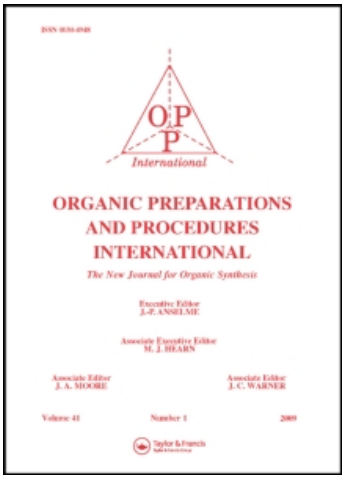

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THE SYNTHESIS OF FLUORINATED HETEROAROMATIC COMPOUNDS. PART 1. FIVE-MEMBERED RINGS WITH MORE THAN TWO HETEROATOMS. A REVIEW

Andrea Pace[a]; Silvestre Buscemi[a]; Nicolò Vivona[a]
[a] Dipartimento di Chimica Organica "E. Paternò", Università degli Studi di Palermo, Palermo, ITALY

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Andrea Pace, Silvestre Buscemi and Nicolò Vivona*

Dipartimento di Chimica Organica "E. Paternò", Università degli Studi di Palermo, Viale delle Scienze-Parco d'Orleans II, I-90128 Palermo, ITALY
e-mail: nvivona@unipa.it

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INTRODUCTION

Fluorinated heterocycles represent an important class of compounds, which are widely applied in many fields.[1,2] From an academic point of view, the possibility of introducing fluorine or fluorinated groups offers the synthetic organic chemist the enthralling opportunity to modify the chemical and physicochemical properties of a given heterocyclic structure. At the same time, such modifications introduced by the presence of the fluorinated moiety open the way to a variety of studies on the new *fluorine-induced* reactivity of such systems. Further, in the industrial field, fluorinated heterocyclic compounds find many applications as agrochemicals, pharmaceuticals, new materials in emerging fluoropolymer sciences and *fluorous* catalysts. For these reasons, one of the most intriguing research areas is devoted to synthetic methodologies leading to targeted fluorinated heterocycles. Under the classification "fluorinated heterocycles" we generally mean two types of compounds: in the first one the fluorine atom is directly linked to an annular carbon of the heterocyclic structure; in the second one, the fluorine atom(s) is located on a substituent linked to the annular carbon or heteroatom (*e.g.* fluoroalkyl or fluoroaryl groups). Clearly, there will be different synthetic approaches to these two classes of fluorinated heterocycles.

Generally, two main strategies have been recognized for this purpose: *i) direct fluorination* where the introduction of the fluorinated moiety into the pre-formed heterocycle occurs through direct substitution of hydrogen (or other groups) with fluorine or the fluorinated group, by halogen exchange reactions, or by modification of functional groups; *ii)* the *building block strategy*, by which the fluorinated heterocyclic structure is built-up from acyclic fluorinated precursors by means of conventional heterocyclization reactions (*e. g.* cycloadditions, cyclocondensations, cyclizations by intramolecular nucleophilic substitutions, electrocyclic reactions). Besides these two strategies, one can also consider the use of heterocyclic rearrangement reactions. This approach introduces the concept of using an easily accessible fluorinated heterocycle as a precursor, which

can be transformed into a different fluorinated heterocyclic structure (through an *in situ* generated open-chain intermediate) by means of thermal or photochemical processes.

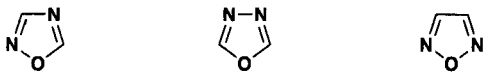
Although the direct methodology may appear the most appropriate, in most cases it is not applicable because of the inertness (or low reactivity) of the heterocyclic structure towards the fluorinating or perfluoroalkylating reagent or, in turn, because of its vulnerability under the experimental conditions to be used. In addition, the presence of particular functional groups can in some cases prevent the use of the *direct fluorination* approach. For these reasons, the *building block strategy* often represents the more suitable methodology, especially for the synthesis of targeted fluorinated structures or compounds containing sensitive functional groups. Within the *building block strategy* one can in principle apply all conventional procedures for heterocyclization reactions and, in this context, the key step consists of the construction of the appropriate fluorinated acyclic precursor. Nevertheless, conventional heterocyclization reactions may present some difficulties due to the modification in reactivity induced by the fluorinated moiety.

Several reviews on the synthesis of fluorinated heterocycles have appeared in the literature,[2] and to them we will refer for general aspects. All these previous reports have been organized focusing on the *general methodologies* used to achieve the fluorinated targets. However, considering the enormous variety of heterocyclic compounds, it is our opinion that a review that points out the state of the art for the *syntheses of a given heterocycle* would be more readily approached by the reader.

In trying to fill this gap, we will present for each heterocycle a significant picture (although not exhaustive) of the methodologies used to obtain the corresponding fluorofunctionalized system. Our project will primarily consider five-membered heterocycles with two or more heteroatoms, and the first part of this review will be focused on heterocycles with more than two heteroatoms (*i.e.* oxadiazoles, thiadiazoles, triazoles and tetrazoles) which often represent the most interesting (for their applications) and more challenging (for their synthesis) systems. Only monocyclic aromatic substrates will be considered; dihydro or tetrahydro compounds will be mentioned when they are involved in a synthesis of particular interest. Experimental details will be described only when they are needed to clarify the kind of processes involved. Our efforts have been devoted to present an update until the end of 2004, and we have mainly considered publications which appeared in the last two decades. Nevertheless, previous papers have been cited when of general interest for the synthetic approach.

I. OXADIAZOLES

The chemistry of 1,2,4-oxadiazoles **1**,[3] 1,3,4-oxadiazoles **2**,[4] and 1,2,5-oxadiazoles (furazans) **3**[5] is widely reported in the literature, and we will refer to the cited references for general aspects on the synthesis and reactivity of these heterocycles. Among oxadiazole systems, it is worthy to note that 1,2,4-oxadiazoles have been receiving great attention in the pharmaceutical industry.[6] On the other hand, 1,3,4-oxadiazoles have recently found extensive application in the field of new materials science for the development of electronic as well as optical devices.[7]



1 2 3

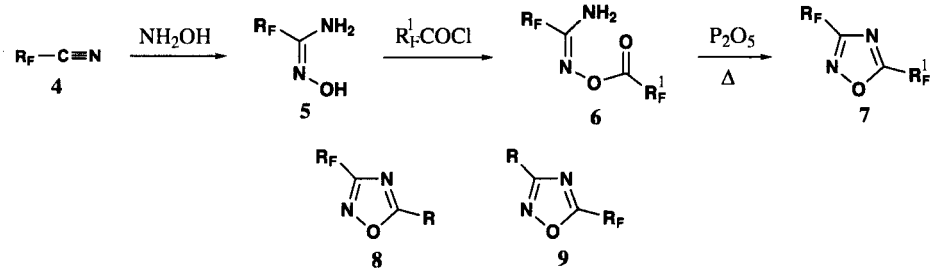
Fig. 1

1. 1,2,4-Oxadiazoles

As far as halogenated 1,2,4-oxadiazoles are concerned, despite the fact that 3- (or 5-) chloro- or bromo- derivatives are known, there is no record of 1,2,4-oxadiazoles having a fluorine atom directly linked to the ring. On the other hand, there are several examples regarding oxadiazoles with fluorinated groups at the C(3) and/or C(5) position of the ring. In none of these cases such systems are obtained by the direct introduction of the fluorinated group on the ring. The synthesis of fluorinated oxadiazoles can be achieved from open-chain fluorinated precursors through conventional heterocyclization reactions. Among the various methodologies, the historical synthesis of the 1,2,4-oxadiazole ring consists of the cyclodehydration of *O*-acylamidoximes and related reactions (*amidoxime route*).[3,8] Another general approach is based on the [3+2] cycloaddition between nitriles and nitrile oxides (*cycloaddition route*).[3] In recent years, some syntheses that take advantage of the annular rearrangements of fluorinated heterocycles (*ring-rearrangement route*) have been reported for particular structures.

a) The Amidoxime Route

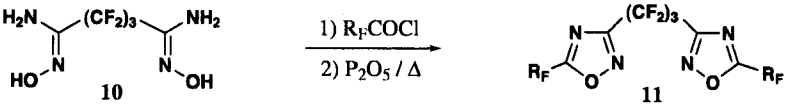
The historical *amidoxime route* towards 1,2,4-oxadiazoles is still the most represented in the literature also for fluorinated structures. Thus, it is possible to obtain oxadiazoles **7** bearing fluorinated groups at both the C(3) and C(5) position of the ring by this method from the appropriate perfluoroalkyl amidoxime **5** (easily prepared by reaction of the corresponding nitrile **4** with hydroxylamine) and a fluorinated acylating reagent (generally acyl chlorides, esters or anhydrides) (*Scheme 1*). Similarly, from suitably fluorinated reagents, one can obtain oxadiazoles **8** or **9** bearing the fluorinated group either at the C(3) or at C(5), respectively. It is obvious



Scheme 1

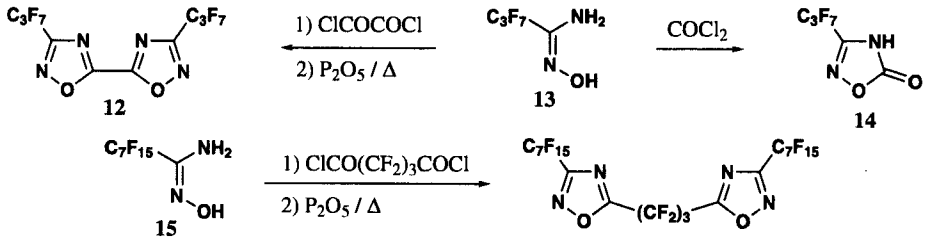
that the experimental conditions to realize the ring closure of the corresponding *O*-acylamidoximes vary as a function of their structures. In some cases, depending on the substrates, the cyclodehydration reaction occurs under the same conditions as the acylation reaction and the open-chain intermediate **6** is not isolated.

Pioneering work on this subject[9] reported the preparation of various perfluoro-alkylamidoximes **5** (R_F = CF_3, C_2F_5, C_3F_7, C_7F_{15}) and their acylation with perfluoro-acylchlorides (R^1_FCOCl) to obtain stable *O*-perfluoroacyl derivatives **6** (R^1_F = CF_3, C_2F_5, C_3F_7, C_7F_{15}) which are cyclodehydrated (by heating with phosphorus pentoxide) to produce 3,5-*bis*(perfluoroalkyl)-1,2,4-oxadiazoles **7** either symmetrically (R_F = R^1_F) or unsymmetrically substituted. By following the same methodology, perfluoro-glutarodiamidoxime **10** produced *bis*-oxadiazoles **11** (R_F = C_2F_5, C_3F_7) (*Scheme 2*). Other examples of this strategy, by which two 1,2,4-oxadiazole moieties can be linearly joined by perfluorinated alkyl chains through the 3,3' annular positions, are reported.[10]



Scheme 2

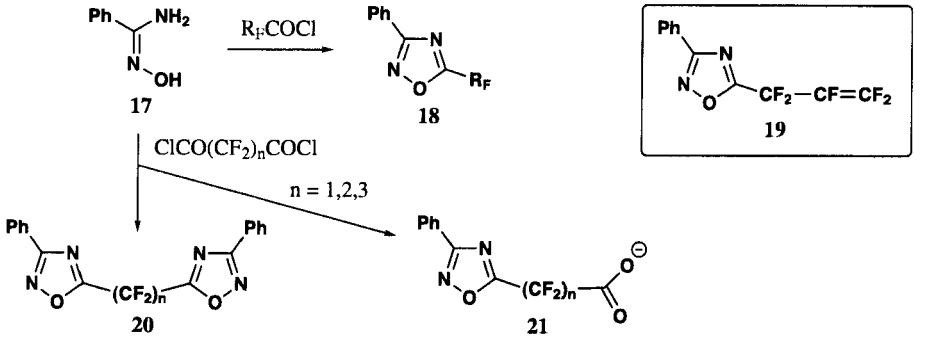
Two perfluoroalkyl substituted oxadiazole moieties linearly joined by the annular 5,5'-positions can be obtained by using the appropriate diacyl chloride. For example, in the reaction of amidoxime **13** with oxalyl chloride, the above cyclodehydration produces the 5,5'-*bis*(1,2,4-oxadiazolyl) system **12**.[9] Note that amidoxime **13** also reacts with phosgene to give stable *O*-chloroformylamidoxime which, heated above 100°C, generates the oxadiazolin-5-one **14** (*Scheme 3*).[9] Furthermore, from the reaction of fluorinated amidoxime **15** and hexafluoroglutaryl chloride, only low yields of the corresponding *O,O'*-hexafluoroglutaryl diamidoxime were isolated.[11] The later was dehydrated by heating with phosphorus pentoxide to give the *bis*-oxadiazole **16** (*Scheme 3*).



Scheme 3

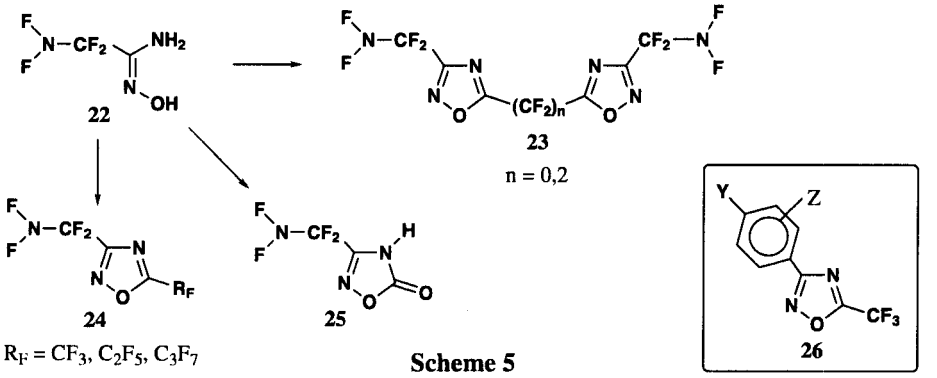
A series of 5-perfluoroalkyl-3-phenyloxadiazoles **18** have been obtained in high yields from the direct reaction of benzamidoxime **17** with perfluoroacylating reagents (perfluoroalkanoyl chloride in the presence of pyridine, or perfluoroalkanoic anhydrides).[11,12] The reaction of arylamidoximes with perfluorodiacyl chlorides was found to depend on experimental conditions as well as on the reagent used. Difluoromalonyl chloride and benzamidoxime **17** directly gave the *bis*-oxadiazolyl-difluoromethane **20** (n = 1). When tetrafluorosuccinyl or hexafluoroglutaryl chloride were used, besides compounds **20** (n = 2, 3), and some of the corresponding diacyl-diamidoximes (which, in their turn, can be cyclodehydrated), the 3-phenyl-1,2,4-oxadiazol-5-yl

perfluoro-alkanoates **21** (n = 2, 3) were isolated.[11] The salt **21** (n = 3), *via* the corresponding perfluorocarboxylic acid, has led also to oxadiazolyl-perfluoroolefin **19** (*Scheme 4*).[13]



Scheme 4

In a similar manner it is possible to obtain fluorinated oxadiazoles bearing the CF_2NF_2 group at C(3). The reaction of difluoroaminodifluoroacetamidoxime **22** with perfluoroalkanoyl chlorides followed by dehydration of the resulting *O*-perfluoroacylamidoximes with P_2O_5 leads to 5-perfluoroalkyl-oxadiazoles **24**. In turn, the reaction of **22** with $COCl_2$ gives the oxadiazolin-5-one derivative **25**, while with perfluorosuccinic acid and phosphorus pentoxide, by heating, the *bis*-oxadiazole **23** (n = 2) is obtained.[14] The same amidoxime **22** with oxalyl chloride will yield *bis*-oxadiazole **23** (n = 0) (*Scheme 5*).[15]



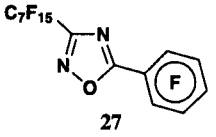
Scheme 5

The cyclodehydration of *O*-acylamidoximes has been exploited also for the synthesis of various 5-alkenyl-3-perfluoroalkyl-1,2,4-oxadiazoles as precursors of fluorinated polymeric structures containing the oxadiazole unit. In this respect, acylation of perfluorooctylamidoxime **15** with methacryloyl chloride and fumaroylchloride, followed by cyclodehydration of the corresponding *O*-acyl-derivatives are reported.[16] Oxadiazoles containing perfluoroalkylether chains at one or both C(3) and C(5) positions are similarly prepared.[17]

A series of 5-trifluoromethyl-3-aryl-1,2,4-oxadiazoles of the general formula **26** are patented as potential pesticides and prepared from the corresponding amidoxime and trifluoroacetic anhydride.[18] [Among these trifluoromethyl-oxadiazoles, compound (**26**; Z = H; Y =

NO_2) is a commercial product]. Similarly, 5-trifluoromethyl-3-(coumarin-4-yl)-oxadiazole has been prepared (in about 50% yield) and tested for biological activity.[19] Furthermore, by analogy with *O*-acylamidoxime cyclodehydration, the reaction between *O*-vinylbenzamidoxime and trifluoroacetic anhydride leads to the 3-phenyl-5-trifluoromethyl-oxadiazole (**26**; Y = Z = H) (49%) through a rather questionable proposed mechanism.[20]

5-Pentafluorophenyl-oxadiazoles **27**, **28**, and **29** (*Fig 2*) have been recently obtained directly from the reaction of the corresponding amidoximes and pentafluorobenzoyl chloride in refluxing toluene in the presence of pyridine.[21,22] These are very interesting substrates: due to the electron deficient character of the oxadiazole [which is more evident at the C(5) position], the *p*-fluoro moiety of the pentafluorophenyl ring is activated towards aromatic nucleophilic substitution by nucleophiles such as amines or alkoxides.[22] Such a reactivity has great potential for the development of other synthetic applications.



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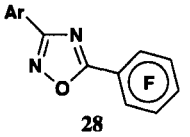

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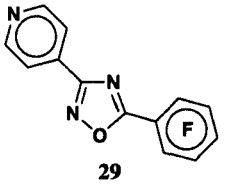
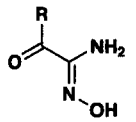


29

Fig. 2

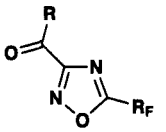
Similarly, 3-benzoyl- **31** (R = Ph)[23] and 3-carboxyethyl-5-perfluoroalkyl-oxadiazole **31** (R = OEt)[24] are prepared from amidoximes (**30**; R = Ph, OEt respectively) and the corresponding perfluoroalkanoyl chlorides (or anhydrides) (*Scheme 6*).



