Fluorinated Triazoles and Tetrazoles

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Abstract The chapter encompasses the synthesis, chemical transformations, properties, and applications of fluorinated monocyclic 1,2,3-, 1,2,4-triazoles and tetrazoles as well as their fused analogs. The heterocycles directly bonded with a fluorine atom (N-F or C-F isomers) as well as trifluoromethyl, perfluoroalkyl, perfluoroaryl, SF_5, NF_2 groups and some other fluorinated fragments were considered.

Keywords Fluorine • Triazole • Tetrazoles • Heterocycle • Synthesis • Application • Biological activity

1 Introduction

Fluorinated polynitrogen heterocycles like 1,2,3-triazoles, 1,2,4-triazoles and tetrazoles differ considerably from the other related heterocyclic systems in the preparation methods and some characteristics. Heterocycles containing three or four endocyclic nitrogen atoms, including one, two, or three N-N bonds combined with a powerful electron-acceptor and energy-consuming substituent like a fluorine atom or perfluoroalkyl groups possess a relatively high enthalpy of formation and notably differ from the other azoles by their chemical properties. Some fluorinated tri- and tetrazoles are well known and find versatile applications [1]. These compounds are widely used in medicine, agriculture, and in material sciences. Thus, several commercially important drugs as well as a lot of bioactive compounds with different types of activity have in their composition fluorinated triazolyl or tetrazolyl groups. Among them there are well-known antidiabetic DPP-IV inhibitors, NK1 receptor antagonist, antifungal agents, herbicides, and some other compounds with useful properties [1–5]. On the other hand these compounds possess a number of unique properties providing a possibility to utilize them in quite different fields of technology. For instance, these compounds are efficient corrosion inhibitors, they can be used as components of energy-rich compounds, ionic liquids, semiconductors, etc. [1, 6]. The applications of fluorinated tri- and tetrazoles will be discussed in more detail in Sect. 6 of this chapter.

Fluorinated derivatives of azoles are known since over half century, the chemical methods of their synthesis and their certain chemical properties are described in many reviews and monographs [1, 6–15]. In general two different ways to incorporate fluorine or perfluoroalkyl groups into a heterocyclic system may be considered:

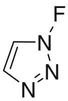
The heterocyclization of fluorine-containing acyclic systems many various types of which are known, or direct introduction of fluorine or a perfluoroalkyl group into existing heterocyclic system [1, 7–15]. So far the problems of the synthesis of highly nitrogenated cyclic systems, especially of 1,2,3-triazoles and tetrazoles have been poorly understood. It should be noted that quite a big number of original publications has appeared in this field within the last decade.

Taking into account the essential difference in the properties and the preparation procedures we consider further in succession compounds having a fluorine atom directly bound to the heterocycle and another fluorine-containing substances, perfluoroalkyl and perfluoroaryl derivatives of 1,2,3-, 1,2,4-triazoles and tetrazoles. The research on the synthesis and the reactivity of tri- and tetrazoles containing as substituents at the endocyclic carbon atom CF_3 or the other perfluoroalkyl groups have been developed since the 1960s. The last decade has been marked with a significant progress in this direction due to some of these compounds have important practical applications. Tri- and tetrazoles containing as substituents perfluoroaryl fragments, SF_5 and NF_2 groups, and also heterocycles involved into fluorobenzo-fused systems are considered separately.

2 Compounds Having Fluorine Bonded Directly to Endocyclic Atoms

2.1 N-F Derivatives

In the case of unsubstituted triazoles and tetrazoles the existence of two isomers is possible for each heterocyclic system. Such derivatives are very different in thermodynamic stability: 1H- and 2H-1,2,3-triazoles and tetrazoles, and also 1H- and 4H-1,2,4-triazoles. By now all parent N-F heterocycles **1**–**6** remain hypothetical. Among substituted derivatives all known N-F heterocycles are only 1H-isomers.



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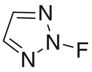

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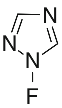

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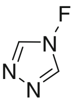

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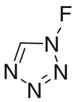

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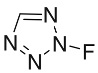

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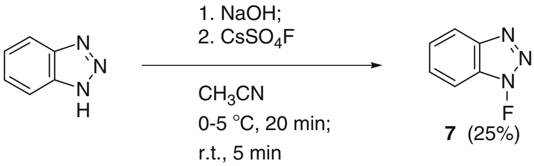
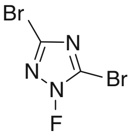
In general the information on the synthesis and properties of the N-fluorinated derivatives of 1,2,3- and 1,2,4-triazoles is very scanty [6]. The data about N-fluorotetrazoles are totally absent today. We discuss below the results of the few publications considering the synthesis of N-fluoro-1,2,3- and 1,2,4-triazoles. This desultory information is difficult to classify since the most of these papers lack any experimental details on the synthesis of the compounds of this type and the proofs confirming the structure.

By now the synthesis of 1-fluoro-benzotriazole **7** is well established fact [16]. Gakh et al. carried out a direct replacement of the hydrogen attached to the nitrogen atom of the “pyrrole” type of benzotriazole by the fluorine. For this aim benzotriazole anion was fluorinated with cesium fluorooxysulfate (CEOX). The cesium fluorooxysulfate discovered by Appelman in 1979 is one of the soft and regioselective reagents for anions fluorination. It requires however a cautious handling for it is prone to spontaneous instant decomposition [8, 9].



7 (25%)

An example of synthesis of N-fluoro-1,2,4-triazole was described in the patent of Strazdina and Grinstein [6, 17]. Here 1-fluoro-3,5-dibromo-1,2,4-triazole **8** was obtained by treating the heterocyclic substrate with the hypohalous acid or its derivatives at −40 to +50 °C in water or an organic solvent in the presence of bases. Langlet and Ostmark in a patent [18] have described the application of isomeric fluoro-triazolones **9, 10** as components of explosive compositions, but the data on the synthesis of these substances have been not reported.



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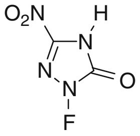

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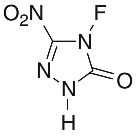
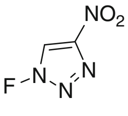
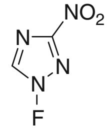


10

Miroshnichenko et al. [19] published results on calorimetric investigation of N-F derivatives of various nitroazoles, in particular, of some N-fluoro derivatives of 1,2,3- and 1,2,4-triazoles **11**–**13** (the values of standard enthalpy of formation ΔH_f^o, kJ/mol are given in parentheses). Regretfully, the methods of the synthesis of N-F triazoles and the data confirming their structure and individuality were not reported in this article.



11 (298.7)



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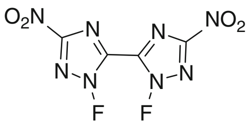
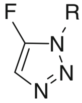


13 (491.2)

According to theoretical calculations the N-F bond in the molecules of N-fluoro-1,2,4-triazoles is rather strong, in contrast to N-Cl (Br, I) bonds [20]. Therefore, it remains possible to prepare a wide range of thermodynamically stable N-fluoro derivatives of 1,2,4-triazole which may be of a practical importance. Thus, using *ab initio* quantum-chemical methods, the structure of salts was investigated that were formed with N-F-1,2,4-triazolium cation and dinitramide anion which might be used for the preparation of exotic energy-rich ionic liquids [21].

2.2 C-F Derivatives

Taking into account that 1,2,3- and 1,2,4-triazole rings contain two carbon atoms, and the tetrazole cycle only a single one, the fluorine atom can be located in two different positions in the isomeric C-F triazoles with nonequivalent substituents **14**–**17** and in a single position in 5-fluorotetrazole **18**. All types of these derivatives are known.



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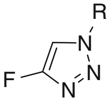

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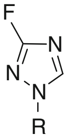

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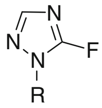

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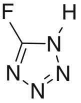
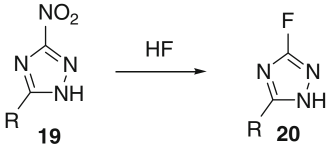


18

The direct incorporation of a fluorine atom in the ring essentially affects versatile physicochemical and chemical characteristics of the heterocyclic system, in particular, its tautomerism, dipole moment, and the acid-base properties. For instance, tautomeric equilibria involving NH-unsubstituted fluoro derivatives of 1,2,3-triazoles [22, 23], 1,2,4-triazoles [24], and tetrazoles [25–28] were explored in a series of theoretical studies. The acid-base properties of these heterocycles (in particular, the CH-acidity of some among them) were also studied [28–30]. These investigations showed that the fluorine atom attached to the heterocyclic system changed significantly the character of the electron density distribution and consequently the polarity of the heterocycle, strongly increased its acidity and decreased its basicity.

The synthetic procedures for the preparation of C-F derivatives of tri- and tetrazoles are more developed compared to the synthesis of the derivatives with the N-F bond. The preparation methods of C-F derivatives are known not only for 1,2,3- and 1,2,4-triazoles, but also for tetrazoles. The C-F bond is successfully formed by the replacement of hydrogen atom or various "leaving" groups under the action of the fluorination reagents. Along with the above methods diverse versions are applied of 1,3-dipolar cycloaddition of azides to dipolarophiles containing fluorine. Also very useful approach is oxidative cyclization of molecules with the linear structure containing a C-F bond.

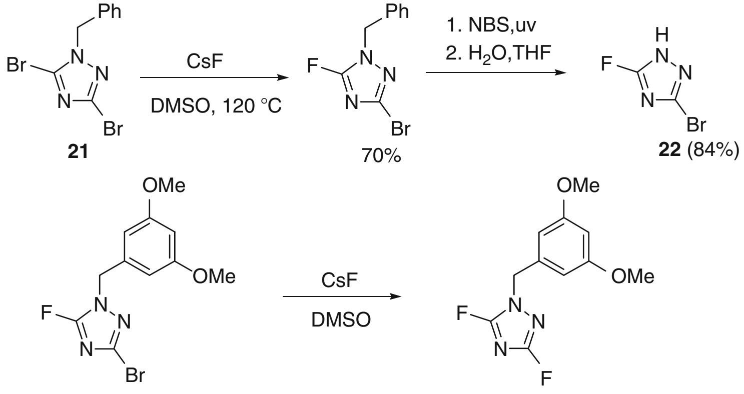
The first report on the preparation of 1,2,4-triazoles fluorinated at the carbon atom of the ring appeared as early as 1973 [31]. In this study the corresponding 3-fluoro-1,2,4-triazoles **20** were obtained in good yields by treatment of 5-R-3-nitro-1,2,4-triazoles **19** with hydrogen fluoride. Nitro group substitution by fluorine under these conditions required a prolonged time (20–48 h) and heating at high temperature (100–150 °C).



