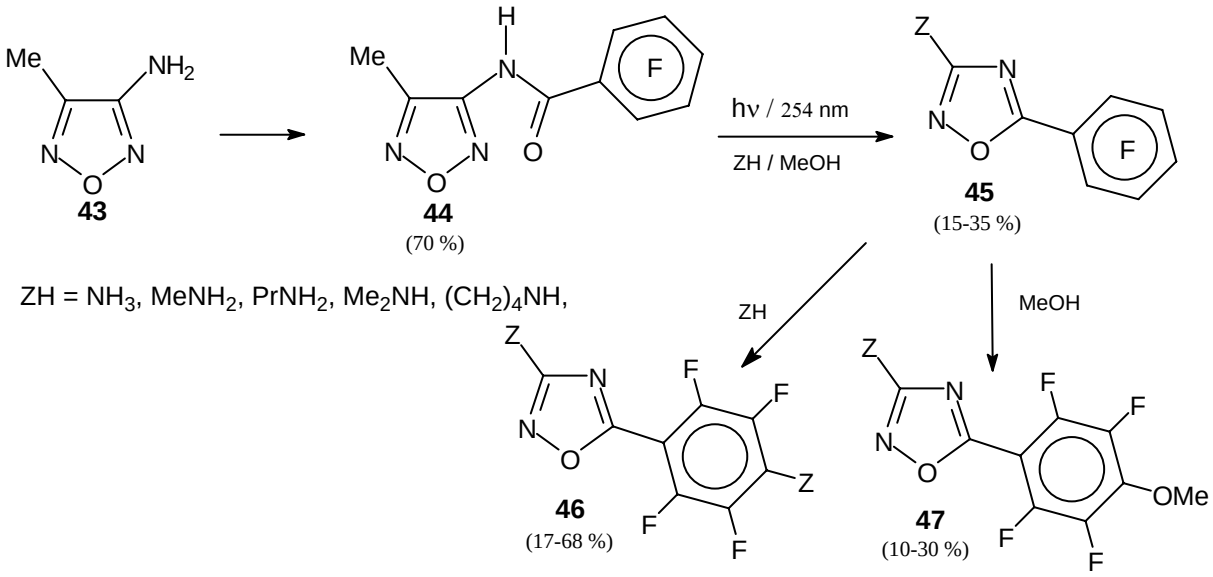
Scheme 10



A similar approach has been applied to the synthesis of 3-amino- (or 3-*N*-substituted amino) 5-pentafluorophenyl-1,2,4-oxadiazoles (**45**) by photolysis of the pentafluorobenzoylaminofurazan (**44**) at λ = 254 nm in methanol and in the presence of either ammonia, primary or secondary aliphatic amines (ZH in Scheme 11).[28] Since the electronic nature of the oxadiazole ring activates the nucleophilic substitution at the 5-perfluorophenyl moiety, thermal displacement of fluoride anion by the nitrogen nucleophile or by

the solvent under reaction conditions produces a series of *para*-substituted polyfluoroaryl-1,2,4-oxadiazoles (**46**) and (**47**) (Scheme 11).