30

R_FCOCl
or $(R_FCO)_2O$

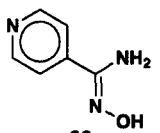
R = Ph, OEt
R_F = CF_3, C_3F_7, C_7F_{15}



31

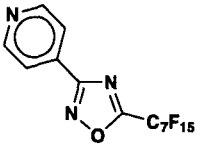
Scheme 6

4-(5-Perfluoroheptyl-1,2,4-oxadiazol-3-yl)pyridine **33** and 3-(5-perfluoroheptyl-1,2,4-oxadiazole-3-yl)pyridine **34**, have been obtained directly (in 90 and 70% yields respectively) from the acylation reaction of the corresponding nicotyl amidoxime (**32**) and isonicotyl amidoxime, respectively, with the perfluoroalkanoyl chloride following the standard procedure (*Scheme 7*).[25] From these derivatives, the corresponding *N*-methyl-pyridinium salts have been prepared for possible applications in designing fluorinated domains.[25]



32

$C_7F_{15}COCl$
Δ



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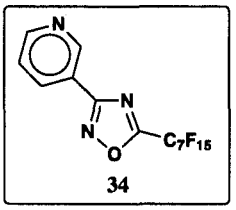

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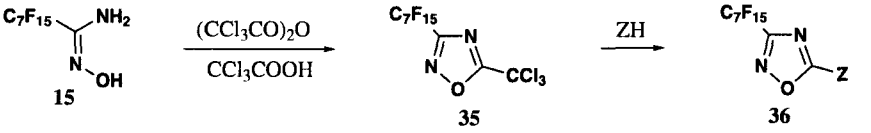
Scheme 7

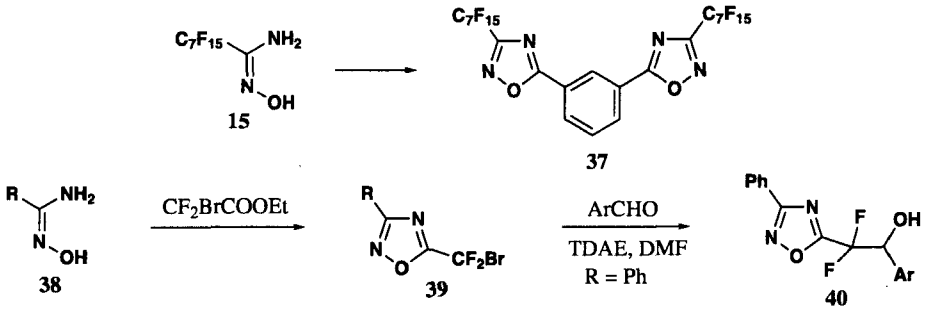
The *O*-acylamidoxime methodology has been used for the synthesis of derivatives differently functionalized at C(5). In this manner, from amidoxime **15** treated with trichloroacetic anhydride in hot trichloroacetic acid, it is possible to obtain the corresponding 5-trichloromethyl-1,2,4-oxadiazole **35**. The latter, in the presence of nitrogenated nucleophiles (ammonia, primary or secondary amines), undergoes an aminolysis reaction leading to **36** (*Scheme 8*).[26]



ZH = NH_3, NH_2Me, $NHMe_2$, $NH(CH_2)_4$, $NH(CH_2)_2(CH_2)_2O$

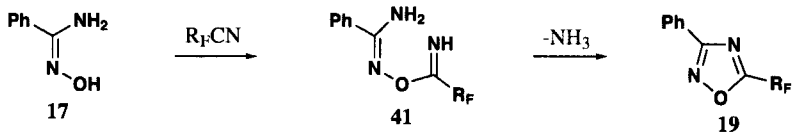
Scheme 8

Examples describing the use of esters as acylating reagents toward amidoximes are also reported (*Scheme 9*). Besides the reaction of amidoxime **15** with diphenyl isophthalate (in DMF at 130°C) to give **37** (in low yield),[11] additional examples have involved the reaction of benzamidoxime or its sodium salt with methyl esters of fluorinated carboxylic acid to give oxadiazoles bearing the fluorinated group at C(5).[27] Amidoximes also react with ethyl bromodifluoroacetate to give 5-(bromodifluoromethyl)oxadiazoles **39** (24-41% depending on R) in one step.[28] From these compounds, through an electron transfer process [mediated by *tetrakis*(dimethylamino)ethylene (TDAE)] in the presence of aromatic aldehydes, a series of β,β-difluoro alcohols such as **40** were obtained (*Scheme 9*).[29]



Scheme 9

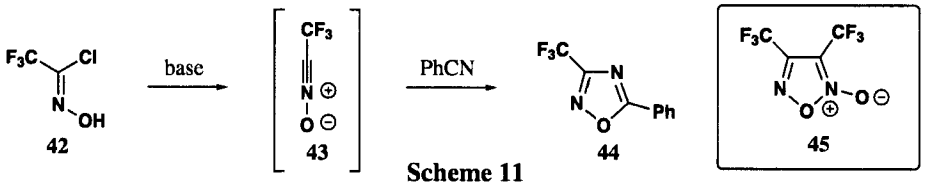
In some cases, nitriles can be used as acylating reagent for amidoximes, and the following heterocyclization involves loss of ammonia in the final step (*Scheme 10*). For this purpose, the reaction is carried out in the presence of an ammonia acceptor reagent (*e. g.*, the perfluorocarboxylic acid, or an excess of the nitrile). For example, from the reaction of benzamidoxime (**17**) with perfluoroalkylnitriles, a series of 5-perfluoroalkyl-1,2,4-oxadiazoles **19** can be obtained.[30] Similarly, reactions with *bis*-amidoximes (*e. g.* terephthalamidoxime) are reported.[30] Some other examples, also including perfluorinated α,ω-*bis*-amidoximes and perfluorinated α,ω-dinitriles containing perfluoroalkylether chains, have been reported as precursors for polymeric structures.[31]



Scheme 10

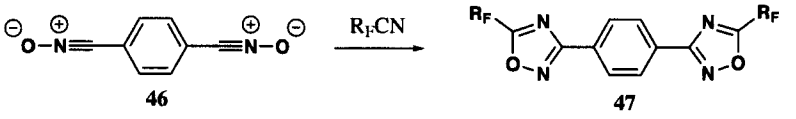
b) The Cycloaddition Route

Another general approach to the synthesis of 1,2,4-oxadiazoles is based on the [3+2] cycloaddition between nitriles and nitrile oxides (with either one or the other containing the fluorinated moiety). By this method, the 3-trifluoromethyl-5-phenyl derivative **44** has been obtained following the mechanism illustrated in *Scheme 11* where the trifluoroacetonitrile oxide **43** is involved.[30] Of course, it is possible to access the same derivative **44** from the corresponding *O*-benzoyl amidoxime. As expected, in the absence of the nitrile component, the corresponding *bis*-trifluoromethylfuroxane **45** is obtained (*Section* I-3). It is to be mentioned that aliphatic nitriles such as the butyronitrile do not undergo cycloaddition to the oxadiazole derivative.[32]



Scheme 11

The method involving cycloaddition between nitriles and nitrile oxides has been employed for the synthesis of complex systems precursors of polymeric materials. For example, terephthaldinitrile oxide **46** was reacted with R_FCN [R_F = nitrile-terminated polyperfluoroalkylether chain (*Scheme 12*)] to give representative **47**.[33]

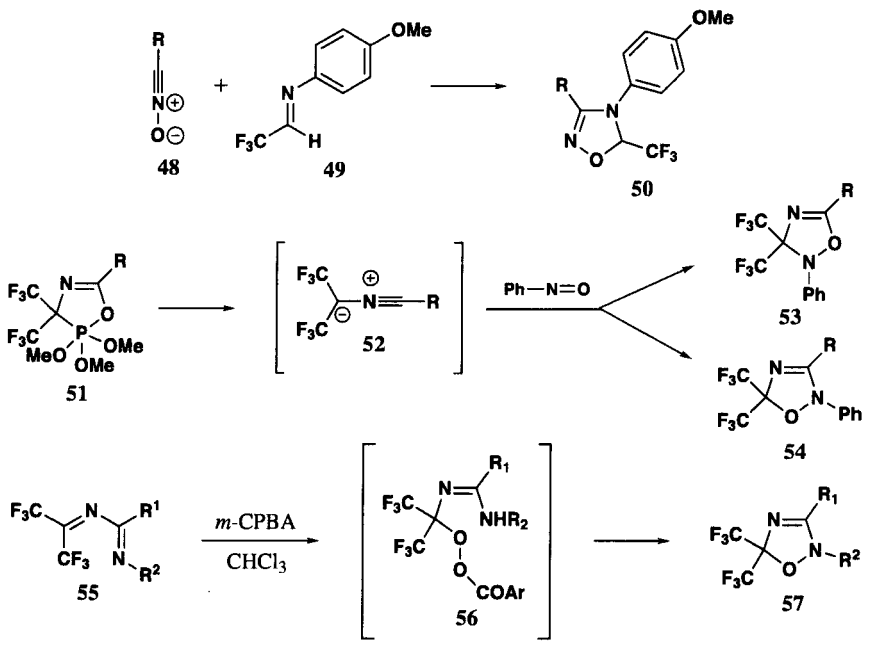


R_F = $-CF_2-(OC_2F_4)_mO(CF_2)_5-O(CF_2CF_2O)_n-CF_2CN$

Scheme 12

With regard to [3+2] cycloaddition reactions, a recent paper reports the regiospecific cycloaddition of nitrile oxides **48** with *N*-substituted trifluoroacetaldimines **49** to give 5-trifluoromethyl-*4H,5H*-dihydro-1,2,4-oxadiazoles **50** (*Scheme 13*).[34] Moreover, a mixture of dihydrooxadiazole regioisomers **53** and **54** is formed by trapping reactions of *bis*(trifluoromethyl)-substituted nitrile ylides **52** (generated by thermolysis of oxazaphospholines **51**), with nitrosobenzene (*Scheme 13*).[35] Furthermore, formation of a series of fluorinated oxadiazolines **57**

is reported (in about 35-60% of yields) from the oxidation reaction of 1,3-diaza-1,3-butadienes **55** with *meta*-chloroperbenzoic acid (*m*-CPBA) through heterocyclization of the presumed intermediate **56** (*Scheme 13*).[36]



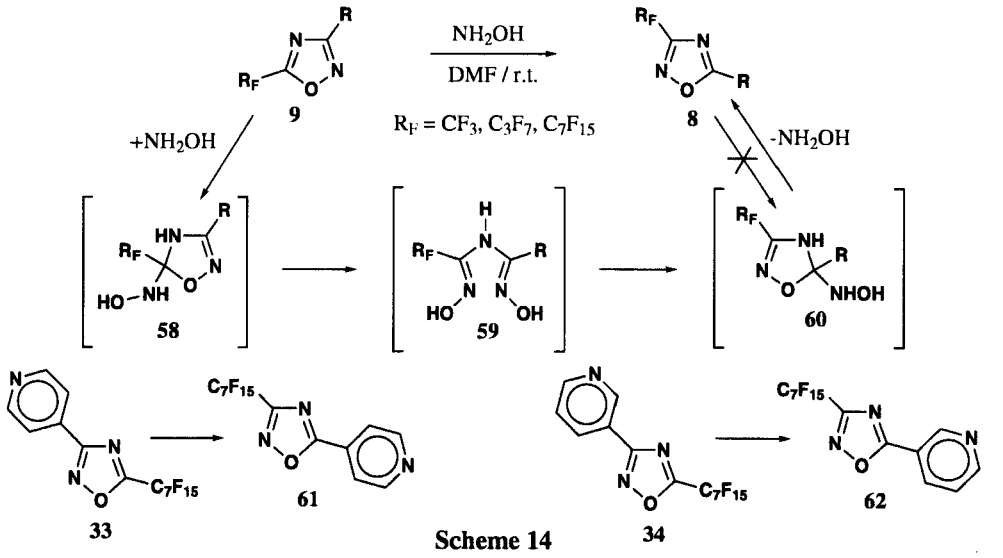
Scheme 13

c) The Ring-rearrangement Route

Some recent results, where ring-rearrangements reactions have been implemented in a synthetic project for fluorinated heterocycles, concern *ANRORC*-like reactions 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.[37] By this approch, an easily accessible fluorinated heterocycle can be transformed into a different one containing the heteroatoms originally belonging to the nucleophilic reagent.

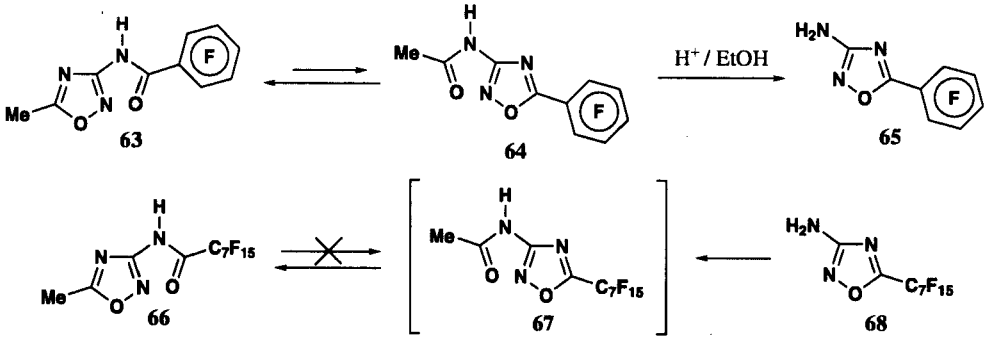
The reaction of 5-perfluoroalkyl-1,2,4-oxadiazoles **9** with hydroxylamine in DMF at room temperature gave excellent yields of 3-perfluoroalkyl-1,2,4-oxadiazoles **8**, resulting in a virtual C(5)-C(3) annular switch (*Scheme 14*).[38] The reaction follows the *ANRORC* pattern, and is determined by the presence of the perfluoroalkyl group which allows the C(5) of the ring (a rather electron-deficient site) to easily undergo the nucleophilic attack of the hydroxylamine to produce **58**. In turn, heterocyclization of dioxime-like intermediate **59** involving displacement of hydroxylamine from **60** is determined by the formation of the more stable 3-perfluoroalkyl-oxadiazoles **8** in an irreversible ring-degenerate process. Experimental results and the proposed mechanism agree with *ab initio* computational data. On this basis, readily accessible 5-perfluoroalkyl-1,2,4-oxadiazoles **9** have been claimed to be efficient synthons for the synthesis of the corresponding 3-perfluoroalkylated 1,2,4-oxadiazoles **8**.[38] By exploitation of this process, the 3-

perfluoroalkyloxadiazoles **61** and **62** have been prepared from easily accessible 5-perfluoroalkyloxadiazoles **33** and **34** (*Scheme 14*).[25]



Scheme 14

The ring rearrangement approach is an efficient methodology also for the synthesis of 3-amino-5-polyfluoroaryl-1,2,4-oxadiazoles. Following the Boulton-Katritzky rearrangement pattern,[39] the ring-degenerate thermal equilibration of **63** (easily accessible from the reaction of 3-amino-5-methyl-1,2,4-oxadiazole with pentafluorobenzoyl chloride) gave a mixture of both the ring degenerate isomers **63** and **64** in a 80:20 ratio as a result of the electron-withdrawing character of the pentafluorophenyl moiety (*Scheme 15*).[40,41] Interestingly, acid hydrolysis of this thermally equilibrated mixture gave the expected 3-amino compound **65** in about 60% yield because

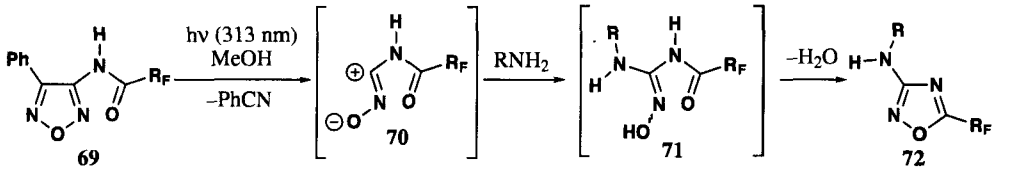


Scheme 15

of the acid induced shift of the ring-degenerate equilibrium. By the same procedure, different 3-amino-5-polyfluorophenyl-1,2,4-oxadiazoles have also been prepared.[41] These results appear of some significance, since attempts to synthesize the same fluorinated oxadiazoles by conventional procedures (*e. g.*, by the acylcyanamide method) were reported to be unsuccessful. Unfortu-

nately, because of the structure-dependent reactivity of 3-acylamino oxadiazoles towards ring-degenerate interconversions, this procedure was not applicable to the synthesis of 5-perfluoroalkyl derivatives **68**. In fact, the equilibration between the ring-degenerate components **66** and **67** is irreversibly shifted towards the perfluoroalkanoylamino component **66**. Eventually, the acetylation of **68** gave **66** directly as a result of the ring-rearrangement of **67** as soon as it is formed (*Scheme 15*).[41]

Nevertheless, photo-induced rearrangements of O-N bond containing azoles[42] can be useful for the synthesis of these 3-amino-5-perfluoroalkyl-1,2,4-oxadiazoles. This procedure exploits the photo-fragmentation pattern of the furazan heterocycle into a nitrile and a nitrile oxide and follows previous results observed for non-fluorinated substrates.[43] Thus, irradiation of 3-perfluoroalkanoylamino compounds **69** at λ = 313 nm in methanol and in the presence of ammonia or primary aliphatic amines gives the corresponding 3-amino- or 3-*N*-alkylamino-5-perfluoroalkyl-1,2,4-oxadiazoles **72** as a result of the heterocyclization of intermediates **71** (*Scheme 16*).[44] Unfortunately, yields of isolated products (about 30-40%) were not very good because of the photo-reactivity of oxadiazoles **72** under irradiation conditions: this however, appears to be the only method which allows these derivatives to be obtained.

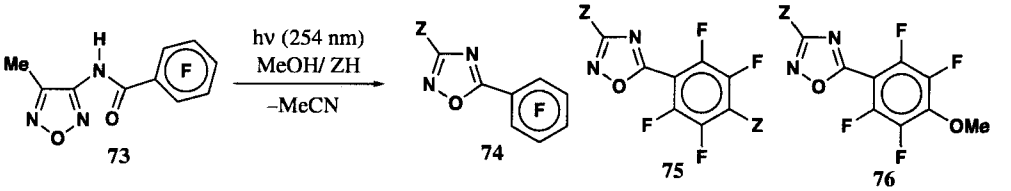


69 **70** **71** **72**

$R_F = C_3F_7, C_7F_{15}$; R = H, Me, Pr, *n*-C_8H_{17}

Scheme 16

A similar method has been applied to the synthesis of 3-amino (or 3-*N* substituted amino) 5-pentafluorophenyl-1,2,4-oxadiazoles **74** by photolysis of the furazan **73** at λ = 254 nm in methanol and in the presence of ammonia, primary or secondary aliphatic amines (ZH in the *Scheme 17*).[45] Since the electronic nature of the oxadiazole ring promotes nucleophilic substitution at the fluorinated phenyl group, non-photochemical post-reaction displacement of fluoride anion by the nitrogen nucleophile or by the solvent under reaction conditions gives a series of 4'-substituted polyfluoroaryl-1,2,4-oxadiazoles **75** and **76**.[45]



73 **74** **75** **76**

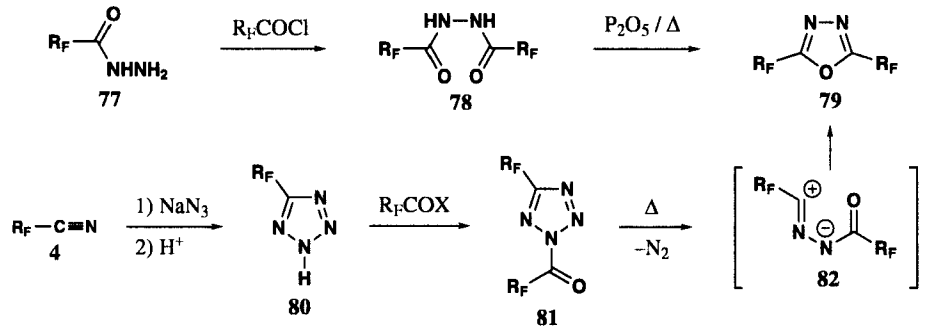
ZH = NH_3, $MeNH_2$, Me_2NH, $PrNH_2$,

Scheme 17

2. 1,3,4-Oxadiazoles

There are several reports in the literature concerning 1,3,4-oxadiazoles bearing a fluorinated group at either or both positions 2 and 5 of the ring and some of these compounds are also commercially available (*e.g.* 2-phenyl-5-trifluoromethyl-1,3,4-oxadiazole). As for oxadiazoles with a fluorine atom directly bond to the ring, although some patents actually claim such derivatives,[46] no description of experimental detail has been reported. Similarly no reports about the direct introduction of a fluorinated group into a preformed heterocycle are evident in the literature. By analogy with the 1,2,4-oxadiazole system, all reported examples describe the ring formation from fluorinated acyclic precursors and belong to the *building-block strategy* category.

