Chemistry of Fluorinated Oxadiazoles and Thiadiazoles

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Contents

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Abstract A literature survey of the chemistry of fluorinated oxadiazoles and thiadiazoles is presented. The core part on synthetic procedures is given by type of heterocycle and includes recent developments up to the end of 2012. Reactivity is discussed when induced by the presence of the fluorinated moiety. Selected examples of bioactive compounds and applications are illustrated.

Keywords Fluorinated azoles • Oxadiazoles • Thiadiazoles • Fluorinated bioactive azoles • Fluorinated materials

1 Introduction

Oxadiazoles and thiadiazoles are a subset of heteroaromatic compounds which are widely applied in many fields, and their chemical and physicochemical properties can be appropriately tuned by the introduction of fluorine or fluorinated groups. This is one of the main reasons of the increasing development of synthetic methodologies leading to targeted fluorinated heterocycles. Additionally, the presence of the fluorinated moiety opens the way to new *fluorine-induced* reactivity with respect to corresponding non-fluorinated systems [1]. Target fluorinated oxadiazoles and thiadiazoles find applications in materials and fluoropolymer science and, in the case of biologically active compounds, their use as agrochemicals or pharmaceuticals is also common. Four types of compounds can be considered under the general classification "fluorinated heterocycles" in this chapter: (i) compounds where the fluorine atom is directly linked to the heterocyclic core; (ii) compounds where the heterocycle is substituted with a mono-, poly- or perfluoroalkyl group; (iii) compounds where the heterocycle is substituted with a mono-, poly- or perfluoroaryl group; (iv) compounds where the fluorine substituent is far from the heterocyclic core. Although the latter category may seem too generally applicable, in several cases the presence of a fluorinated group not directly linked to the heterocyclic core can strongly affect the heterocyclic moiety chemical behaviour. Most of the literature refers to (per)fluoroalkyl and (per)fluoroaryl derivatives and reported examples have been selected on the basis of general interest or major breakthrough. Our efforts have been devoted to present an update until the end of 2012, mainly considering publications appeared in the last two decades. Previous papers have been cited when of general interest for the synthetic approach.

2 Synthetic Routes to Fluorinated Oxadiazoles and Thiadiazoles

2.1 1,2,3-Oxadiazoles

With the exception of mesoionic compounds such as sydnone **1** (Fig. 1) [2], fluorinated 1,2,3-oxadiazole systems are rare and often included as structures in patent's Markush, without sufficient experimental details [3].

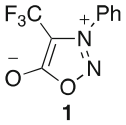

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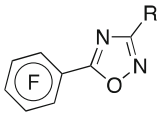
Fig. 1 A reported example of fluorinated 1,2,3-oxadiazole system



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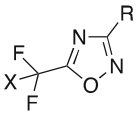

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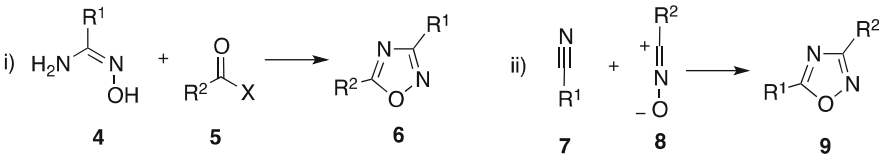
Fig. 2 Examples of 1,2,4-oxadiazole reagents

2.2 1,2,4-Oxadiazoles

Fluorinated 1,2,4-oxadiazoles find their application in both the pharmaceutical industry and materials science. Recently, 3-substituted 5-pentafluorophenyl-1,2,4-oxadiazoles **2** (Fig. 2) have been used as fluorinated oxadiazole arylating reagents (FOXARs) for the attachment of fluorinated moieties to nucleophilic pendants of polymers [4] and macromolecules [5]. Fluorinated 1,2,4-oxadiazoles **3** (Fig. 2) have been employed as reagents to introduce the difluoromethylene moiety into organic compounds [6]. To date, despite the fact that 3- (or 5-) chloro- or bromo- derivatives are known, there is still no literature on the synthesis of 1,2,4-oxadiazoles bearing a fluorine atom directly linked to the oxadiazole ring.

The synthesis of fluorinated oxadiazoles can be achieved from open-chain fluorinated precursors through conventional heterocyclization reactions such as the *amidoxime route* (i in Scheme 1) and the *cycloaddition route* (ii in Scheme 1), both necessitating of a nitrile precursor [7].

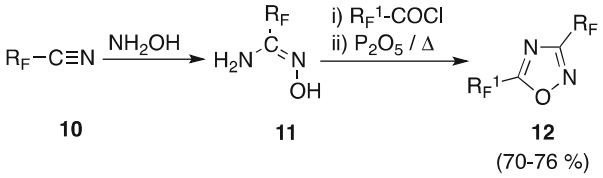


4 5 6 7 8 9

Scheme 1 1,2,4-oxadiazole synthesis by (i) the amidoxime route; (ii) the cycloaddition route

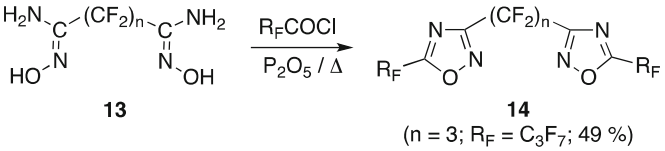
2.2.1 The Amidoxime Route

The historical *amidoxime route* towards 1,2,4-oxadiazoles is still the most represented in the literature also for fluorinated structures. Oxadiazoles **12**, bearing fluorinated groups at both the C(3) and C(5) can be obtained from the appropriate perfluoroalkyl amidoxime **11** and a fluorinated acylating reagent (Scheme 2). Similarly, from suitably fluorinated reagents, one can obtain oxadiazoles bearing the fluorinated group either at the C(3) or at C(5), respectively.



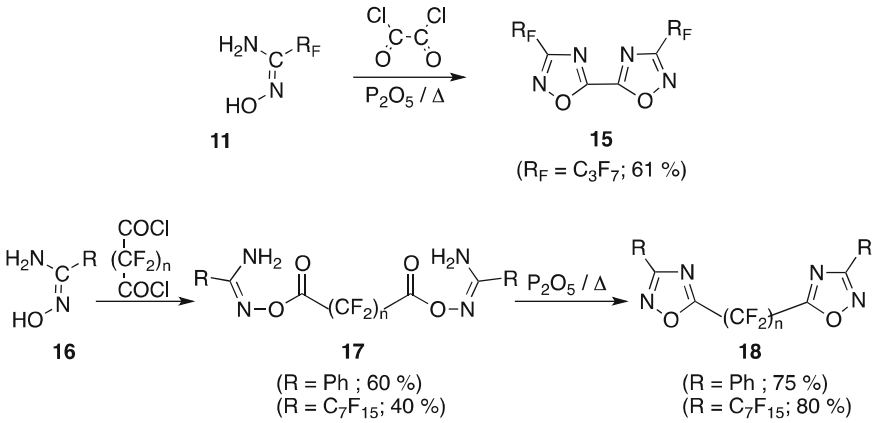
Scheme 2 Synthesis of 1,2,4-oxadiazoles bearing fluorinated groups at both the C(3) and C(5) by the amidoxime route

Pioneering work on this subject [8] reported the preparation of various perfluoro-alkylamidoximes **11** (R_F=CF_3, C_2F_5, C_3F_7, C_7F_{15}) and their acylation with perfluoro-acylchlorides (R_F^1COCl) followed by cyclodehydration to produce 3,5-bis(perfluoroalkyl)-1,2,4-oxadiazoles **12** either symmetrically (R_F=R_F^1) or unsymmetrically substituted. By following the same methodology, bis-oxadiazoles **14** (n=3) could be obtained (Scheme 3) [8, 9].



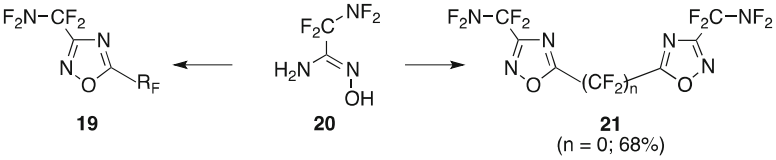
Scheme 3 Synthesis of perfluoroalkylated bis-oxadiazoles **14** by the amidoxime route

Perfluoroalkyl substituted oxadiazoles joined by the annular 5,5′- positions can be obtained by using the appropriate diacyl chloride. For instance, in the reaction of amidoxime **11** with oxalyl chloride, the 5,5′-bis(1,2,4- oxadiazolyl) compound **15** is produced (Scheme 4) [8]. Furthermore, the corresponding O,O′-hexafluoroglutaryl diamidoxime **17** (n=3) was isolated in acceptable yields by the reaction of amidoxime **16** and hexafluoroglutaryl chloride [10]. Subsequent dehydration by heating with phosphorus pentoxide gave the corresponding bis-oxadiazole **18** in good yields (Scheme 4).



Scheme 4 Bis-oxadiazoles **15** and **18** obtained by the amidoxime route followed by dehydration step with P_2O_5

Various 5-perfluoroalkyl-3-phenyloxadiazoles have been obtained from the direct reaction of benzamidoxime **16** (R=Ph) with perfluoroacylating reagents [10, 11]. Difluoromalonyl chloride and benzamidoxime directly gave the bis-oxadiazolyl-difluoromethane **18** (n = 1). Similarly, the reaction of difluoroaminodifluoroacetamidoxime **20** with perfluoroalkanoyl chlorides followed by dehydration of the resulting *O*-perfluoroacylamidoximes with P_2O_5 leads to 5-perfluoroalkyl-oxadiazoles **19**. When heating amidoxime **20** with perfluorosuccinic acid and phosphorus pentoxide, the bis-oxadiazole **21** (n = 2) is obtained [12]. The same amidoxime **20** with oxalyl chloride will yield bis-oxadiazole **21** (n = 0) (Scheme 5) [13].



Scheme 5 Synthesis of perfluoroalkyl 1,2,4-oxadiazole **19** and bis-oxadiazole **21**

5-Pentafluorophenyl-oxadiazoles of general formula **22** (Fig. 3) can be obtained directly from the reaction of the corresponding amidoximes and pentafluorobenzoyl chloride in refluxing toluene in the presence of pyridine [14].

Similarly, 3-benzoyl- **24** (R=Ph) [15] and 3-carboxyethyl-5-perfluoroalkyl-oxadiazole **24** (R=OEt) are prepared from amidoximes (**23**; R=Ph, OEt respectively) and the corresponding perfluoroalkanoyl chlorides (or anhydrides) (Scheme 6).

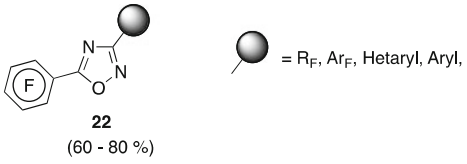
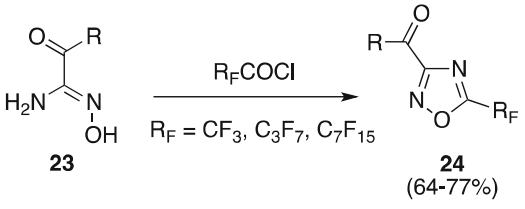
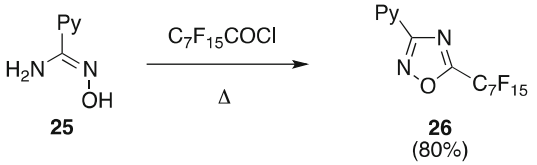


Fig. 3 Examples of synthetically available FOXARs



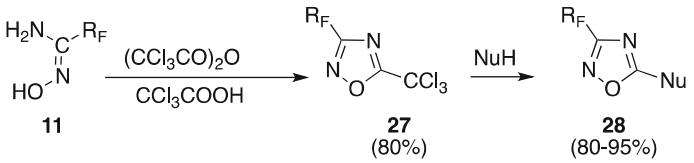
Scheme 6 Synthesis of 5-perfluoroalkyl 1,2,4-oxadiazole **24**

4-(5-Perfluoroheptyl-1,2,4-oxadiazol-3-yl)pyridine or 3-(5-perfluoroheptyl-1,2,4- oxadiazole-3-yl)pyridine **26,** have been obtained directly (in 90 and 70 % yields, respectively) from the acylation reaction of the corresponding nicotyl amidoxime and isonicotyl amidoxime (Scheme 7) [16]. From these derivatives, the corresponding *N*-methyl-pyridinium salts have been prepared for possible applications as *S*elf-*O*rganized *F*unctional *O*rganic *S*alts (SOFOS) [16].



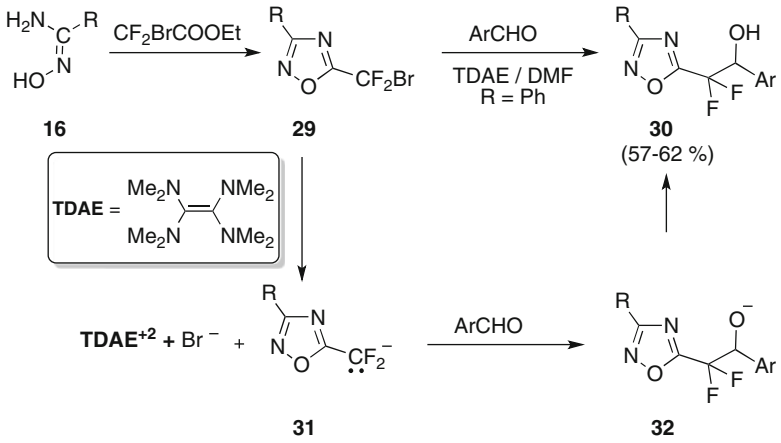
Scheme 7 Synthesis of 3- and 4-(5-perfluoroheptyl-1,2,4-oxadiazol-3-yl)pyridine **26**

The *amidoxime route* has been used for the synthesis of derivatives differently functionalized at C(5). Amidoxime **11** treated with trichloroacetic anhydride in hot trichloroacetic acid, lead to the corresponding 5-trichloromethyl- 1,2,4-oxadiazole **27.** The latter, in the presence of nitrogen nucleophiles (ammonia, primary or secondary amines), undergoes an aminolysis reaction leading to **28** (Scheme 8) [17].