19 **20**

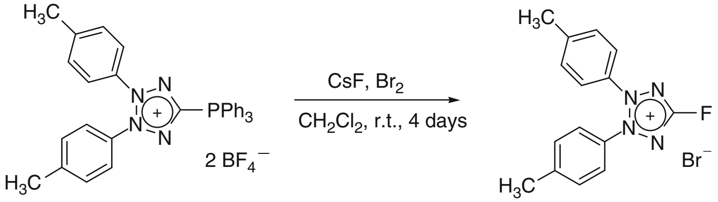
R	Temperature,°C	Time, h	Yield, %
H	150	48	80
Br	100	36	98
CO_2Me	100	20	70
OH	100	36	21

The nucleophilic exchange of one bromine atom in 1-benzyl-3,5-dibromo-1,2,4-triazole **21** with fluorine under the action of CsF followed by the photoinitiated elimination of the benzyl protective group led to the formation of 3-bromo-5-fluoro-1H-1,2,4-triazole **22** in 59 % overall yield. The alkylation of this substrate gave 1-alkyl-3-fluoro-1,2,4-triazoles for the first time. Both bromine atoms were substituted to provide the corresponding difluoro derivative **24** under the same reaction conditions, but using 1-(3,5-dimethoxybenzyl)-3,5-dibromo-1,2,4-triazole **23** as substrate for fluorination [32].



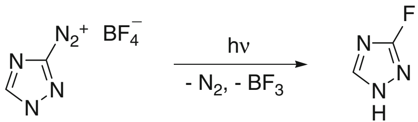
21 70% **22** (84%) **23** **24** (73%)

Cesium fluoride was also used in the synthesis of 2,3-di(*p*-tolyl)-5-fluorotetrazolium bromide **25** from the corresponding 5-triphenylphosphoniotetrazolium salt [33].



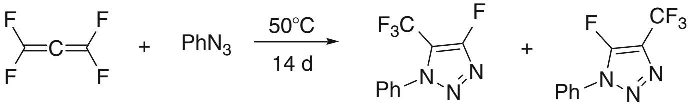
25 (73%)

Another example of the direct introduction of the fluorine atom into a heterocycle was demonstrated in [34]. Here 3-fluoro-1,2,4-triazole **26** was obtained by the photochemical decomposition of hetaryldiazonium tetrafluoroborate in solution oversaturated with $NaBF_4$.

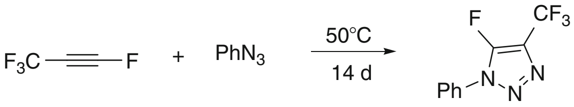


26 (39%)

A widely used method of the preparation of versatile 1,2,3-triazoles and tetrazoles consists in the reaction of azides with fluorine-containing compounds with multiple bonds. For example, this approach afforded N-substituted 4(5)-fluoro-1,2,3-triazoles **27, 28** by the 1,3-dipolar cycloaddition of perfluoropropadiene to phenyl azide [35]. In the course of the reaction a mixture of regioisomeric 1,2,3-triazoles was formed; 1-phenyl-4-fluoro-5-trifluoromethyl-1,2,3-triazole **27** was considerably prevailed. On the contrary, the reaction of phenyl azide with the perfluoropropyne resulted in predominantly the isomer that was minor in the previous scheme.

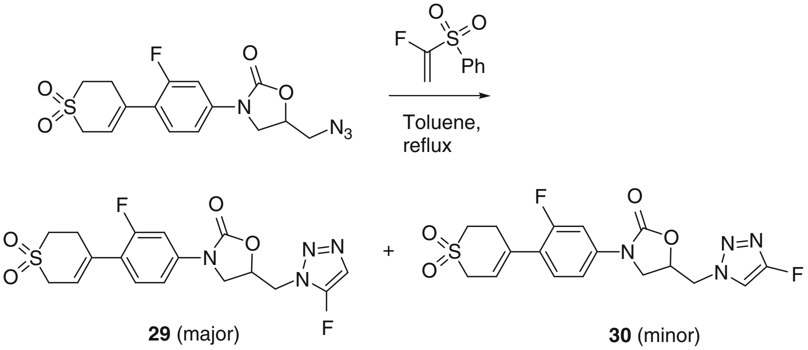


27 (25%) **28** (3%)



28 (32%)

Reck et al. demonstrated that phenylsulfinic acid was eliminated in course of 1,3-dipolar cycloaddition involving 1-fluoro-1-(phenylsulfonyl)ethylene and (5R)-3-[4-(1,1-dioxo-3,6-dihydro-2H-thiopyran-4-yl)-3-fluorophenyl]-5-(azidomethyl)oxazolidin-2-one. As a result a mixture of regioisomeric 4- and 5-fluoro-1,2,3-triazoles **29, 30** in 7:1 ratio was formed in 28 % overall yield. Compounds **29, 30** may be regarded as effective antimicrobial agents [36].



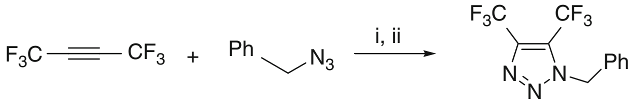
29 (major) **30** (minor)

Apparently the simplest 5-fluorotetrazole **18** and its derivatives can be synthesized by the reaction of 2 + 3 dipolar cycloaddition of azides to cyanogen fluoride or by some other method. Yet we failed to find the mention of such synthesis in available publications. The possibility of this reaction and its mechanism were assessed theoretically [37]. Publications are known where compound **18** is used as a component of the energy-rich compositions [38].

3 Trifluoromethyl and Perfluoroalkyl Derivatives

3.1 1,2,3-Triazoles

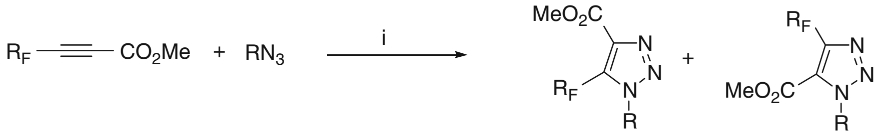
The most common synthetic procedure for the preparation of perfluoroalkylated 1,2,3-triazole derivatives is 1,3-dipolar cycloaddition of azides to diverse unsaturated dipolarophiles containing perfluoroalkyl substituents. Thus, in 1966 Carpenter et al. carried out the cycloaddition of benzyl azide to perfluoroalkyl substituted acetylene derivatives leading to the formation of trifluoromethyl-1,2,3-triazolines and 1,2,3-triazoles [39]. In this paper a synthesis of l-benzyl-4,5-bistrifluoromethyl-l,2,3-triazole **31** from hexafluoro-2-butyne was described.



i, test tube chilled to -70 °C
ii, 2 days, r.t.

31 (5%)

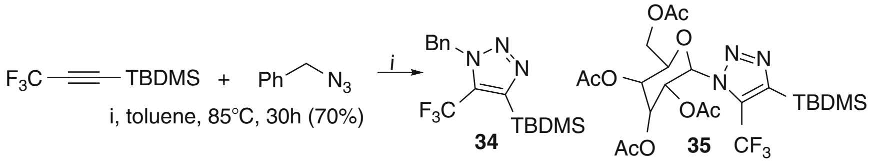
The regioselectivity of 1,3-cycloaddition of benzyl azide to unsymmetrical acetylenes containing CF_3 substituent at one carbon atom of the fragment $C \equiv C$ and CO_2Et group at the other carbon was analyzed [40]. The formation of regioisomeric mixtures of 1,2,3-triazoles **32, 33** was observed. This study was further developed recently. Zhang et al. published the results of a research on the 1,3-dipolar cycloaddition of benzyl azide and some other aryl azides to methyl perfluoroalkylalkynoate. It was shown that the ratio of regioisomers is governed by two factors: the orbital control (the role of the frontier orbitals was established) and also spatial interaction of the perfluoroalkyl and aryl (or benzyl) groups [41].



i, ^{t}BuOH, 80°C or r.t. **32** **33**

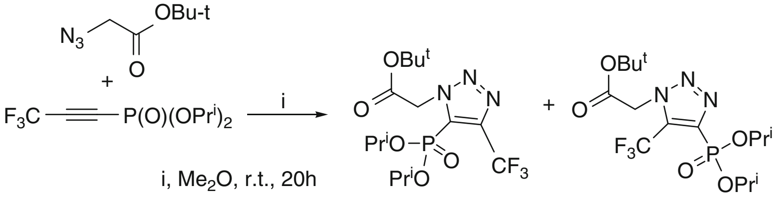
R_F	R	ratio **32:33**	Yield,%
CF_3	$C_6H_5CH_2$	1:0.7	91
C_2F_5	p-$MeOC_6H_4CH_2$	1:0.9	82
C_3H_7	p-$MeOC_6H_4CH_2$	1:1.2	83
CF_3	C_6H_5	1:2.1	85

The influence of the steric effects on the regioselectivity of the cycloaddition was studied in detail by an example of the 1,3-dipolar cycloaddition of benzyl azide to trifluoromethylacetylene containing a TBDMS (*tert*-butyldimethylsilyl) protecting group. The regioselective formation in this case of the single isomer of 1,2,3-triazole **34** was explained by the presence in the structure of dipolarophile of a bulky substituent (TBDMS) [42]. Such an approach made it possible to perform a regioselective synthesis of nucleosides analogs containing in their molecular structure a trifluoromethyl-1,2,3-triazolyl fragment **35** [42].



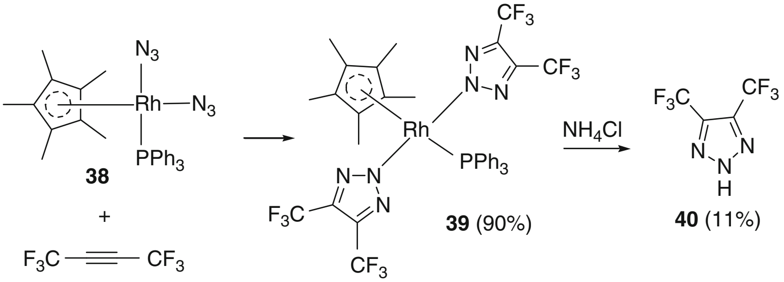
i, toluene, 85°C, 30h (70%) **34** **35**

The reaction of *tert*-butyl azidoacetate with diisopropyl-3,3,3-trifluoroprop-1-ynylphosphonate gave regioisomeric diisopropyl(1-*tert*-butoxycarbonylmethyl-4-trifluoromethyl-1H-l,2,3-triazol-5-yl)phosphonate **36** and disopropyl(l-*tert*-butoxycarbonylmethyl-5-fluoromethyl-lH-l,2,3-triazol-4-yl)phosphonate **37** in 75:25 ratio (90 % overall yield) [43].

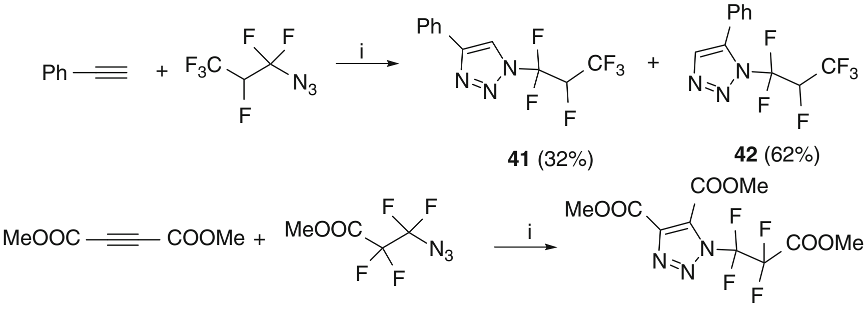


i, Me$_2$O, r.t., 20h **36** **37**

Pentamethylcyclopentadienylrhodium (or iridium) azido complexes **38** react with ditrifluoromethylacetylene to give the corresponding 1,2,3-triazole rhodium complex **39**. Subsequent treatment with NH_4Cl opened the route to free NH-triazole **40** [44].