The most widely used methodologies are *i*) the cyclodehydration of fluorinated diacylhydrazines **78** (*Scheme 18*); *ii*) the ring-transformation of fluorinated 2-acyl-tetrazoles **81** which can be directly realized by acylation of tetrazoles **80**. The mechanism of this ring-transformation (also known as the Huisgen reaction)[47] involves the decomposition (by loss of a nitrogen molecule) of the acylated tetrazole ring leading to a nitrilimine species **82** from which a 1,5-heterocyclization reaction will produce 1,3,4-oxadiazoles **79** (*Scheme 18*). Besides these general methodologies, some syntheses of particular 1,3,4-oxadiazoles through photo-induced ring-rearrangements have been reported as well.

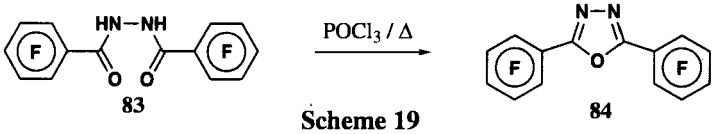


Scheme 18

By the use of the first approach, symmetric fluorinated diacylhydrazines **78** [which can be obtained either by reaction of hydrazides **77** with perfluoroalkanoyl chlorides or anhydrides or by direct acylation of hydrazine with perfluoroalkanoyl chlorides] will produce symmetric 2,5-disubstituted 1,3,4-oxadiazoles. In turn, asymmetric derivatives can be prepared from asymmetric diacylhydrazines obtained from hydrazides **77**. Of course, both methodologies allow the construction of 1,3,4-oxadiazole derivatives, where either one or both substituents can be a fluorinated group, by simple selection of the appropriate (fluorinated or not) nitrile (as a tetrazole precursor by the reaction with sodium azide followed by acid treatment), and the appropriate (fluorinated or not) acylating reagent (*Scheme 18*).

a) The Diacylhydrazine Route

Historical examples of syntheses by cyclodehydration of *bis*-perfluoroacylhydrazines with P_2O_5 leading to **79** ($R_F = CF_3$, C_2F_5, C_3F_7, C_7F_{15}) are reported by Brown and co-workers[48] as well as by Chambers and Coffman.[49] Other examples involving a dehydration of 1,2-*bis*-polyfluoroacylhydrazines carried out with oleum are also reported.[50] By using the same approach, a series of symmetrically and asymmetrically substituted 2,5-*bis*(polyfluoroaryl)-1,3,4-oxadiazoles can be prepared in excellent yields.[51] Symmetric diaroylhydrazines are obtained directly from the reaction of the aroyl chloride with hydrazine; asymmetric diaroylhydrazines are prepared by aroylation of the monoaroylhydrazine (obtained from the corresponding esters).[51] A typical synthesis of the 2,5- *bis*(pentafluorophenyl)oxadiazole (**84**) (74%) is illustrated in *Scheme 19*.



83 **84**

Scheme 19

Recently, oxadiazoles **85** (*Fig. 3*), which are useful energetic plasticizers, have been prepared by reaction of *N*-polynitroacyl-*N'*-perfluoroacylhydrazines in 1,2-dichloro-ethane in the presence of PCl_5.[52] The same method has been used for the preparation of oxadiazoles **86** which contain a combination of SF_5-perfluoroalkyl, SF_5-alkyl-, perfluoroalkyl-, and polynitroalkyl substituents (*Fig. 3*).[53]

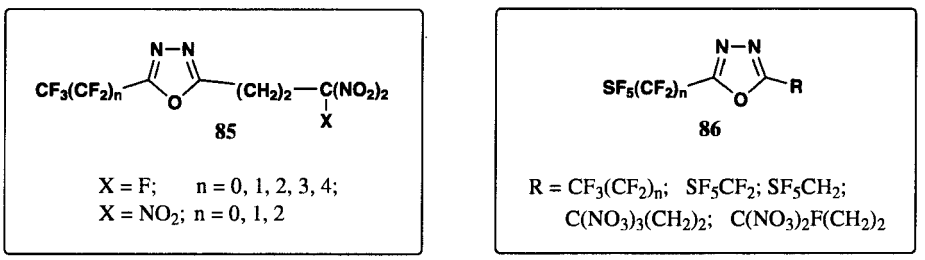
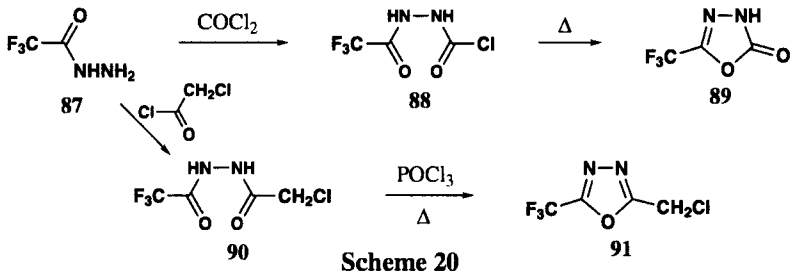


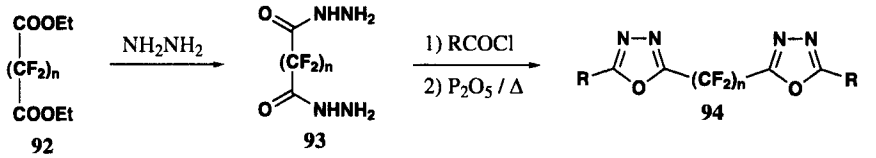
Fig. 3

Similarly, trifluoroacethydrazide **87** has been used to obtain the 2-trifluoromethyl-5-one derivative **89** (by a reaction with phosgene)[54] and the chloromethyl derivative **91** (*Scheme 20*); from the latter compound, other heterocyclic structures containing the trifluoromethyl group have been obtained by typical *ring opening-ring closure* reactions in the presence of nucleophiles.[55]



Scheme 20

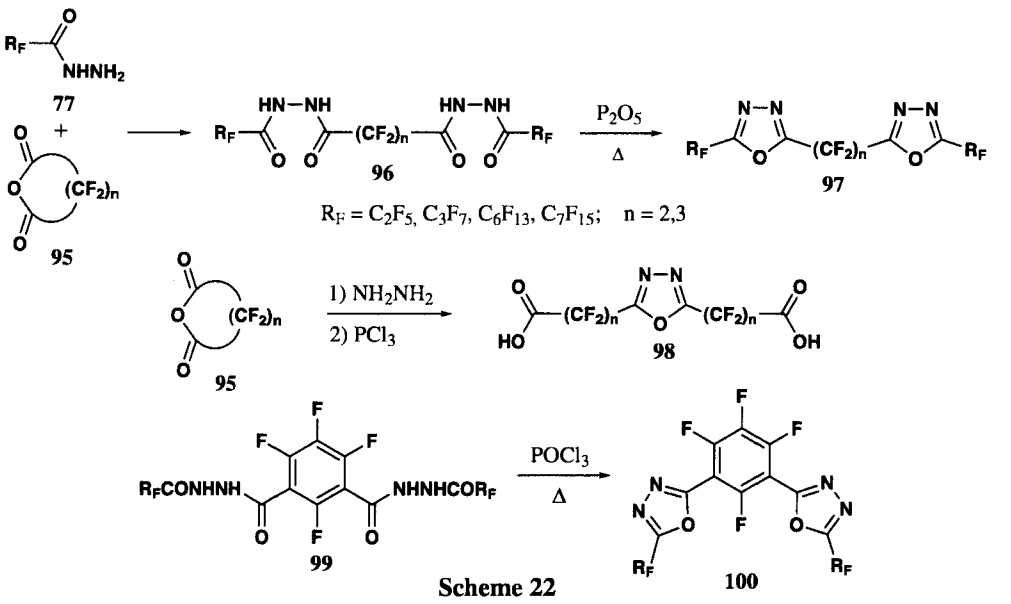
An interesting application of this methodology uses the dihydrazides **93** which upon acylation with fluorinated (or not) reagents, and cyclodehydration with P_2O_5, yield *bis*-oxadiazoles **94** (*Scheme 21*).[56] *bis*-Oxadiazoles **97** interspaced by a perfluoroalkyl chain are also



R = C_3F_7, Pr, Ph; n = 3, 4, 8

Scheme 21

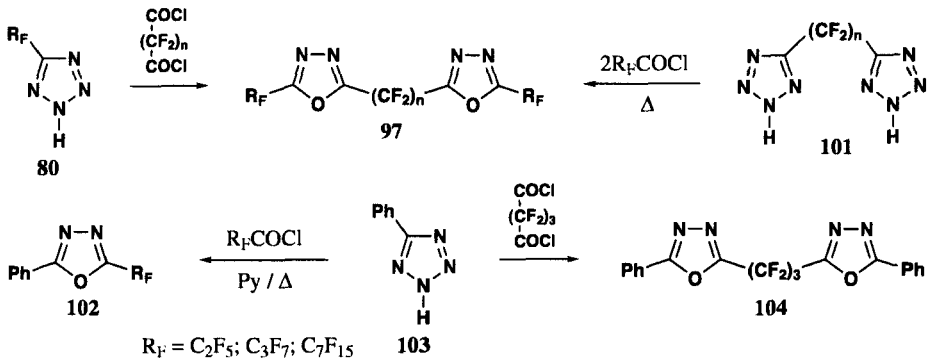
obtained by dehydration of *bis*-diacylhydrazines **96** originating from **77** and cyclic perfluoroanhydrides **95** (*Scheme 22*).[57] Similarly, the cyclodehydration of diacylhydrazines (from hydrazine and anhydrides **95**) leading to **98** is also reported.[58] *bis*-Oxadiazoles **100**, which have a good thermal stability and are used in heat transfer fluids, are prepared by cyclodehydration of the corresponding tetrafluoroisophthaloyl *bis*(perfluoroacylhydrazines) **99** (*Scheme 22*).[59] In the same work, tetrafluoroterephthaloyl derivatives are also reported.[59]



Scheme 22

b) The Acyl-tetrazole Rearrangement Route

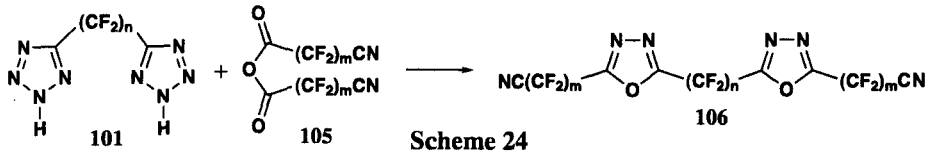
2,5-*Bis*(perfluoroalkyl)-1,3,4-oxadiazoles **79** (R_F = CF_3, C_3F_7) are reported to be prepared also from perfluoroalkyltetrazoles **80** and perfluoroacyl chlorides following the Huisgen reaction approach (*Scheme 18*).[60] By the same methodology, *bis*-oxadiazole **97** (R_F = C_3F_7; n = 3) is prepared either from perfluoropropyltetrazole **80** (R_F = C_3F_7) and glutaryl chloride or, in better yields, from the ditetrazole **101** (n = 3) (obtained from the perfluoroglutaronitrile) and perfluorobutyryl chloride (*Scheme 23*); similarly compound **97** (R_F = C_3F_7; n = 0) is prepared from perfluoropropyltetrazole **80** (R_F = C_3F_7) and oxalyl chloride.[60] Both 5-perfluoroalkyl-2-phenyl-1,3,4-oxadiazoles **102** and the diheterocyclic compound 1,3-*bis*(2-phenyl-1,3,4-oxadiazol-5-yl)hexafluoropropane **104** can be obtained by reaction of 5-phenyltetrazole **103** with perfluoroacyl chloride or perfluoroglutaryl chloride respectively (*Scheme 23*).[11] Additional examples of this methodology involve the synthesis of oxadiazoles bearing perfluoroalkylether chains.[61]



80 97 101 102 103 104

Scheme 23

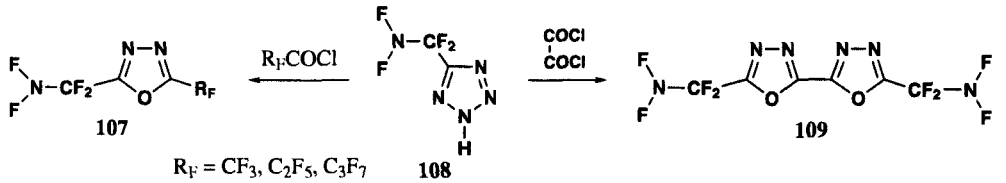
For the construction of polymeric structures, bifunctional reagents have been examined. Thus, the reaction of α,ω-*bis*(tetrazol-5-yl)perfluoroalkane **101** with ω-cyanoperfluoroanhydrides **105** (at 150°C) produces *bis*-oxadiazoles **106** from which further functionalization may be added on the two end-chain nitriles (*Scheme 24*).[62,63]



101 105 106

Scheme 24

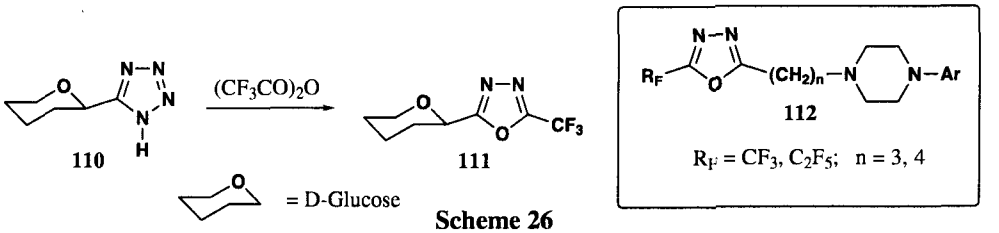
By the use of the same methodology, the *N,N*-difluoroaminodifluoromethyl-tetrazole **108** reacts with perfluoroacyl chlorides or oxalyl chloride leading to the corresponding oxadiazoles **107** or *bis*-oxadiazole **109** respectively (*Scheme 25*).[15]



107 108 109

Scheme 25

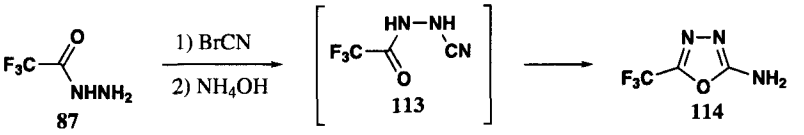
The above examples demonstrated how the *tetrazole transformation* methodology is a very versatile and quite general approach. Any nitrile can be easily transformed into a tetrazole precursor which (by reaction with a perfluoroacylating reagent) will eventually lead to a perfluoroalkyl-1,3,4-oxadiazole. A couple of examples are represented (*Scheme 26* where, for the sake of clarity, none of the substituents on the sugar units were indicated) by the synthesis of *O*-acylated 5-(β-D-glucopyranosyl)-2-trifluoromethyl-1,3,4-oxadiazoles **111**[64] and the synthesis of piperazine derivatives **112** of pharmaceutical interest.[65]



Scheme 26

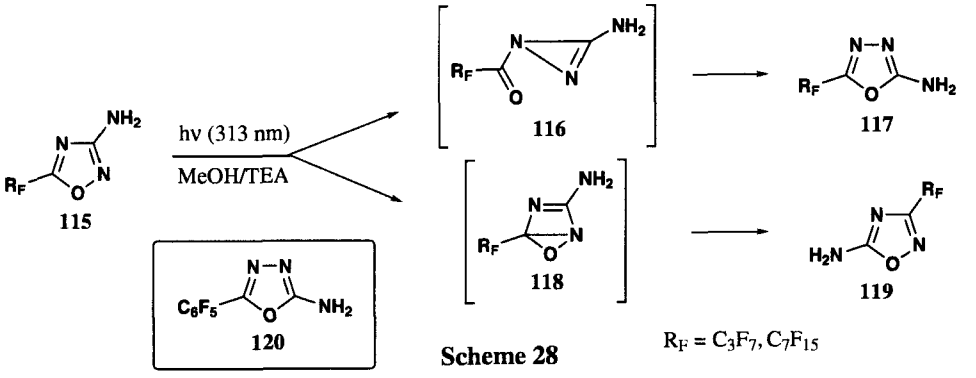
c) The Photo-induced Ring-rearrangement Approach

As far as functional groups are concerned, a particular mention goes to the synthesis of amino or alkylamino derivatives. The 2-amino-5-trifluoromethyl-1,3,4-oxadiazole **114** is prepared following one of the conventional methods for the synthesis of aminooxadiazoles which involves the reaction of acylhydrazines with BrCN (*Scheme 27*).[66] For other amino derivatives, a photochemical approach has been reported which takes advantage of the photo-induced rearrangements of fluorinated 1,2,4-oxadiazoles.[42]



Scheme 27

In fact, 3-amino-5-pefluoroalkyl-1,2,4-oxadiazoles **115**, upon UV irradiation at 313 nm in methanol and in the presence of triethylamine (TEA), produce the corresponding 2-amino-5-perfluoroalkyl-1,3,4-oxadiazoles **117** (53-61% of yields), following the typical *ring contraction-ring expansion* route involving a supposed diazirine intermediate **116**.[67-69] In the same reaction, amounts of 5-amino-1,2,4-oxadiazole derivatives **119** are also formed through a competing process following the *internal cyclization-isomerization* route (*Scheme 28*).[67,69]

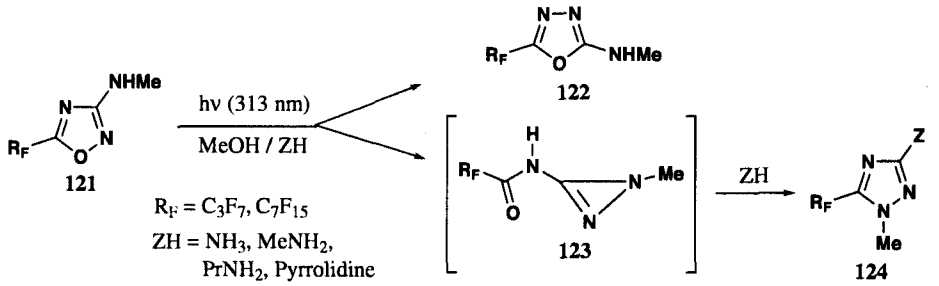


Scheme 28

The photo-induced transformation of some 3-amino-5-polyfluorophenyl-1,2,4-oxadiazoles (irradiated at 254 nm in the presence of TEA) into the corresponding 1,3,4-oxadiazoles, (*e. g.*, the pentafluorophenyl-1,3,4-oxadiazole **120**), is also reported to take place in lower yield.[67]

In turn, the oxadiazole **120** can also be obtained (in low yield)[67] through the conventional method which involves the oxidative cyclization of the pentafluorobenzaldehyde semicarbazone with lead tetraacetate.[70]

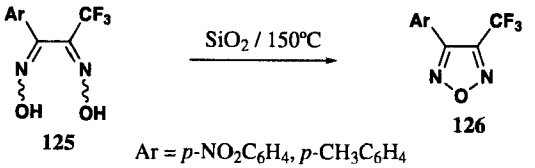
In the case of 3-methylaminooxadiazoles **121**, irradiation in the presence of nucleophilic base (ZH in the *Scheme*) gave, besides the expected 1,3,4-oxadiazoles **122**, 1,2,4-triazoles **124** through the *exocyclic* diazirine intermediate **123** (*Scheme 29*).[71]



Scheme 29

3. 1,2,5-Oxadiazoles

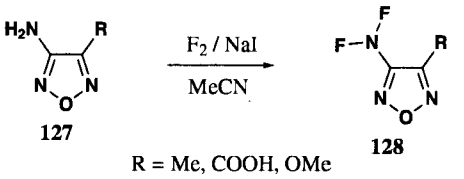
There are not many examples regarding the synthesis of fluorinated 1,2,5-oxadiazole (furazan) systems in the literature. A recent report describes the synthesis of trifluoromethyl furazans **126** by dehydration of dioximes **125** in the presence of silica (*Scheme 30*).[72] Since the presence of silica is fundamental for this process, the author suggests that an interaction between the substrate and the silanol groups assists the cyclization reaction. Electron-withdrawing *p*-nitrophenyl group is more effective than the *p*-tolyl group in favoring the cyclization step and higher yields (77%) of the final product are obtained.