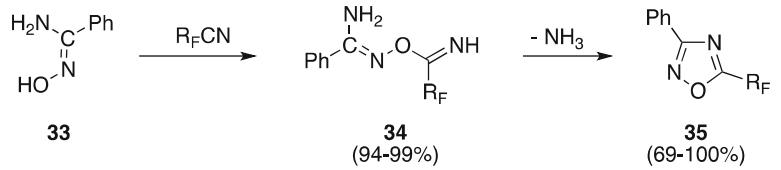
Scheme 8 Synthesis of 5-trichloromethyl- 1,2,4-oxadiazole **27** and its aminolysis leading to **28**

Amidoximes also react with ethyl bromodifluoroacetate to give 5-(bromodifluoromethyl)oxadiazoles **29** [18]. A series of difluoro alcohols such as **30** were obtained by an electron transfer process in the presence of aromatic aldehydes starting from compounds **29** (Scheme 9). The reactions occurs through an initial formation of a red colored charge-transfer complex between TDAE (donor) and bromo derivative **29** (acceptor). A temperature increase from −20 °C to rt allows to complete an electron transfer process producing difluoromethylene anion **31**, which is stable enough to react with aromatic aldehydes, finally leading to the corresponding alcohols **30** [19].



Scheme 9 Synthesis of 5-(bromodifluoro-methyl)oxadiazoles **29** and difluoro alcohols **30**

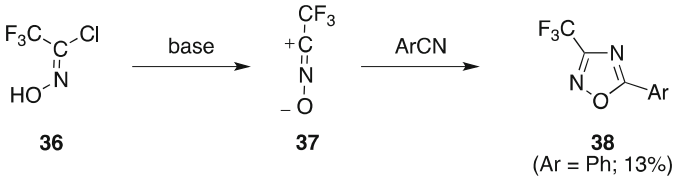
Nitriles themselves can be also used as acylating reagent for amidoximes in some cases. Subsequent heterocyclization involves loss of ammonia in the final step (Scheme 10). For this purpose, the reaction is carried out in the presence of an ammonia acceptor reagent (e. *g.* the perfluorocarboxylic acid, or an excess of the nitrile). For example, from the reaction of benzamidoxime with perfluoroalkylnitriles, a series of 5-perfluoroalkyl-1,2,4-oxadiazoles **35** can be obtained [20].



Scheme 10 Synthesis of 5-perfluoroalkyl-1,2,4-oxadiazoles **35**

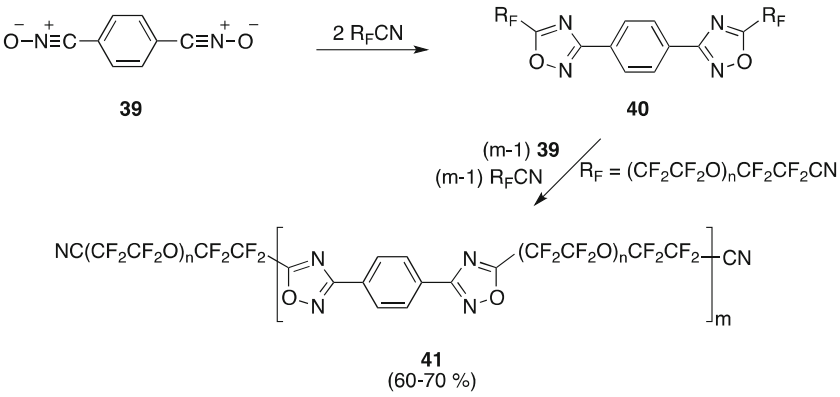
2.2.2 The Cycloaddition Route

Another general approach to the synthesis of fluorinated 1,2,4-oxadiazoles is based on the [3+2] cycloaddition between nitriles and nitrile oxides (each component of the reaction can contain the fluorinated moiety). Cycloaddition of the trifluoroacetonitrile oxide **37** produced the 3-trifluoromethyl-5-phenyl derivative **38** (Ar=Ph) (Scheme 11) [21]. Unfortunately, aliphatic nitriles such as the butyronitrile do not undergo cycloaddition into the oxadiazole derivative [21].



Scheme 11 Synthesis of 3-trifluoromethyl-5-phenyl derivative **38** by the Cycloaddition Route

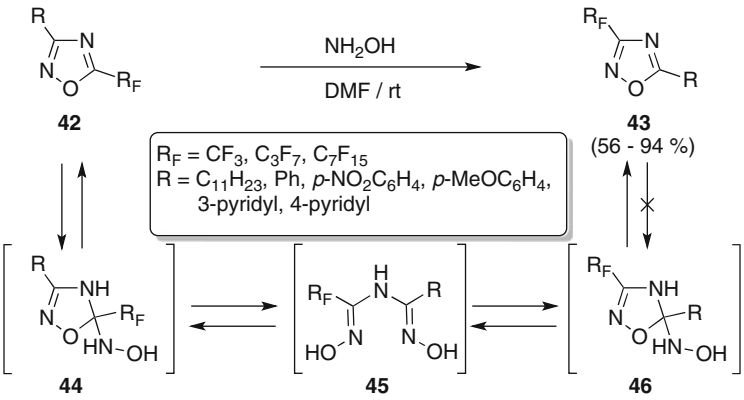
The method involving cycloaddition between nitriles and nitrile oxides has also been employed for the synthesis of complex systems precursors of polymeric materials. For example, terephthaldinitrile oxide **39** was reacted with R_FCN (Scheme 12) to give representative oxadiazole **40**. In the case of R_F=nitrile-terminated polyperfluoroalkylether chain, the presence of several nitrile pendants as curing sites can lead to further functionalized oligomers **41** [22].



Scheme 12 Synthesis of functionalized oligomers **41**

2.2.3 The Ring-Rearrangement Route

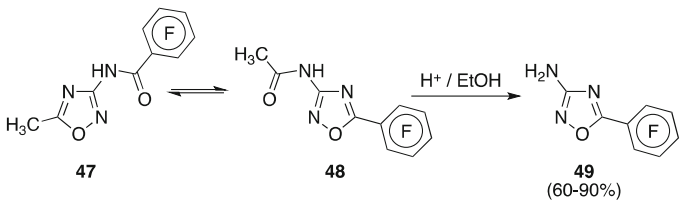
More than a decade from our laboratories demonstrated how heterocyclic rearrangements can be fruitfully implemented for the synthesis of fluorinated heterocycles. ANRORC-like reactions, which consists of the **Addition** of a **Nucleophile** to a electron deficient heterocycle, followed by **Ring-Opening** and **Ring- Closure** steps [23], represent a valuable strategy to transform an easily accessible fluorinated heterocycle into a different one containing the heteroatoms originally belonging to the nucleophilic reagent. The reaction of 5-perfluoroalkyl-1,2,4-oxadiazoles **42** with hydroxylamine in DMF at room temperature gave excellent yields of 3-perfluoroalkyl-1,2,4-oxadiazoles **43,** resulting in a virtual C(5)-C(3) annular switch (Scheme 13) [24].



Scheme 13 ANRORC-like reactions: the C(5)-C(3) annular switch

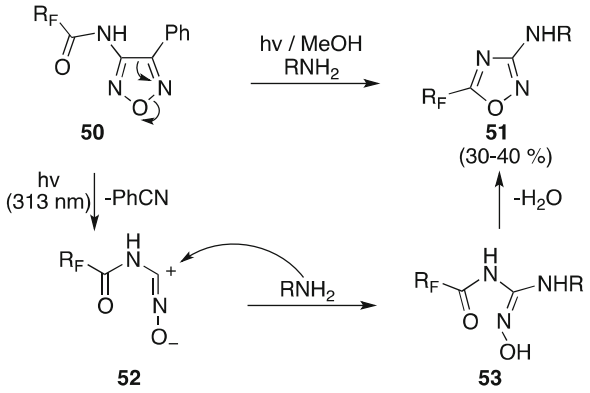
The ring-degenerate ANRORC rearrangement has been successfully applied also for the synthesis of perfluoroalkylated 1,2,4-oxadiazolyl-pyridines **43** (R_F=C_7F_{15}; R=3- or 4-pyridyl), suitable precursors of the corresponding *N*-methylated salts [16].

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, the ring-degenerate thermal equilibration of **47** (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 **47** and **48** in a 80:20 ratio as a result of the electron-withdrawing character of the pentafluorophenyl moiety (Scheme 14) [25]. Interestingly, acidic hydrolysis of this thermally equilibrated mixture gave the expected 3-amino compound **49** in about 60 % yield because 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 [25]. 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.



Scheme 14 The Boulton-Katritzky ring-degenerate thermal equilibration of **47**

Unfortunately, because of the structure-dependent reactivity of 3-acylamino oxadiazoles towards ring- degenerate interconversions, this procedure is not applicable to the synthesis of 5-perfluoroalkyl derivatives [25]. Nevertheless, these compounds can be obtained through photo-induced rearrangements of O-N bond containing azoles [26] involving the photo-fragmentation of 3-perfluoroalkanoylamino furazans **50** at λ = 313 nm in methanol and in the presence of ammonia or primary aliphatic amines giving the corresponding 3-amino- or 3-N-alkylamino-5- perfluoroalkyl-1,2,4-oxadiazoles **51** as a result of the involvement of the added amine in the reaction of photofragmented intermediates (Scheme 15) [27].



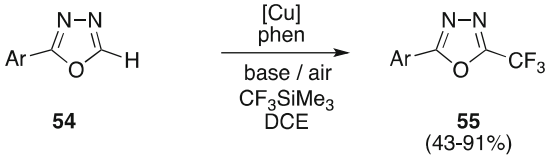
Scheme 15 Synthesis of 3-N-alkylamino-5- perfluoroalkyl-1,2,4-oxadiazoles **51** by photo-fragmentation of 3-perfluoroalkanoylamino furazans **50**

In order to maximize yields, the irradiated solution needs to stand in the dark overnight, to complete the final cyclization step of **53** into **51**. Although yields are not optimal due to the subsequent photoreactivity of compounds **51** at the used irradiation wavelength (see Sect. 2.3.3), this route appears to be the most accessible synthetic method for the synthesis of 3-(alkyl) amino-5-perfluoroalkyl-1,2,4-oxadiazoles.

2.3 1,3,4-Oxadiazoles

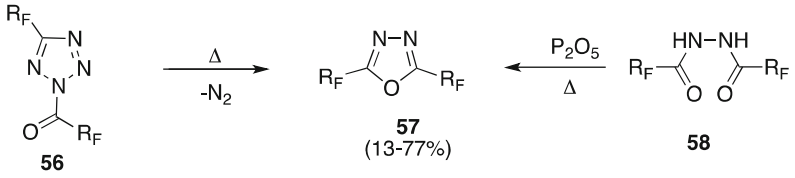
There are several reports in the literature concerning 1,3,4-oxadiazoles bearing a fluorinated group at either or both positions 2 and 5 of the ring. Some trifluoromethyl-1,3,4-oxadiazoles are also commercially available. As for oxadiazoles with a fluorine atom directly bond to the ring, although some patents actually claim such derivatives [28], no description of experimental detail has been reported.

Recently, the direct trifluoromethylation of 1,3,4-oxadiazoles has been achieved by reaction with trifluoromethyltrimethylsilane through direct C-H activation of oxadiazole **54** using copper acetate as catalyst under oxidative conditions (Scheme 16) [29].



Scheme 16 Synthesis of trifluoromethyl-1,3,4-oxadiazole **55** by copper acetate catalysis

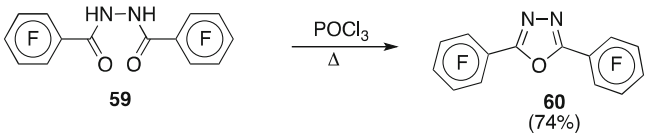
Beside this direct approach, the most widely used methodologies to obtain fluorinated 1,3,4-oxadiazole derivatives are: (i) the cyclodehydration of fluorinated diacylhydrazines **58** (Scheme 17); (ii) the ring-transformation of fluorinated 2-acyltetrazoles **56** (Huisgen reaction) [30] involving the loss of a nitrogen molecule of the acylated tetrazole ring leading to a nitrilimine intermediate which will finally produce 1,3,4-oxadiazoles **57** (Scheme 17). Besides these general methodologies, some syntheses of particular 1,3,4-oxadiazoles through photoinduced ring-rearrangements have been reported as well (see Scheme 26 in Sect. 2.3.3).



Scheme 17 Synthesis of perfluoroalkylated 1,3,4-oxadiazoles **57** by cyclodehydration of fluorinated diacylhydrazines **58** and Huisgen reaction of fluorinated 2-acyltetrazoles **56**

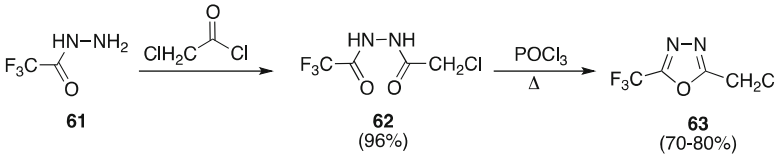
2.3.1 The Diacylhydrazine Route

Historical examples of syntheses by cyclodehydration of bis-perfluoro-acylhydrazines with P_2O_5 were reported by Brown et al. [31] as well as by Chambers and Coffman [32]. By using the same approach, a series of symmetrically and asymmetrically substituted 2,5-bis(polyfluoroaryl)-1,3,4-oxadiazoles **60** can be prepared in excellent yields (Scheme 18) [33].