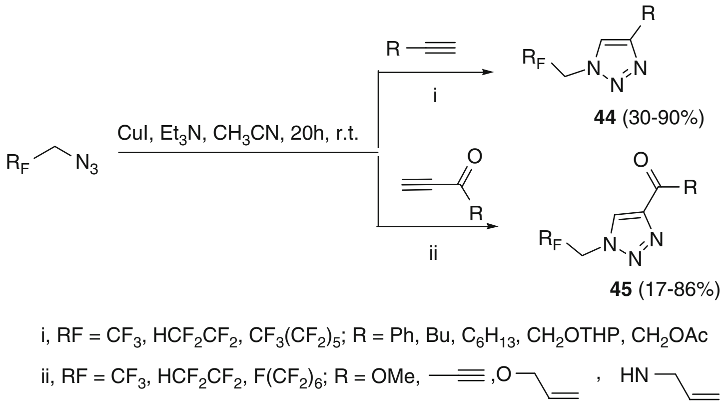


Lermontov et al. reported some successful reactions of two α,α-difluoroazides, namely, 2-hydroperfluoropropyl azide and the methyl ester of 3-azidoperfluoropropanoic acid, with various acetylene compounds, and described some properties of the resulting products [45]. Thus, phenylacetylene reacts with 2-hydroperfluoropropyl azide to give the corresponding 4-phenyl-1-(2H-perfluoropropyl)-1,2,3-triazole **41** and 5-phenyl-1-(2H-perfluoropropyl)-1,2,3-triazole **42** in 1/2 ratio. Disubstituted acetylenes also react with these azides to give the corresponding 1H-1,2,3-triazoles [45]. Thus in the case of triazole **43** the yield is close to the quantitative.



i, steel bomb, 130°C 6h

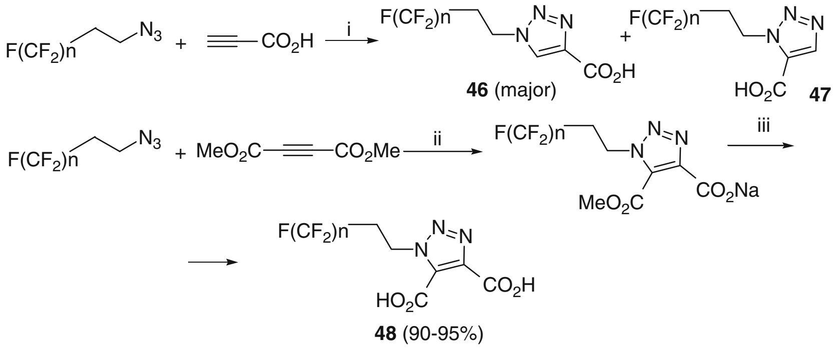
In the paper [46] of Wu, Chen et al. a method for the preparation of the fluoroalkylated 1,4-disubstituted-1,2,3-triazoles by the 1,3-dipolar cycloaddition of fluoroalkylated azides to terminal alkynes in the presence of Cu(I) salt as catalyst at room temperature was described. All these reactions were highly regioselective giving 1,4-disubstituted **44, 45**, no 1,5-disubstituted products. The structure of key compounds was confirmed both by the NOSEY spectra and an X-ray diffraction study.



i, RF = CF_3, HCF_2CF_2, $CF_3(CF_2)_5$; R = Ph, Bu, C_6H_{13}, CH_2OTHP, CH_2OAc

ii, RF = CF_3, HCF_2CF_2, $F(CF_2)_6$; R = OMe,

A series of fluoroalkylated amphiphilic 1,2,3-triazoles **46**, **47**, **48** was synthesized by efficient 1,3-dipolar cycloaddition of 2-perfluoroalkylethyl azides and acetylenic acids or esters [47].

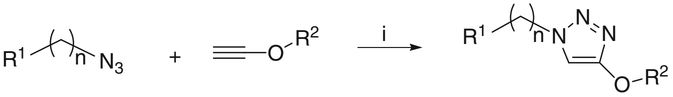


i, acetone, reflux, 24 h; n = 4, yield 75% (90/10), 6, yield 85% (86/14), 8, yield 90% (95/5)

ii, acetone, 2M NaOH, 5 min, n = 4 - 6

iii, 1M HCl, until pH = 1, n = 4-6

Recently Yi et al. also utilized 2-perfluoroalkylethyl azides as 1,3-dipoles in the 1,3-dipolar cycloaddition to phenyl- or butylacetylenes [48]. As a result in the presence of copper(I) salt the corresponding 1-fluoroalkyl-4-substituted 1,2,3-triazoles were obtained in about 60 % yield. Note that in this case only anti- isomers were obtained: 1-fluoroalkyl-4-aryl- or 1-fluoroalkyl-4-butyl-1,2,3-triazoles. The authors do not explain the high selectivity of the process, although it may be attributed to the steric effect of the bulky substituents (aryl, butyl). Yi et al. note the relatively high efficiency of the fluoroalkyl 1,4-disubstituted-1,2,3-triazoles as catalysts of aldol condensation which may be easily recovered and reused [48]. Read et al. [49] virtually simultaneously with [48] published the results of their proper exploration of the copper salts catalyzed 1,3-dipolar cycloaddition of fluorinated alkyl azides to acetylenes. This research extended the methodology formerly suggested by Wu et al. [46] who were among the first to apply the catalytic system based on Cu(I). It was shown that practically for the generation of the Huisgen-Meldal catalyst the system $CuSO_4$ $5H_2O$ – sodium ascorbate was preferable. Just under these reaction conditions a wide range of 1,2,3-triazoles **49** was obtained having the perfluoroalkyl groups at the atoms in the positions *1* and *4* [49]. It was also shown that the higher rate of the process and the higher yield of cycloaddition products were achieved both in the presence of copper salts and at the microwave acceleration.



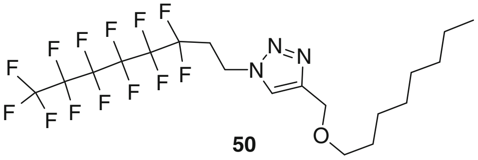
49 (50-97%)

i, $CuSO_4$ $5H_2O$, Na ascorbate, DMSO, heat

$R^1 = C_4F_9, C_6F_{13}, C_8F_1$; n = 2; $R^2 = C_8H_{17}$; etc.

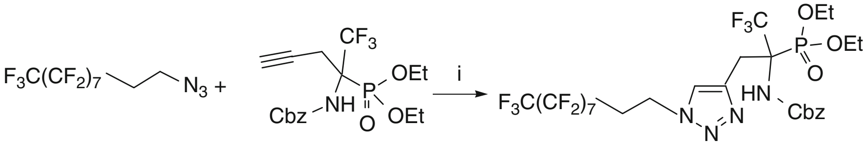
$R^1 = C_4H_9, C_6H_{13}, C_8H_{17}, C_9H_{19}, CH_2Ph$; n=0; $R^2 = CH_2CH_2C_6F_{13}$, etc.

1,3-Dipolar cycloaddition of fluoroalkyl azides to acetylenes in the version of the click-chemistry involving the above mentioned catalytic system ($CuSO_4$ $5H_2O$ – sodium ascorbate) essentially extended the set of the known fluoroalkyl derivatives of 1,2,3-triazole; some 1,2,3-triazole derivatives previously regarded as exotic became relatively accessible. Read et al. recently reported on the results of research of the effect on the *m*-xylene surface tension of the additives of exotic surfactants based on fluoroalkyl derivatives of 1,2,3-triazoles, e.g., compound **50** [50]. The synthesis of fluoroalkyl-1,2,3-triazoles using the above mentioned procedure was also described in the earlier publication of the same team [51].



50

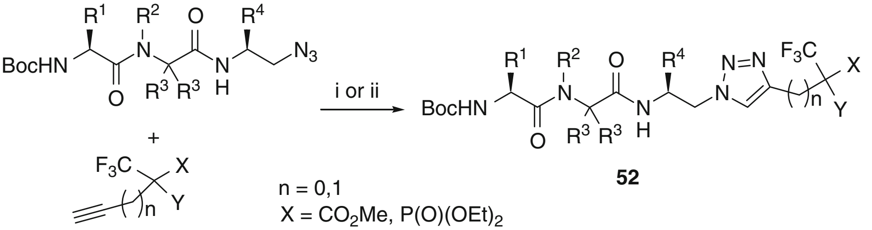
A convenient method for the preparation of 1,2,3-triazole-containing CF_3-α-aminophosphonates **51** via copper-catalyzed (3 + 2)-cycloaddition of α-CF_3-α-aminophosphonates bearing an alkynyl group at the α-carbon atom to different organic azides has been described [52].



i, *t*-BuOH - H_2O, r.t., 8h, yield 92%

51

A convenient and simple method for the synthesis based on copper-catalyzed 1,3-dipolar cycloaddition of azidopeptides to acetylenes of tetrapeptide surrogates containing CF_3-alkyl-1,2,3-triazolyl moiety **52** having ester of phosphonates functionalities or have been developed by Nenajdenko et al. [53, 54].



52

n = 0,1

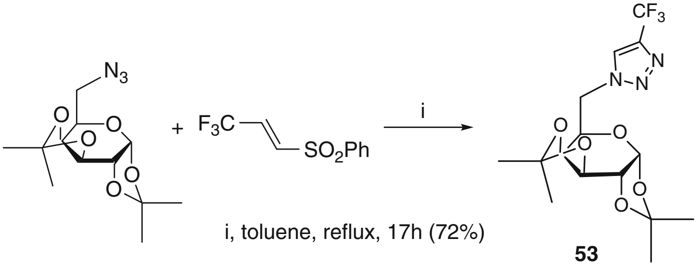
X = CO_2Me, P(O)(OEt)$_2$

Y = NHBoc, NHCbz, OH

i, sodium ascorbate (40%), $CuSO_4$ $5H_2O$ (10%), CH_2Cl_2/H_2O (10:1), 40°C, 3-5 h (70-97%)

ii, sodium ascorbate (30%), $CuSO_4$ $5H_2O$ (5%), *t*-BuOH/H_2O (1:1), r.t. or 90°C, 2 h (57-96%)

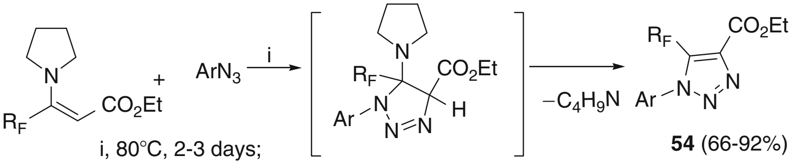
Some approaches to the synthesis of trifluoromethyl-1,2,3-triazoles by the azidation of compounds containing not a triple but a double C=C bond were described. In this case apparently a functional group elimination occurs *in situ* to provide the formation of an additional carbon-carbon bond. For instance, Miethchen et al. described a synthesis of 4-trifluoromethyl-1,2,3-triazole **53** linked to the C^6-atom of D-galactose and D-altrose. 1,3-Dipolar cycloaddition using the monosaccharide azides and the perfluoroalkyl- substituted phenylvinylsulfones was performed [55, 56].



i, toluene, reflux, 17h (72%)

53

A number of 5-fluoroalkylated 1H-1,2,3-triazoles **54** was synthesized in good yield by the 100 % regioselective 1,3-dipolar cycloaddition of (*Z*)-ethyl-3-fluoroalkyl-3-pyrrolidino-acrylates with aryl or benzyl azides [57].