Scheme 30

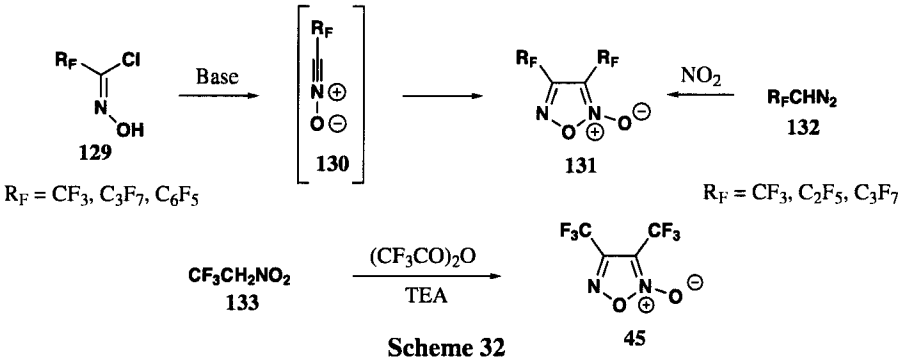
For some 3-aminofurazans **127**, direct fluorination has been reported (by using molecular fluorine in MeCN and in the presence of NaI) to yield *N,N*-difluoroamino derivatives **128** (31-42%) (*Scheme 31*).[73]

Furazan-*N*-oxides (furoxanes) **131** (*Scheme 32*) are isolated as a result of the nitrile oxide dimerization when chlorooximes **129** are treated with bases in the absence of dipolarophiles.[32,74,75] Furoxane **131** ($R_F = C_6F_5$) can be also formed from lead tetraacetate oxidation of



Scheme 31

the pentafluorobenzaldehyde oxime.[74] The involvement of nitrile oxide dimerization has been also suggested in the formation of furoxanes **131** by reaction of perfluoroalkyldiazomethanes **132** (R_F = CF_3, C_2F_5, C_3F_7) with nitrogen dioxide,[76] and in the formation of the 3,4-*bis*(trifluoromethyl) derivative **45** from the dehydration reaction of trifluoromethylnitromethane **133** with trifluoroacetic anhydride (*Scheme 32*).[77]



Scheme 32

II. THIADIAZOLES

In this section we will consider 1,2,4-thiadiazoles **134**,[78] 1,3,4-thiadiazoles **135**,[79] and 1,2,5-thiadiazoles **136**[80] (*Fig. 4*). For general aspects regarding the chemistry of these heterocycles see the cited literature. As for fluorinated thiadiazoles, in many cases their synthesis is patented, confirming the industrial importance of such compounds (also for their application as agrochemicals and pharmaceuticals). For this reason, in some cases it is very difficult to find available experimental details about preparative procedures.

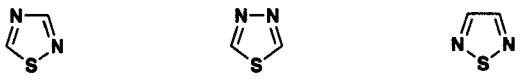
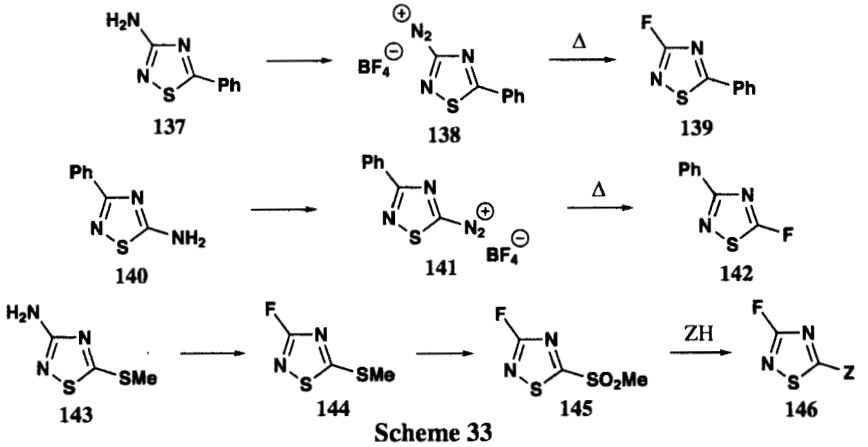


Fig. 4

1. 1,2,4-Thiadiazoles

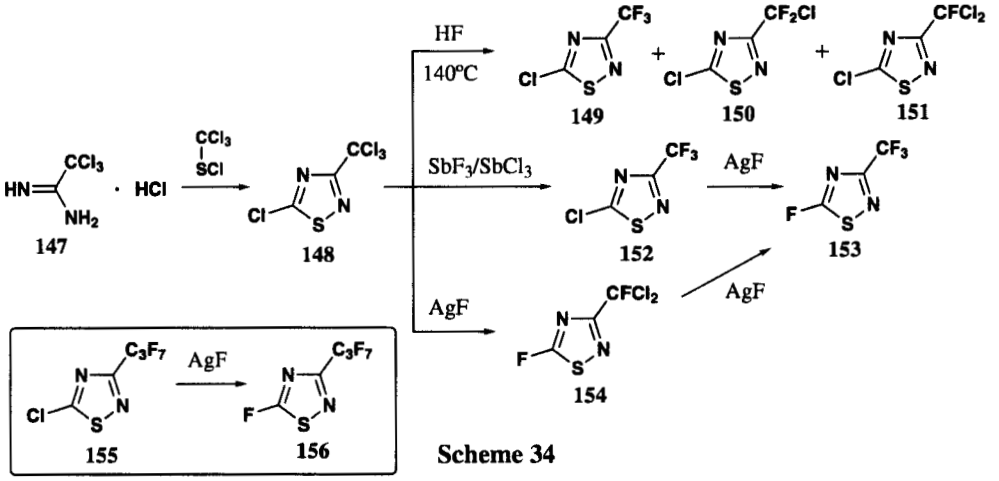
The introduction of a fluorine atom directly bonded to the ring can be achieved by the generally applied decomposition of diazonium tetrafluoroborates **138** and **141** leading to 3-fluoro-5-phenyl- (**139**) (67%) or the regioisomer 5-fluoro-3-phenylthiadiazole (**142**) (18%), respectively[81] (*Scheme 33*). The same methodology has been utilized for the preparation of 3-fluoro-5-

methylthiothiadiazole **144** which can be obtained in a 33% yield.[82] In turn, this 5-methylthio derivative **144** can be oxidized to the 5-sulfonylthiadiazole **145** which is a precursor of a series of compounds of industrial interest (of the general type **146**) obtained through nucleophilic substitution reactions with appropriate reagents (ZH in the *Scheme*) (*Scheme 33*).



Scheme 33

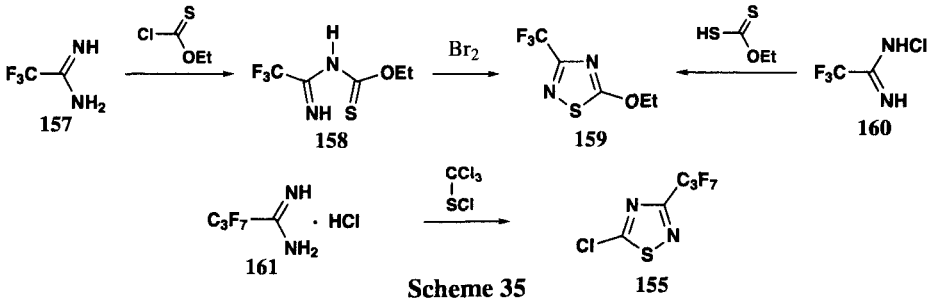
The introduction of fluorine has also been described through nucleophilic substitutions or fluorination of functional groups already bonded to the ring. For instance, 5-chloro-3-trichloromethylthiadiazole **148** can be fluorinated with different reagents.[83] Fluorination of **148** by using HF at 140°C leads to a mixture of polyfluorinated thiadiazoles (*Scheme 34*).[84] By the use of the $SbF_3/SbCl_3$ fluorinating mixture, only the trichloromethyl group is fluorinated to yield the trifluoromethyl derivative **152**. The annular 5-chloro moiety undergoes substitution and partial fluorination of the 3-trichloromethyl moiety is also observed with AgF. Further reactions of derivatives **152**, **154** and **155** with AgF lead to perfluorinated compounds **153** and **156**.



Scheme 34

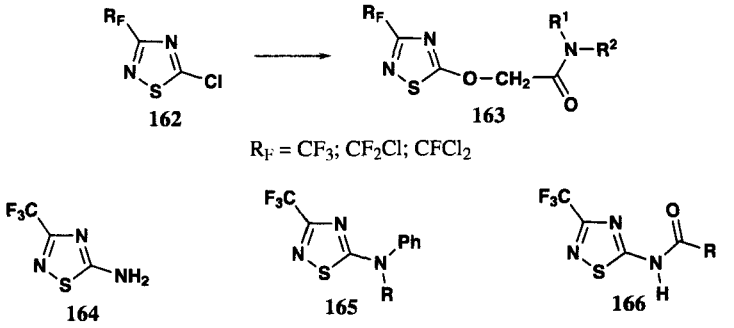
With regard to the syntheses from fluorinated acyclic precursors, an approach to fluorinated 1,2,4-thiadiazoles utilizes the oxidative heterocyclization of fluorinated thioacylamidines.

For example, trifluoroacetamidine **157** and ethyl chlorothiocarbonate will form the open-chain intermediate **158** which, upon oxidation with bromine, leads to 5-ethoxy-3-trifluoromethyl-1,2,4-thiadiazole **159** (*Scheme 35*).[85]



Scheme 35

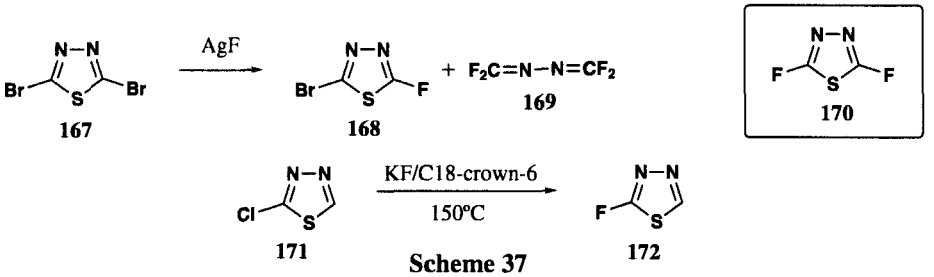
A direct heterocyclization into the thiadiazole **159** takes places from the reaction of the fluorinated *N*-chlorotrifluoroacetamidine **160** with ethyl xanthate.[86] In addition, the 3-perfluoropropyl-5-chlorothiadiazole **155** is obtained in 52% yield from the reaction of heptafluorobutyramidine hydrochloride **161** with trichloromethylsulfenyl chloride in the presence of a base.[83] Because of their reactivity towards nucleophiles, 5-chlorothiadiazole derivatives **162** are used as precursors for the synthesis of various compounds (*e. g.*, **163**) and are patented.[84] For the same reasons the reactions which take advantage of 5-amino-3-trifluoromethyl-1,2,4-thiadiazole **164** reactivity are also patented.[87] 5-Amino and 5-chloro derivatives bearing a fluorinated group at C(3) are very important reagents which can bind a fluorinated thiadiazole moiety to different systems (as in the case of target molecules **163**, **165**, or **166**) for several applications.[84,87]



Scheme 36

2. 1,3,4-Thiadiazoles

In the case of 1,3,4-thiadiazoles, a fluorine atom can also be introduced on the ring through substitution or modification of other functional groups. An example of this approach is represented by the reaction of the 2,5-dibromo derivative **167** with AgF, leading to the monofluorinated compound **168** in low yield (16%) and the perfluorinated open-chain compound **169**. The latter probably originated from the ring-cleavage of the unisolated **170** (*Scheme 37*),[83]



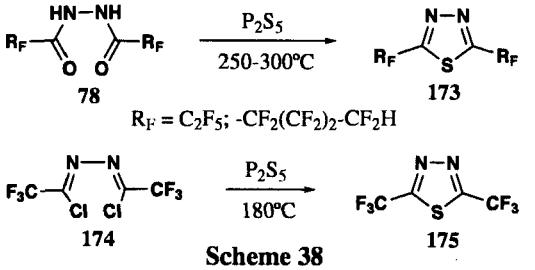
167 168 169 170 171 172

Scheme 37

though any attempt to obtain the difluoro derivative **170** through the diazotization of the 2,5-diaminothiadiazole was unsuccessful.

A recent Japanese patent reports the synthesis of a series of derivatives, having the fluorine atom bonded to an annular carbon, through substitution reactions. *Inter alia*, the reaction of 2-chloro-1,3,4-thiadiazole **171** with KF (in the presence of 18-crown-6 ether at 150°C) leading to the 2-fluoro derivative **172** (15%) is claimed. Other patents[46] claim thiadiazoles bearing fluorine or fluorinated functionalities without reporting any experimental detail.

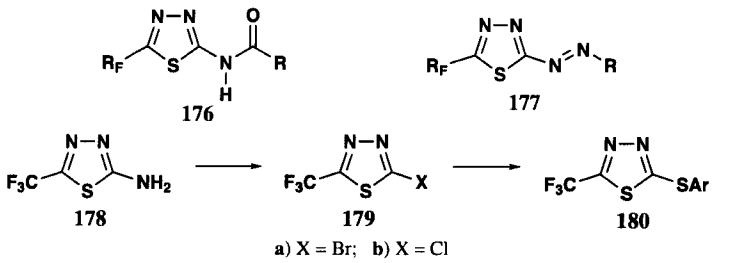
In analogy to what was observed in the case of 1,3,4-oxadiazoles, the sulfuration of *N,N'*-diacylhydrazines **78** with P_2S_5 represent a general methodology for the synthesis of 2,5-*bis*(perfluoroalkyl)-1,3,4-thiadiazoles **173** which, in the reported examples, are obtained in 56-75% yields depending on the nature of R_F (*Scheme 38*).[49] Excellent yields are obtained in the synthesis of 2,5-*bis*(trifluoromethyl)-1,3,4-thiadiazole **175** from the reaction of dichloroazine **174** with P_2S_5 (*Scheme 38*).[89]



78 173 174 175

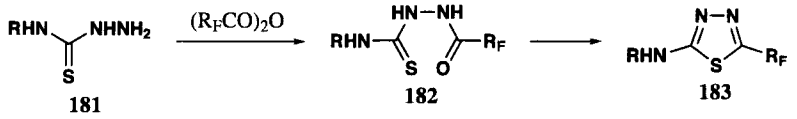
Scheme 38

Particular importance should be given to some fluorinated thiadiazoles which contain functionalities such as amino or methylthio groups. It is worth noting that 2-amino-5-trifluoromethylthiadiazole **178** is a commercial product which is widely employed to link the fluorinated thiadiazole to several targets through its amino group by means, for example, of an acylation reaction, as in the case of **176**. Several patents on the synthesis of pharmaceuticals and agrochemicals take advantage of this of type of reaction.[90] In some cases, the amino group is involved in a diazotation reaction followed by a coupling reaction (leading to **177**)[91] or a nucleophilic substitution.[92] For example, 2-bromo (**179a**) and 2-chloro (**179b**) derivatives can be prepared *via* diazonium salts from 2-amino-5-trifluoromethylthiadiazole **178** (*Scheme 39*).[92] Also 2-arylthio derivatives **180** are obtained through a nucleophilic substitution reaction.[93]



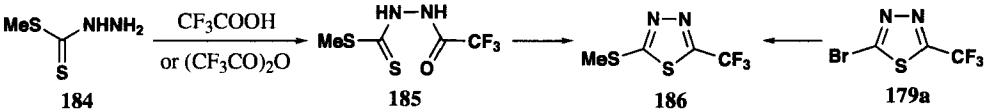
Scheme 39

Besides the industrial production, the synthesis of these aminothiadiazoles is based on the heterocyclization of acylthiosemicarbazides with yields depending on experimental conditions. In some cases the heterocyclization into the thiadiazole derivative occurs directly during the acylation reaction. In this manner, from the reaction of thiosemicarbazide with trifluoroacetic anhydride, the formation of **178** is reported in a 30% yield;[94] however, in the reaction carried out in the presence of $POCl_3$, the yield increases to 93%.[95] Reactions between thiosemicarbazides **181** and trifluoroacetic acid or anhydride in the presence of PPA were used for the synthesis of 2-amino and 2-methylamino derivatives **183** ($R_F = CF_3$) (*Scheme 40*).[96] Other 2-amino-5-perfluoroalkyl derivatives **183** (R = H) were synthesized and employed for the preparation of acaricides through acylation reactions with pyrazol-5-carboxylic acid chlorides or thiazole-5-carboxylic acid chlorides.[97]