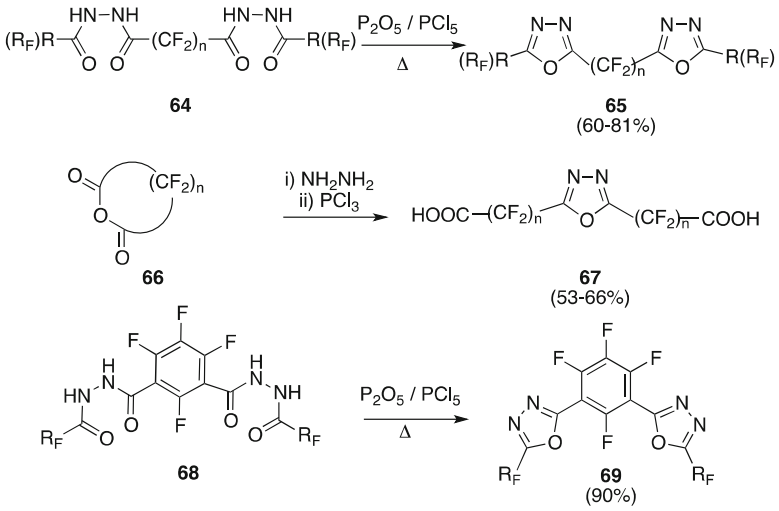
Scheme 18 Synthesis of 2,5-bis(polyfluoroaryl)-1,3,4-oxadiazoles **60** by cyclodehydration of bis-perfluoro-acylhydrazines with P_2O_5

Chloromethyl derivative **63**, a useful precursor for other trifluoromethylated heterocycles [34] can be obtained by reaction of **61** with chloroacetylchloride followed by cyclization of the resulting diacylhydrazide with phosphorus oxychloride **62** (Scheme 19) [35].



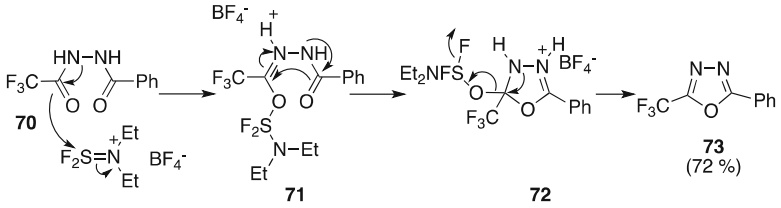
Scheme 19 Synthesis of chloromethyl derivative **63**

An interesting application of the cyclodehydration approach is the synthesis of bis-oxadiazoles **65** by dehydration of bis-diacylhydrazines **64** [36, 37]. Similarly, reaction of perfluoroanhydride **66** leading to **67** is also reported [38]. Bis-oxadiazoles **69**, which have a good thermal stability, are prepared by cyclodehydration of the corresponding tetrafluoroisophthaloyl bis(perfluoroacyl-hydrazines) **68** (Scheme 20) [39].



Scheme 20 Synthesis of bisoxadiazoles **65** and **69** and oxadiazoles **67** by the cyclodehydration approach

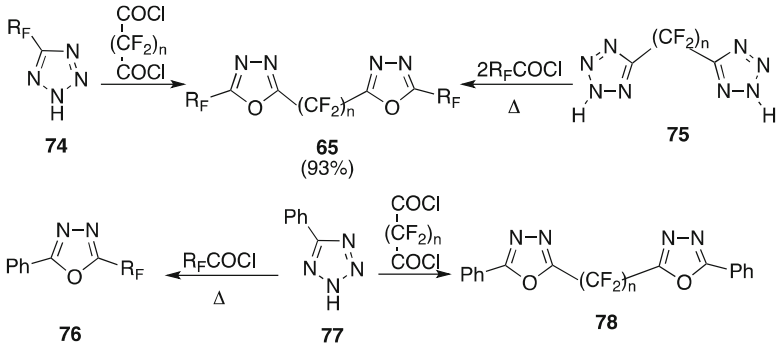
More recently, the synthesis of 1,3,4-oxadiazoles **73**, including fluorinated derivatives, from 1,2-diacylhydrazines was reported by using $[Et_2NSF_2]BF_4$ as a convenient cyclodehydration agent (Scheme 21) [40].



Scheme 21 Synthesis of 1,3,4-oxadiazoles **73** by using $[Et_2NSF_2]BF_4$ as a cyclodehydration agent

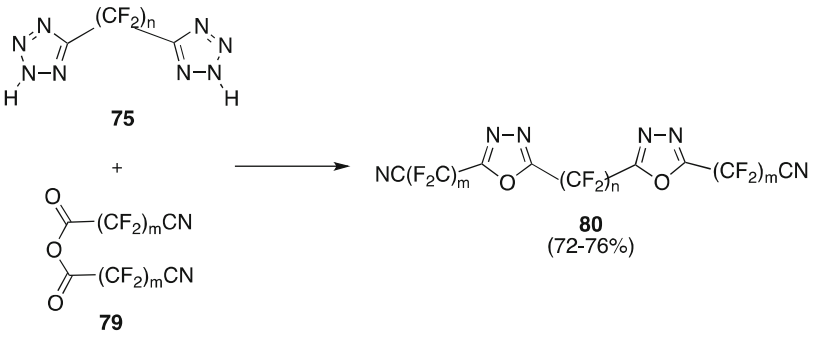
2.3.2 The Acyl-Tetrazole Rearrangement Route

Some of the previously illustrated fluorinated 1,3,4-oxadiazoles, such as **57** (R_F=CF_3, C_3F_7) and **65** (R=C_3F_7; n = 3), can be alternatively obtained by the Huisgen reaction approach [41]. Both 5-perfluoroalkyl-2-phenyl-1,3,4-oxadiazoles **76** and the diheterocyclic compound 1,3-bis(2-phenyl-1,3,4-oxadiazol-5- yl)hexafluoropropane **78** (n = 3) can be obtained by reaction of 5-phenyltetrazole **77** with perfluoroacyl chloride or perfluoroglutaryl chloride respectively (Scheme 22) [10].



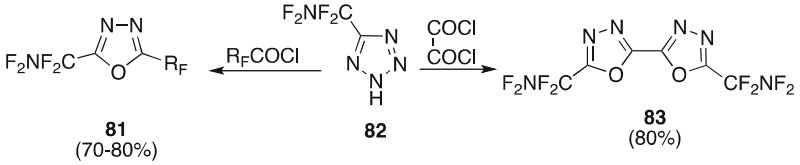
Scheme 22 The Acyl-Tetrazole Rearrangement Route in the synthesis of fluorinated 1,3,4-oxadiazoles **65**, 5-perfluoroalkyl-2-phenyl-1,3,4-oxadiazoles **76** and 1,3-bis(2-phenyl-1,3,4-oxadiazol-5- yl)hexafluoropropane **78**

Bifunctional reagents have been considered for the construction of polymeric structures. The reaction of α,ω-bis(tetrazol-5-yl)perfluoroalkane **75** with ω-cyanoperfluoroanhydrides **79** (at 150 °C) produces bis-oxadiazoles **80** from which further functionalization may be added on the two terminal nitriles (Scheme 23) [42, 43].



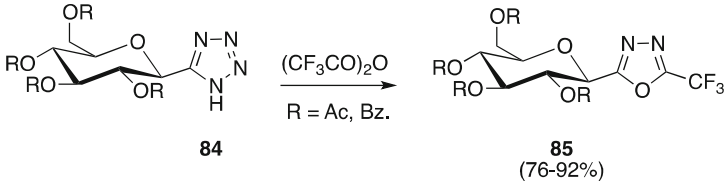
Scheme 23 Bifunctional reagents in the construction of polymeric structures

By the use of the same methodology, the *N,N-difluoroaminodifluoromethyl-tetrazole* **82** reacts with perfluoroacyl chlorides or oxalyl chloride leading to the corresponding oxadiazoles **81** or bis-oxadiazole **83**, respectively (Scheme 24) [13].



Scheme 24 Synthesis of perfluoroalkyl oxadiazoles **81** and bis-oxadiazole **83**

Overall, the *tetrazole transformation* methodology is a quite general approach. Almost any nitrile can be transformed into the corresponding tetrazole precursor which can lead to a perfluoroalkyl-1,3,4-oxadiazole. One example is represented in Scheme 25 for sugar-linked system **85** obtained from the corresponding D-glucose tetrazole derivative (Scheme 25) [44].

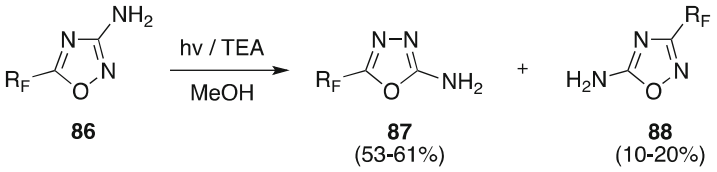


Scheme 25 Sugar-linked system **85** obtained by the *tetrazole transformation* methodology

2.3.3 The Photoinduced Ring-Rearrangement

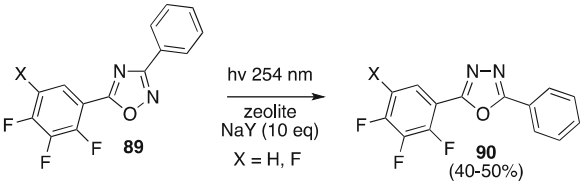
Although simple derivatives such as the 2-amino-5-trifluoromethyl-1,3,4-oxadiazole **87** (R_F=CF_3) can be prepared by reaction of trifluoroacetylhydrazine with BrCN, an interesting alternative is represented by the photorearrangement of the corresponding 1,2,4-oxadiazoles [26, 45].

As far as functional groups are concerned, in solution this approach is restricted to 1,2,4-oxadiazoles bearing a tautomerizable group at C(3) [7]. For instance, 3-amino-5-pefluoroalkyl-1,2,4-oxadiazoles **86** produced the corresponding 2-amino-5- perfluoroalkyl-1,3,4-oxadiazoles **87** (53–61% of yields) upon UV irradiation at 313 nm in methanol and in the presence of triethylamine (TEA). The reaction followed the typical ring contraction-ring expansion route [46]. In the same reaction, amounts of 5-amino-1,2,4-oxadiazole derivatives **88** are formed also through a competing process following the internal cyclization-isomerization route (Scheme 26) [46].



Scheme 26 Competing photoinduced ring-rearrangement: the ring contraction-ring expansion route and the internal cyclization-isomerization route

Very recent unpublished studies from our laboratories showed also the possibility to exploit the intrazeolite photorearrangement of 1,2,4-oxadiazoles [45] for the preparation of fluorinated diaryl-1,3,4-oxadiazole derivatives **90** (Scheme 27).

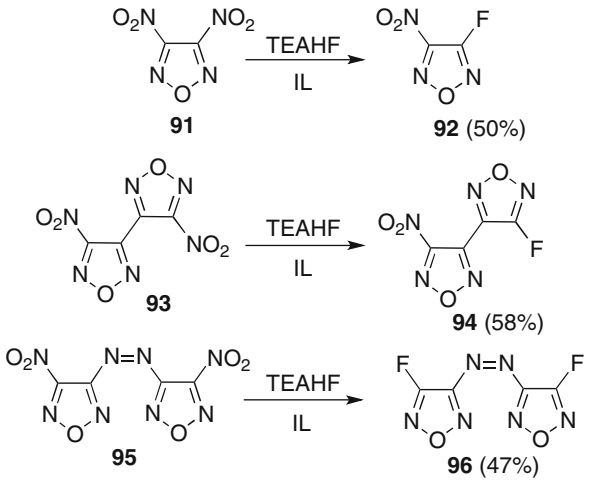


Scheme 27 Intrazeolite photorearrangement of 1,2,4-oxadiazoles

2.4 1,2,5-Oxadiazoles

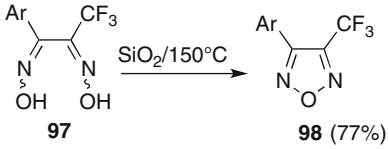
There are not many examples regarding the synthesis of fluorinated 1,2,5-oxadiazole (furazan) systems in the literature. Furazans bearing fluoro atoms were easily obtained by nucleophilic displacement of a nitro group at the furazan ring by using

a fluoride source and a ionic liquid (IL) as a medium [47]. Treatment of dinitro derivatives **91** and **93** with triethylamine hydrofluoride (TEAHF), by using butylmethylimidazolium salts (IL) as solvent, gave monofluorinated furazans **92** and **94** in 50–58 % yields (Scheme 28). Unfortunately, formation of the corresponding difluoro derivatives was observed in traces, with the double substitution of the nitro groups, just obtained in the case of diazo-derivative **96** (47 % yield) from the corresponding dinitro derivative **95**.