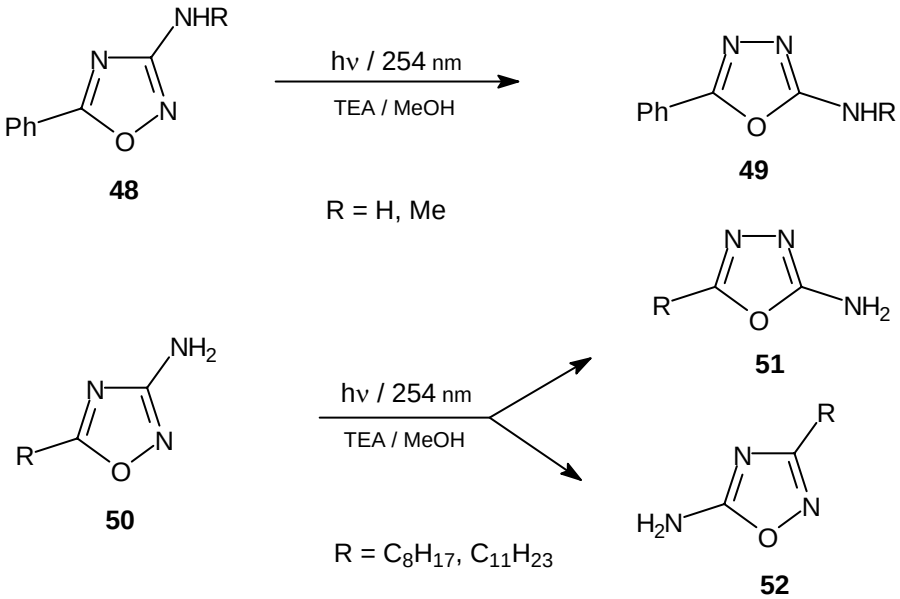
Scheme 11



3.2. The Photochemistry of 1,2,4-Oxadiazoles

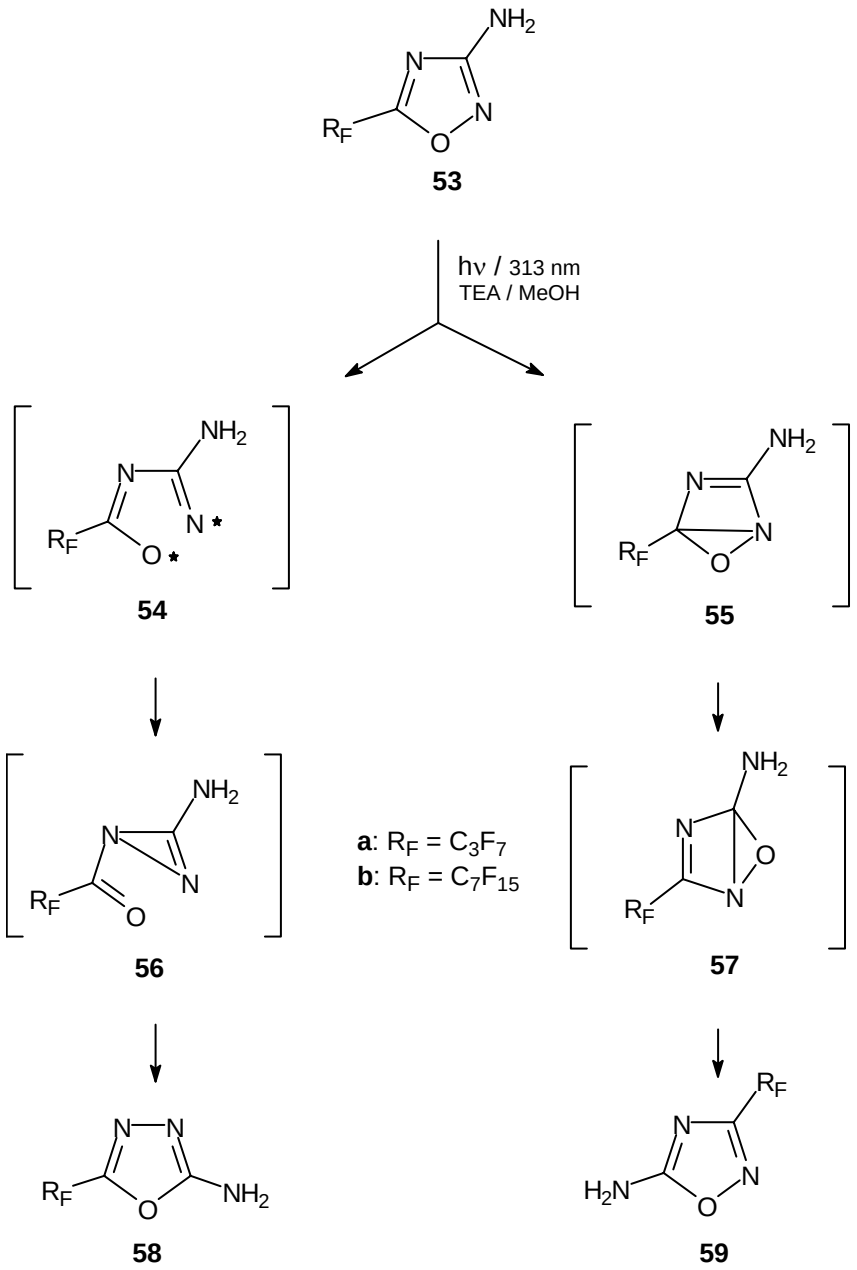
It is well known that the photochemistry of the 1,2,4-oxadiazole heterocycle is characterized by the cleavage of the weakest O-N bond of the ring, producing open chain intermediates which then develop into different products. The products formed depend upon the nature and position of substituents in the ring, as well as the presence of an interacting reagent able to generate precursors for subsequent heterocyclization reactions.[21,24-26] A particular example of photoreactivity of 1,2,4-oxadiazoles is represented by the ring-photoisomerization into 1,3,4-oxadiazoles by the *ring contraction–ring expansion* route.[29-31]

Scheme 12



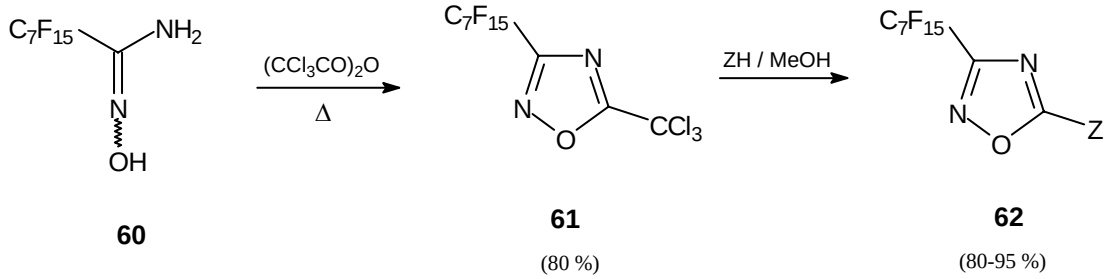
The occurrence of this process appears to be restricted to 1,2,4-oxadiazoles bearing an XH group (such as NH_2 or NHR) at C(3) and was found to be favored by the presence of a base in the photoreaction medium (Scheme 12).[30] Interestingly, in the case of the 3-amino-5-alkyl-1,2,4-oxadiazoles (**50**) irradiated at λ = 254 nm in methanol and in the presence of TEA, two competing pathways have been observed:[31] formation of the 1,3,4-oxadiazoles (**51**) on one hand and the 5-amino ring-degenerate 1,2,4-oxadiazoles (**52**) on the other. The formation of the ring degenerate isomers has been explained by assuming the occurrence of a competing *internal cyclization-isomerization* route, involving a N(2)-C(5) bond formation in the first step, followed by sigmatropic shift and isomerization (see later).