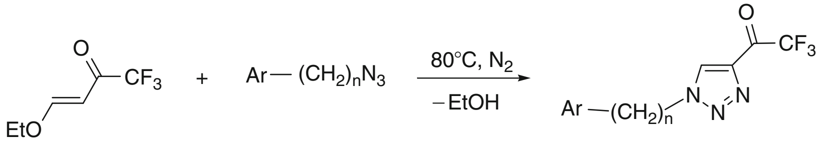


i, 80°C, 2-3 days;

54 (66-92%)

R_F = $ClCF_2$, $BrCF_2$, CF_3, $Cl(CF_2)_3$; Ar = Ph, 4-$CH_3OC_6H_4$,4-$NO_2C_6H_4$

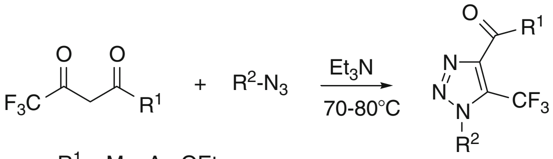
1,3-Dipolar cycloaddition of aryl (or benzyl) azides to 1,1,1-trifluoro-4-ethoxy-3-butene-2-one proceeded smoothly by heating without solvent. As a result 1-substituted 4-trifluoroacetyl-1*H*-1,2,3-triazoles **55** were formed regioselectively in good yield [58]. These compounds were readily hydrated at air exposure.



55

n=0; Ar = C_6H_5, 66h, yield 51%; 4-MeC_6H_4, 48h, yield 80%,
4-$NO_2C_6H_4$, 66h, yield 78%, 4-ClC_6H_4, 44h, yield 73%,2-$CH_3C_6H_4$, 144h, yield 68%.
n=1; Ar= C_6H_5, 35h, yield 69%, Ar=4-OMe, 24h, yield 79%; Ar=4-NO_2, 72h, yield 88%.

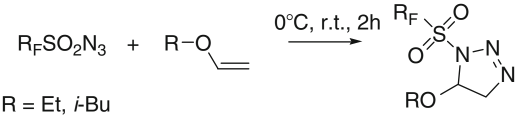
Recently Nenaidenko et al. carried out reactions of a variety alkyl and aryl azides with 1-trifluoromethylated 1,3-dicarbonyl compounds what lead 100 % regioselectively to a single 4-acyl-5-trifluoromethyl-1,2,3-triazoles **56** isomer in good yields [59]. The reaction represents a general and highly selective method for the synthesis of 1,2,3-triazoles otherwise difficulty available. The observed regioselectivity can be explained by selective enolization of trifluoromethyl ketone fragment to form enolate with double bond conjugated to the CF_3 group.



R^1 = Me, Ar, OEt
R^2 = Alk, Ar

56 (up to 92%)

Fluoroalkanesulfonyl azides in reactions with alkenes are more reactive than alkyl azides because of strong electron-acceptor properties of the sulfonyl group. Thus, Zhu, He et al. shown that the reaction of vinyl ethers with 1-fluoroalkanesulfonyl azides proceeded in mild conditions to afford 1-fluoroalkanesulfonyl-5-alkoxy-1,2,3-triazolines in good yields (≈70 %) [60, 61]. The authors point out that the cycloaddition is extremely regioselective. Only the 5-alkoxy derivative of 1,2,3-triazoline **57** has been obtained, whereas the corresponding 1,4-isomer has not been detected.

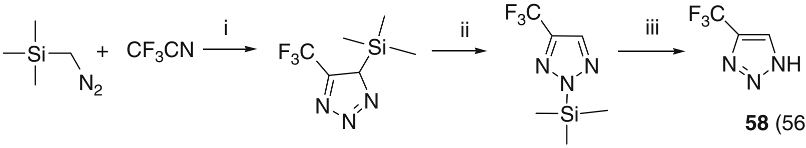


57

R = Et, *i*-Bu
R_F = $ICF_2CF_2OCF_2CF_2$, $ClCF_2CF_2OCF_2CF_2$, $Me_2CHO_2CCF_2$, C_4H_9

According to Shreeve et al., 4-trifluoromethyl-1,2,3-triazole **58** may be synthesized as a result of 1,3-dipolar cycloaddition of $TMSN_3$ to trifluoropropyne in the presence of Cu(I) [62]. The synthesis of perfluoroalkyl-1,2,3-triazoles was also described in the earlier cited paper of Taylor et al. [35]. In this study the reaction was investigated between perfluoropropadiene with phenyl azide resulting in regioisomeric 1,2,3-triazole containing at the endocyclic carbon atoms both the fluorine atom and the CF_3-group.

Below we described some other, less wide spread methods as compared to 1,3-dipolar cycloaddition used in the preparation of perfluoroalkyl derivatives of 1,2,3-triazoles. For instance, Haszeldine et al. [63] developed an original method of the synthesis of trifluoromethyl-1,2,3-triazole about 40 years ago. The reaction of diazomethyltrimethylsilane with trifluoroacetonitrile led to the formation of an intermediate adduct rearranged into 2-trimethylsilyl-4-trifluoromethyl-1,2,3-triazole **59**. This compound being treated with aqueous ethanol liberated the trimethylsilane to yield 4-trifluoromethyl-1,2,3-triazole **58**.

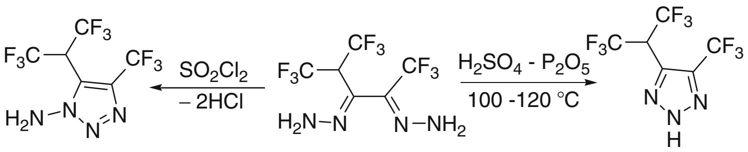


i -196°C; ii r.t., 12 week; iii ethanol aq.

59

58 (56%)

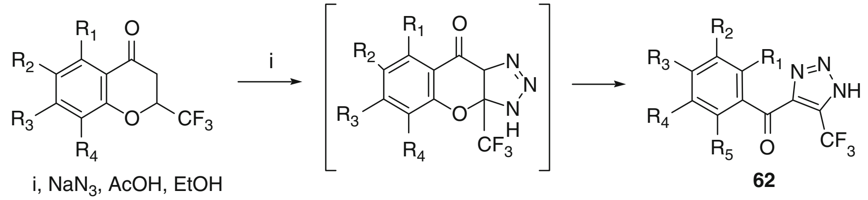
Bargamov and Bargamova reported on new polyfluorinated 1-amino-1,2,3-triazoles **60** which were obtained by oxidation of the bis-hydrazones of aliphatic polyfluorinated α-dicarbonyl compounds with sulfuryl chloride, bromine, or selenium dioxide in an aprotic solvent [64, 65]. In a later article these authors described an oxidation of a dihydrazone of 1,1,1,5,5,5-hexafluoro-4-trifluoromethylpentane-2,3-dione in the presence of the $H_2SO_4 - P_2O_5$ mixture (molar ratio 3:1) to 4-(1,1,1,3,3,3-hexafluoroisopropyl)-5-trifluoromethyl-2*H*-1,2,3-triazole **61** (no yield was given) [66].



60 (82%)

61

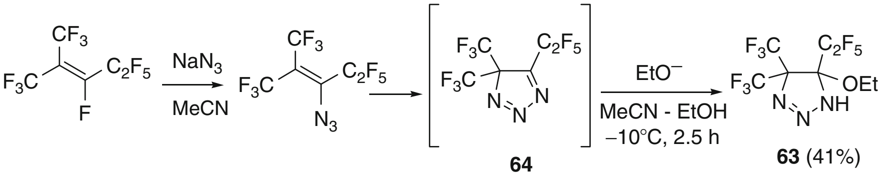
The reactions of 2-trifluoromethylchromones and 2-trifluoromethyl-4H-chromen-4-imines with sodium azide in the presence of acetic acid gave ketone (or imine) derivatives of 5(4)-trifluoromethyl-1,2,3-triazole **62** in high yields [67].



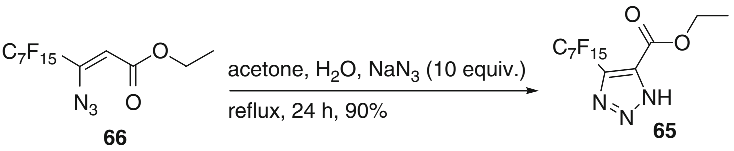
$R^1 = R^3 = R^4 = H, R^2 = NO_2$ (86%) $R^1 = R^3 = H, R^2 = R^4 = Br$ (50%)

$R^1 = R^3 = R^4 = H, R^2 = Cl$ (68%) $R^1 = R^3 = Me, R^2 = R^4 = NO_2$ (66%)

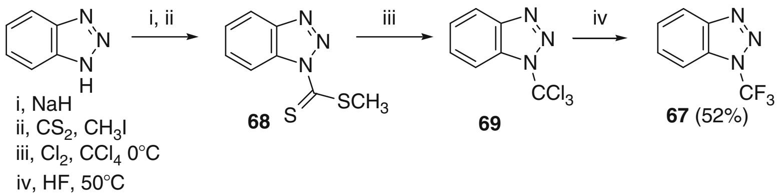
Furin et al. (2001) published a method for the synthesis of 4,4-bis(trifluoromethyl)-5-ethoxy-5-pentafluoroethyl-1,2,3-triazoline **63** based on the electrocyclic cyclization of linear vinyl azide as a precursor [68]. In the first stage of this process the perfluoro-2-methyl-2-pentene reacted with sodium azide in acetonitrile–ethanol mixture at −20 °C furnishing the vinyl azide, which at −10 °C underwent an intramolecular cyclization into an unstable intermediate **64**. In the presence of ethanol a nucleophilic attack of ethoxy anion on C=N bond of intermediate **63** occurs to form a stable product **64** [68].



Bozkurt et al. demonstrated that 5-(perfluoroheptyl)-3H-1,2,3-triazole-4-carboxylate **65** is formed in a high yield by the intramolecular cyclization of ethyl 3-azido-3-(perfluorheptyl)propenoate **66** in presence of a significant excess of sodium azide [69].