Scheme 28 Synthesis of furazans bearing fluoro atoms by nucleophilic displacement in ionic liquids

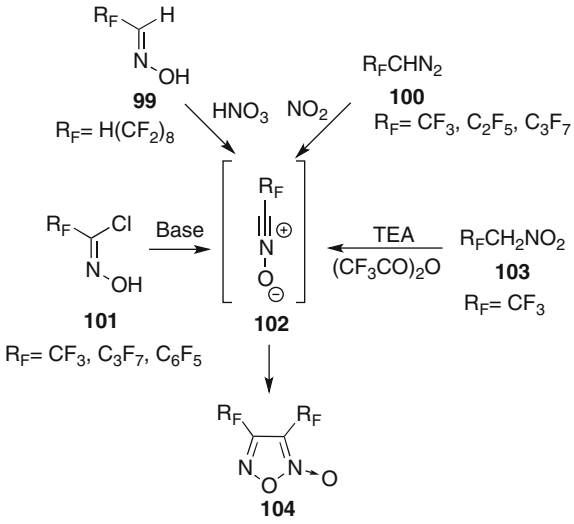
The synthesis of trifluoromethyl furazans **98** was described by Kamitori through the dehydration of dioximes **97** in the presence of silica (Scheme 29) [48]. Since the presence of silica is fundamental for this process, the author suggests that an interaction between the substrate and the silanol groups assists the cyclization reaction. The final products were obtained in higher yields (77 %) in presence of electron-withdrawing *p*-nitrophenyl group which facilitated reaction more effectively than the *p*-tolyl group in favoring the cyclization step.



Scheme 29 Synthesis of trifluoromethyl furazans **98** through the dehydration of dioximes **97** in the presence of silica

Furazan-*N*-oxides (furoxanes) **104** (Scheme 30) are isolated as a result of the nitrile oxide dimerization when chloro-oximes **101** are treated with bases in the absence of dipolarophiles [21, 49, 50]. Oxidation of aldoxime **99** with nitric acid gives furoxan **104** [R_F=H$(CF_2)_8$] in 50 % yield [51]. Similarly, furoxane **104** (R_F=C_6F_5)

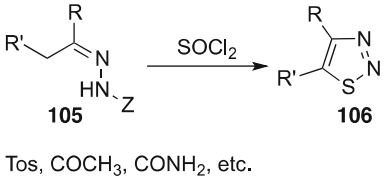
can be also formed from lead tetraacetate oxidation of the pentafluorobenzaldehyde oxime [49]. The involvement of nitrile oxide dimerization has been also suggested in the formation of furoxanes **104** by reaction of perfluoroalkyldiazomethanes **100** (R_F=CF_3, C_2F_5, C_3F_7) with nitrogen dioxide [52], and in the formation of the 3,4-*bis*(trifluoromethyl) derivative **104** (R_F=CF_3) from the dehydration reaction of trifluoromethylnitromethane **103** with trifluoroacetic anhydride (Scheme 30) [53]. More recently, the unstable trifluoroacetonitrile *N*-oxide molecule, CF_3CNO, has been generated in high yield in the gas phase from the corresponding bromo-oxime [54]. Cold trapping of this molecule followed by slow warming forms the stable bis (trifluoromethyl)furoxan **104** (R_F=CF_3), and the mechanism of the dimerization process to the furoxan ring was studied with density functional theory.



Scheme 30 Synthesis of the 3,4-*bis*(trifluoromethyl) furoxan **104**

2.5 1,2,3-Thiadiazoles

The synthesis of fluorinated 1,2,3-thiadiazole was not widely investigated and is essentially related to the general scheme of the Hurd-Mori reaction [55], i.e. the treatment of hydrazone derivatives with thionyl chloride (Scheme 31).



Scheme 31 Hurd-Mori reaction to 1,2,3-thiadiazole

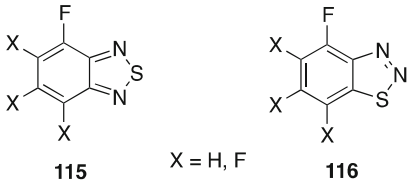
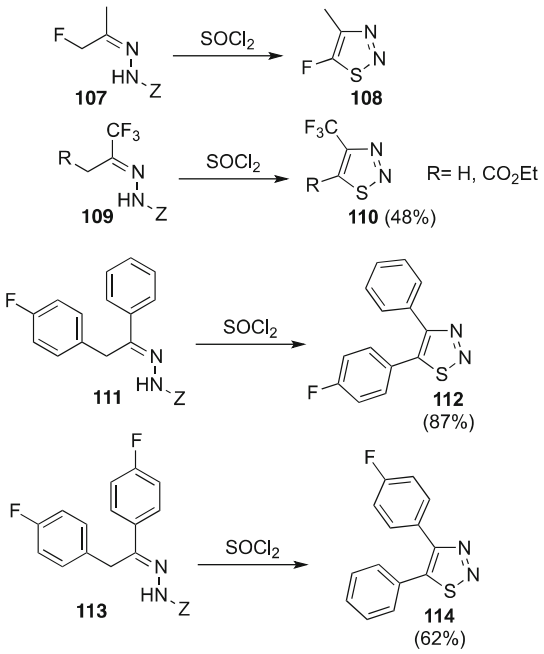


Fig. 4 Structure of fluorinated benzothiadiazoles

By applying this method some representative fluorinated 1,2,3-thiadiazoles were obtained from the corresponding hydrazone derivatives (Scheme 32) [56].

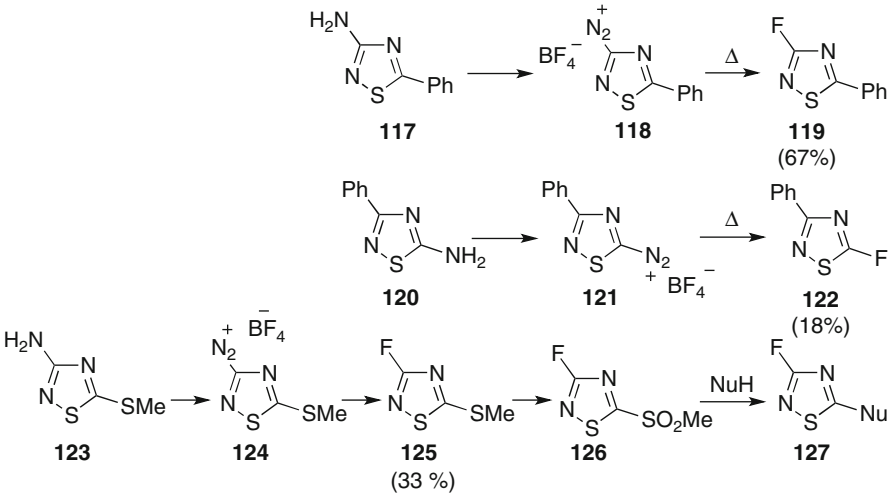


Scheme 32 Synthesis of fluorinated 1,2,3-thiadiazole by the Hurd-Mori reaction

Concerning benzocondensated derivatives, despite the largely cited use of fluorinated 2,1,3-benzothiadiazoles **115** in electronic devices [57], due also to the redox properties and anion stability of 2,1,3-benzothiadiazole systems such as **115** (Fig. 4) [58], the preparation of fluorinated 1,2,3-benzothiadiazoles such as **116** (Fig. 4), used for application as agrochemical, are rarely reported [59].

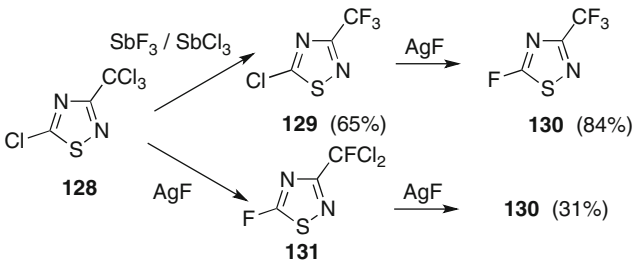
2.6 1,2,4-Thiadiazoles

When aminoderivatives such as **117** or **120** are available, the introduction of a fluorine atom directly bonded to the ring can be achieved by the generally applied decomposition of diazoniumtetrafluoroborates **118** and **121** leading to 3-fluoro-5-phenyl- **119** (67 %) or the regioisomer 5-fluoro-3-phenylthiadiazole **122** (18 %), respectively [60] (Scheme 33). The same methodology has been utilized for the preparation of 3-fluoro-5-methylthiothiadiazole **125** which can be obtained in a 33 % yield [61]. In turn, this 5-methylthio derivative **125** can be oxidized to the 5-sulfonylthiadiazole **126** which is a precursor of a series of compounds of industrial interest (of the general type **127**) obtained through nucleophilic substitution reactions with appropriate reagents (NuH in the Scheme 33).



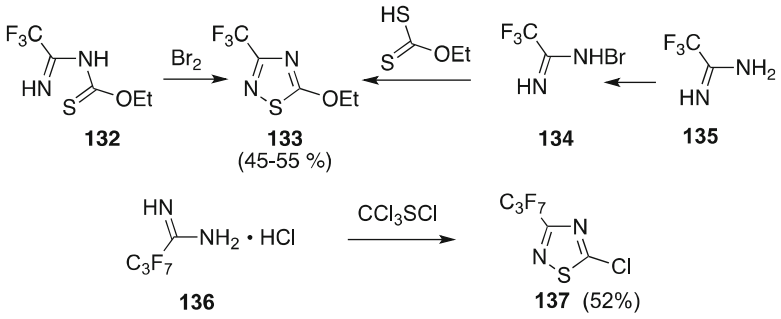
Scheme 33 Introduction of a fluorine atom directly bonded to the 1,2,4-thiadiazole ring

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 **128** can be fluorinated with different reagents (Scheme 34) [62]. By the use of the $SbF_3/SbCl_3$ fluorinating mixture, only the trichloromethyl group is fluorinated to yield the trifluoromethyl derivative **129**. The annular 5-chloro moiety undergoes substitution and partial fluorination of the 3-trichloromethyl moiety is also observed with AgF. Further reactions of derivatives **129** and **131** with AgF lead to perfluorinated compound **130**.



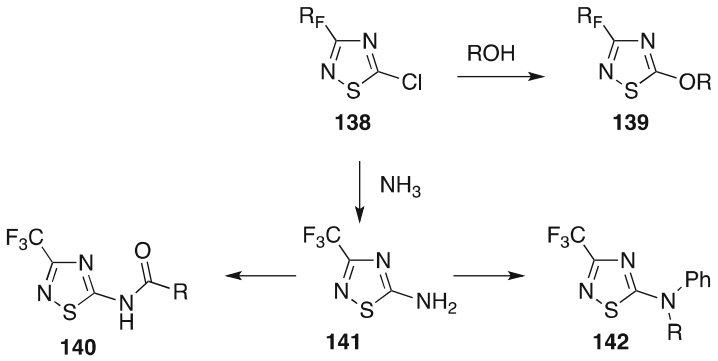
Scheme 34 Introduction of fluorine in 1,2,4-thiadiazole systems through nucleophilic substitution or fluorination of functional groups already bonded to the ring

With regard to the syntheses from fluorinated acyclic precursors, an approach to fluorinated 1,2,4-thiadiazoles utilized the oxidative heterocyclization of fluorinated thioacyl-amidines. For example, trifluoroacetamidine and ethyl chlorothiocarbonate will form the open-chain intermediate **132** which, upon oxidation with bromine, leads to 5-ethoxy-3-trifluoromethyl-1,2,4-thiadiazole **133** (Scheme 35) [63]. A direct heterocyclization into the thiadiazole **137** takes places from the reaction of the fluorinated *N*-bromotrifluoroacetamidine **134**, prepared by selective bromination of the corresponding trifluoroacetamidine **135**, with ethyl xanthate [64]. In addition, the 3-perfluoropropyl-5-chlorothiadiazole **137** is obtained in 52 % yield from the reaction of heptafluorobutyramidine hydrochloride **136** with trichloromethylsulfenyl chloride in the presence of a base (Scheme 35) [62].



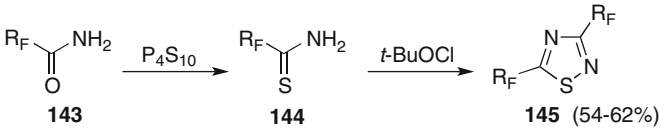
Scheme 35 Synthesis of fluorinated 1,2,4-thiadiazole from fluorinated acyclic precursors

Due to their reactivity towards both O- and N- nucleophiles, 5-chlorothiadiazole derivatives **138** are used as precursors for the synthesis of various compounds such as **139** [65]. Further reactions of 5-amino-3-trifluoromethyl-1,2,4-thiadiazole **141** into target compounds **140** and **142** are also patented (Scheme 36) [66].



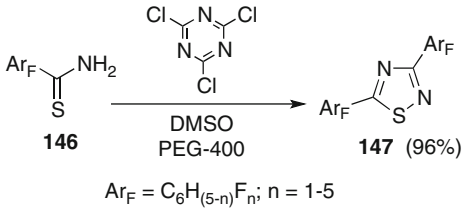
Scheme 36 5-chlorothiadiazole derivatives **138** as precursors for the synthesis of fluorinated 1,2,4-thiadiazoles

Reaction of polyfluoroalkylthioamide **144**, prepared by sulfur insertion on the appropriate polyfluoroalkylcarboxamide, give rise to 1,2,4-thiadiazoles **145** in 54–62% yields (Scheme 37) [67, 68].