Scheme 13



These peculiar photoreactivities have been exploited for fluorinated structures. Thus, studying the irradiation of 3-amino-5-perfluoroalkyloxadiazoles (**52**) a marked photoreactivity was observed, and this behavior was ascribed to a sinergic effect of the amino group at C(3) and the perfluoroalkyl group at C(5), which determines a significant red-shift in the UV absorption spectra of about 30 nm for the fluorinated substrates compared with the non-fluorinated analogues.[32,33] The irradiation of compounds (**53**) at λ = 313 nm in methanol containing TEA followed the expected competing routes leading to 2-amino-5-perfluoroalkyl-1,3,4-oxadiazoles (**58**) as the major component (50-60 %) and the 5-amino-3-perfluoroalkyl-1,2,4-oxadiazoles (**59**) (15-20 %) (Scheme 13).[33] Also in this case, the photochemical methodology in synthesis of 2-amino-5-perfluoroalkyl-1,3,4-oxadiazoles has been emphasized. In turn, for 5-amino substituted 3-perfluoroalkyl-1,2,4-oxadiazoles or the 5-*N*-substituted amino derivatives (**62**), a general synthetic methodology was reported by aminolysis of the 5-trichloromethyl-3-perfluoroheptyloxadiazole (**61**) with primary or secondary aliphatic amines (Scheme 14).[32]

Scheme 14

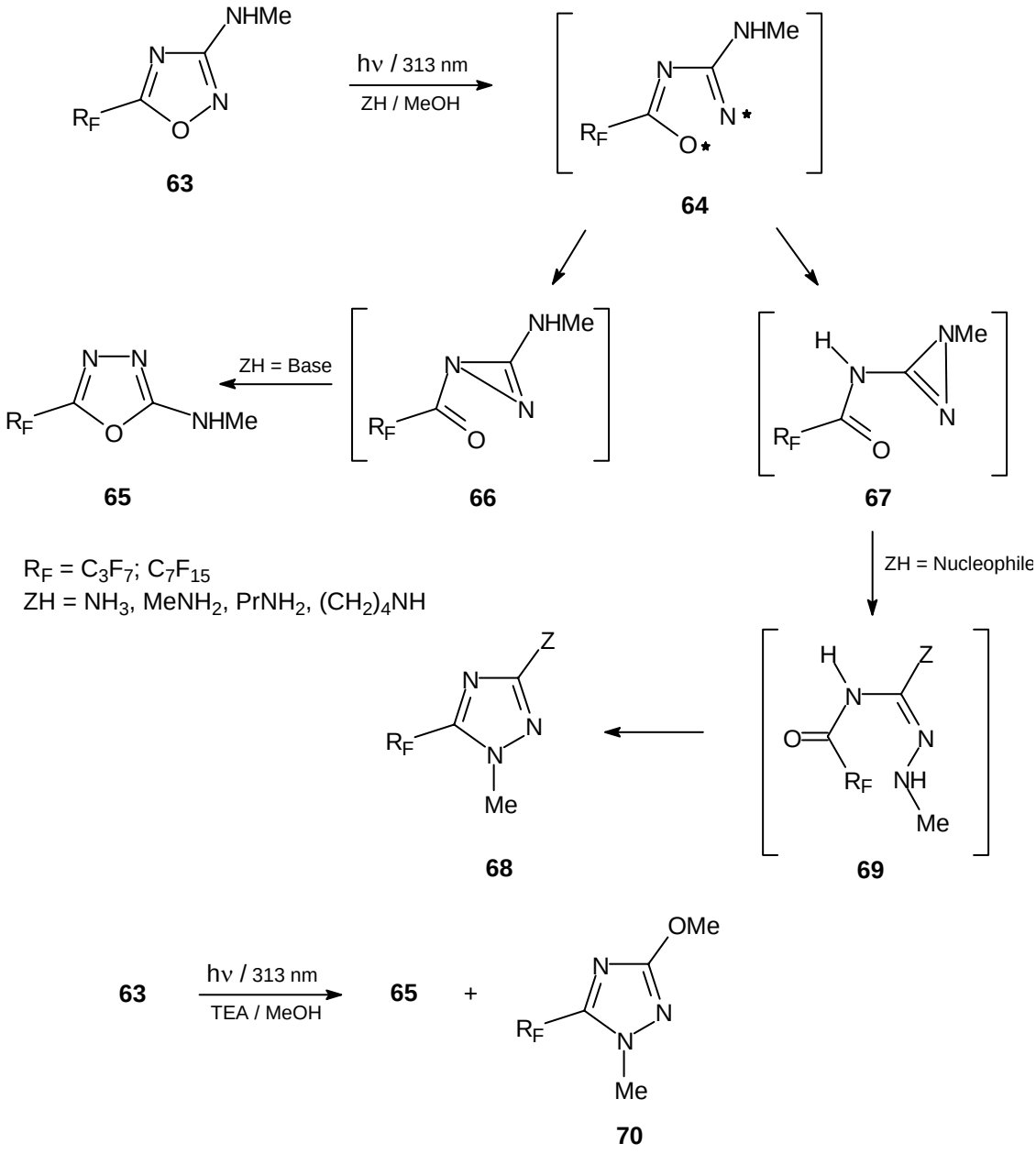


60 **61** (80 %) **62** (80-95 %)

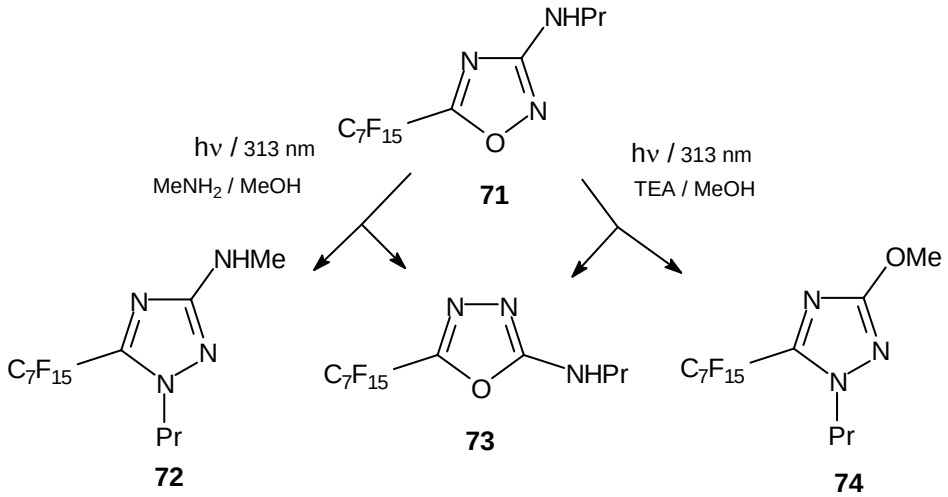
ZH = NH_3, $MeNH_2$, Me_2NH, CH_2=CH-CH_2NH_2, $(CH_2)_4NH$