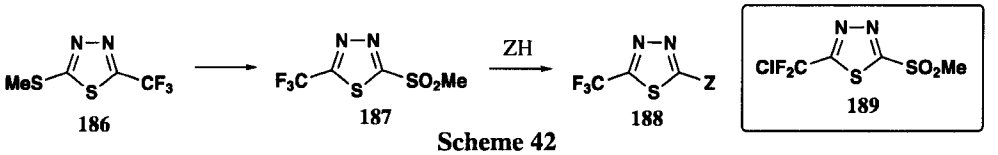
Scheme 40

Several patents report the synthesis (or in some cases just a purification methodology) of 5-trifluoromethyl-2-methylthiothiadiazole **186** which can be prepared through the reaction of **184** with trifluoroacetic acid or anhydride (*Scheme 41*).[98] The same compound **186** can also be obtained from the 2-bromo derivative **179a**.[99]



Scheme 41

The methylthiothiadiazole **186** can be oxidized easily to the corresponding sulfonyl derivative **187** (*Scheme 42*). Some patents have also focussed on the optimization of this oxidation which usually is carried out with hydrogen peroxide in acetic acid and in the presence of

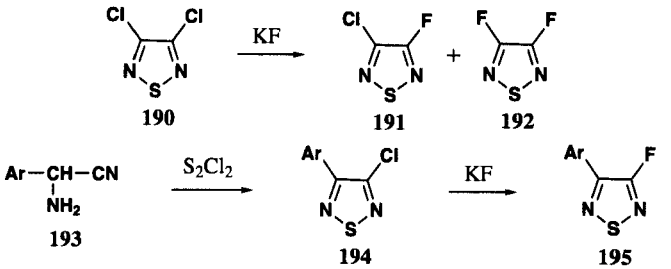


Scheme 42

different catalytic species (boric acid, metal salts, etc.).[100] The importance of this oxidation and of the possibility to obtain the sulfonyl derivative stems from the ability of such a group to undergo nucleophilic substitution with several nucleophiles (ZH in the *Scheme*). In this way, it is possible to introduce the trifluoromethylthiadiazole moiety into target compounds for potential industrial applications.[101] Similar reactions are reported for the chlorodifluoromethyl derivative **189**, which is used as a precursor for the preparation of herbicides.[102]

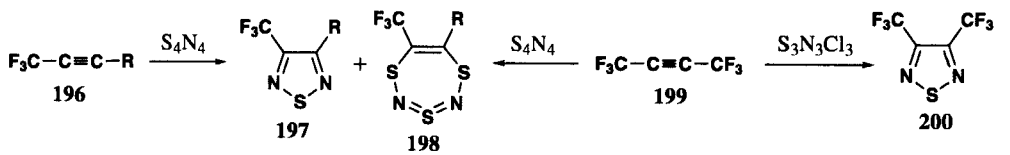
3. 1,2,5-Thiadiazoles

Similarly to other thiadiazoles, the direct introduction of fluorine on the 1,2,5-thiadiazole can be achieved *via* substitution reactions on the corresponding chloro derivatives. Thus, from the commercial 4,5-dichloro-thiadiazole **190** by a reaction with KF in sulfolane at 180°C, it is possible to obtain both the monofluoro compound **191** (24%) and difluorothiadiazole **192** (48%) (*Scheme 43*).[103] Similarly, 3-aryl-4-fluoro-1,2,5-thiadiazoles (**195**) have been prepared by treating the corresponding 4-chloro derivatives **194** (obtained by standard reactions [80a] involving α-aminonitriles **193** and sulfur monochloride) with KF at high temperatures (*Scheme 43*).[104]



Scheme 43

A synthesis of fluorinated 1,2,5-thiadiazoles from acyclic precursors utilizes the reaction of particular fluorinated substrates with tetrasulfur tetranitride (S_4N_4) in a (3 + 2) synthetic pattern.[80,105] For instance, 4,4,4-trifluoro-2-butyronitrile **196** (R = CN) and ethyl 4,4,4-trifluoro-2-butynoate **196** (R = COOEt) treated with S_4N_4 in dichloromethane at 150°C produced trifluoromethyl substituted thiadiazoles **197** (30-55%)[106] (*Scheme 44*). Interestingly, the reaction is

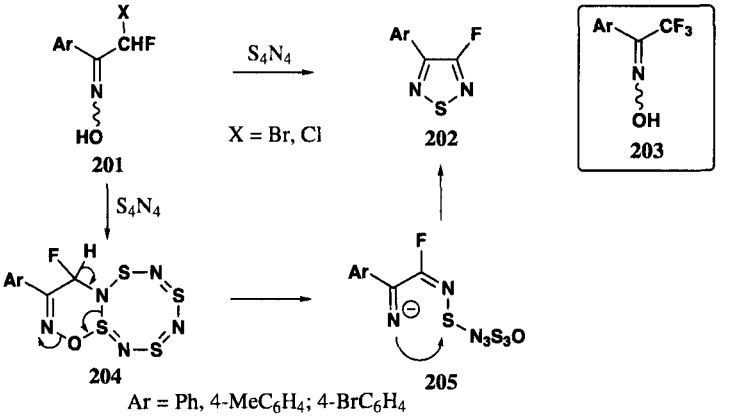


Scheme 44

accompanied by the formation of trithiadiazepine **198**. In the case of the reaction with hexafluorobutyne **199**, only the corresponding trithiadiazepine derivative **198** (R = CF_3) is isolated, although the authors assumes that the *bis*(trifluoromethyl)thiadiazole **200** is formed also and lost during the reaction work-up because of its volatility. The formation of **200** is claimed in 58% yield from the reaction of hexafluorobutyne **199** with the more electrophilic trithiazyl trichloride ($S_3N_3Cl_3$) reagent.[107] In this case, the addition of two NSCl moieties to the triple bond and the loss of SCl_2 during the heterocyclization is suggested. The same *bis*(trifluoromethyl) derivative

200 had been suggested to be involved in the reaction of **199** with thiazyl fluoride (NSF).[108]

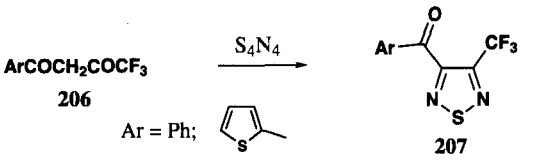
Cyclization with tetrasulfur tetranitride has been employed with the 1-aryl-2,2-dihaloethanone oximes **201**. From the reaction carried out in refluxing dioxane, 3-aryl-4-fluoro thiadiazoles **202** have been obtained in fair yields (32-65%) and the mechanistic aspects which involve the species **204** have been discussed (*Scheme 45*).[109] It has to be noted that the same reaction performed on 1-aryl-2,2,2-trifluoroethanone oximes **203** does not result in cyclization to thiadiazole.[110]



Ar = Ph, 4-MeC_6H_4; 4-BrC_6H_4

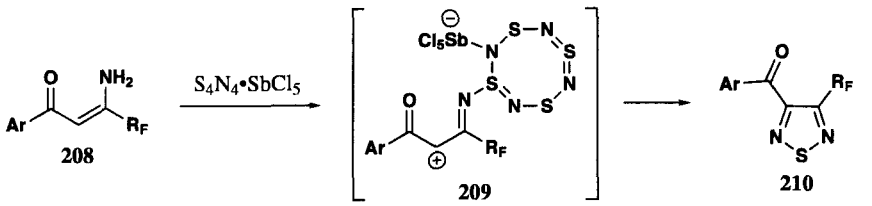
Scheme 45

The reaction of benzyl ketones with tetrasulfur tetranitride provided a method for the synthesis of 3,4-diaryl- and 3-alkyl-4-aryl-1,2,5-thiadiazoles.[111] Similarly, in the case of fluorinated substrates, 3-aroyl-4-trifluoromethylthiadiazoles **207** have been obtained in 40-50% yields from the reaction of aroyltrifluoroacetylmethanes **206** with S_4N_4 in refluxing toluene (*Scheme 46*).[112]



Scheme 46

Enaminones **208** have also been utilized as suitable substrates for the cyclization into 1,2,5-thiadiazoles **210** (21-51%).[113] The reaction has been realized using $S_4N_4/SbCl_5$ complex in toluene at 100°C, and a key intermediate **209** has been suggested (*Scheme 47*).

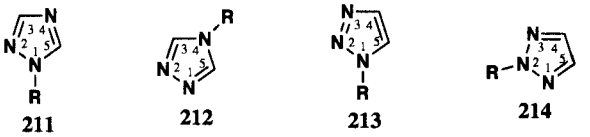


$R_F = CF_3$; Ar = Ph, 2-thienyl, 2-naphtyl
$R_F = C_3F_7$; Ar = 4-ClC_6H_4

Scheme 47

III. TRIAZOLES

Two classes of aromatic triazoles are structurally possible: 1,2,4-triazoles and 1,2,3-triazoles (*Fig. 5*). For each class, two series of *N*-substituted derivatives may be recognized, namely *1H-* (**211**) and *4H-* (**212**) forms in the case of 1,2,4-triazoles, and *1H-* (**213**) and *2H-* (**214**) forms



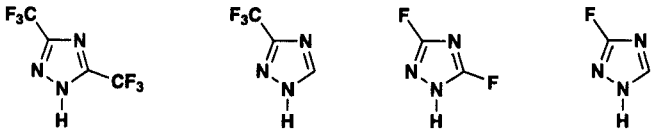
211 **212** **213** **214**

Fig. 5

in the case of 1,2,3-triazoles. It is worth noting that, in the case of *1H*-triazoles, the C(3) and C(5) monosubstituted 1,2,4-triazoles [as well as the C(4) and C(5) monosubstituted 1,2,3-triazoles] will be tautomeric forms. The chemistry of both 1,2,4-triazoles[114] and 1,2,3-triazoles[115] is well documented, and we will refer to these reports for general aspects regarding these heterocycles.

1. 1,2,4-Triazoles

The structure, basicity and thermodynamic properties of 3,5-*bis*(trifluoromethyl)- **215** and 3(5)-trifluoromethyl-1,2,4-triazole **216** have been examined by *ab initio* computational methods and have been related to the properties of the parent compound.[116] Calculations showed that *1H* tautomers are more stable than the *4H* ones, whereas in the case of the monosubstituted trifluoromethyl derivative, the *1H*-5-CF_3 form is only slightly less stable than the tautomer *1H*-3-CF_3. MNDO calculations on tautomeric forms of 3,5-difluoro-(**217**) and 3(5)-fluoro-1,2,4-triazole (**218**) suggest that the *1H*-3,5-difluoro tautomer and the *1H*-3-fluoro tautomer, respectively, are the predominant forms (*Fig. 6*).[117]

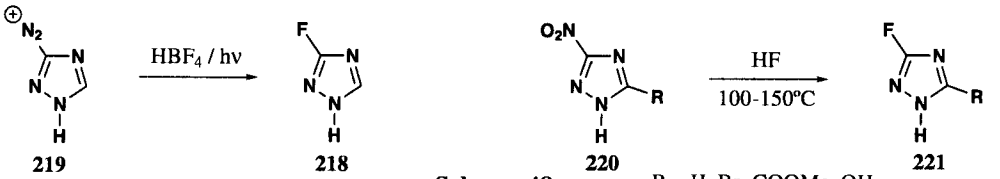


215 **216** **217** **218**

Fig. 6

The preparation of 1,2,4-triazoles bearing an annular fluorine atom is based more on the substitution of functional groups already present as ring substituents than on direct fluorination reactions. A typical example involves the 3-fluoro derivative **218**, obtained in 39% yields from irradiation of 3-diazonium-1,2,4-triazole **219** in concentrated tetrafluoroboric acid.[118] Moreover, the reaction of 3(5)-nitro derivatives **220** with pure hydrogen fluoride at 100-150°C (depending on the substituent) produces the corresponding 3(5)-fluorotriazoles **221** (70-98%); much lower yields are obtained when R = OH)[119] (*Scheme 48*).

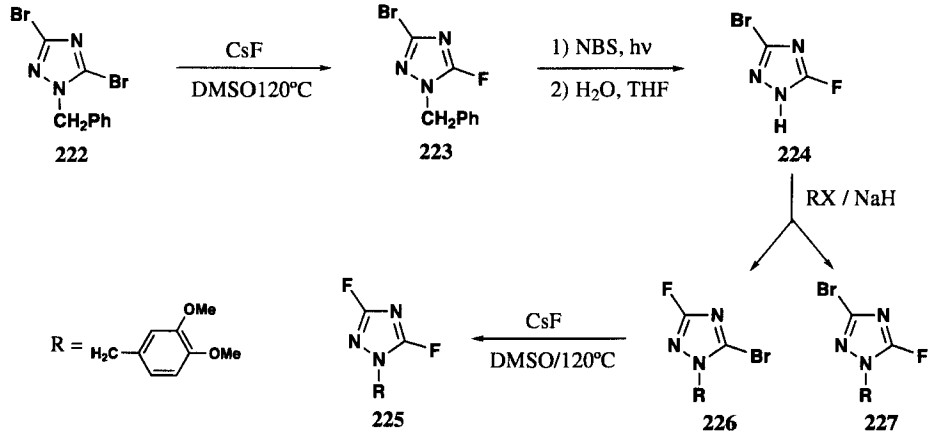
A nucleophilic substitution reaction with CsF is described in the case of the 3,5-dibromo compound **222**.[120] This reaction, conducted with an excess of CsF in DMSO at 120°C,



219 **218** **220** **221**

Scheme 48

produces the 3-bromo-5-fluoro-1,2,4-triazole **223** (87%) (*Scheme 49*). The observed selectivity for the C(5) halogen substitution is in agreement with the known higher reactivity of this position with respect to the C(3). Debenzylation of **223** (which could be easily accomplished by bromination followed by aqueous hydrolysis) and alkylation of resulting **224** afforded a mixture of isomers where 1-alkyl-5-bromo-3-fluorotriazoles **226** were the main products. From these compounds, which once again contain a 5-bromo moiety, a series of reactions with different nucleophiles produces various 5-substituted-1-alkyl-3-fluoro-1,2,4-triazoles. Interestingly, the reaction of representative **226** with CsF in DMSO produced the 3,5-difluorotriazole **225** (73%) (*Scheme 49*).[120] A patented example claims compounds containing 5-fluorotriazole structures, without experimental details, for the introduction of the fluoro moiety into the 1,2,4-triazole ring.[121] Finally, a direct *N*-difluoromethylation of a 1-phenyl-1,2,4-triazolin-5-one is reported by using chlorodifluoromethane as a reagent in a DMF/K_2CO_3 medium.[122]



222 **223** **224** **225** **226** **227**

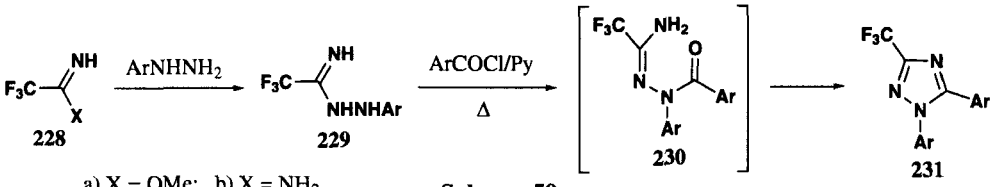
Scheme 49

Besides these examples, the most widely applied methodologies for the synthesis of fluorinated 1,2,4-triazoles involve the heterocyclization of open-chain fluorinated precursors, and ring-rearrangement reactions.

a) Heterocyclization Reactions

Following one of the general methodologies for the construction of the 1,2,4-triazole ring, 1,5-diaryl-3-trifluoromethyltriazoles **231** are prepared by reaction of amidrazones **229** (obtained from iminoether **228a** and arylhydrazines) with aroyl chlorides in dioxane/pyridine

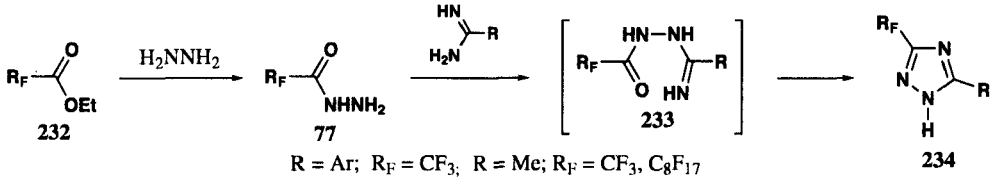
(*Scheme 50*).[123] In describing the same procedure for the preparation of trifluoromethyltriazoles **231** as potential cyclooxygenase-2 inhibitors, recent papers report the use of amidrazones **229** prepared from trifluoroacetamidine **228b** and arylhydrazines.[124]



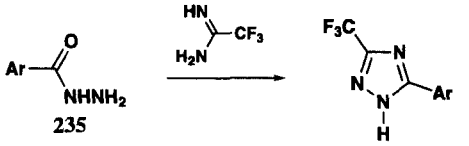
a) X = OMe; b) X = NH_2

Scheme 50

A one-pot synthesis of 5-substituted-3-perfluoroalkyl-1,2,4-triazoles **234** is reported *via* a three-component condensation reaction of ethyl perfluoroalkanoate **232**, hydrazine and amidines.[125,126,127] The reaction involves the initial formation of hydrazides **77** which then react with the amidine component (*Scheme 51*). A similar reaction is involved in the synthesis of 3-trifluoromethyltriazoles **236** from arylhydrazides **235** and trifluoroacetamidine.[128] Derivatives **234** (R = Me; $R_F = CF_3$, C_8F_{17}) are alkylated at N(1) through the corresponding sodium salt, and subsequently quaternized at N(4).[127]

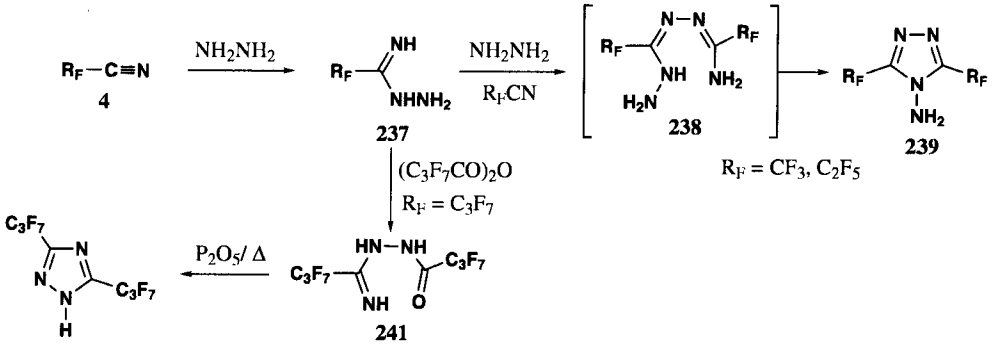


R = Ar; $R_F = CF_3$; R = Me; $R_F = CF_3$, C_8F_{17}



Scheme 51

N-Amino perfluoroalkyltriazoles **239** ($R_F = CF_3$, C_2F_5) are claimed to be obtained directly from the reaction of perfluoroalkylnitriles with hydrazine.[129] A reaction pathway is postulated and shown in *Scheme 52*. In the case of the reaction of perfluorobutyronitrile **4** (R_F =

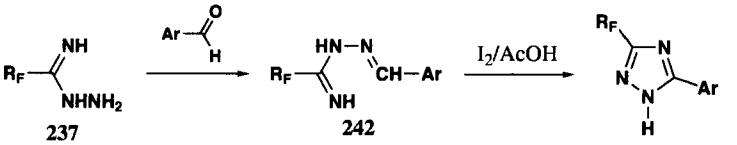


4 237 238 239 240 241

Scheme 52

C_3F_7) with hydrazine, the corresponding amhydrazone **237** (R_F = C_3F_7) has been isolated. Its acylation with pefluorobutyric anhydride and subsequent cyclodehydration of the open-chain intermediate **241** with P_2O_5 lead to the 3,5-*bis*(perfluoropropyl)triazole **240** (*Scheme 52*).