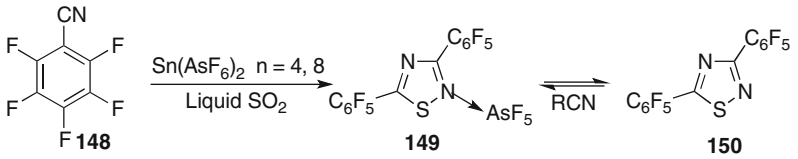
Scheme 37 Synthesis of 3,5-perfluoroalkyl-1,2,4-thiadiazoles **145**

Another convenient strategy for the synthesis of 3,5-diaryl-1,2,4-thiadiazoles is the oxidative dimerization of arylthioamides by using 2,4,6-trichloro-1,3,5-triazine and dimethylsulfoxide in polyethylene glycol 400 (PEG-400) as solvent at ambient temperature. This methodology can be applied to various fluoroarylated systems (Ar_F=mono-, poly-, or perfluorophenyl). The reaction give rise to 4-fluoro substituted derivatives **147** during 8 min in yields of 96 % (Scheme 38) [69]. The same reaction has been recently reported by using 1-butyl-3-methylimidazolium tetrafluoroborate as eco-friendly reaction medium at room temperature [70].



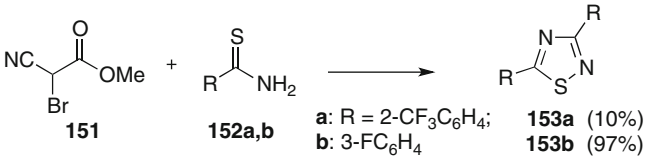
Scheme 38 Synthesis of 3,5-diaryl-1,2,4-thiadiazoles **147** by oxidative dimerization of arylthioamides

Concerning perfluoroaryl-1,2,4-thiadiazoles synthesis, C_6F_5CN reacts with $Sn(AsF_6)_2$ (n=4,8) in liquid SO_2 to give 3,5-bis(perfluorophenyl)-1,2,4-thiadiazole **150** in mixture with its precursor **149** (Scheme 39) [71].



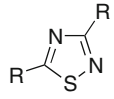
Scheme 39 Synthesis of 3,5-diaryl-1,2,4-thiadiazoles **150** by oxidative dimerization of arylnitriles

A new and efficient method for the synthesis of the 3,5-diaryl-1,2,4-thiadiazole system including fluorophenyl and trifluoromethylphenyl derivatives was investigated. The appropriate aryl thioamide **152a, b**, undergo a very rapid condensation in the presence of methyl bromocyanoacetate **151** in methanol to provide the corresponding fluorinated 3,5-diaryl-1,2,4-thiadiazoles **153a, b** with yields from low to quantitative (Scheme 40) [72].



Scheme 40 Synthesis of fluorinated 3,5-diaryl-1,2,4-thiadiazoles **153a, b** by condensation of the aryl thioamide

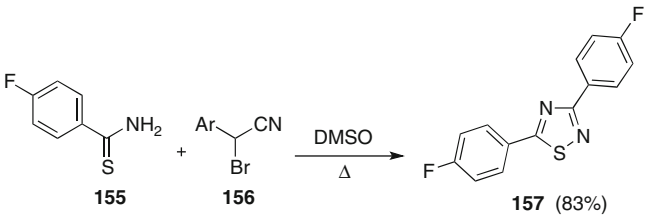
A similar approach has been exploited by Cushman and coworkers to obtain a series of thiadiazole **154**, for pharmaceutical applications as analogues of resveratrol, in quantitative yields (Fig. 5) [73].



154
(95-100%)
R = 2-FC_6H_4, 3-FC_6H_4, 4-F-C_6H_4, 2-$CF_3C_6H_4$, 4-$CF_3C_6H_4$.

Fig. 5 Fluorinated thiadiazoles used as pharmaceutical analogues of resveratrol

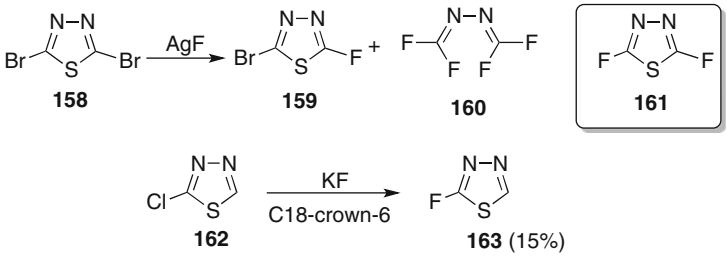
Alternatively, a simple and fast route reported for the preparation of 3,5-bis(fluoroaryl)-1,2,4-thiadiazoles **157**, consists in the reaction of benzothioamides **155** and 2-bromo-2-phenylacetamide derivatives **156** at 60 °C in DMSO (Scheme 41) [74].



Scheme 41 Synthesis of 3,5-bis(fluoroaryl)-1,2,4-thiadiazoles **157**

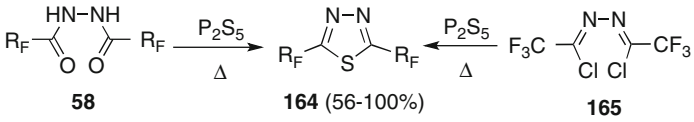
2.7 1,3,4-Thiadiazoles

In the case of 1,3,4-thiadiazoles, a fluorine atom can be directly introduced on the ring through nucleophilic substitution of other halogens. An example of this approach is represented by the reaction of the 2,5-dibromo derivative **158** with AgF, leading to the monofluorinated compound **159** (although in low yield; 16 %) and the perfluorinated open-chain compound **160**. The latter probably originated from the ring-cleavage of the unisolated **161** (Scheme 42) [62], although any attempts to obtain the difluoro derivative **161** through the diazotization of the 2,5-diaminothiadiazole were unsuccessful. A relatively 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 **162** with KF (in the presence of 18-crown-6 ether at 150 °C) leading to the 2-fluoro derivative **163** (15 %) is claimed [75].



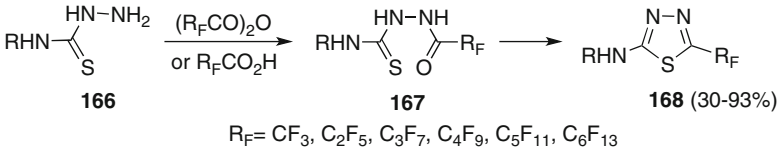
Scheme 42 Introduction of a fluorine atom on the 1,3,4-thiadiazole ring through nucleophilic substitution

In analogy to what was observed in the case of 1,3,4-oxadiazoles, the sulfuration of *N,N′*-diacylhydrazines **58** with P_2S_5 represent a general methodology for the synthesis of 2,5-*bis*(perfluoroalkyl)-1,3,4-thiadiazoles **164** which, in the reported examples, are obtained in 56–75 % yields depending on the nature of R_F (Scheme 43) [32]. Quantitative yields were observed in the synthesis of 2,5-*bis*(trifluoromethyl)-1,3,4-thiadiazoles **164** (R_F=CF_3) by the reaction of dichloroazine **165** with P_2S_5 (Scheme 43) [76]. More recently, Lawesson's reagent has been also employed for the obtainment of 2-phenyl-5-trifluoromethyl-1,3,4-thiadiazole in moderate yield (54 %) [77].



Scheme 43 Synthesis of 2,5-*bis*(perfluoroalkyl)-1,3,4-thiadiazoles **164** by sulfuration with P_2S_5

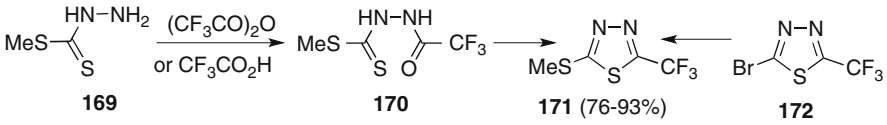
Particular importance has been payed to fluorinated thiadiazoles which contain functionalities such as amino or methylthio groups due to their industrial production. The synthesis of aminothiadiazoles **168** is based on the heterocyclization of acylthiosemicarbazides **167** with yields depending on experimental conditions (Scheme 44). In some cases the heterocyclization into the thiadiazole derivative occurs directly during the acylation reaction. In this manner, the reaction of thiosemicarbazide with trifluoroacetic anhydride lead to the formation of 2-amino-5-trifluoromethylthiadiazole **168** (R_F=CF_3, R=H) in a 30 % yield [78]. However, reaction carried out in the presence of $POCl_3$ permitted to obtain the yield increased to 93% [79]. Reactions between thiosemicarbazides **166** and trifluoroacetic acid or anhydride in the presence of PPA were also used for the synthesis of 2-amino and 2-methylamino derivatives **168** (R_F=CF_3) [80].



Scheme 44 Synthesis of aminothiadiazoles **168** by heterocyclization of acylthiosemicarbazides **167**

Several patents report the synthesis (or in some cases just a purification methodology) of 2-methylthio-5-trifluoromethyl-1,3,4-thiadiazole **171** which can be prepared through the reaction of **169** with trifluoroacetic acid or anhydride

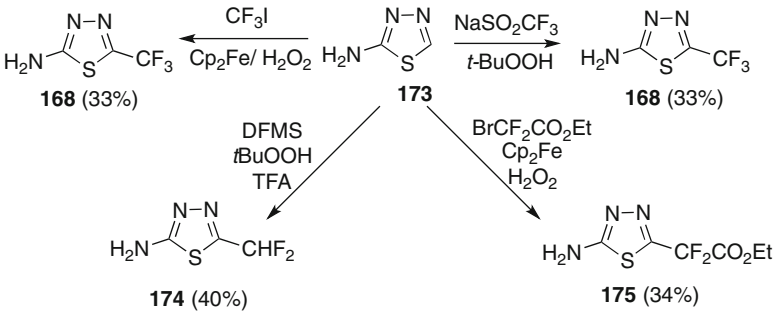
(Scheme 45) [81]. The same compound **171** can also be obtained from the 2-bromo derivative **172** [82].



169 **170** **171** (76-93%) **172**

Scheme 45 Synthesis of 2-methylthio-5-trifluoromethyl-1,3,4-thiadiazole **171**

Very recently, direct trifluoromethylation of the pre-formed 1,3,4-thiadiazole ring has been reported. In all the cases the trifluoromethyl radical is involved as electrophilic species attacking the ring. Generation of the reactive radical could be achieved from CF_3I in the presence of ferrocene (Cp_2Fe) and hydrogen peroxide [83] or by using CF_3SO_2Na (Langlois reagent) in the presence of *t*-BuOOH [84]. This quite interesting reactivity was just evidenced for the obtainment of 2-amino-5-tryfluoromethyl-1,3,4-thiadiazole **168** from the corresponding 2-amino derivative **173** and unfortunately in low yields. Similarly, radical fluoroalkylation of amine **173** was also achieved by using the new difluoromethylating agent $Zn(SO_2CF_2H)_2$ (DFMS) [85] or $BrCF_2CO_2Et$ [86] as CF_2R radical sources (Scheme 46).



168 (33%) **173** **168** (33%)

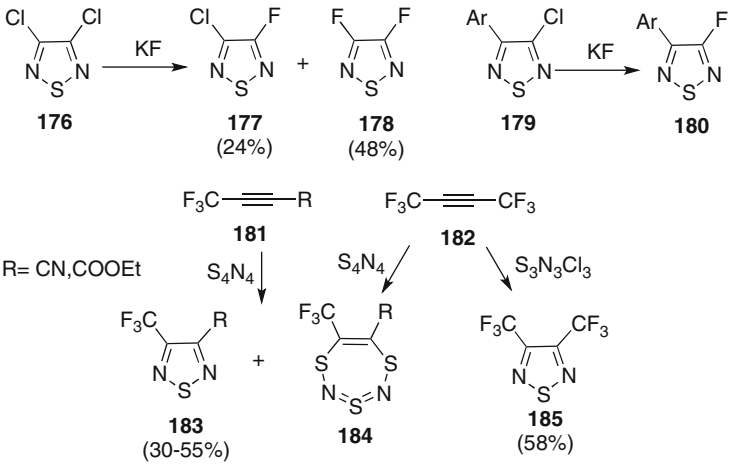
174 (40%) **175** (34%)

Scheme 46 Synthesis of fluorinated 1,3,4-thiadiazoles by radical fluoroalkylation of amine **173**

2.8 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, reaction of the commercially available 4,5-dichloro-thiadiazole **176** with KF in sulfolane at 180ºC allow to obtain both the monofluoro compound **177** (24%) and difluorothiadiazole **178** (48%) (Scheme 47) [87].

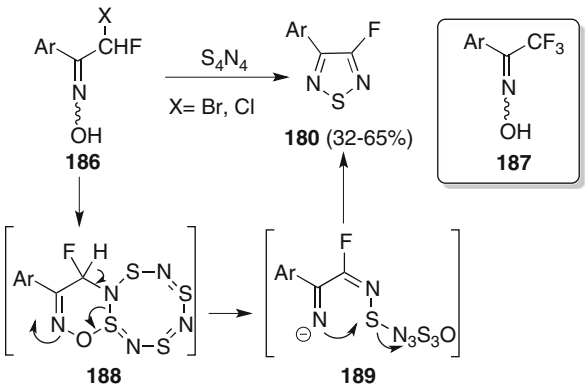
Similarly, 3-aryl-4-fluoro-1,2,5-thiadiazoles **180** have been prepared by treating the corresponding 4-chloro derivatives **179** with KF at high temperatures (Scheme 47) [88]. A synthesis of fluorinated 1,2,5-thiadiazoles from acyclic precursors utilizes the reaction of particular fluorinated substrates with tetrasulfur tetranitride (S_4N_4) in a (3 + 2) synthetic pattern. For instance, trifluorobutynonitrile **181** (R=CN) and ethyl 4,4,4-trifluoro-2-butynoate **181** (R=COOEt) treated with S_4N_4 in dichloromethane at 150ºC produced trifluoromethyl substituted thiadiazoles **183** (30–55 %) (Scheme 47)[89]. Interestingly, the reaction was accompanied by the formation of trithiadiazepine **184**. In the case of the reaction with hexafluorobutyne **182**, only the corresponding trithiadiazepine derivative **184** (R=CF_3) was isolated, although the authors assumed that the *bis*(trifluoromethyl)thiadiazole **185** was formed also and lost during the reaction work-up because of its volatility. The formation of **185** was claimed in 58 % yield from the reaction of hexafluorobutyne **182** with the more electrophilic trithiazyl trichloride ($S_3N_3Cl_3$) reagent.[90] In this case, the addition of two NSCl moieties to the triple bond and the loss of SCl_2 during the hetero-cyclization is suggested. The same *bis*(trifluoromethyl) derivative **185** had been suggested to be involved in the reaction of **182** with thiazyl fluoride (NSF) [91]. Bis(trifluoromethyl)thiadiazole **185** was also obtained from the photochemical decomposition of bis(trifluoromethyl)-1,3,2-dithiazol-2-yl radical [92].