Photoreactivity of 3-*N*-methylamino-5-perfluoroalkyl-1,2,4-oxadiazoles (**63**) has been found to be different from that observed for the 3-amino compounds (**53**).[34] In fact, irradiation of compounds (**63**) in the presence of various nitrogen reagents produces competing pathways leading to the 1,3,4-oxadiazoles (**65**) (27-53 %) (ZH acting as a base) and the 1,2,4-triazoles (**68**) (21-27 %) (ZH acting as a nucleophile). A ring contraction route involving the endocyclic nitrogen [to the diazirine (**66**)] on one hand and the involvement of the exocyclic nitrogen [to the diazirine (**67**)] on the other has been suggested (Scheme 15). In addition, irradiation of **63** in the presence of TEA produced both the expected compounds **65** (36-38 %) and the corresponding 3-methoxytriazoles (**70**) (17-32 %) arising from the involvement of the solvent methanol as nucleophile (Scheme 15). Similar photoreactions have also been applied to the 3-*N*-propylaminooxadiazole (**71**) irradiated in the presence of $MeNH_2$ [leading to **72** (22 %) and **73** (50 %)] or in the presence of TEA [leading to **73** (36 %) and **74** (37 %)] (Scheme 16).[34]

Scheme 15



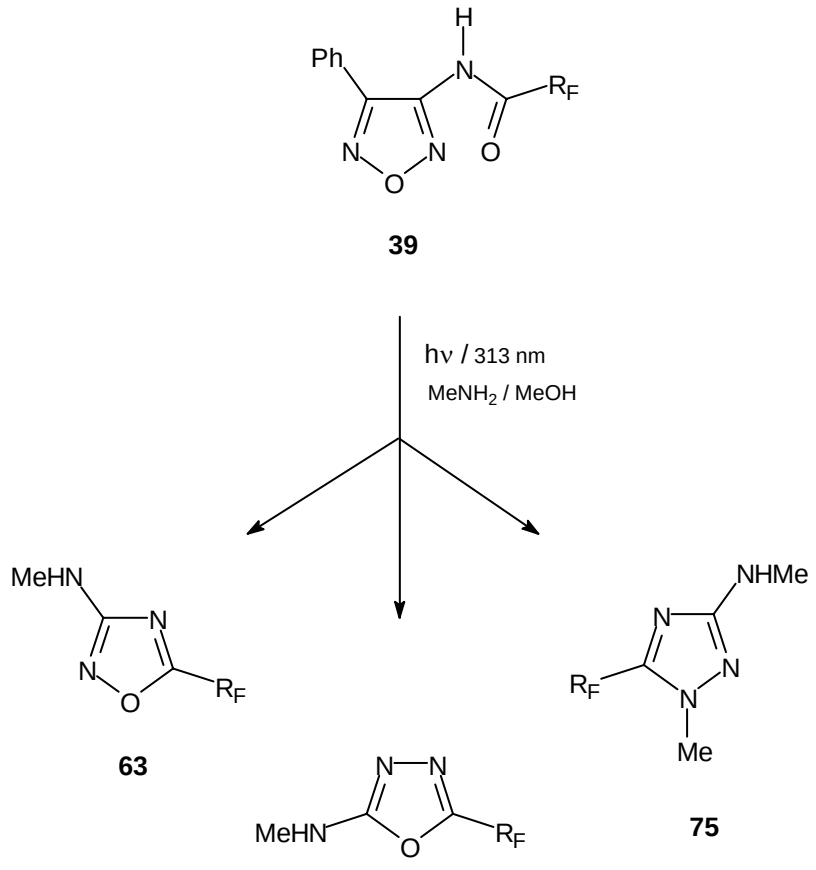
Scheme 16



Furthermore, considering the synthetic procedure leading to 3-*N*-alkylamino-5-perfluoroalkyl-1,2,4-oxadiazoles (that is, irradiation of 3-perfluoroalkanoylaminofurazans in the presence of primary aliphatic amines, see Scheme 10),[27] irradiation of the perfluoroalkanoylaminofurazans (**39**) in the presence of an excess of methylamine has been re-evaluated with the intention to perform a one-pot phototransformation. In a typical experiment, irradiation of compound (**39a**) in the presence of an excess of methylamine, besides the 3-*N*-methylamino-1,2,4-oxadiazole (**63a**) (8%), produced the 2-*N*-methylamino-1,3,4-oxadiazole (**65a**) (45 %) and the 3-*N*-methylamino-1,2,4-triazole (**75a**) (10 %). Similarly, prolonged irradiation of **39b** in the presence of an excess of methylamine produced **63b** (42 %), **65b** (25 %) and **75b** (16 %) (Scheme 17).[34]