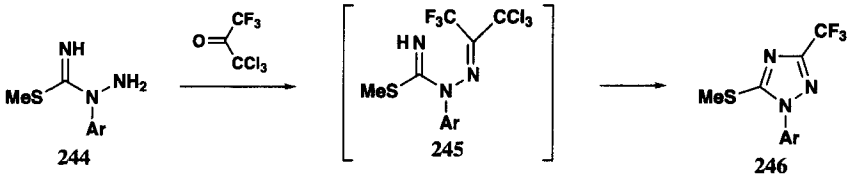
From perfluoroalkylamidrazones **237**, it is possible to obtain the arylidene derivatives **242**. Their oxidative heterocyclization with iodine in acetic acid allows the synthesis of perfluoroalkyltriazoles **243** (*Scheme 53*).[130] Another example of oxidative cyclization of trifluoromethyl-*N*-alkylamidrazones derivatives with *t*-butyl hypochlorite has also been reported.[131]



237 242 243

Scheme 53

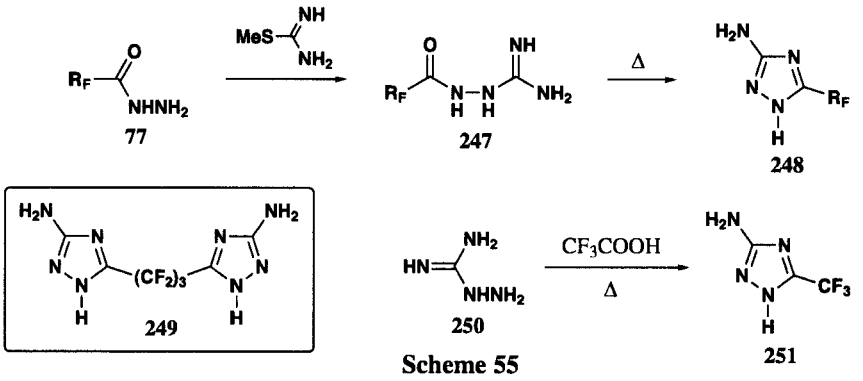
Synthetic procedures which use thiosemicarbazones may also be related to the methods described above. The reaction of *S*-methyl-2-arylisothiosemicarbazides **244** with 1,1,1-trichloro-3,3,3-trifluoroacetone produces 5-methylthiotriazoles **246** (*Scheme 54*).[132] Another recent example is the reaction of 4-arylthiosemicarbazides with methyl trifluoroacetate as acylating reagent in the presence of sodium methoxide leading to 3-trifluoromethyl-4-aryl-1,2,4-triazol-5-thiones.[133]



244 245 246

Scheme 54

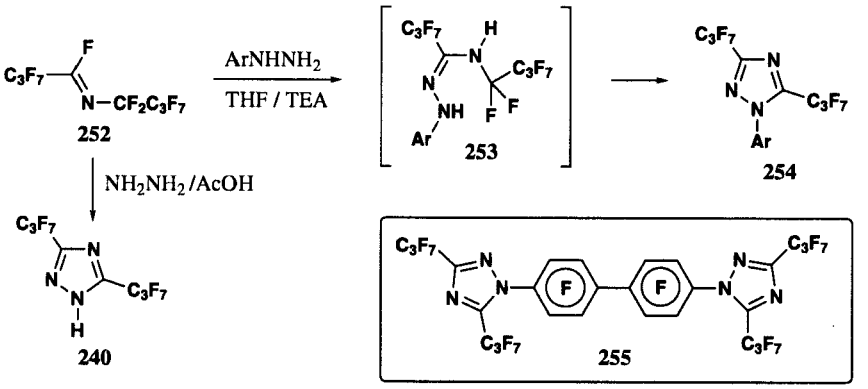
A synthesis of 3(5)-amino-5(3)-perfluoroalkyltriazoles **248** with optimal yields from the thermal cyclodehydration of perfluoroalkanoyl derivatives of *N*-aminoguanidine **247** obtained from perfluoroacylhydrazines **77** and *S*-methylisothiourea has been reported (*Scheme 55*).[134]



Scheme 55

Amino-*bis*-triazoles **249**, linked by a perfluoroalkyl chain at the 5,5' (or 3,3') positions, are obtained in a similar way by using *bis*-hydrazides of perfluoroglutaric acid.[134] The 3(5)-amino-5(3)-trifluoromethyltriazole **251**, is obtained in high yields (80%) by acylation of *N*-aminoguanidinium carbonate with trifluoroacetic acid in refluxing toluene (*Scheme 55*).[135]

An interesting methodology takes advantage of the reactivity of perfluoroaldimines **252** towards arylhydrazines, where the aryl group can either be totally, partially or not at all fluorinated.[136] The reaction, carried out in THF and in the presence of triethylamine (TEA) leads to 1,2,4-triazole derivatives **254** (*Scheme 56*). Similarly, the reaction of **252** with hydrazine in acetic

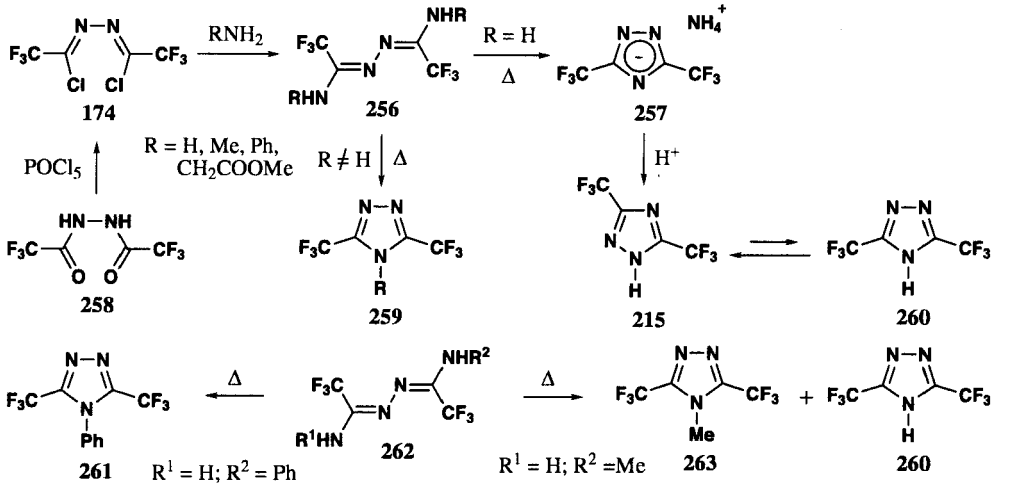


Scheme 56

acid gave the 3,5-*bis*(perfluoropropyl)triazole **240**. When the 4,4'-dihydrazinooctafluorobiphenyl is used as reagent, both hydrazine groups are involved in the reaction which leads finally to the perfluorinated triazole **255**.[136] This reaction is rationalized by the addition of the arylhydrazine to the imine double bond in the first step followed by elimination of HF leading to **253**. The heterocyclization of this intermediate (again with HF elimination) and the subsequent aromatization (with loss of another HF molecule) leads to the final product (*Scheme 56*); there is no evidence to support the exact sequence of this process.

The dichlorodiazadiene **174**, obtained by treating the diacylhydrazine **258** with phos-

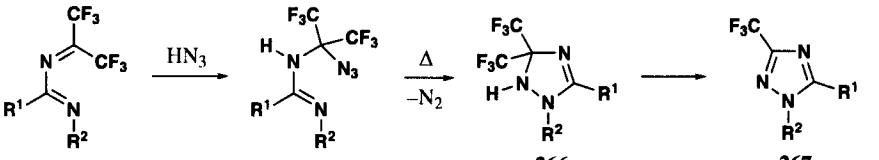
phoryl chloride, has been used for the synthesis of various 3,5-*bis*(trifluoromethyl)-1,2,4-triazoles in good yields.[137] From the reaction of **174** with an excess of ammonia, the diamino azine **256** (R = H) is obtained and then undergoes thermal cyclization at 150°C to give the ammonium 3,5-*bis*(trifluoromethyl)-1,2,4-triazolate **257** (*Scheme 57*). This compound, upon tratment with hydrochloric acid, will finally give triazole **215** (the less stable *4H* tautomer **260**[137a] was initially proposed).[137c] The same reaction is described for primary amines with formation of 4-substituted triazoles **259**.[137] From the unsubstituted triazole, addition reactions of alkynes, activated alkenes and diazomethane are reported to lead to the corresponding 1-substituted derivatives.[138] Moreover, the triazolate anion **257** is used in nucleophilic substitution on halides and pentafluoropyridine (which will undergo substitution in its 2- and/or 4-positions) regiospecifically leading to the corresponding 1-substituted triazoles.[138]



Scheme 57

From the thermolysis of asymmetric diamino azines **262**, the direction of the cyclization to the triazole derivative is a function of final product stability rather than the nucleophilic character of the amino nitrogens or the leaving ability of the amino group. As an example, the thermolysis of 2-amino-5-anilino derivative **262** (R^1 = H, R^2 = Ph) in refluxing ethanol leads to the 4-phenyl derivative **261**. In the case of 2-amino-5-methylamino derivative **262** (R^1 = H, R^2 = Me) the solvent-free thermolysis lead to the competitive elimination of ammonia or methylamine, with formation of the 4-methyl derivative **263** (main product) and of the unsubstituted **260** (minor product, mainly as a methylammonium salt) (*Scheme 57*).[137c]

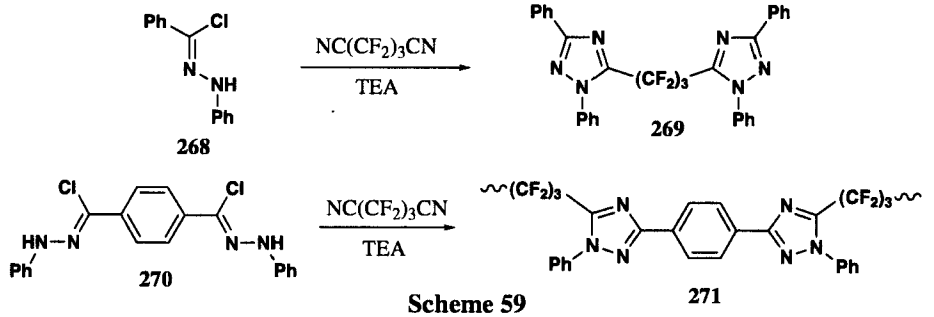
A triazole synthesis illustrated in *Scheme 58* involves the reaction of 1,3-diaza-1,3-dienes **264** with hydrazoic acid and subsequent decomposition of the resulting azide **265** into the



Scheme 58

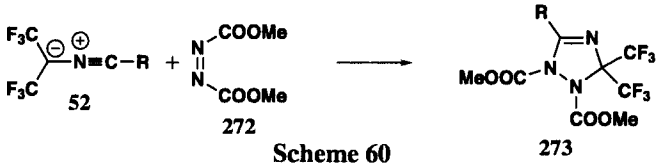
cyclized 5,5-*bis*(trifluoromethyl) derivative **266**.[139] The thermolysis of the latter compound in the presence of a radical initiator in toluene will give the triazole derivative **267** with loss of CHF_3 (even if yields are good in the latter step, the triazole cyclization is reported to proceed with modest overall yields).

The methodology involving a cycloaddition between a nitrile and a nitrilimine dipole is used for the synthesis of **269** from the reaction of hydrazonoyl halide **268** and perfluoroglutaronitrile in the presence of TEA.[140] Using the *bis*(acid) hydrazide chloride **270** and the same perfluorodinitrile, some polymeric structures are reported (*Scheme 59*).[140]



Scheme 59

Similarly, a trifluoromethylated nitrilimine (from a hydrazonoyl bromide) reacts with the C=N double bond of sodium cyanate to give a trifluoromethyl-triazolin-5-one.[141] In another example of 1,3-dipolar cycloaddition, the *bis*(trifluoromethyl) ylide **52** reacts with dimethyl azodicarboxylate **272** to give triazolines **273** (*Scheme 60*).[142]

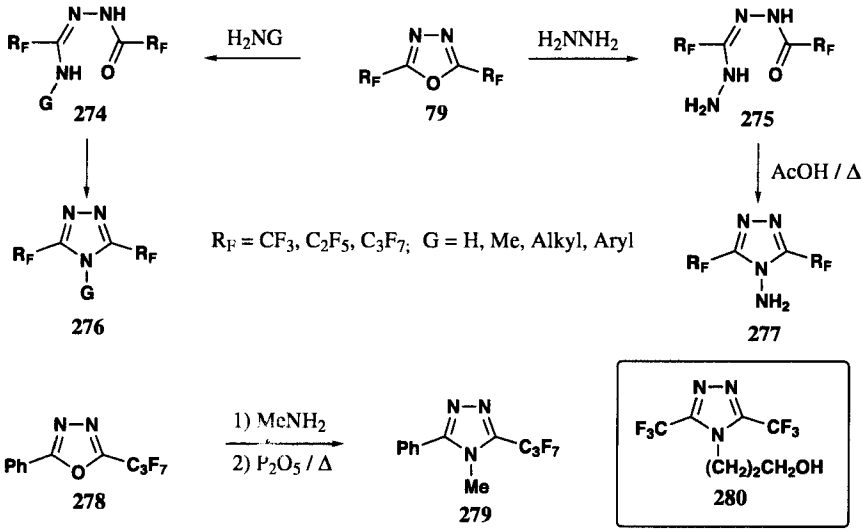


Scheme 60

b) Ring-rearrangement Reactions

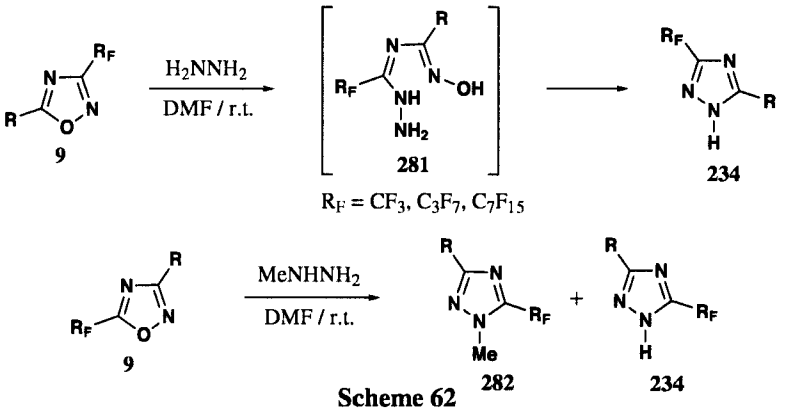
An example of ring-rearrangement is the already mentioned *ANRORC* process (***Section I, 1, c***). The reaction of 2,5-*bis*(perfluoroalkyl)-1,3,4-oxadiazoles **79** with nitrogen nucleophiles such as ammonia or amines on one hand,[143] or hydrazine,[144] on the other, leads to the open-chain

intermediates **274** or **275**, respectively, which can then undergo a heterocyclization reaction into 3,5-*bis*(perfluoroalkyl)-1,2,4-triazoles **276** or **277** under different experimental conditions depending on the nature of the intermediates [Note that in the case of **276** (G = H), the more stable form would be the *1H*-tautomer[116,137c]] (*Scheme 61*). In some aminolysis cases, the heterocyclization process is so favored that the intermediate is not isolated and the final triazole is obtained directly.[143b] On the contrary, sterically hindered or electron-deficient anilines require more drastic conditions to yield the final triazoles **276** (G = aryl).[143b] Similarly, the reaction of 2-perfluoropropyl-5-phenyl-1,3,4-oxadiazole **278** with methylamine gave an open-chain intermediate which underwent cyclodehydration to **279** by treatment with P_2O_5 (*Scheme 61*).[11] This methodology has been employed recently for the synthesis of target triazole **280** which was obtained in acceptable overall yields (39%).[145] It is worth noting that this ring transformation can represent a generally applicable approach for the synthesis of perfluoroalkyl or of 3,5-*bis*(perfluoroalkyl)-1,2,4-triazoles susbstituted at the N(4) ring atom.



Scheme 61

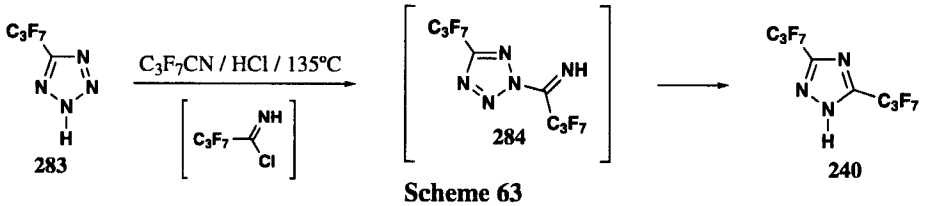
An *ANRORC* process on 5-perfluoroalkyl-1,2,4-oxadiazoles **9** allows the synthesis of perfluoroalkyl-1,2,4-triazole derivatives.[146] For instance, hydrazinolysis of oxadiazoles **9** in DMF at room temperature gives good yields of **234** (represented in the scheme by an arbitrary 3-perfluoroalkyl tautomeric form). These results are explained by formation of an open-chain intermediate **281** which eventually undergoes a ring-closure process involving the β-nitrogen of the hydrazine and the C(3) of the original oxadiazole ring (*Scheme 62*). The *ANRORC* reaction



Scheme 62

takes place also with methylhydrazine and, in this case, mixtures of 1-methyl (**282**) (major component) and *1H* (**234**) triazoles (minor component) are obtained (*Scheme 62*). The formation of the *1H* derivative is explained by assuming a demethylation step in the re-aromatization which follows the ring closure. The observed product ratio is a function of the substituents and reflects the different regioselectivity of the unsymmetrical nucleophilic reagent toward the C(5) of the oxadiazole ring.