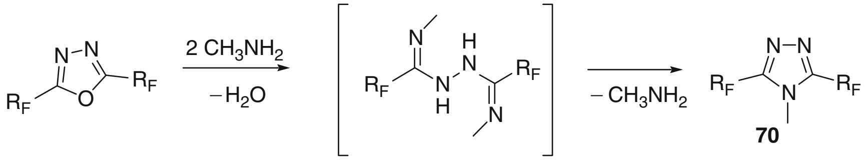


An example of the "direct" incorporation of a perfluoroalkyl group into the structure of an already formed 1,2,3-triazole was given [70]. In this paper a method of synthesis of 1-trifuoromethyl-substituted benzotriazole **67** is described by the chlorination of the corresponding methyl 1-azoledithiocarboxylates **68** followed by the fluorination of the resulting 1-trichloromethyl derivatives **69** using anhydrous HF [70].



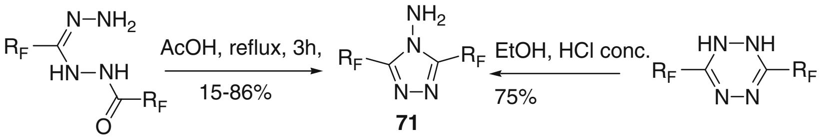
3.2 1,2,4-Triazoles

Perfluoroalkyl-1,2,4-triazoles are often formed by rearrangement of other heterocycles or by cyclization of carboxylic acid hydrazides or their analogues. In 1962 Brown and Cheng described for the first time the synthesis of 3,5-bis(perfluoroalky1)-1,2,4-triazoles **70** by treatment of bis(perfluoroalkyl)-1,3,4-oxadiazoles with methylamine [71]. The method for the synthesis of NH-unsubstituted 3,4-bis(perfluoropropyl)-l,2,4-triazole by the action of P_2O_5 on the corresponding hydrazine was also reported in this paper. Thirty years later Threadgill et al. [72] prepared 3,5-bis(trifluoromethyl)-4-(3-benzyloxypropyl)-4H-l,2,4-triazole by the reaction of 2,5-bis(trifluoromethyl)-l,3,4-oxadiazole with 3-benzyloxypropylamine in methanol (reflux, 9 days).

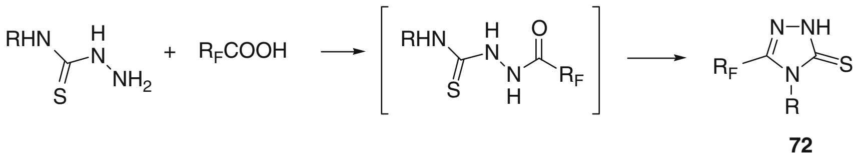


$R_F = CF_3$ (93%), C_2F_5 (94%), C_3F_7 (68%)

Brown et al. also suggested a version of the synthesis of 3,5-bis(perfluoroalkyl)-4H-1,2,4-triazoles **71** from perfluoroalkylhydrazides and from bis-(perfluoroalkyl)-1,2-dihydro-1,2,4,5-tetrazines [73].



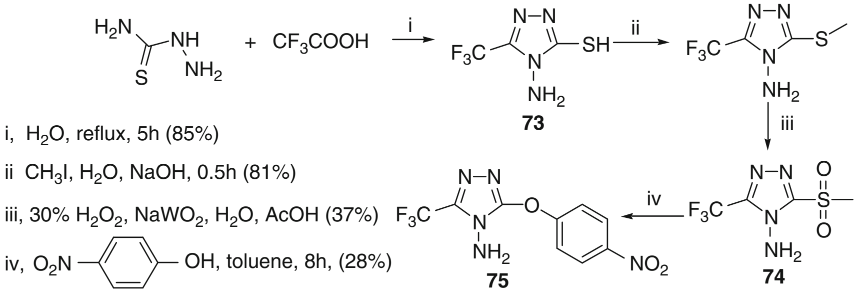
Charushin et al. demonstrated that 4-substituted thiosemicarbazides react with di- and trifluoroacetic acids to give the corresponding 3-fluoroalkyl-4,5-dihydro-1,2,4-triazole-5(1H)-thiones **72** [74].



72

R_F	R	Yield, %	R_F	R	Yield, %
CHF_2	1-pyrrolidino	36	CF_3	$4\text{-}CH_3C_6H_4$	55
CHF_2	Ph	45	CF_3	$4\text{-}FC_6H_4$	88
CF_3	piperidino	50	CF_3	Ph	70
CHF_2	$3,4\text{-}(MeO)_2C_6H_3$	35			

It should be noted that in 1998 El-Sayed and Khodairy recognized that thiones **72** are versatile substrates for the synthesis of fused and spiroheterocyclic systems [75]. Recently Chen et al. synthesized 4-amino-5-(trifluoromethyl)-4H-1,2,4-triazole-3-thiol **73** from thiocarbohydrazide [76]. The latter compound in its turn served as a reagent for the preparation of new functional triazole derivatives **74** and **75** [76].



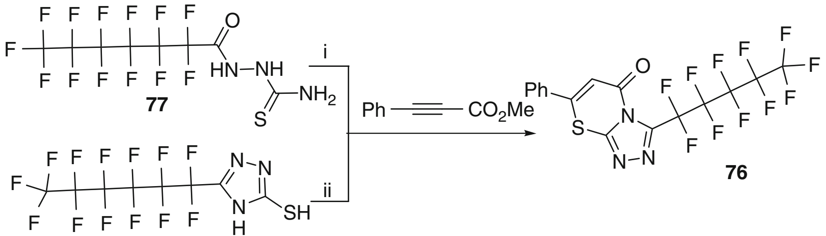
i, H_2O, reflux, 5h (85%)

ii CH_3I, H_2O, NaOH, 0.5h (81%)

iii, 30% H_2O_2, $NaWO_2$, H_2O, AcOH (37%)

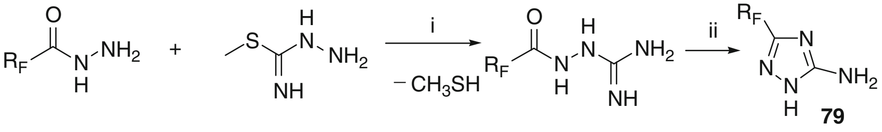
iv, $O_2N-C_6H_4-OH$, toluene, 8h, (28%)

Ivin et al. obtained 3-(perfluorohexyl)-7-phenyl-5H-[1, 2, 4]triazolo[3,4-b][1,3] thiazin-5-one **76** as a result of a reaction of methyl phenylpropynoate with a linear 1-(perfluoroheptanoyl)thiosemicarbazide **77** or a cyclic 5-(perfluorohexyl)triazole-3-thiol **78**. In both cases the reaction conditions were practically identical, and the yields of compounds containing the trifluorohexyl group in the position *3* of the 1,2,4-triazole ring were comparable [77].



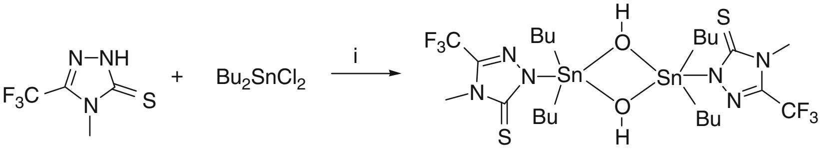
i, AcOH, reflux, 5 h, yield, 68%; ii, the same conditions, yield, 72%

Lopyrev et al. developed an original method for the synthesis of 3-perfluoroalkyl-5-amino-1,2,4-triazoles **79** in nearly quantitative yields based on the cyclization of perfluoroacylaminoguanidines that in their turn were obtained in good yields (60–81 %) from hydrazides of perfluorocarboxylic acids and S-methylisothiourea [78].



$R_F = CF_3, C_2F_5, C_3F_7, CF_3OCF_2CF_2$ i, 0.1 N NaOH, r.t., 72h; ii, 170°C, 30 min

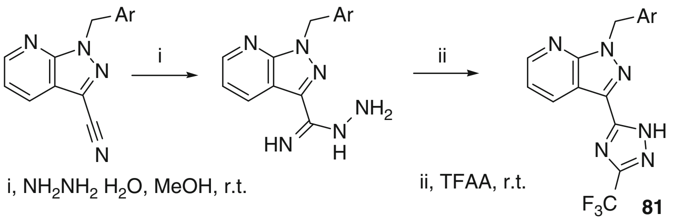
New organotin(IV) compounds with 4-methyl-5-trifluoromethyl-4H-1,2,4-triazoline-3(2H)-thione fragments **80** have been synthesized and characterized [79]. The central tin atoms of complexes is five-coordinated with distorted trigonal bipyramidal geometry.



i, EtONa, benzene, 12h, 40°C

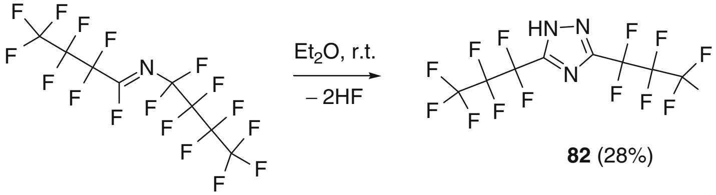
80 (85%)

The synthesis of potentially biologically active substances whose structure contained a fragment of 5-trifluoromethyl-1,2,4-triazole linked to pyrazolo- or imidazolopyridine core **81** were presented in the article of Roberts et al. [80]. One of the typical schemes of the synthesis of such compounds includes a hydrazinolysis of the cyano group. Subsequent acylation with trifluoroacetic anhydride (TFAA) followed by the closure of the triazole ring afforded **81** (yields unknown).



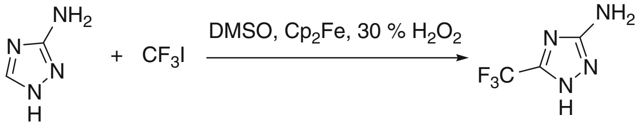
i, NH_2NH_2 H_2O, MeOH, r.t. ii, TFAA, r.t.

Siedle et al. established that the hydrazinolysis of corresponding fluoroimine occurred via particular mechanism “nucleophilic addition – HF elimination” leading to the formation of 3,5-bis(heptafluoropropyl)-1,2,4-triazole **82** [81].



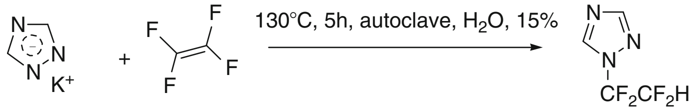
82 (28%)

An original procedure of a “direct” incorporation of a trifluoromethyl group into molecules of heteroaromatic substrates was developed by Jamakawa et al. Using this procedure 3-amino-1,2,4-triazole was trifluoromethylated by trifluoromethyl iodide in DMSO in presence of hydrogen peroxide-ferrocene system [82] to obtain 3-amino-5-trifluoromethyl-1,2,4-triazole **83**.



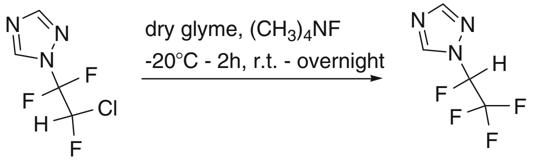
83

Yagupolskii et al. developed various versions of the alkylation of 1,2,4-triazolate anion with fluoroethylene [83] to form 1-(1,1,2,2-tetrafluoroethyl)-1,2,4-triazole **84** in a low yield.