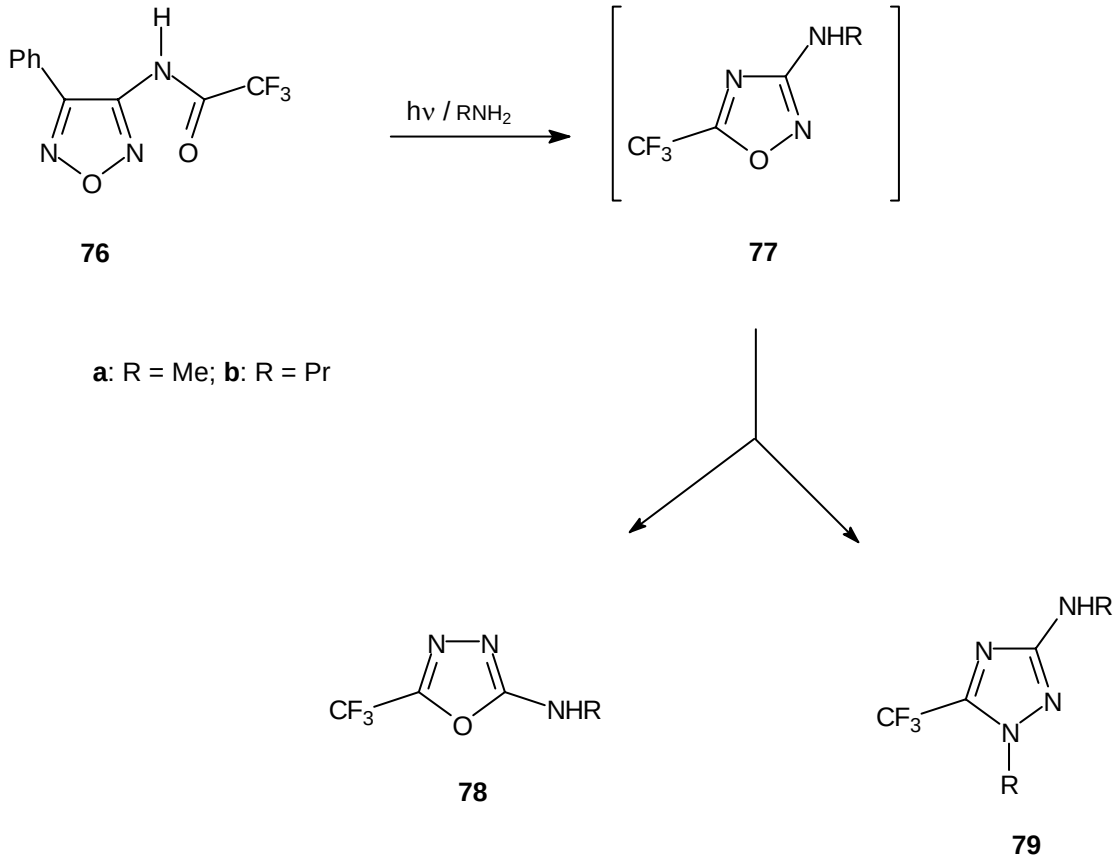
This general one-pot methodology has been successfully used also in the case of trifluoromethylated compounds for which 1,2,4-oxadiazoles were difficult to isolate. As expected, irradiation of compound (**76**) in the presence of an excess of methylamine or propylamine produced the 2-*N*-alkylamino-5-trifluoromethyl-1,3,4-oxadiazoles (**78**) (32 %) (whose structure was also confirmed by X-ray analysis performed on **78a**) and 1-alkyl-3-*N*-alkylamino-1,2,4-triazoles (**79**) (15-27 %) (Scheme 18).[34]

Scheme 17



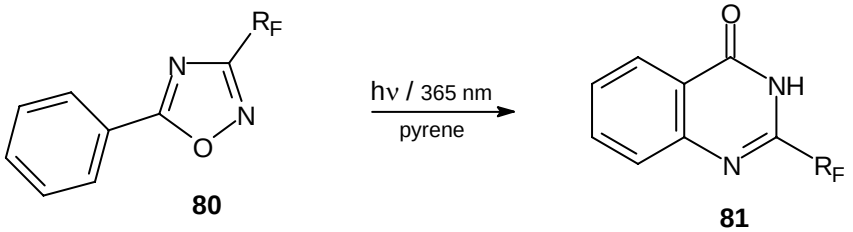
a: $R_F = C_3F_7$; **b**: $R_F = C_7F_{15}$

Scheme 18

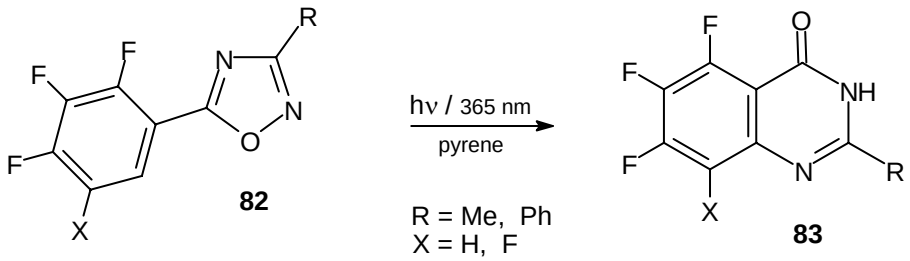


The photochemistry of 1,2,4-oxadiazoles was also reported as a way to synthesize quinazolin-4-ones containing a perfluoroalkyl group at C(2) or a polyfluorinated benzofused moiety.[35] Similarly to what was reported for non-fluorinated substrates,[26] irradiation of 3-perfluoroalkyl-5-phenyl- 1,2,4-oxadiazoles **80** or of 5-polyfluorophenyl-1,2,4-oxadiazoles **82** at λ = 365 nm in acetonitrile and in the presence of pyrene, produced the fluorinated quinazolin-4-ones **81** or **83**, respectively, in acceptable preparative scale yields (in the range of 35-75%) (Scheme 19). A plausible explanation of these photoreactions assumes a photoinduced electron-transfer process from excited pyrene to the ground state oxadiazole. An energy transfer process from excited pyrene to the oxadiazole has been ruled out on the basis of singlet state energies of oxadiazole substrates. The resulting oxadiazole radical-anion will be the species undergoing the cleavage of the ring O-N bond. Subsequent hetrocyclization of open chain intermediates at the phenyl or polyfluorophenyl moiety will involve a back-electron transfer process (Scheme 20). The same phototransformation (with lower yields, however) has also been obtained by irradiating oxadiazoles **80** or **82** at λ = 313 nm in MeOH/TEA medium. In this case the electron-transfer process involves the excited oxadiazole component and TEA as the electron donor species.