Scheme 47 Synthesis of fluorinated 1,2,5-thiadiazole by direct introduction of fluorine on the ring through nucleophilic substitution or starting from fluorinated acyclic precursors

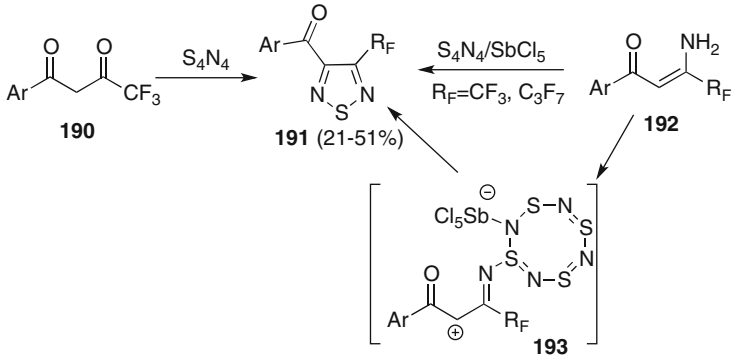
Cyclization with tetrasulfur tetranitride has been employed with the 1-aryl-2,2-dihaloethanone oximes **186**. From the reaction carried out in refluxing dioxane, 3-aryl-4-fluorothiadiazoles **180** have been obtained in fair yields (32–65%) and

the mechanistic aspects which involve the species **188** have been discussed (Scheme 48) [93]. It has to be noted that the same reaction performed on 1-aryl-2,2,2-trifluoroethanone oximes **187** does not result in cyclization to thiadiazole [94].



Scheme 48 Mechanistic aspects of the synthesis of fluorinated 1,2,5-thiadiazole by cyclization with tetrasulfur tetranitride

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 [95]. Similarly, in the case of fluorinated substrates, 3-aroyl-4-trifluoromethylthiadiazoles **191** have been obtained in 40–50 % yields from the reaction of aroyltrifluoroacetylmethanes **190** with S_4N_4 in refluxing toluene [96]. Enaminones **192** have also been utilized as suitable substrates for the cyclization into 1,2,5-thiadiazoles **191** (21–51 %) [97]. The reaction has been realized using $S_4N_4/SbCl_5$ complex in toluene at 100 °C and **193** as a key intermediate has been suggested (Scheme 49).

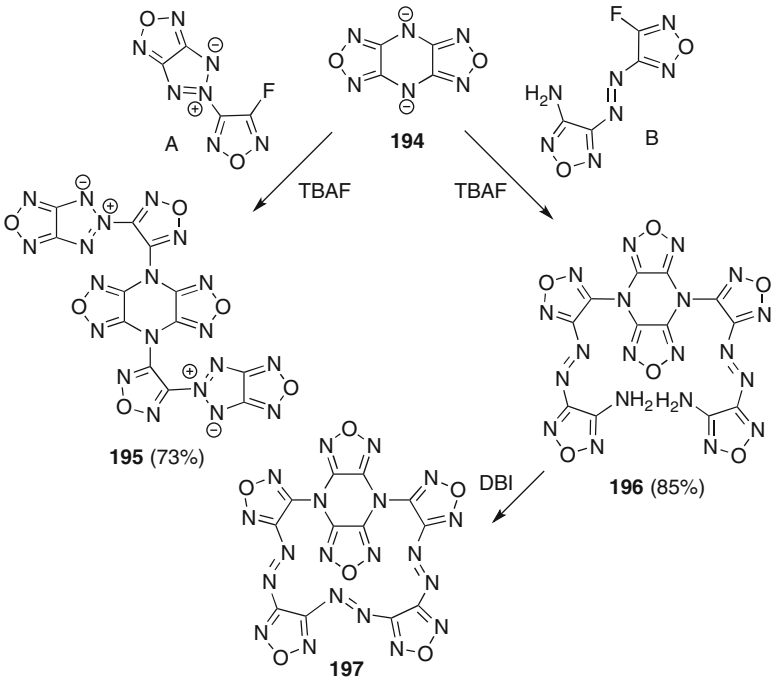


Scheme 49 Synthesis of 3-aroyl-4-trifluoromethylthiadiazoles **191**

3 Fluorine-Induced Reactivity of Fluorinated Oxadiazoles and Thiadiazoles

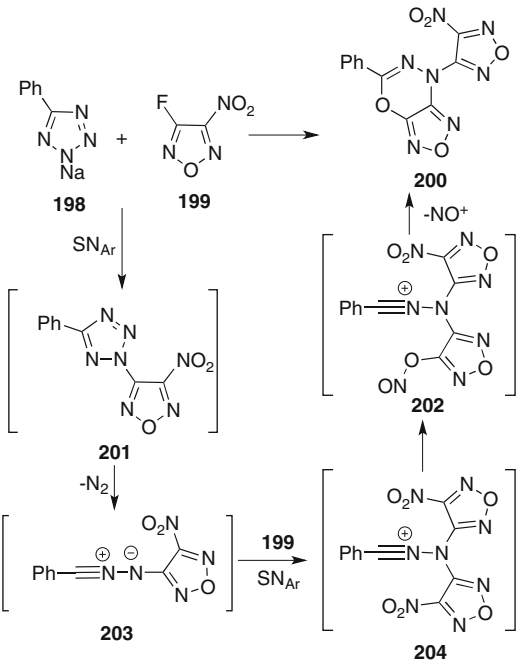
3.1 Ring-Fluorinated Derivatives

Few examples are reported in the literature regarding the reactivity of fluorinated 1,2,5-oxadiazoles. As for many azoles, the nucleophilic substitution of a fluorine atom is relatively easy and provided high yields. Fluorofurazans **A** react with bisfurazanopyrazine dianion **194** yielding a disubstituted compound **195** (73 %) containing two tris (furazanyl)-amino moieties [98]. The same reaction performed on fluoroderivative **B** gave compound **196** (85 %), the precursor of macrocycle **197** synthesised by oxidative cyclization with dibromoisocyanurate (DBI) (Scheme 50).



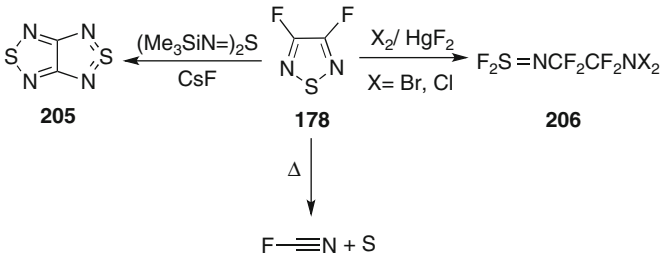
Scheme 50 Reactivity of fluorinated 1,2,5-oxadiazoles: the nucleophilic substitution of a fluorine atom

Displacement of fluoride from furazan **199** is the initial step of a new ring cleavage/ring closure reactions of tetrazole which provides a route to the new furazano[3,4-e]-1-oxa-3,4-diazine system **200** [99]. Interestingly, the nucleophilic substitution on a second molecule of fluorinated furazan **199** is one of the key steps of the suggested mechanism outlined in Scheme 51.



Scheme 51 Suggested mechanism for a route to furazano[3,4-e]-1-oxa-3,4-diazine system **200**

Concerning the reactivity of fluorinated 1,2,5-thiadiazoles, the only reported examples are related to the 3,4-difluoro-1,2,5-thiadiazole **178**. This compound show nucleophilic displacement by fluoride ion-induced condensation with $(Me_3SiN=)_2S$, giving [1, 2, 5]thiadiazolo[3,4-c][1, 2, 5]thiadiazole **205** in 62 % yield [100]. Electrochemical generation of **205** radical anion might be of interest to materials science as a building block for molecular ion-based conductors and/or magnets. Ring-opening reactions of **178** were performed with molecular chlorine and/or bromine in the presence of HgF_2 giving open-chain compounds $F_2S{=}NCF_2CF_2NX_2$ **206** (X=Cl, Br) (Scheme 52) [101].

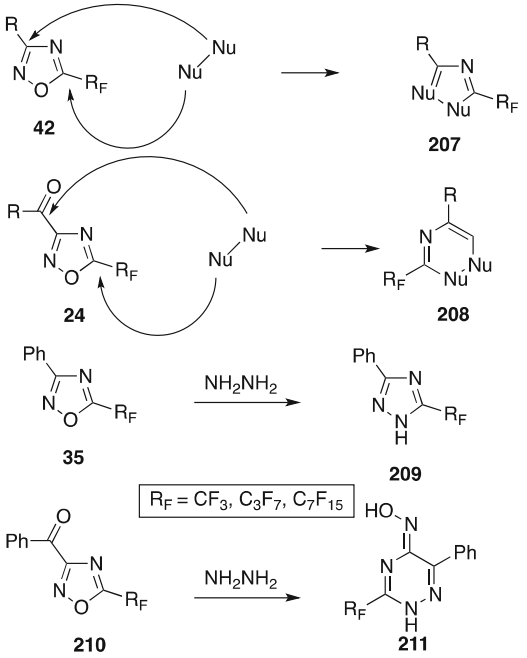


Scheme 52 Ring-opening reactions of **178**

The gas-phase generation and spectroscopic identification of nitrile sulfides by thermolysis of 1,2,5-thiadiazole precursors was attempted, but in all cases the thiadiazoles were found to produce sulfur and the corresponding nitrile [102]. Interestingly, compound **178** was indicated as the most stable derivative, giving not decomposition up to 900 °C.

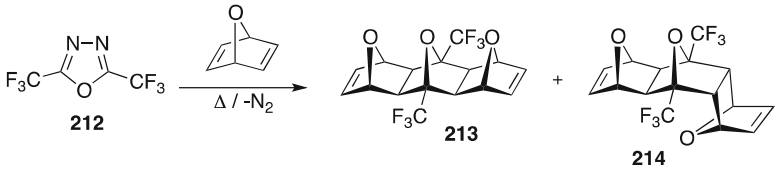
3.2 Ring-Fluoroalkylated Derivatives

The C(5) position is the most electrophilic site of the heterocycle in perfluoroalkyl-1,2,4-oxadiazoles due to the electron- withdrawing effect of both O(1) and N(4) [7]. In the presence of a perfluoroalkyl group linked at the C(5) of the oxadiazole the first step of the addition of a nucleophile–ring opening–ring closure (ANRORC) reaction of 5-perfluoroalkyl-1,2,4-oxadiazoles is strongly favoured (Scheme 53). Depending on the nature of the 3-substituent, the cyclization step of the open-chain intermediate can involve either the C(3) or an electrophilic site of the original C(3)-linked side-chain, leading to other five- **207** or six-membered ring **208** heterocycles, respectively [15, 16, 24, 103, 104]. Besides ring-degenerate rearrangement leading to regioisomeric 1,2,4-oxadiazoles (Scheme 13 in Sect. 2.2.3), this ANRORC reactivity has been exploited for the synthesis of fluorinated triazoles **209** and triazines **211** (Scheme 53) [103].



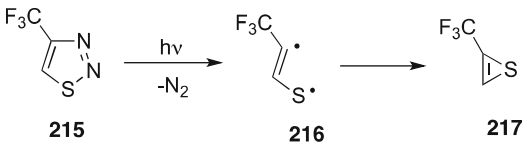
Scheme 53 The ANRORC reactivity in the synthesis of fluorinated triazoles **209** and triazines **211**

The reaction of the 2,5-bis-trifluoromethyl-1,3,4-oxadiazole **212** with oxanorbornene derivatives has been recently re-evaluated for its stereoselectivity aspects, through a combination of experimental and computational studies [105]. In particular, the theoretical model was able to explain the origin of stereoselectivity towards the bent product **214** caused by repulsive lone pair interactions between oxygen bridges in the transition state of the 1,3-dipolar addition (Scheme 54).



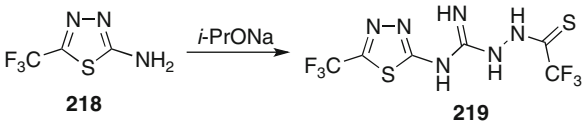
Scheme 54 Stereoselectivity towards the bent product **214** in the reaction of the 2,5-bis-trifluoromethyl-1,3,4-oxadiazole **212** with oxanorbornene derivatives

An interesting photochemical ring contraction has been reported for trifluoromethylated 1,2,3-thiadiazoles. Thiirene **217** was obtained by the argon matrix photolysis at 265 nm of 1,2,3-thiadiazoles **215** at 8 K. Interestingly, trifluoromethyl group exert a stabilizing effect on the highly unstable 4π-electron ring system (Scheme 55) [56b].