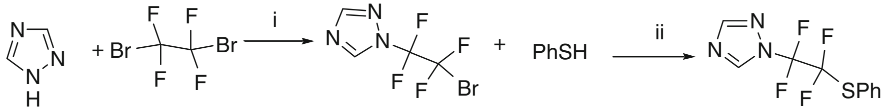
84

The same authors developed an original method of the synthesis of 1-(1,2,2,2-tetrafluoroethyl)-1,2,4-triazole **85** by treatment of N-(2-chloro-1,1,2-trifluoro)-1,2,4-triazole with tetramethylammonium fluoride [83]. The assumed reaction mechanism consist of several steps. In the first stage elimination of HF and the formation of 2-chloro-1,2-difluoroethylene derivative takes place. Further chlorine atom is replaced by fluorine with the formation of 1,2,2-trifluoroethylene-1,2.4-triazole. Finally addition of HF gave the final product **85**.



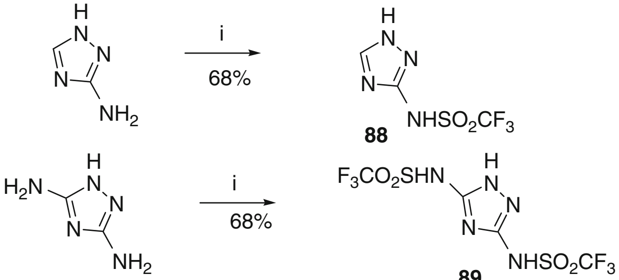
85 (40%)

In extension of this study the sodium salt of 1,2,4-triazole was alkylated with 1,2-dibromotetrafluoroethane (Freon 114B2) to obtain N-(2-bromotetrafluoroethyl)-1,2,4-triazole **86**. This compound was then subjected to photoinduced (UV-irradiation) reaction with thiophenol in liquid ammonia. Selective nucleophilic substitution of bromine with thiophenol residue was achieved under these conditions. As a result N-(2-phenylthiotetrafluoroethyl)-1,2,4-triazole **87** was obtained in a high yield [84, 85].



i, DMF, NaH, Bu_4NI, 2h, 55°C, 63% **86** ii, NH_3, hν, (Hg, 950w), 86% **87**

Lately Garg and Shreeve suggested a simple synthesis of trifluoromethanesulfonamide derivatives of 3-amino- and 3,5-diamino-1,2,4-triazoles **88, 89** from the corresponding aminoazoles and trifluoromethanesulfonyl fluoride [86].

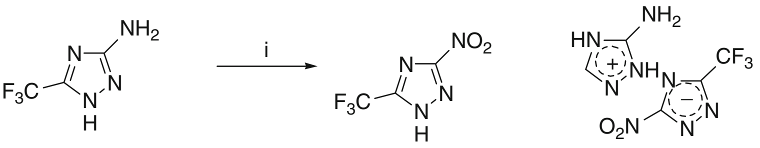


88

89

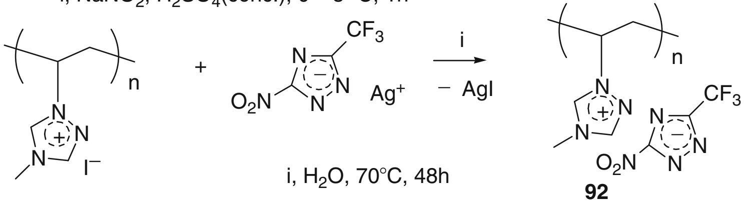
i, CF_3SO_2F, MeCN, Et_3N, r.t., 10-12 h

New energetic materials were prepared from by perfluoroalkyl-1,2,4-triazoles. For instance, Shreeve et al. obtained 3-nitro-5-trifluoromethyl-1,2,4-triazole **90** by the diazotization of 3-amino-5-trifluoromethyl-1,2,4-triazole in the concentrated sulfuric acid [87]. In its turn 3-amino-1,2,4-triazole and 3-nitro-5-trifluoromethyl-1,2,4-triazole were used in the preparation of energetic 3-amino-1,2,4-triazolium 3-nitro-5-trifluoromethyl-1,2,4-triazolate **91**. Energetic polymeric material **92** was synthesized containing in the monomer unit ions of 3-nitro-5-trifluoromethyl-1,2,4-triazolate. The yield of polymer is unknown [88].



90 (55%) **91**

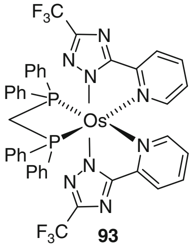
i, $NaNO_2$, H_2SO_4(conc.), 0 – 5 °C, 1h



i, H_2O, 70°C, 48h

92

The perfluoro-1,2,4-triazoles are known to be effective ligands. For instance, a number of charge neutral Os(II) pyridyl-1,2,4-triazolate complexes with either bis(diphenylphosphino)methane **93** or *cis*-1,2-bis(diphenylphosphino)ethene **94** chelates were synthesized, and their structural, electrochemical, photophysical properties and thermodynamic relationships were established [89, 90]. Chi, Carty et al. synthesized 6-(3-trifluoromethyl-1,2,4-triazolyl)-2,2'-bipyridine and built up on this basis tridentate 6-azolyl-2,2′-bipyridine chelate complex compounds of Ga and In **95** [91].



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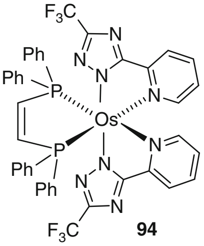

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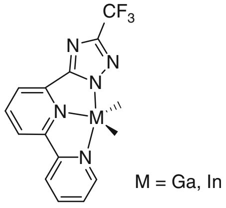
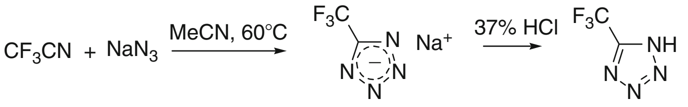


95

Among trifluoromethyl-derivatives of 1,2,4-triazole, an efficient inhibitors of dipeptidyl peptidaze IV (sitagliptin and its derivatives) have been found (see Sect. 6.1).

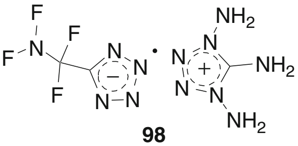
3.3 Tetrazoles

5-Trifluoromethyltetrazole **96** – the simplest of tetrazoles containing a perfluoroalkyl substituent – was prepared for the first time by Norris in 1962 by the cycloaddition of the azide-anion to the trifluoroacetonitrile [92]. This reaction occurred with a considerable heat evolution. The conversion of corresponding anion **97** into the neutral form required the use of concentrated mineral acids due to the relatively high NH-acidity of tetrazole **96** (pK_{BH+} 1.1) [28, 93]. It was shown later that the 5-trifluoromethyltetrazole **96** could be obtained reacting CF_3CN with coordinated azides similarly to the synthesis of 4,5-bistrifluoromethyl-1,2,3-triazole **40** [44].



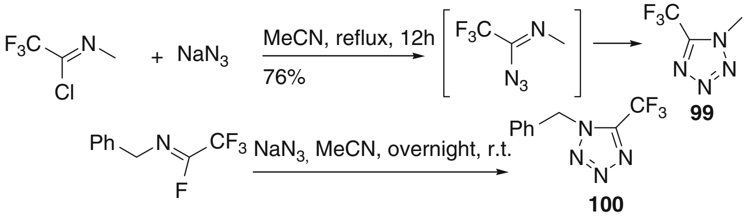
97 (75%) **96** (83%)

To explore the properties of some energetic salts **98**, in a series of publications Shreeve et al. described the procedure of the synthesis of NH-5-difluoroaminodifluoro methyltetrazole by same manner for which F_2NCF_2CN was used as a precursor [94].

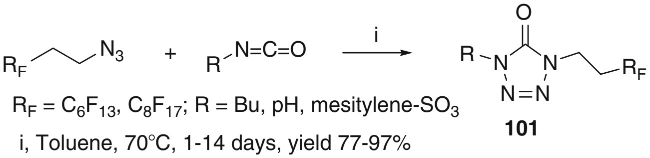


98

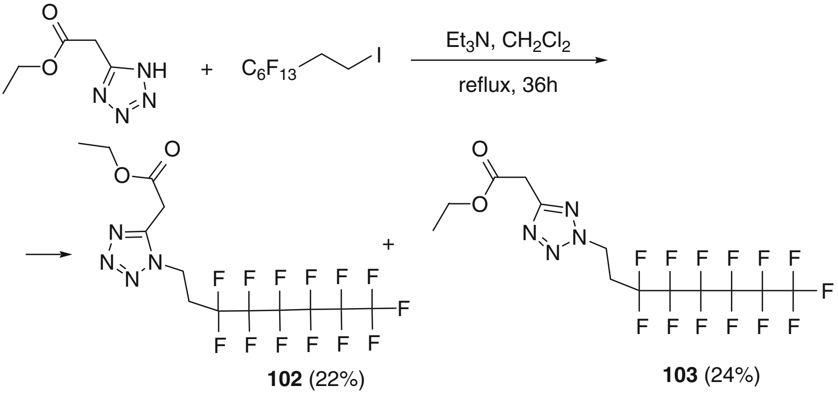
The 1-substituted 5-trifluoromethyltetrazoles may be also obtained by the azidation of imidoyl halides. For instance, the nucleophilic substitution of the chlorine for the azide group in the N-methylimidoyl chloride provided the corresponding imidoyl azide (azidoazomethine), which suffered a cyclization into 1-methyl-5-trifluoromethyltetrazole **99** [95]. Carpenter et al. synthesized 1-benzyl-5-trifluoromethyltetrazole **100** by replacing the fluorine atom in N-benzyltrifluoroacetimidoyl fluoride by an azide group followed by electrocyclic cyclization of the intermediate imidoyl azide (azidoazomethine). The yield of purified product **100** is unknown [39].



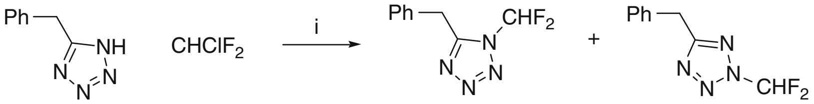
1,3-Dipolar cycloaddition of perfluoroalkylethyl azides to isocyanates afforded 1-perfluoroalkyl-4-(*n*-Bu, phenyl or mesitylsulfonyl) tetrazol-5-ones **101** in good yields [96].



The synthesis of surfactants in the series of fluoroalkyltetrazoles **102**, **103** and the study of their effect on the surface tension of *m*-xylene was described by Read et al. [50, 97].