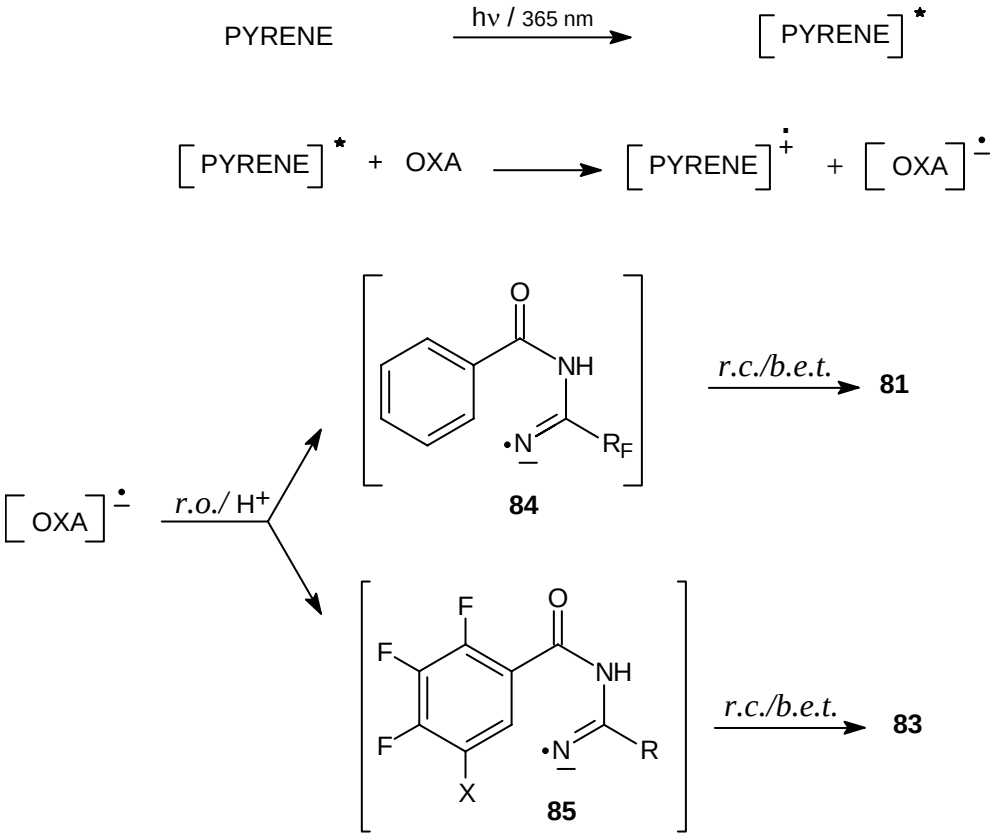
Scheme 19



R_F = CF_3, C_3F_7, C_7F_{15}, C_6F_5



Scheme 20



OXA = oxadiazole; *r.o.* = ring opening;
r.c. = ring closure; *b.e.t.* = back electron transfer

4. CONCLUDING REMARKS

In conclusion, we wish to emphasize that the heterocyclic rearrangement pattern of O-N bond containing azoles could be generally exploited for the synthesis of fluorinated heterocycles. This is valid both in the case of the thermal approach and in the case of photoinduced processes. Although in some photoinduced reactions yields of desired products are not excellent, the photochemical approach still represents a valid alternative for obtaining targeted fluorinated heterocyclic compounds when thermal or conventional procedures present some difficulties.

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6. REFERENCES

1 *Inter alia*, *see*: (*a*) M. Hudlicky, *Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, 1976; (*b*) R. Filler, *Organofluorine Chemicals and their Industrial Applications*, ed. by R. E. Banks, Ellis Horwood, Chichester, 1979; (*c*) R. Filler and Y. Kobayashi, *Biomedical Aspects of Fluorine Chemistry*, Kodansha & Elsevier Biomedical, Tokyo, 1982; (*d*) J. T. Welch, *Tetrahedron*, 1987, **43**, 3123; (*e*) D. W. Reynolds, P. E. Cassidy, C. G. Johnson, and M. L. Cameron, *J. Org. Chem*., 1990, **55**, 4448; (*f*) R. Filler, Y. Kobayashi, and L. M. Yagupolskii, *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, Elsevier, Amsterdam, 1993; (*g*) M. Hudlicky and A. E. Pavlath, eds, *Chemistry of Organic Fluorine Compounds II. A Critical Review*, ACS Monograph 187, American Chemical Society, Washington, DC, 1995.

2 (*a*) R. D. Chambers and C. R. Sargent, *Adv. Heterocycl. Chem*., 1981, **28**, 1; (*b*) E. Differding, W. Frick, R. W. Lang, P. Martin, C. Schmit, S. Veenstra, and H. Greuter, *Bull. Soc. Chim. Belg*., 1990, **99**, 647; (*c*) M. J. Silvester, *Adv. Heterocycl. Chem*., 1994, **59**, 1; (*c*) K. Burger, U. Wucherpfennig,

and E. Brunner, *Adv. Heterocycl. Chem*., 1994, **60**, 1; (*d*) G. G. Furin, *Targets in Heterocyclic Systems*, ed. by O. A. Attanasi and D. Spinelli, Società Chimica Italiana: Roma, 1998; Vol. 2, pp 355-442; (*e*) S. Z. Zhu, Y. L. Wang, W. M. Peng, L. P. Song, and G. F. Jin, *Current Organic Chemistry*, 2002, **6**, 1057.