Scheme 55 Thiirene **217** by photochemical ring contraction of trifluoromethylated 1,2,3-thiadiazoles

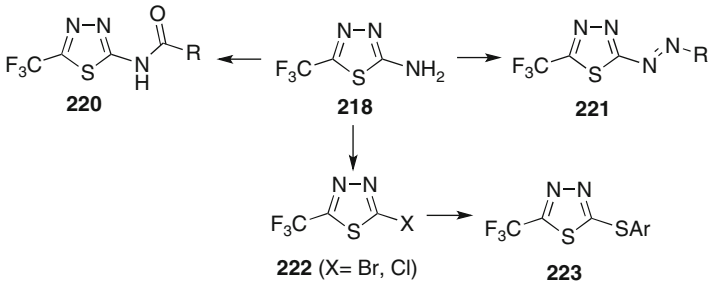
Regarding the reactivity of fluorinated 1,3,4-thiadiazoles, rare examples of peculiar reaction due to the presence of fluorinated moieties are reported in the literature, and all involve the thiadiazole ring-opening. Beside the above discussed obtainment of perfluorinated open-chain compound **160**[62] the only example is related to the treatment 2-amino-5-trifluoromethyl-1,3,4-thiadiazole **218** with an alcoholate, causing dimerization with opening of a thiadiazole ring and formation of **219** in 34 % yield (Scheme 56) [106].



Scheme 56 Reactivity of fluorinated 1,3,4-thiadiazoles: dimerization with opening of a thiadiazole ring and formation of **219**

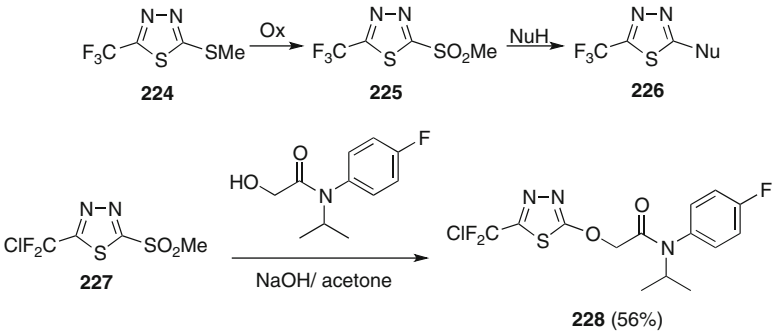
On the other hand, reactivity of other functionalities linked to the thiadiazole ring is not affected by the presence of fluorinated moieties, therefore fluorinated 1,3,4-thiadiazoles behave as unfluorinated congeners. Also in this case, particular attention to fluorinated thiadiazoles which contain amino or methylthio groups has been given, due to their the industrial importance.

It is worth noting that 2-amino-5-trifluoromethylthiadiazole **218** 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 **220**. Several patents on the synthesis of pharmaceuticals and agrochemicals take advantage of this of type of reaction [107]. In some cases, the amino group is involved in a diazotation reaction followed by a coupling reaction (leading to **221**) [108] or a nucleophilic substitution [109]. For example, 2-halo derivatives **222** can be prepared *via* diazonium salts from 2-amino-5-trifluoromethylthiadiazole **218** (Scheme 57) [109]. Also 2-arylthio derivatives **223** are obtained through a nucleophilic substitution reaction [110].



Scheme 57 Reactivity of fluorinated thiadiazoles which contain amino groups

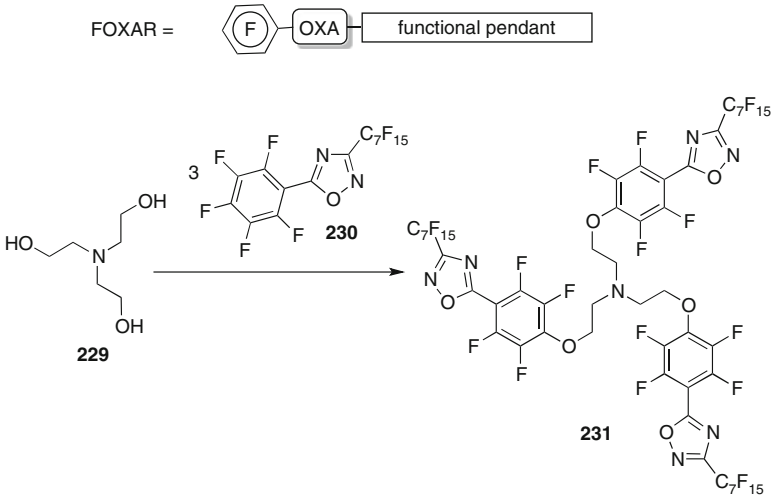
The methylthiothiadiazole **224** can be oxidized easily to the corresponding sulfonyl derivative **225** (Scheme 58). Some patents have also focused on the optimization of this oxidation which usually is carried out with hydrogen peroxide in acetic acid and in the presence of different catalytic species (boric acid, metal salts, etc.) [111]. The importance of this oxidation is related to the possibility to obtain the sulfonyl derivative system, due the ability of such a group to undergo nucleophilic substitution with several nucleophiles (NuH in the Scheme 58). In this way, it is possible to introduce the trifluoromethylthiadiazole moiety into target compounds for potential industrial applications [112]. Similar reactions are reported for the chlorodifluoromethyl derivative **227**, which is used as a precursor for the preparation of herbicides such as **228** [113]. The latter showed very strong preemergent and strong postemergent herbicidal activity.



Scheme 58 Reactivity of fluorinated methylthiothiadiazoles

3.3 Ring-Fluoroarylated Derivatives

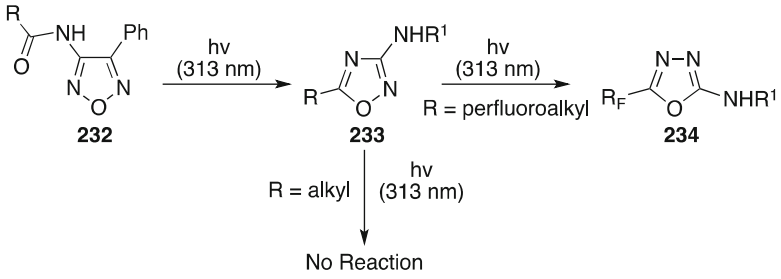
As mentioned above, the 1,2,4-oxadiazole is one of the most electron-withdrawing azole having a very activated C(5) position. In turn, when the electronic demand can be distributed over conjugated aromatic rings, the 1,2,4-oxadiazoles can activate the nucleophilic aromatic substitution. Indeed, 5-fluoroaryl-1,2,4-oxadiazoles are ideal examples for this concept. 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. Such a reactivity has great potential for the development of other synthetic applications and for the functionalization of macromolecules with nucleophilic pendants (Scheme 59) [5, 7]. In fact, a series of variously substituted 5-pentafluorophenyl-1,2,4-oxadiazoles have been used for the arylation of polymers, calixarenes, and tripodal ligands such as highly fluorinated system **231** [5b].



Scheme 59 Fluoroaryl 1,2,4-oxadiazoles in the functionalization of macromolecules with nucleophilic pendants

3.4 Systems Containing Fluorine Far from the Heterocyclic Core

Due to the presence of labile O-N bonds, the furazan system possess also an interesting photochemical reactivity. As discussed previously (Scheme 15 in Sect. 2.2.3 and Scheme 26 in Sect. 2.3.3), 3-perfluoroacylamino-1,2,5-oxadiazoles **50** are useful precursor for the obtainment of fluorinated 3-amino-1,2,4-oxadiazoles [27]. However, differently from non-fluorinated analogues **233** (R=alkyl) which are stable at the irradiation wavelength, perfluoroalkylated 1,2,4-oxadiazoles can undergo a subsequent photorearrangement into the corresponding 1,3,4-oxadiazole system [46]. Due to this peculiar reactivity of fluorinated derivatives, synthesis of fluorinated heterocycles involving photochemical steps must be carefully monitored in order to avoid unwanted reactivity not evidenced in unfluorinated substrates (Scheme 60).



Scheme 60 Photorearrangements in the perfluoroalkylated oxadiazole series

4 Biological Activity of Fluorinated Oxadiazoles and Thiadiazoles

A series of 5-trifluoromethyl-1,2,4-oxadiazoles are patented as potential pesticides [114] and tested for biological activity [115]. More recently, trifluoromethyl-1,2,4-oxadiazole derivatives such as **235** have been evaluated as cannabinoid antagonists [116] Besides these recent reports, one of the major debated bioactivity concerning fluorinated azoles is the efficiency of PTC124, also known with the name of *Ataluren* **236**, which was claimed to promote the readthrough of nonsense premature stop codons (Fig. 6) [117, 118].

Fluorinated 1,2,5-oxadiazoles have also been considered as important fragments in the field of medicinal chemistry, but only very recently compounds with considerable activity have been discovered. Some fluoroaryl substituted furoxans derivatives (Fig. 7), developed in the frame of SAR studies on *Furoxan*, were reported as inhibitors of thioredoxin glutathione reductase (TGR), with nitric oxide (NO) donor ability, acting as efficacious antischistosomal agents [119]. In particular, compounds **238** and **239** displayed an inhibition activity comparable to that of lead compound,

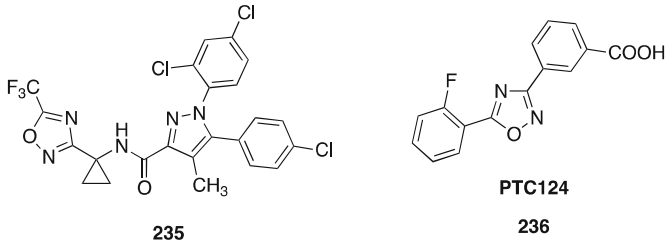


Fig. 6 Examples of fluorinated biologically active 1,2,4-oxadiazoles

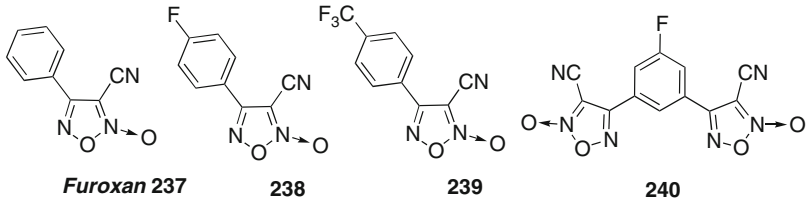
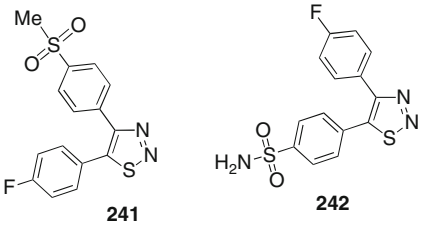


Fig. 7 Examples of fluorinated biologically active 1,2,5-oxadiazoles

Fig. 8 Examples of fluorophenyl thiadiazoles as potential COX-2 inhibitors



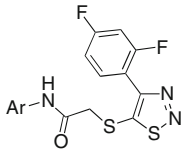
while fluorinated bis-furoxan **240** is a better TGR inhibitor than *Furoxan* **237** (IC_{50} = 0.48 μM vs 6.3 μM) with improved NO donation and ADME (solubility, Caco-2 permeability) properties.

Fluorinated 4,5-diaryl thiadiazoles **241** and **242** were evaluated as cyclooxygenase-2 (COX-2) inhibitors (Fig. 8). They showed good cell viability but poor inhibitor activity [120].

Difluorophenyl derivatives **243** were synthesized and tested in the frame of a SAR study on 1,2,3-Thiadiazole thioacetanilides as HIV non-nucleoside reverse transcriptase inhibitors. They showed the ability to protect MT-4 cells from viral cytopathogenicity in the low-micromolar range, but resulted less active than the chlorinated analogues to be further considered (Fig. 9) [121].

During the discovery of a series of pyrrolidine-2,4-dicarboxylic acid amides, which have 1-(sulfur-containing hetero-aryl)piperazin-4-yl carbonyl as a substituent of the L-prolyl moiety, and are novel and stable DPP-IV inhibitors, the 1,2,4-thiadiazole **244** (Fig. 10) was found to be acceptable in the desired enzyme pocket, but its

Fig. 9 Example of an anti-HIV fluoroarylated thiadiazole



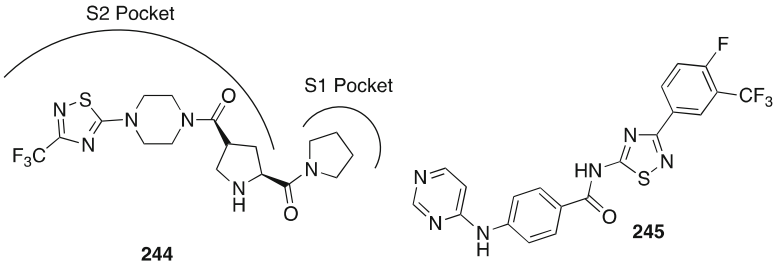


Fig. 10 Examples of fluorinated biologically active 1,2,4-thiadiazoles

inhibitory activity in plasma decreased along with an increase of lipophilicity [122]. In a series of pyrimidine benzamide-based thrombopoietin receptor agonists [123], in which the lead molecule contains a 2-amino-5-unsubstituted thiazole (a group that has been associated with idiosyncratic toxicity), the potential for metabolic oxidation at C-5 of the thiazole, the likely source of toxic metabolites, was removed by substitution at C-5 or by replacing the thiazole with a thiadiazole. In particular, the 4-F-3-CF_3 analog **245** (Fig. 10) is active and only slightly less potent than the corresponding 2-amino-4-arylthiazole lead.