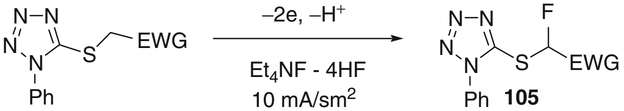
The synthesis of N-fluoroalkyltetrazoles may be carried out also by the alkylation of the corresponding NH-unsubstituted tetrazoles. Jończyk et al. showed that 5-benzyl-1H-tetrazole reacted with chlorodifluoromethane in the presence of concentrated aqueous sodium hydroxide and a catalyst, benzyltriethylammonium chloride (TEBAC), in THF with the formation of regioisomeric N-difluoromethyl substituted derivatives **104, 105** [98].



i, 50% aq NaOH, TEBAC, THF, CH_2Cl_2

104 (23%) **105**(15%)

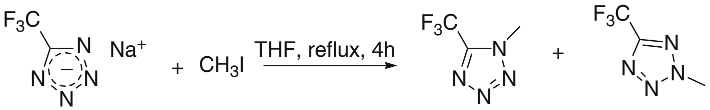
An interesting approach to the synthesis of tetrazoles with fluorine atoms in the side chain was suggested by Fuchigami et al. who performed an anodic monofluorination of 1-substituted 5-tetrazolyl sulfides containing an α-electron-withdrawing group (EWG) leading to the formation of the corresponding C-F derivatives **105** [99].



105

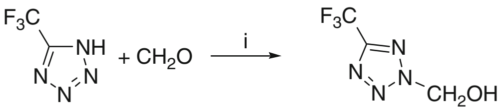
EWG, Solvent, Yield, %: Ph, DME, 38; CO_2Et, MeCN, 46; CN, MeCN, 20

Norris in his pioneering article described also some chemical transformations of 5-trifluoromethyltetrazole **96** [92]. For instance, the alkylation of anion **97** with methyl iodide resulted in regioisomeric N-methyl-5-trifluoromethyltetrazoles **106**, **107** with 2-methyl isomer **107** prevailing. Also a direct halogenation was performed of the 5-trifluoromethyltetrazole sodium salt with the molecular chlorine furnishing the N-chloroderivative of 5-trifluoromethyltetrazole that was found an explosive extremely dangerous at handling [92].



97 **106** (9.8%) **107** (55%)

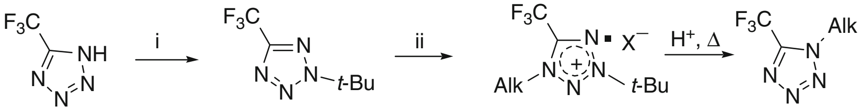
The high regioselectivity of tetrazolate **97** alkylation in the environment of aqueous acetone giving predominantly the 2H-isomer was later noted also by Spear et al. [100]. 5-Trifluoromethyltetrazole **96** slowly reacts with formaldehyde in water solution at pH 5 giving 2-hydroxymethyl-5-trifluoromethyltetrazole **108** [101]. Later the role of the electronic effects of the substituents at the endocyclic carbon of the tetrazole, and also the influence of the solvation effects on the alkylation regioselectivity of tetrazoles was treated in detail in quite a number of theoretic and experimental publications [28, 102].



96 **108**

i, H_2O, r.t., 72h, 80%

Uncompromising regioselectivity of exhaustive alkylation of 2-substituted 5-trifluoromethyltetrazoles was exploited in a recently developed elegant procedure for the synthesis of 1-alkyltetrazoles starting from *N*-unsubstituted ones. This three-step reaction sequence utilizing an N^2-regioselective *t*-butylation (the product is compound **109**) in the first step, was reported to provide isomerically pure products **110** in high to nearly quantitative yields [103, 104].

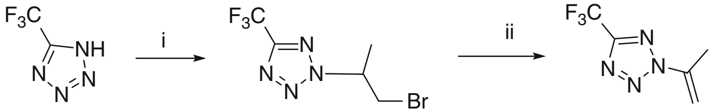


96 **109** **110**

i, *t*-BuOH, 96% H_2SO_4, r.t., 40 min, 92%

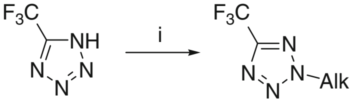
ii, AlkX, Alk = Me, Et, *n*-Bu; X = OSO_2OMe, OSO_2Ph, TsO, OEt_2 BF_3

2-(1-Methylvinyl)-5-trifluoromethyltetrazole **111** was obtained by the regioselective alkylation of 5-trifluoromethyltetrazole with 3-bromopropene in sulfuric acid followed by dehydrohalogenation of the intermediate products [105].



96 **111**

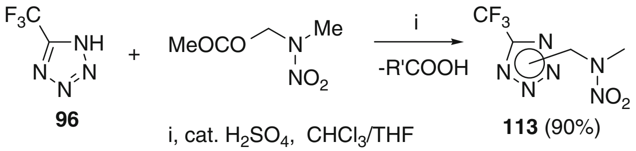
Generally, alcohols, readily generating carbenium cations in the presence of acidic catalysts, were found to react with *NH*-unsubstituted 5-trifluoromethyltetrazole **96** yielding N^2-alkylated products **112** [28, 103]. The reaction can be carried out in neutral organic solvents (chloroform, dichloromethane, acetonitrile, nitromethane) in the presence of catalytic amounts of sulfuric or *p*-toluenesulfonic acids as well as Lewis acids like boron trifluoride etherate or zinc triflate.



96 **112**

i, *t*-BuOH, $CHCl_3$, H_2SO_4 cat., yield 85%

Alkylation of 5-trifluoromethyltetrazole **96** with esters of 2-nitro-2-azapropanol in the presence of catalytic amounts of sulfuric acid was described [106]. Here the regioselectivity of the process was not assessed and a mixture of 1- and 2-alkyltetrazoles **113** (the ratio is unknown) was obtained.

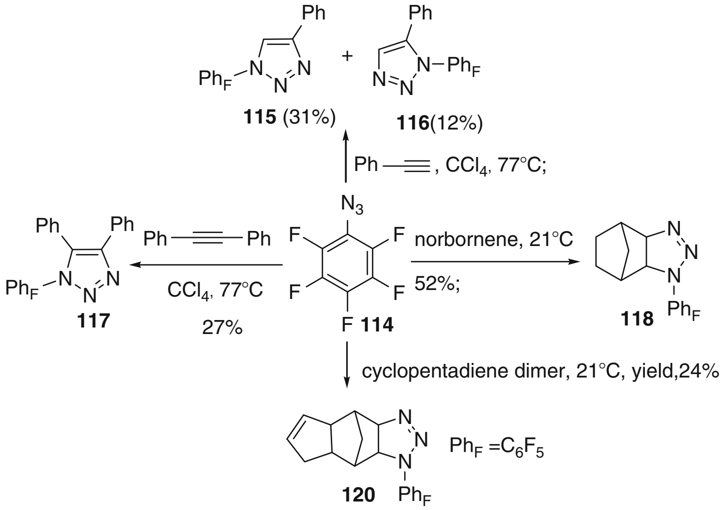


Gaponik et al. found that the NH-unsubstituted 5-trifluoromethyltetrazole in the systems containing transition metal salts formed water-soluble polymeric complexes [107].

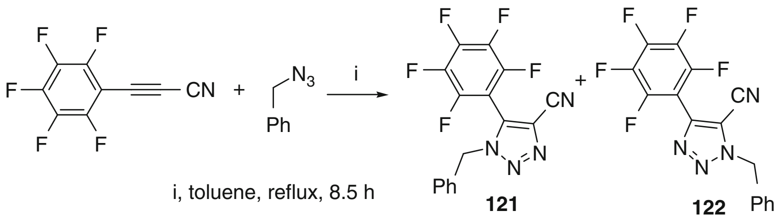
4 Perfluoroaryl and Fluorobenzo-Fused Heterocycles

4.1 1,2,3-Triazoles

Banks and Prakash were first to demonstrate the wide opportunities of the 1,3-dipolar cycloaddition of 1-azido-2,3,4,5,6-pentafluobenzene **114** to acetylenes as the general method of the synthesis of 1,2,3-triazoles **115–120** containing a perfluorophenyl group at the endocyclic nitrogen atom [108].

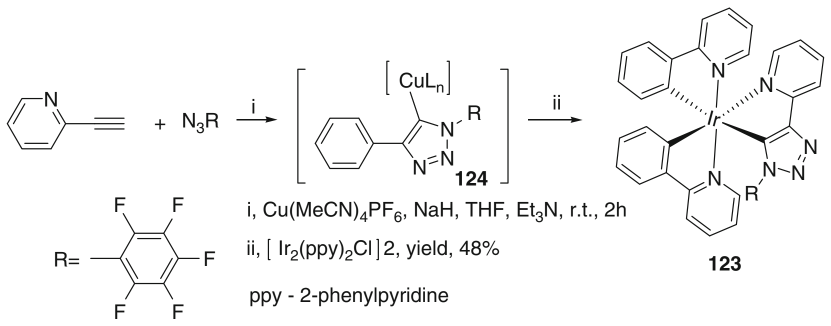


1,3-Dipolar cycloaddition of benzyl azide to 3-(2,3,4,5,6-pentafluorophenyl) propynenitrile resulted in the formation of isomeric 1,2,3-triazoles **121, 122** in 17 and 61 % yield respectively [109].



i, toluene, reflux, 8.5 h

Swager et al. synthesized various Ir(III) complexes **123**, among them complexes containing a perfluoroaryl substituent [110]. The method of building up these structures is underlain by the "click-reaction" leading to the formation of the corresponding Cu(I)-triazolide intermediate **124**.

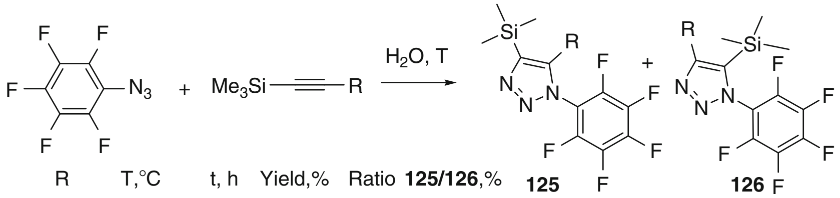


i, Cu(MeCN)$_4$PF$_6$, NaH, THF, Et$_3$N, r.t., 2h

ii, [Ir$_2$(ppy)$_2$Cl]2, yield, 48%

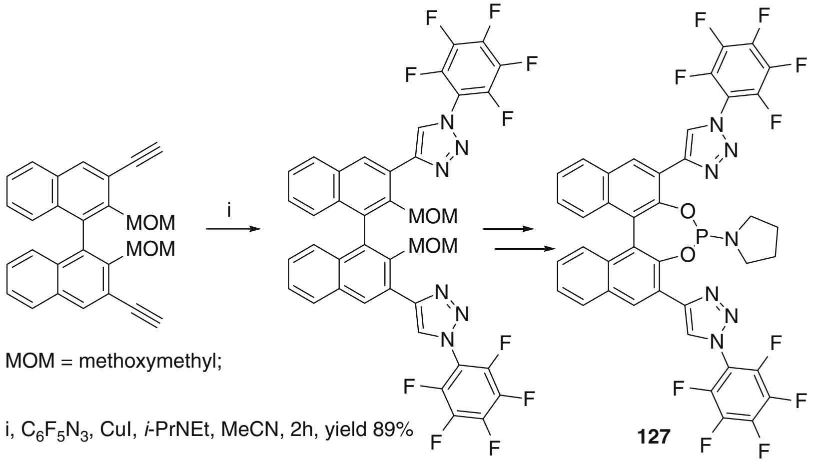
ppy - 2-phenylpyridine

Schubert et al. subjected to a systematical examination reactions of 1,3-[3 + 2]-cycloaddition of substituted aromatic azides to trimethylsilylacetylenes in water affording regioisomeric 1,2,3-triazoles, in particular, those containing a perfluoroaryl substituent at endocyclic atoms of the heterocycle **125, 126** [111].