3 For heterocyclic rearrangements, see: (*a*) H. C. Van der Plas, *Ring Transformations of Heterocycles*; Academic: New York, 1973, Vol. 1 and 2; (*b*) A. J. Boulton, A. R. Katritzky, and A. M. Hamid, *J. Chem. Soc. C,* 1967, 2005; (*c*) A. S. Afridi, A. R. Katritzky, and C. A. Ramsden, *J. Chem. Soc., Perkin Trans. 1,* 1976, 315; (*d*) M. Ruccia, N. Vivona, and D. Spinelli, *Adv. Heterocycl. Chem*., 1981, **29**, 141; (*e*) G. L'abbé, *J. Heterocycl. Chem*., 1984. **21**, 627; (*f*) N. Vivona, S. Buscemi, V. Frenna, and G. Cusmano, *Adv. Heterocycl. Chem.,*1993, **56**, 49.

4 H. C. Van der Plas, *Adv. Heterocycl. Chem*., 1999, **74**, 1.

5 For photoinduced rearrangements of five-membered heterocycles, see: (*a*) A. Padwa, In *Rearrangements in Ground and Excited States*, ed. by P. de Mayo, Academic Press, New York, 1980, Vol III, pp. 501-547; (*b*) M. D'Auria, *Heterocycles*, 1999, **50**, 1115; (*c*) M. D'Auria, In *Targets in Heterocyclic Systems*, ed. by O. A. Attanasi and D. Spinelli, Società Chimica Italiana: Roma, 1999; Vol. 2, pp. 233-279; (*d*) M. D'Auria, *Adv. Heterocycl. Chem*., 2001, **79**, 41.

6 For recent papers on mechanistic studies on azole-to-azole interconversion reactions of the Boulton-Katritzky type, see: (*a*) B. Cosimelli, S. Guernelli, D. Spinelli, S. Buscemi, V. Frenna, and G. Macaluso, *J. Org. Chem*., 2001**, 66**, 6124; (*b*) B. Cosimelli, V. Frenna, S. Guernelli, C. Z. Lanza, G. Macaluso, G. Petrillo, and D. Spinelli, *J. Org. Chem*., 2002, **67**, 8010 and references cited therein for several papers on this series from the Spinelli's research group.

7 S. Buscemi, A. Pace, V. Frenna, and N. Vivona, *Heterocycles*, 2002, **57**, 811.

8 For ring degenerate rearrangements involving 1,2,4-oxadiazole derivatives and three side-chain atoms, see: (*a*) N. Vivona, G. Cusmano, M. Ruccia, and D. Spinelli, *J. Heterocycl. Chem*., 1975, **12**, 985; (*b*) N. Vivona, M. Ruccia, G. Cusmano, M. L. Marino, and D. Spinelli, *J. Heterocycl. Chem*., 1975, **12**, 1327; (*c*) G. La Manna, S. Buscemi, V. Frenna, N. Vivona, and D. Spinelli, *Heterocycles*,

1991, **32**, 1547; (*d*) V. G. Andrianov, S. V. Makushenkov, and A. V. Eremev, *Mendeleev. Commun*., 1992, 129; (*e*) S. Buscemi, V. Frenna, N. Vivona, G. Petrillo, and D. Spinelli, *Tetrahedron*, 1995, **51**, 5133; (*f*) G. La Manna, S. Buscemi, and N. Vivona, *J. Mol. Struct. (Theochem)*, 1998, **452**, 67; (*g*) S. Buscemi, V. Frenna, A. Pace, N. Vivona, and D. Spinelli, *Eur. J. Org. Chem*., 2002, 1417.

9 G. Westphal and R. Schmidt, *Z. Chem*., 1974, **14**, 94.

10 (*a*) N. Vivona, S. Buscemi, V. Frenna, and M. Ruccia, *J. Chem. Soc., Perkin Trans. 1*, 1986, 17; (*b*) S. Buscemi, G. Macaluso, V. Frenna, and N. Vivona, *J. Heterocycl. Chem*., 1986, **23**, 1175.

11 A. Pace, I. Pibiri, A. Palumbo Piccionello, S. Buscemi, and N. Vivona, *Book of Abstracts of IX Joint Meeting on Heterocyclic Chemistry*, Urbino (Italy), 2004, p. O22.

12 *Inter alia*, see: (*a*) R. G. Dickinson and N. W. Jacobsen, *Aust. J. Chem*., 1975, **28**, 2435; (*b*) A. Rykowski and E. Wolinska, *Tetrahedron Lett.*, 1996, **37**, 5795; (*c*) A. Rykowski and D. Branowska, *Heterocycles*, 1996, **43**, 2095; (*d*) O. N. Chupakhin, V. N. Kozhevnikov, D. N. Kozhevnikov, and V. L. Rusinov, *Tetrahedron Lett.*, 1999, **40**, 6099; (*e*) O. N. Chupakhin, V. N. Kozhevnikov, A. M. Prokhorov, D. N. Kozhevnikov, and V. L. Rusinov, *Tetrahedron Lett.*, 2000, **41**, 7379.

13 (*a*) A. Hetzheim and K. Mockel, *Adv. Heterocycl. Chem*., 1966, **7**, 183; (*b*) J. R. Reid and N. D. Heindel, *J. Heterocycl. Chem*., 1976, **13**, 925; (*c*) J. Sandstrom, *Adv. Heterocycl. Chem*., 1968, **9**, 165; (*d*) J. Suwinski, W. Pawlus, E. Salwinska, and K. Swierczek, *Heterocycles*, 1994, **37**, 1511.

14 (*a*) D. B. Reitz and M. J. Finkes, *J. Heterocycl. Chem*., 1989, **26**, 225. (*b*) D. B. Reitz and M. J. Finkes, *J. Org. Chem*., 1989, **54**, 1760.