The synthesis of 3,5-*bis*(perfluoropropyl)-1,2,4-triazole **240** from the decomposition of 5-perfluoropropyl-tetrazole **283** in the presence of C_3F_7CN and HCl can be also included in the class of heterocyclic transformations;[60] the reaction scheme, which involves the *in situ* formation of the imidoyl chloride, is reminiscent of the synthesis of 1,3,4-oxadiazoles from the decomposition of 2-acyl-tetrazoles (***Section I, 2, b***). The formation of the imidoyl chloride is the determining step, since in the absence of hydrochloric acid the formation of the final triazole does not take place.



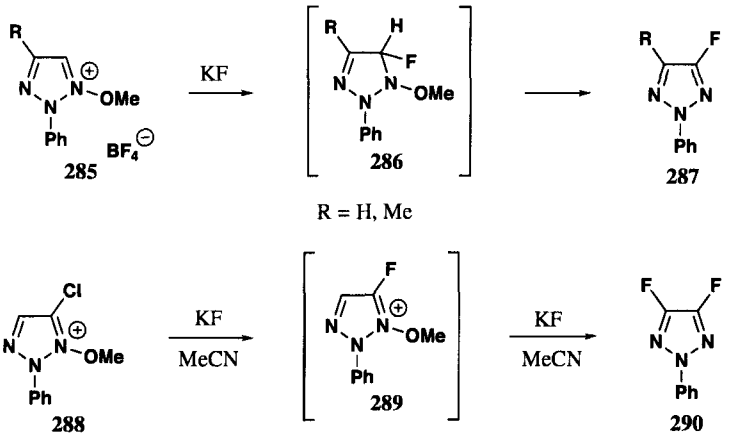
Scheme 63

As an additional example of the ring-rearrangement approach, it is worth of note that 3-methylamino-5-perfluoroalkyl-1,2,4-oxadiazoles **121** have been found to be precursors of 3-substituted 5-perfluoroalkyl-1,2,4-triazoles **124** in a photo-induced rearrangement pattern[70] (***Section I, 2, c***).

2. 1,2,3-Triazoles

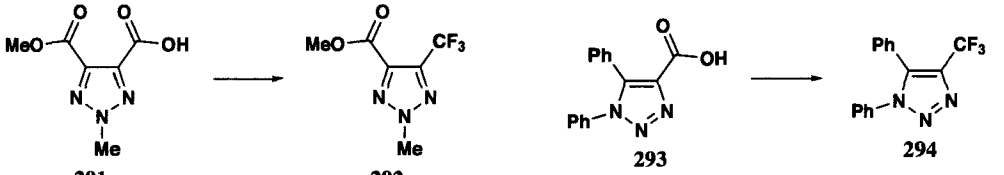
The tautomeric forms of fluoro derivatives, have been studied by means of MNDO calculations in the 1,2,3-triazoles series as well.[117] Therein, as far as the introduction of a fluorine atom as a substituent directly bonded to the heterocyclic ring is concerned, the literature reports

an addition/elimination reaction of tetrafluoroborates **285** with KF resulting in the formation of fluoro derivatives **287** in about 60% yields (*Scheme 64*).[147] A similar example involves 5-chloro compound **288** which, in the presence of fluoride, leads to 4,5-difluoro derivative **290** (14% yields) through intermediate **289** (*Scheme 64*).[148]



Scheme 64

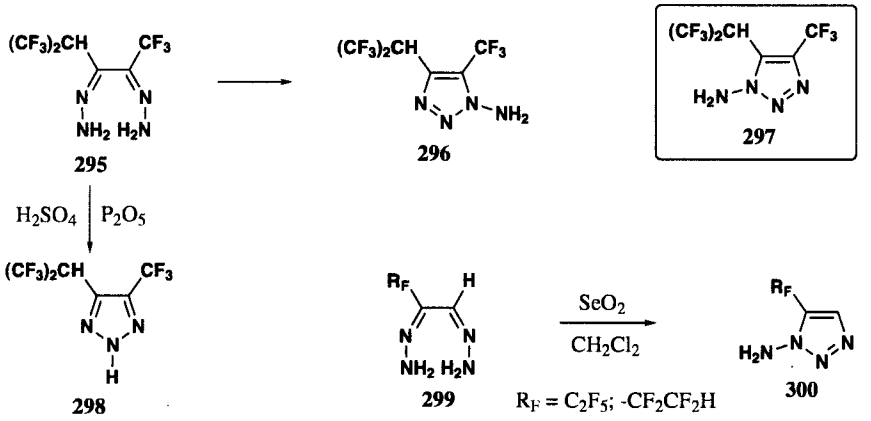
A fluorofunctionalization of triazole systems by modification of ring substituents is represented by the fluorination of carboxylic acids **291**[149] and **293**,[150] which have been transformed into the corresponding trifluoromethyl derivatives **292** and **294**, respectively (*Scheme 65*).[151]



Scheme 65

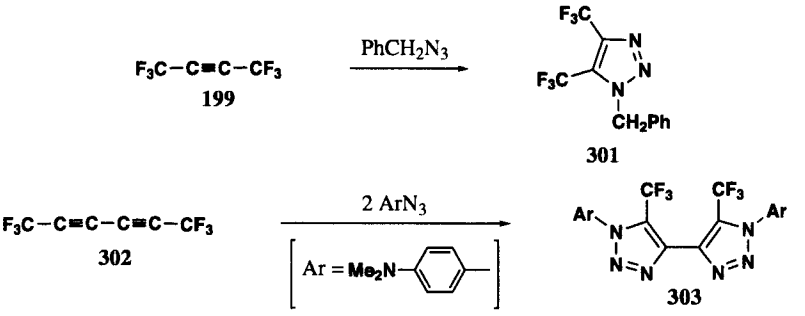
a) Heterocyclization Reactions

Following a mechanistic pattern observed for non-fluorinated analogues,[152] the oxidative heterocyclization of fluorinated *bis*-hydrazone **295**, with sulfuryl chloride or with bromine in aprotic solvents, resulted in the formation of *N*-amino triazole **296**[153] whose structure was confirmed by X-ray analysis (in a previous paper,[154] however, the regioisomer structure **297** had been wrongly assigned) (*Scheme 66*). Similarly, oxidation of *bis*-hydrazones **299** with selenium dioxide produced 1-amino-5-perfluoroalkyl-triazoles **300**.[153a] Triazole derivative **298** is claimed to be formed by treatment of *bis*-hydrazone **295** with a sulfuric acid/phosphoric anhydride mixture at 120°C.[155]



Scheme 66

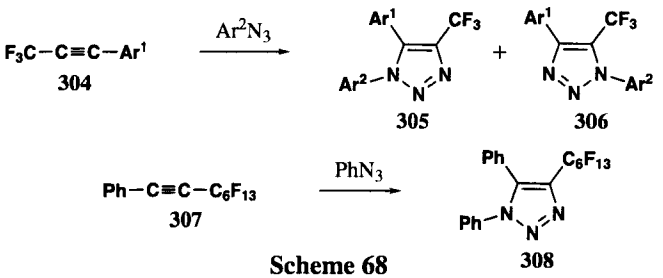
The most widely applied methodology leading to 1,2,3-triazoles consists of the addition of azides to acetylenic compounds and, in this context, there are several examples where the fluorinated moiety is present on both the azide and the triple bond components of the reaction. Some pioneering examples involve the synthesis of 1-benzyl-4,5-*bis*-trifluoromethyl-1,2,3-triazole **301** from hexafluorobutyne **199** and benzyl azide[156] and the preparation of *bis*-triazole **303** from hexafluoro-2,4-diyne **302** with two equivalents of *p*-(dimethylamino)-phenyl azide[157] (*Scheme 67*).



Scheme 67

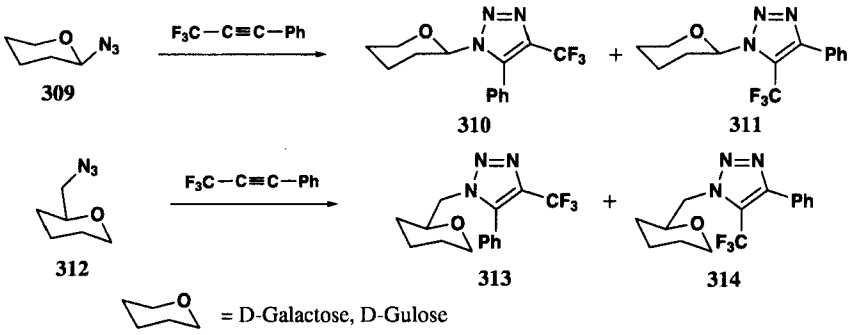
Interesting results are reported from the study of the reaction between aryl azides and aryltrifluoromethylacetylenes **304** upon heating for several hours in a high boiling aromatic solvent (usually toluene).[150,158] The general outcome of this reaction is the formation (in 65-95% yields) of regioisomeric triazole derivatives [*i. e.* 4-trifluoromethyl- **305** and 5-trifluoromethyltriazoles **306**] in variable ratios, which depend on the nature of the substituents, with an average (~4:1) predominance of the 4-trifluoromethyl derivatives **305** (*Scheme 68*). In this reaction, the observed regioselectivity has been explained on the basis of HOMO/dipole-LUMO/dipolarophile control.[158] The same result may be also predicted by taking into consideration the electronic effect of the trifluoromethyl group in the polarization of the acetylenic counterpart. In the reac-

tion between phenyl azide and 1-perfluorohexyl-2-phenylacetylene **307** the exclusive formation of 1,5-diphenyl-substituted triazole **308** is claimed.[159]



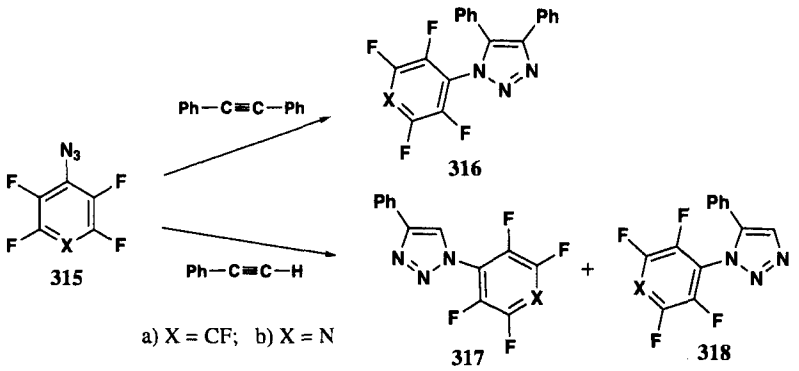
Scheme 68

Trifluoromethyl substituted 1,2,3-triazoles linked to *D*-galactose and *D*-gulose were synthesized by cycloadditions of trifluoromethylphenylacetylene to suitably protected azido sugars **309** and **312** carried out in refluxing toluene (79-83% yields)[160] (*Scheme 69* where, for the sake of clarity, none of the substituents on the sugar units were indicated). As expected, always two regioisomeric products were obtained and the 4-trifluoromethyl substituted triazoles **310** and **313** were the predominant component (about 1.5:1 ratio) The assignment of the structures of the regioisomeric pairs was based on ^{1}H NOE measurements, NMR data and X-ray analyses. Deprotection of the carbohydrate moieties in the final triazole derivative is carried out by conventional methodologies.



Scheme 69

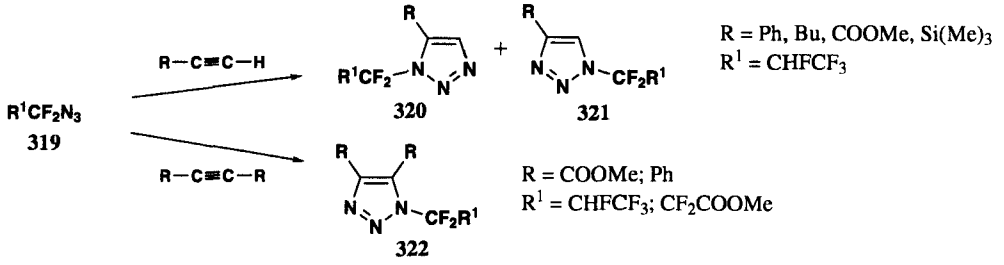
From the cycloaddition reaction of pentafluorophenyl azide **315a** with diphenylacetylene or phenylacetylene (carried out in CCl_4 under prolonged reflux heating) it is possible to obtain the trisubstituted 1,2,3-triazole derivative **316a** (27%) and a mixture of the two 1,4-disubstituted **317a** (31%) and 1,5-disubstituted regioisomer **318a** (12%), respectively (*Scheme 70*).[161]



Scheme 70

4-Azidotetrafluoropyridine **315b** behaves similarly during cycloaddition reactions with acetylenic compounds (*Scheme 70*). The reaction with diphenylacetylene gave low yields of the corresponding 4,5-diphenyl substituted triazole **316b** (11.5%), while the reaction with phenylacetylene gave both 4-phenyl substituted triazole **317b** and 5-phenyl substituted triazole **318b** in 42 and 24% yields, respectively.[162] From the reaction of 4-azidotrifluoropyrimidine with phenylacetylene, only the formation of 4-phenyl-1-(2,5,6-trifluoro-4-pyrimidinyl)-1,2,3-triazole is reported.[163]

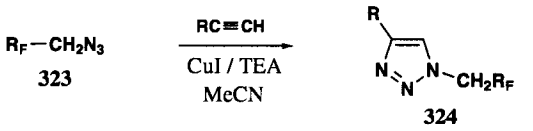
The reaction of α,α-difluoroazides **319** with different acetylenes produces 1,2,3-triazoles in high yields. The reaction with terminal alkynes affords a mixture of the expected regioisomers **320** and **321** in a ratio that is dependent on the nature of the substituent on the triple bond. In the case of the trimethylsilyl derivative, only the 1,4-disubstituted regioisomer was detected (although in 50% yield).[164] Azides **319** react with disubstituted triple bonds, such as dicarbomethoxy- or diphenylacetylene (the latter requiring higher temperature), leading to 4,5-disubstituted compounds **322** (*Scheme 71*). The stability of triazoles containing the CF_2-R moiety linked to the ring nitrogen has been rationalized by the involvement of the nitrogen lone-pair into the heteroaromatic ring, preventing its influence on α-fluorine atoms.[164]



Scheme 71

A series of polyfluoroalkyl azides **323** reacts with various terminal alkynes at room temperature in acetonitrile and in the presence of CuI, giving 1,4-disubstituted polyfluoroalkyl triazoles **324** in moderate to good yields through a highly regioselective cycloaddition (*Scheme 72*).[165]

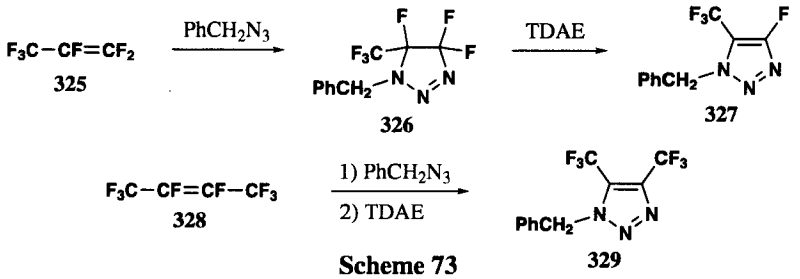
Interestingly, no 1,5-disubstituted product was formed and this result was explained by the CuI catalysis which involves the initial formation of copper acetylide as previously observed in non-fluorinated systems.[166]



R_F = CF_3; CF_2CF_2H; $(CF_2)_5CF_3$; $(CF_2)_7CF_3$; $(CF_2)_nCF_2Cl$

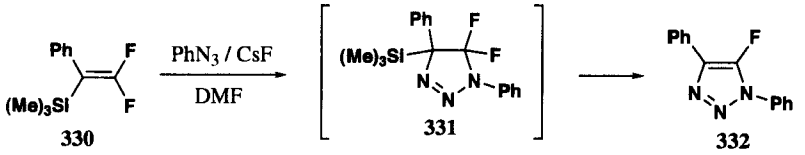
Scheme 72

The cycloaddition of azides can involve activated double bonds and be followed by aromatization. Some examples include the reaction of perfluoropropene **325** or perfluorobutene **328** with benzyl azide at 150°C.[156] Triazole derivatives **327** and **329**, respectively, can be obtained from the corresponding triazoline precursors by treatment with *tetrakis*(dimethylamino)ethylene (TDAE), a reagent which is reported[167] to be capable of halogen abstraction (*Scheme 73*). In the addition of phenyl azide to some *bis*-trifluoromethylalkenes, only one of the possible triazoline regioisomers is claimed.[168]



Scheme 73

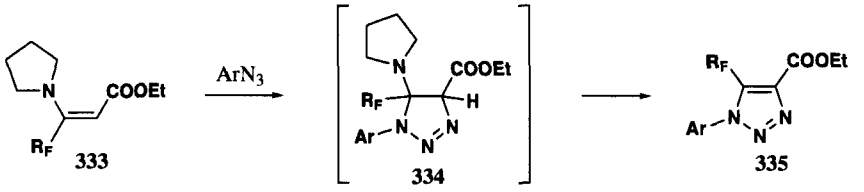
The isolation of 5-fluoro-1,4-diphenyl-1,2,3-triazole **332**, from the trimethylsilyl compound **330** and phenyl azide in DMF and in the presence of CsF,[169] can be related to the same reactivity illustrated above (*Scheme 74*). In this case, the initial cycloaddition into **331** can be assumed; on the other hand, from the observation that defluorosilylation of **330** with CsF also leads to an oligomer of 1-fluoro-2-phenylacetylene.[169]



Scheme 74

The cycloaddition reaction of aryl or benzyl azides with 3-fluoroalkyl-3-pyrrolidinoacrylates **333** (which possess an enamine-like structure where the electron-donating character of the pyrrolidine group determines the regiochemistry of the reaction) opens the way to the regiospecific synthesis of the corresponding 5-fluoroalkylated-*1H*-1,2,3-triazoles **335** (structure

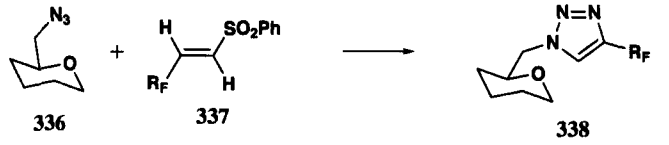
supported by X-ray analyses) (*Scheme 75*).[170] The reaction is carried out at 80-90°C in the absence of solvent and in the presence of an excess of azide.



$R_F = CF_3$; CF_2Cl; CF_2Br; $CF_2CF_2CF_2Cl$

Scheme 75

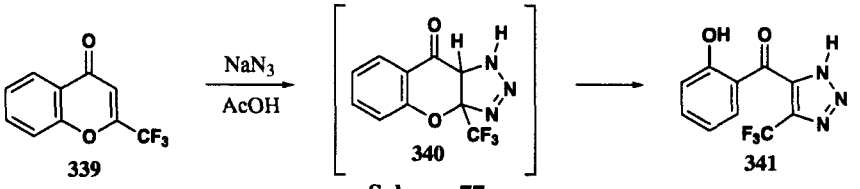
Perfluoroalkyl substituted vinyl sulfones **337** are used as dipolarophiles in the cyloaddition with suitably protected monosaccaride azides **336**, to afford 4-perfluoroalkyl substituted 1,2,3-triazoles linked at the C-6 of *D*-galactose or *D*-altrose entities **338** in 70-75% yields (*Scheme 76*).[171] The reaction is carried out in refluxing toluene and is regiospecific. From the initial cycloadduct, the aromatization is a spontaneous process, driven by the presence of a good leaving group. The triazoles obtained were then deprotected by usual procedures.