Recently, several fluorinated 1,3,4-thiadiazoles have been considered as Drugs. Through a highthroughput biochemical screening of more than 340,000 synthetic compounds, the thiadiazole derivative **XCT790** (**246** in Fig. 11) has been identified as an estrogen-related receptor α (ERRα)–specific inverse agonist, validating ERRα as a promising therapeutic target in the treatment of metabolic disorders, including diabetes and obesity [124]. This compound could also be used in pathologies such as breast cancer [125], enhancing the efficacy of Fulvestrant **247** – an estrogen receptor antagonist with no agonist effects, already clinically used for the treatment of metastatic breast cancer in postmenopausal women [126]. Moreover, **XCT790** itself is a perspective drug for the treatment of hormone-related tumors such as prostate and breast cancer [127].

A patent from *Janssen Pharmaceutica* disclosed compound **248**, and other trifluoromethyl-1,3,4-thiadiazole derivatives, as fast dissociating dopamine 2 receptor antagonists with a pIC_{50} value > 5.0 when tested for *in vitro* binding affinity for human D2L receptor [128]. Compound **248** should be useful for treating or

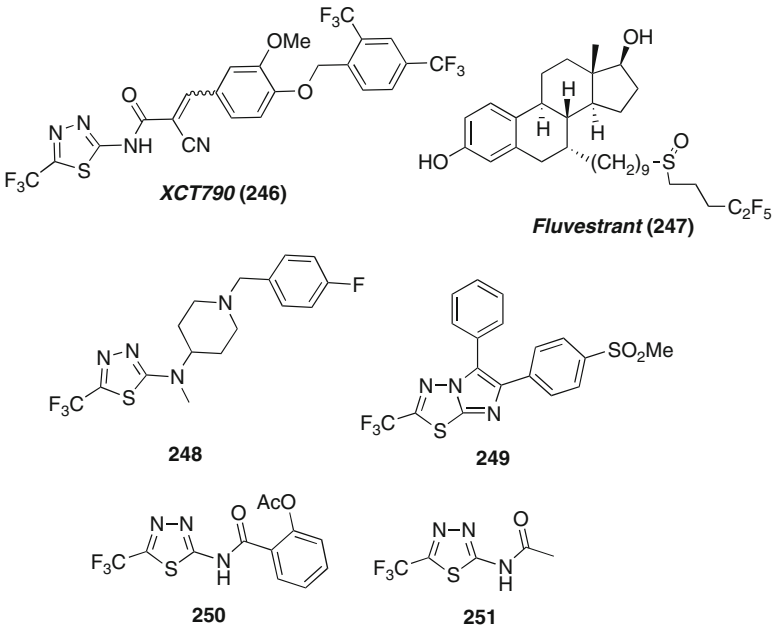


Fig. 11 Examples of fluorinated biologically active 1,3,4-thiadiazoles

preventing central nervous system disorders, for example schizophrenia, by exerting an antipsychotic effect without motor side effects. Also in the field of non-steroidal anti-inflammatory drugs (NSAIDs) fluorinated thiadiazoles appear. Compound **249** showed appreciable cyclooxygenase-2 (COX-2) selective inhibitory activity [129]. This compound also exhibited significant *in vivo* anti-inflammatory activity, comparable to that of the reference compound *Celecoxib*. 5-Trifluoromethyl-1,3,4-thiadiazolyl-amide **250** has been considered for anti-parasitic activity against *Sarcocystis neurona* [130], an obligate intracellular parasite that causes equine protozoal myeloencephalitis (EPM), and *Cryptosporidium parvum* [131], responsible for diarrhea in immunocompetent children and adults (cryptosporidiosis). Compound **250** is more active than reference compound nitazoxanide (NTZ) and seems promising for the treatment of both threats. In the field of anti-fungal compound, derivative **251** has been recently highlighted as a chitinase inhibitor for the fungal pathogen *Aspergillus fumigates* [132]. Despite the weak inhibitory activity, it could represent an interesting lead for future inhibitor development.

Regarding biological applications of fluorinated 1,2,5-thiadiazoles, compounds **180** were investigated for their nematocidal activity [88], while compound **252** was highlighted as antiviral agent, showing an EC_{50} of 0.008 μg/mL *in vitro*, protecting HIV-infected MT-4 cells from death [133] (Fig. 12).

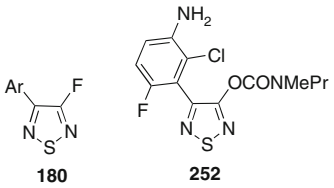


Fig. 12 Examples of fluorinated biologically active 1,2,5-thiadiazoles

5 Applications of Fluorinated Oxadiazoles and Thiadiazoles

Potential artificial oxygen carriers, based on new water-soluble fluorinated polymers, were obtained by using FOXARs (see also Scheme 59 in Sect. 3.3) to introduce fluorinated pendants in the α,β-poly(N-2-hydroxyethyl)-DL-aspartamide (PHEA) and polyethylenglycol–PHEA (PHEA– PEG) biocompatible polymers. The introduction of the fluorinated moiety increased the polymer's oxygen-dissolving ability without compromising its biocompatibility which was checked by an in vitro viability assay[4].

Fluorinated ionic liquid crystals (ILC) were synthesized by quaternization of pyridyl-1,2,4-oxadiazoles with CH_3I [134]. Interestingly, replacing the rigid perfluoroalkyl moiety with a more disordered alkyl chain resulted in a dramatic change of the salt's physico-chemical properties. In the field of supramolecular interactions involving fluorinated heterocyclic systems, a very recent study was performed on a series of perfluoroalkyl-1,2,4-oxadiazolyl-pyridines as H-bond acceptors in protic ionic liquids [135]. Interestingly, self-assembling capability of 1,3,4-oxadiazoles **256** (Fig. 13) allowed the obtainment of tubular crystals of size controllable through sublimation protocols [136].

Other examples regarding applications of fluorinated oxadiazoles in the field of sensoring and optoelectronics are illustrated in Fig. 13. In some cases the luminescent properties of a system can be designed to be a function of a measure such as the concentration of a given species in solution. For example, the fluorescence of the star-shaped molecule similar to **253** (Fig. 13) is self-quenched by the tertiary amino moiety of its core and is strongly dependant on the medium's acidity [5b] Additionally, the derivative **253** has been recently developed as fluorescent sensor for mercuric ion in aqueous media [137]. Starburst oxadiazole **254** is a precursor of dendritic emitter [138]. Finally, compound **255** represents the simplest oligomer of highly fluorinated polyarylene systems with fluoride anion sensing ability [139].

The application of fluorinated furazan is rather limited for synthesis and reactivity. Most studied derivative is 3-amino-4-trifluoromethyl-1,2,5-oxadiazole, which is commercially available. Nevertheless, in recent years, some perspective applications have been envisaged. In the agrochemical field a large library (more than 300 derivatives) of *N*-(4-trifluoromethyl-1,2,5-oxadiazol-3-yl)benzamides **257** has been prepared and considered for herbicidal activity [140], while 1-(4-fluoro-1,2,5-oxadiazol-3-yl)pyrazole derivatives **258** were claimed as herbicides and plant growth regulators (Fig. 14) [141].

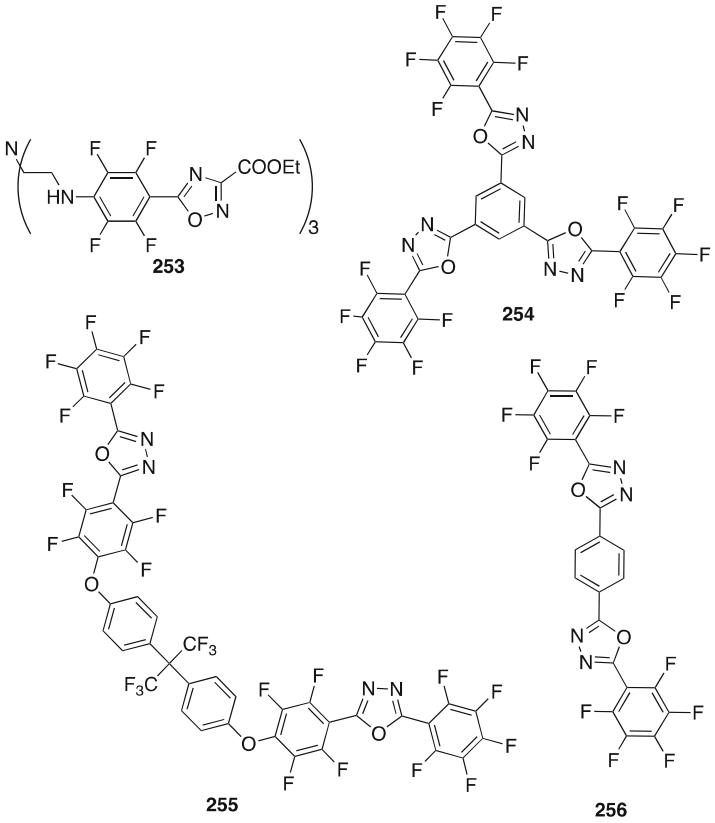
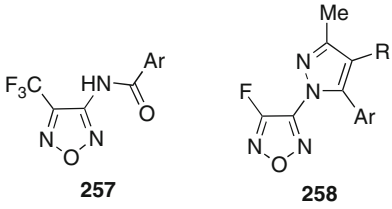


Fig. 13 Examples of fluorinated oxadiazoles for sensoring and optoelectronics

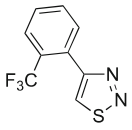
Fig. 14 Examples of fluorinated 1,2,5-oxadiazoles agrochemicals



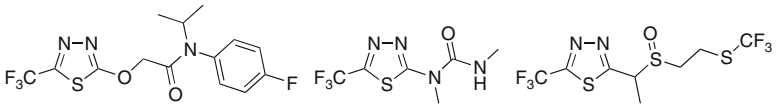
Many fluorinated thiadiazoles have been applied as agrochemicals. For instance, thiadiazole **259** is an antidote for acetanilide herbicides, protecting sorghum and wheat against phytotoxicity without affecting green foxtail control by these herbicides (Fig. 15) [142].

As outlined above, fluorinated 1,3,4-thiadiazoles are widespread applied in many fields as agrochemicals, drugs and materials. It is noteworthy that in the agrochemical field some 1,3,4-thiadiazole derivatives have reached the market, in particular, *Flufenacet* **260** and *Thiazafluron* **261** (Fig. 16).

Fig. 15 A fluorinated 1,2,3-thiadiazole herbicide

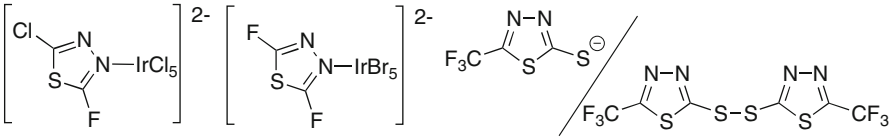


259



***Flufenacet* (260)** ***Thiazafluron* (261)** **262**

Fig. 16 Examples of commercial fluorinated 1,3,4-thiadiazole agrochemicals



263 **264** **265**

Fig. 17 Examples of fluorinated 1,3,4-thiadiazoles applied in materials science

Flufenacet (brand names: Artist®, Axiom®, Cadou®, Define®, Liberator®, Radius®, Tiara®, Terano®) was introduced by Bayer AG and is an oxyacetanilide herbicide applied before crops have emerged [143]. Is an inhibitor of cell division acting on very-long-chain-fatty-acid (VLCFA) synthesis. Applied for crop protection (Corn, Rice, Wheat, Potatoes, Soybeans) presents a spectrum of activity on infesting annual grasses like *Alopecurus myosuroides, Apera spica-venti, Digitaria spp., Echinochloa crus-galli, Poa annua, Setaria spp*.

Thiazafluron (other names: Erbotan® GS 29696, Thiazfluron) is an herbicide introduced by Ciba-Geigy AG [144]. *Thiazafluron* is believed to be obsolete for use as pesticides is one of 320 pesticides to be withdrawn in July 2003. Recently, other trifluoromethyl-1,3,4-thiadiazole derivatives such as **262** (Fig. 16) have been claimed useful for fighting or controlling invertebrate pests in agricultural as well as veterinary applications [145].

In the field of materials for photography, metal complexes containing fluorothiadiazoles as monodentate ligand have been used. Emulsion layer contains Ag halide and the iridium complex **263** provides high-speed development method with high-quality images free from pressure-derived fogs [146], while the emulsion containing the iridium complex **264** showed high sensitivity and contrast, preventing reciprocity law failure in broader exposure range (Fig. 17) [147].

Also in the field of reagents for materials characterization fluorinated 1,3,4-thiadiazoles have found some applications. In fact, the couple 5-trifluoromethyl-2-mercapto-1,3,4-thiadiazolate/5,5′-bis(2-trifluoromethyl-1,3,4-thiadiazole) disulfide **265** was employed as organic redox couple in nonaqueous media to perform capacitance measurements through Electrochemical Impedance Spectroscopy (EIS) on semiconductive materials (Fig. 17) [148].

6 Concluding Remarks

Due to the peculiar features introduced by fluorinated moieties, the synthesis, the reactivity, and the application of fluorinated oxadiazoles and thiadiazoles still are challenging research topics. Therefore, the updated synthetic guidelines reported in this chapter will represent a useful tool for both the experienced synthetic chemists and those willing to embrace the study of fluorinated azoles. For this reason, it is the authors' opinion that synthetic information organized by kind of heterocycle is better approached by the reader for faster consultation. On the other hand, reactivity has been presented by focusing on the type and position of the fluorinated moiety, in the attempt to provide general concepts transferable also to other heterocyclic systems. Finally, examples of fluorinated oxadiazoles and thiadiazoles used in materials chemistry or as bioactive compounds have been briefly illustrated to suggest the potential application of newly synthesized compounds.

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