15 J. P. Critchley and J. S. Pippett, *J. Fluorine Chem*., 1973, **2**, 137.

16 S. Buscemi, A. Pace, I. Pibiri, N. Vivona, and D. Spinelli, *J. Org. Chem*., 2003, **68**, 605.

17 S. Buscemi, A. Pace, I. Pibiri, N. Vivona, C. Z. Lanza, and D. Spinelli, *Eur. J. Org. Chem*., 2004, 974.

18 (*a*) L. B. Clapp, *Adv. Heterocycl. Chem*., 1976, **20**, 65; (*b*) J. C. Jochims, In *Comprehensive Heterocyclic Chemistry II*, ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Pergamon,

Elsevier Science, 1996, Vol. 4, pp. 179-228; (*c*) U. Kraatz, In *Houben-Weyl E 8c, Heteroarenes III/3*; Georg Thieme Verlag: Stuttgart, 1994, pp. 409-525.

19 For methodologies to synthesizing fluorinated 1,2,4-oxadiazoles, see: (*a*) H. C. Brown and C. R. Wetzel, *J. Org. Chem*., 1965, **30**, 3734; (*b*) K. J. L. Paciorek, R. H. Kratzer, J. Kaufman, and R. W. Rosser, *J. Fluorine Chem*., 1975, **6**, 241; (*c*) K. J. L. Paciorek, R. H. Kratzer, J. Kaufman, J. H. Nakahara, R. W. Rosser, and J. A. Parker, *J. Fluorine Chem*., 1977, **10**, 119; (*d*) K. J. L. Paciorek, T. I. Ito, J. H. Nakahara, J. Kaufman, R. H. Kratzer, and R. W. Rosser, *J. Fluorine Chem*., 1980, **16**, 51; (*e*) W. J. Middleton, *J. Org. Chem*., 1984, **49**, 919; (*f*) E. O. John and J. M. Shreeve, *Inorg. Chem*., 1988, **27**, 3100; (g) O. Rohr and F. Zumstein, 1988, Jpn Patent 63162680 (*Chem. Abstr*., 1989, **110**, 75518). (*h*) E. O. John, R. L. Kirchmeir, and J. M. Shreeve, *J. Fluorine Chem*., 1990, **47**, 333; (*i*) E. V. Kabakchi, V. V. Il'in, A. V. Ignatenko, and V. A. Ponomarenko, *Izv. Akad. Nauk. Ser. Khim*., 1992, 1863 (*Chem. Abstr*., 1993, **118**, 124429).

20 For recent methodologies for synthesizing 1,2,4-oxadiazoles by the amidoxime route, see, also: (*a*) J. R. Young and R. J. De Vita, *Tetrahedron Lett*., 1998, **39**, 3931; (*b*) N. Hébert, A. L. Hannah, and S. C. Sutton, *Tetrahedron Lett*., 1999, **40**, 8547; (*c*) A. R. Gangloff, J. Litvak, E. J. Shelton, D. Sperandio, V. R. Wang, and K. D. Rice, *Tetrahedron Lett*., 2001, **42**, 1441; (*d*) A. Hamzé, J. F. Hernandez, P. Fulcrand, and J. Martinez, *J. Org. Chem*., 2003, **68**, 7316; (*e*) A. Hamzé, J. F. Hernandez, and J. Martinez, *Tetrahedron Lett*., 2003, **44**, 6079.

21 (*a*) S. Buscemi, V. Frenna, T. Caronna, and N. Vivona, *Heterocycles*, 1992, **34**, 2313. (*b*) N. Vivona and S. Buscemi, *Heterocycles*, 1995, **41**, 2095 and references cited therein.

22 S. Buscemi, N. Vivona, and T. Caronna, *J. Org. Chem*., 1995, **60**, 4096.

23 S. Buscemi, N. Vivona, and T. Caronna, *Synthesis*, 1995, 917.

24 S. Buscemi. N. Vivona, and T. Caronna, *J. Org. Chem.*, 1996, **61**, 8397.

25 N. Vivona, S. Buscemi, S. Asta, and T. Caronna, *Tetrahedron*, 1997, **53**, 12629.

26 S. Buscemi, A. Pace, N. Vivona, T. Caronna, and A. Galia, *J. Org. Chem*., 1999, **64**, 7028.

27 S. Buscemi, A. Pace, and N. Vivona, *Tetrahedron Lett*., 2000, **41**, 7977.

28 S. Buscemi, A. Pace, R. Calabrese, N. Vivona, and P. Metrangolo, *Tetrahedron,* 2001, **57**, 5865.

29 (*a*) S. Buscemi, M. G. Cicero, N. Vivona, and T. Caronna, *J. Heterocycl. Chem*., 1988, **25**, 931. (*b*) S. Buscemi, M. G. Cicero, N. Vivona, and T. Caronna, *J. Chem. Soc., Perkin Trans. 1,* 1988, 1313.

30 S. Buscemi, A. Pace, N. Vivona, and T. Caronna, *J. Heterocycl. Chem*., 2001, **38**, 777.

31 S. Buscemi, A. Pace, I. Pibiri, and N. Vivona, *J. Org. Chem*., 2002**, 67**, 6253.

32 S. Buscemi, A. Pace, I. Pibiri, and N. Vivona, *Heterocycles*, 2002, **57**, 1891.

33 S. Buscemi, A. Pace, I. Pibiri, N. Vivona, and T. Caronna, *J. Fluorine Chem*., 2004, **125**, 165.

34 A. Pace, I. Pibiri, S. Buscemi, N. Vivona, and L. Malpezzi, *J. Org. Chem*., 2004, **69**, 4108.

35 S. Buscemi, A. Pace, A. Palumbo Piccionello, I. Pibiri, and N. Vivona, *Heterocycles*, 2004, **63**, 1619.