O = D-Galactose, D-Altrose $R_F = CF_3$; C_4F_9; C_6F_{13}

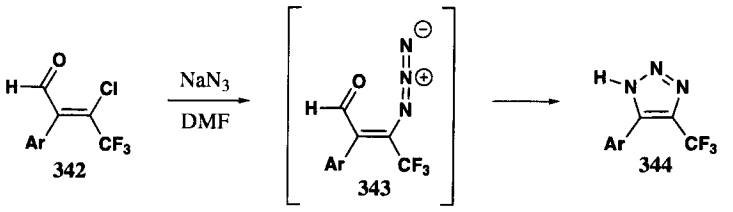
Scheme 76

An example of cycloaddition of hydrazoic acid (from sodium azide in acetic acid) is reported with 2-trifluoromethylchromone **339**.[172] In this case, the initial cycloadduct evolves towards the final product **341** through a spontaneous ring-opening process (*Scheme 77*).



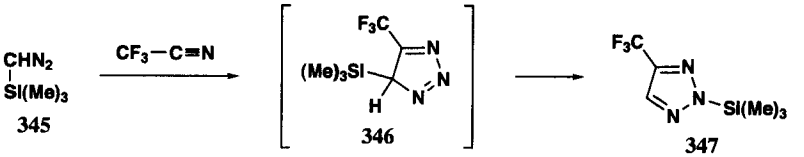
Scheme 77

The β-chloro-β-perfluoroalkyl substituted acroleins **342** have been used as olefinic substrates in the reaction with sodium azide (*Scheme 78*).[173] From this reaction, conducted at room temprerature in DMF, 4,5-disubstituted-1,2,3-triazoles **344** are obtained presumably through a reaction route involving the initial formation of azide **343** and subsequent heterocyclization (from its hydrated form) with elimination of formic acid.



Scheme 78

An example of cycloaddition of a diazoalkane with a fluorinated nitrile has also been reported.[174] The reaction of diazomethyltrimethylsilane **345** with trifluoroacetonitrile produces the 4-trifluoromethyl-2-trimethylsilyl-1,2,3-triazole **347** whose formation suggests the migration of the trimethylsilyl group in the initially formed cycloadduct **346** (*Scheme 79*).



Scheme 79

IV. TETRAZOLES

Tetrazole is an aromatic azapyrrole ring which may exist in two tautomeric *1H* (**349**) and *2H* (**350**) forms, from which two series (namely 1,5- and 2,5-) of disubstituted tetrazoles **351** and **352** are originated (*Fig. 7*).

For general aspects of the chemistry of the tetrazole system, see the cited literature.[175] A recent report deals with a theoretical study of the tautomerism and ionization of a series of 5-substituted tetrazoles.[176] Comparative semi-empirical calculations of 1-, 2-, 1,5- and 2,5-substituted

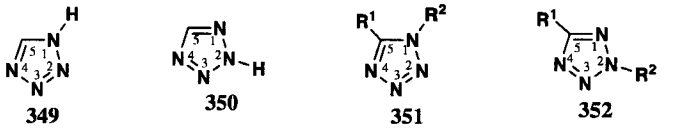
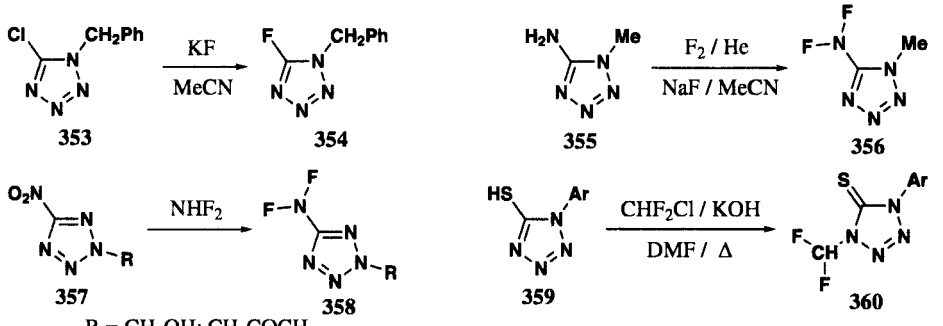


Fig. 7

tetrazoles have also been reported.[177] MNDO calculations, comparing heats of formation and dipolar moments with those of other fluoroazoles, have been performed on both tautomers of 5-fluorotetrazole without leading to convincing conclusions on the stability of the two tautomeric forms.[117] The 5-fluorotetrazole has also been cited in a patent regarding carbon dioxide laser fuels; however, no experimental data are reported regarding its preparation.[178]

The synthesis of fluorinated tetrazoles is essentially a *building block strategy* based on starting from fluorinated acyclic precursors. Among those few cases where the fluorinated moiety is instead introduced directly on the pre-formed tetrazole ring we may cite: *i*) the nucleophilic substitution on 5-chloro-1-benzyltetrazole **353** with potassium fluoride in acetonitrile in the pres-

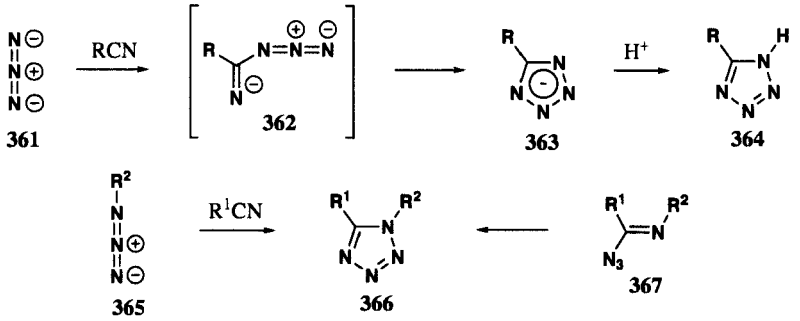
ence of crown-ethers;[179] *ii*) the fluorination of 5-amino-1-methyltetrazole **355** with fluorine in the presence of sodium fluoride leading to the corresponding 5-*N,N*-difluoroamino compound **356**;[180] *iii*) the nucleophilic substitution of a nitro group in 5-nitro-2-substituted-tetrazoles **357** leading to the corresponding 5-*N,N*-difluoroamino derivatives **358**[180] (*Scheme 80*). (In this context, the potentially explosive behavior of difluoroamino tetrazoles should be noted). A difluoromethylation reaction of tetrazoles **359** is also reported:[181] depending on experimental conditions, the *N*-difluoromethyl derivatives **360** or *S*-difluoromethyl derivatives were obtained (*Scheme 80*).



Scheme 80

The *building block strategy* for the synthesis of fluorinated tetrazoles utilizes general methods consisting of: *i*) the addition of azide ion to nitriles, which is the more general approach to 5-monosubstituted tetrazoles **364**; *ii*) the cycloaddition of azides to nitriles which is regioselective in forming 1,5-disubstituted derivatives **366**; *iii*) the *in situ* generation of *N*-substituted imidoyl azides **367** followed by cyclization to 1,5-disubstituted compounds **366** (*Scheme 81*).

Regarding the first approach, the literature reports a recent mechanistic study based on density functional theory calculations.[182] The reaction very likely proceeds through the formation

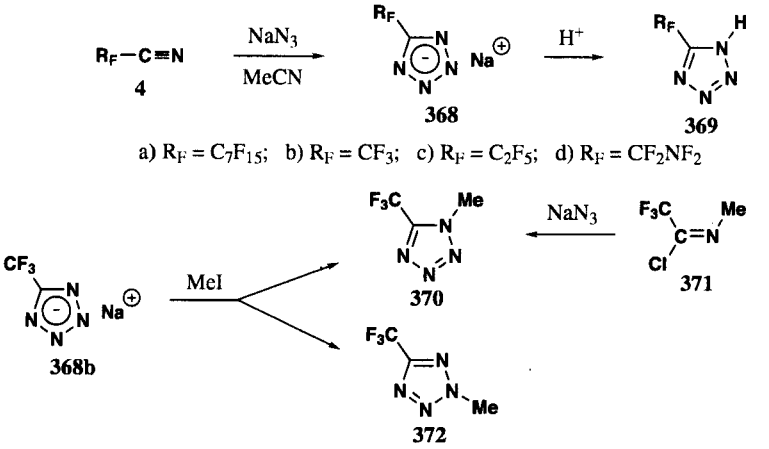


Scheme 81

of an imidoyl azide **362** which then cyclizes to give the tetrazole, and the activation barriers are found to correlate with the electron-withdrawing potential of the substituent linked to the nitrile moiety. In general, the reaction is favored by the presence of an electron-withdrawing group which, in this case, is represented by a fluorinated group. Even if the reaction stoichiometry indi-

cates the addition of hydrazoic acid (HN_3), the synthetic protocol actually involves the use of an azide salt (*e. g.* NaN_3) followed by acid treatment.

An example employing such a methodology is represented by the synthesis of the 5-perfluoroheptyltetrazole **369a** (obtained in quantitative yields) through the reaction of the corresponding perfluoroalkylnitrile with sodium azide in DMF at 100°C.[183] Similarly, from trifluoroacetonitrile and NaN_3 in MeCN, the 5-trifluoromethyltetrazole **369b** is obtained[184] (*Scheme 82*).



4 368 369

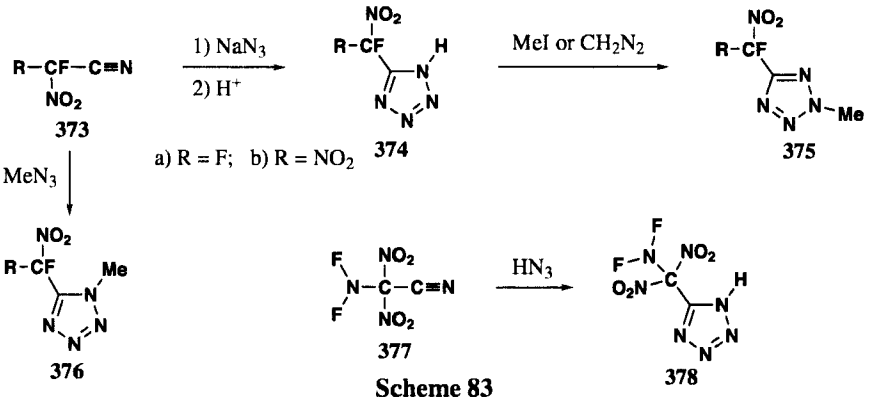
a) $R_F = C_7F_{15}$; b) $R_F = CF_3$; c) $R_F = C_2F_5$; d) $R_F = CF_2NF_2$

368b 370 371 372

Scheme 82

Methylation of the sodium salt **368b** with methyl iodide leads to a mixture of the two 1-methyl- (**370**) and 2-methyltetrazole (**372**) isomers in a 1:6 ratio, and this result is in agreement with the electron-withdrawing effect of the substituent at the C(5) position, which drives the reaction towards the formation of the 2-substituted derivative.[185] In turn, 1,5-disubstituted derivative **370** can be prepared by the reaction of NaN_3 with trifluoroacetyliminium chloride **371** (*Scheme 82*).[184] The 5-perfluoroethyltetrazolate anion **368c** and 5-(*N,N*-difluoroamino)difluoromethyltetrazolate anion **368d**, similarly prepared from the corresponding nitriles, have also been utilized as organic ligands in the formation of complexes.[186,187]

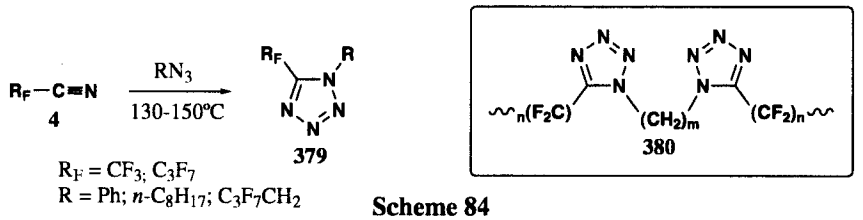
Other examples of sodium azide addition to nitriles are: *i*) the synthesis of **374** from which mainly 2-methyl derivatives **375** can be obtained by methylation with diazomethane or methyl iodide (again, 1-methyl derivatives **376** can be obtained by the reaction of nitriles **373** with methyl azide)[188,189] (*Scheme 83*); *ii*) the synthesis of 5-(*N,N*-difluoroamino)dinitromethyltetrazole **378** from nitrile **377** with hydrazoic acid in diethyl ether[190] (*Scheme 83*). Furthermore, for other syntheses of 5-perfluoroalkyl tetrazoles, which have been prepared to be used as precursors in the synthesis of fluorinated 1,3,4-oxadiazoles, see Section I, 2b.



Scheme 83

1,5-Disubstituted derivatives can be obtained from the cycloaddition of azides to nitriles. In contrast with the facile [2+3] cycloaddition of an azide to an acetylenic compound (RN_3 + RC≡CR), only certain highly electron-deficient nitriles are known to undergo an easy intermolecular cycloaddition in the case of the analogous [2+3] cycloaddition of an azide to a nitrile leading to tetrazoles.[175c,182,191] In fact, it has been demonstrated that increasing the electron-withdrawing strength of the substituent on the nitrile (as in the case of perfluoroalkylnitriles) will increase its rate of cycloaddition to azides.[182,191]

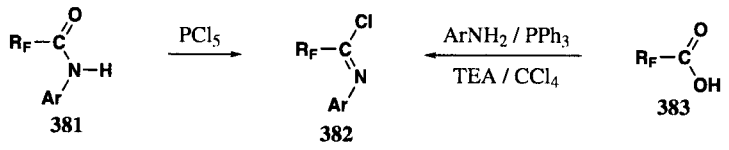
A historical example of this approach involves the reaction of alkyl or aryl azides with perfluoroalkylnitriles leading to **379** (*Scheme 84*);[192] see also the cited reaction of **373** with methyl azide, or the reaction of the fluorodinitroacetonitrile **373b** with *n*-hexyl azide.[189] Other



Scheme 84

examples of alkyl azide cycloaddition with CF_3CN are reported.[193] Polymeric structures such as **380** are reported[194] to arise from the reaction of perfluorodinitriles (for example perfluoroglutaronitrile, n = 3) and diazides (for example hexamethylene diazide, m = 6) (*Scheme 84*).

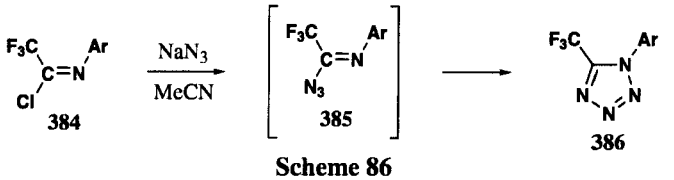
Perfluoroalkyl imidoyl chlorides **382** represent useful precursors of perfluoroalkyl tetrazoles. This synthesis is particularly successful because of the ready availability of such reagents. Besides the methodology which involves the reaction of amides **381** with PCl_5, an easy and widely applied method has been developed using the reaction of the carboxylic acid **383** with a primary amine in the presence of PPh_3, TEA and CCl_4 (or CBr_4) (*Scheme 85*).[195]



381 382 383

Scheme 85

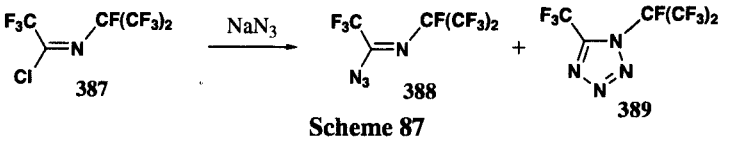
The reaction of imidoyl chlorides **384** with sodium azide in water/acetone, acetonitrile or DMF at room temperature, produces directly 1-substituted-5-trifluoromethyltetrazoles **386** in moderate to excellent yields (higher yields were obtained when electron-rich aryl groups were present) (*Scheme 86*).[196]



384 385 386

Scheme 86

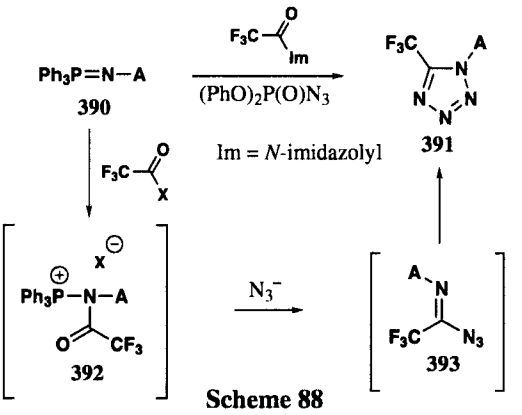
In this context, the cyclization of imidoyl azide **385** may be affected by geometry related steric restrictions (the lone pair of the imino nitrogen and the azido group must be in a *cis* configuration) and by the electron density of the imino nitrogen.[175a-c,196] In fact, it is well known that electron-withdrawing groups affect the ring-chain azido-tetrazole equilibrium.[175a-c] Significantly, from the reaction of the imidoyl chloride **387** with azide ion, an equilibrium mixture of the azide **388** and tetrazole **389** (where the tetrazole is the favored component) is observed.[197]



387 388 389

Scheme 87

Other examples of syntheses utilizing imidoyl chlorides involve the formation of 5-trifluoromethyltetrazoles from *N*-alkyl- or *N*-benzyltrifluoroacetimidoyl chloride and NaN_3 in acetonitrile.[156,184,192] A similar reaction pattern may be envisaged in a patented synthesis of 5-trifluoromethyltetrazoles from trifluoroacetyl-*N*-arylamino derivatives.[198] Furthermore, a recent patent reports the synthesis of 5-trifluoromethyltetrazoles of general formula **391**, where *A* indicates an alkyl, cycloalkyl, aryl or hetaryl group.[199] This approach is analogous to a general methodology of tetrazole synthesis[200] and involves the trifluoroacetylation of triphenyl iminophosphoranes **390** (in this case, the 1-trifluoroacetylimidazole acts as a trifluoroacetylating reagent) and the subsequent reaction with diphenylphosphoryl azide (as an azide ion source) leading to the azide **393** precursor of the final tetrazole **391** (*Scheme 88*).



Scheme 88

V. CONCLUDING REMARKS

As already mentioned in the introduction, the synthesis of fluorinated heterocyclic systems is a challenging research field. The authors hope that their efforts in collecting the information presented in this review will be helpful in the planning of straightforward synthetic strategies for specific heterocyclic targets. In the upcoming second part, we will focus on fluorinated five-membered heterocycles with two heteroatoms. Nevertheless, because of the growing importance of five-membered heterocycles with more than two heteroatoms in the construction of new materials and in new applications, we plan to reserve some space in the next review for recent updates on this topic.

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