R	T,°C	t, h	Yield,%	Ratio **125/126**,%
Mesityl	110	30	61	>91
p-NO$_2$C$_6$H$_4$	110	17	28	87
CO$_2$Et	85	5	92	22

Recently, a number of chiral phosphoramidite ligands **127** containing 1,2,3-triazole ring at the 3,3′-positions of the binol scaffold were synthesized by McErlean et al. [112].

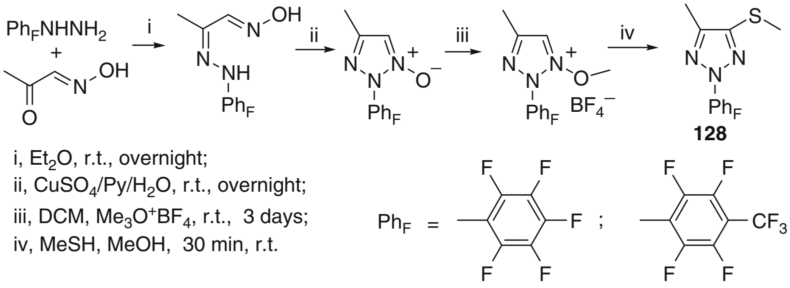


MOM = methoxymethyl;

i, $C_6F_5N_3$, CuI, *i*-PrNEt, MeCN, 2h, yield 89%

127

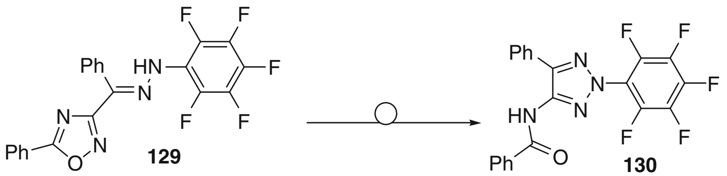
O'Mahony et al. [113] advanced an alternative version of cyclization resulting in perfluoroaryl-1,2,3-triazoles. These authors demonstrated that 2-(2,3,4,5,6-pentafluorophenyl)-4-methyl-5-methylthio-1,2,3-triazole **128** obtained by this procedure (yield is unknown) possessed considerable pesticide activity.



128

i, Et_2O, r.t., overnight;
ii, $CuSO_4/Py/H_2O$, r.t., overnight;
iii, DCM, $Me_3O^+BF_4$, r.t., 3 days;
iv, MeSH, MeOH, 30 min, r.t.

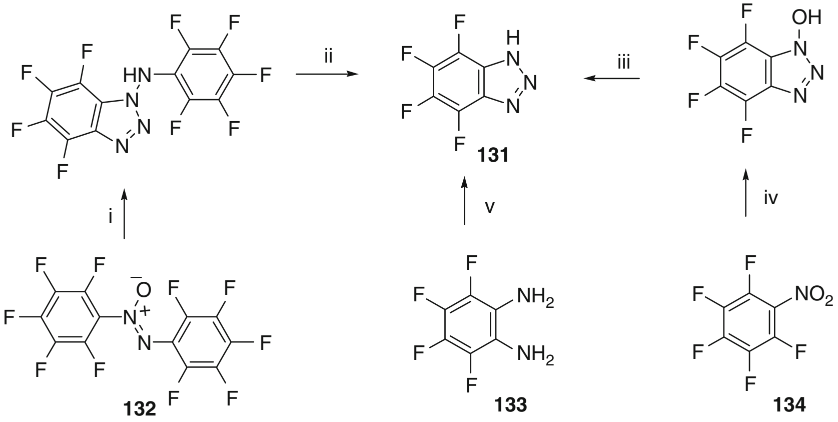
The paper of Frenna, Spinelli et al. contained data on the kinetics of the rearrangement of 3-benzoyl-5-phenyl-1,2,4-oxadiazole **129** into the corresponding 2-aryltriazoles **130** (Boulton–Katritzky reaction) [114].



129

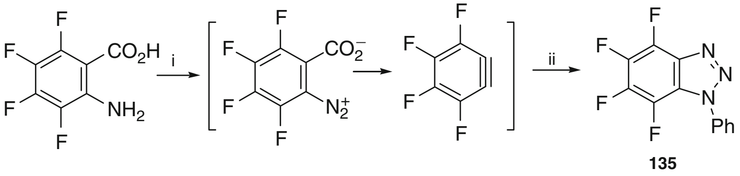
130

Haszeldine in 1970 developed several routes for the synthesis of perfluorobenzo-fused 1,2,3-triazole **131** from decafluoroazoxybenzene **132**, tetrafluoro-o-phenylenediamine **133**, and 2,3,4,5,6-pentafluoronitrobenzene **134** [115]. More than a quarter of a century later Heaton et al. suggested a similar version of the synthesis of tetrafluorobenzotriazole **131** from 1,2,3,4-tetrafluoro-5,6-dinitrobenzene and 3,4,5,6-tetrafluoro-1,2-phenylenediamine that were regarded as versatile semiproducts in the synthesis of various tetrafluorobenzoheterocycles [116].



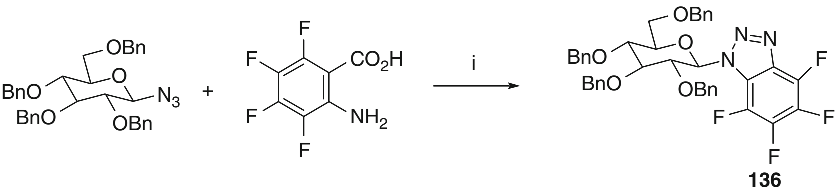
i, NH_2NH_2 H_2O, EtOH, yield, 28%; ii, HI, yield, 22%; iii, HI, almost 100%;
iv, $NH_2NH_2H_2O$, EtOH, yield,14%; v, HNO_2, yield, 84%

The synthesis of 1-phenyl-4,5,6,7-tetrafluorobenzotriazole **135** from tetrafluoroanthranilic acid through tetrafluorodehydrobenzene as intermediate is described by Yakobson et al. in 1967 [117].



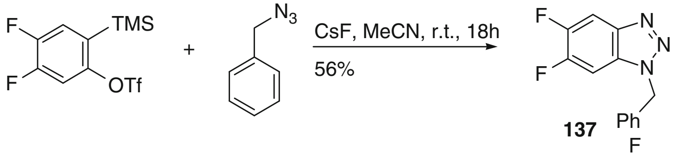
i, BuONO, CH_2Cl_2,2h, reflux ii, $C_6H_5N_3$, acetone, yield 35%

Williams et al. reports that 1-(2,3,4,5-tetra-O-benzyl-β-*D*-glucosyl)-3,4,5,6-tetrafluoro-1–H-benzo[d][1,2,3]-triazole **136** can be prepared from available anomeric azide and 2-amino-3,4,5,6-tetrafluorobenzoic acid through “click” methodology [118].



i, 1 equiv. azide, 3 equiv. of anthranilic acid, dioxane, 5 equiv. isoamil nitrite (CH_2Cl_2), 30 min, reflux under N_2, yield 42%

Recently “click-chemistry” approach to the preparation of fluorobenzo-fused 1,2,3-triazole **137** was demonstrated in the paper of Larock et al. [119]. Zhang and Moses developed a special version of one-pot “click-chemistry” for the preparation of monofluoro derivatives of benzotriazole **138**, **139** from *p*-methoxyaniline and *o*-fluoroanthranilic acid with two *in situ* generated intermediates: *p*-methoxyphenyl azide and fluorobenzyne [120].



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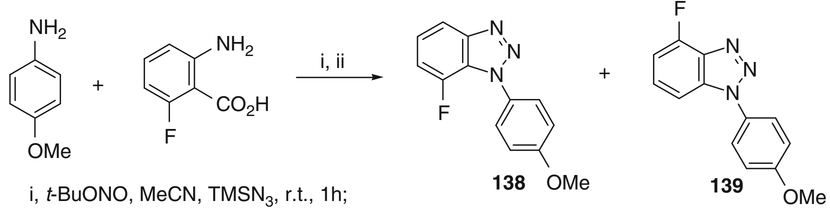
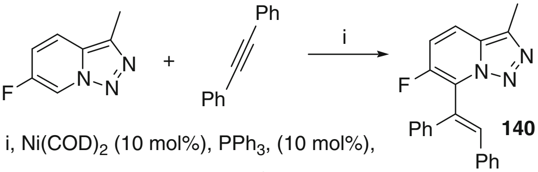


138 **139**

i, *t*-BuONO, MeCN, $TMSN_3$, r.t., 1h;

ii, *o*-fluoroanthranilic acid, *t*-BuONO, MeCN, reflux, 15h, yield, 36%, **138/139** =1:1

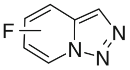
Driver et al. explored the Ni-catalyzed C7-alkenylation of 6-fluorotriazolopyridine with diphenylacetylene applying bis-(1,5-cyclooctadiene)nickel(0) ($Ni(COD)_2$) leading to the formation of fluorobenzotriazole **140** [121]. It was underlined in the article that the crucial importance for the high conversion of the reagents and the sufficient yields of the alkenylation products had the selection of the Lewis acid which was $AlMe_3$ in this study.



140

i, $Ni(COD)_2$ (10 mol%), PPh_3, (10 mol%), $AlMe_3$ (1.2 eq), toluene, 70°C, yield, 71%

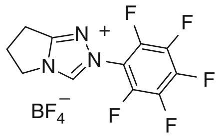
Some isomers of fluorobenzotriazoles are capable of ring-chain rearrangements with the opening of the triazole ring. Elguero, Alkorta et al. performed a quantum-chemical investigation of the ring-chain isomerization of fluoro derivatives of 1,2,3-triazolopyridines **141** [122].



141

4.2 1,2,4-Triazoles

Efficient enantioselective catalysts of various organic reactions were found among pentafluoroaryl-1,2,4-triazoles. Tetrafluoroborates of 2-(2,3,4,5,6-pentafluorophenyl)-1,2,4-triazolium **142–147** are practically useful compounds. The synthesis and application examples of these catalysts are presented in the series of publications [123–129].



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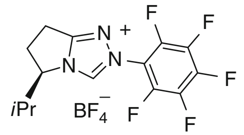

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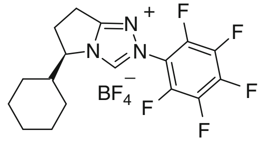

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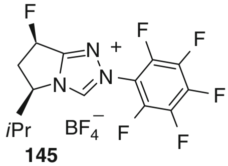

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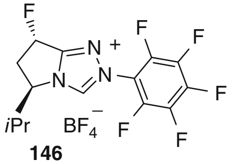

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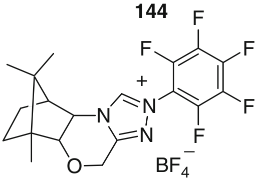
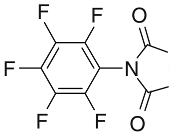


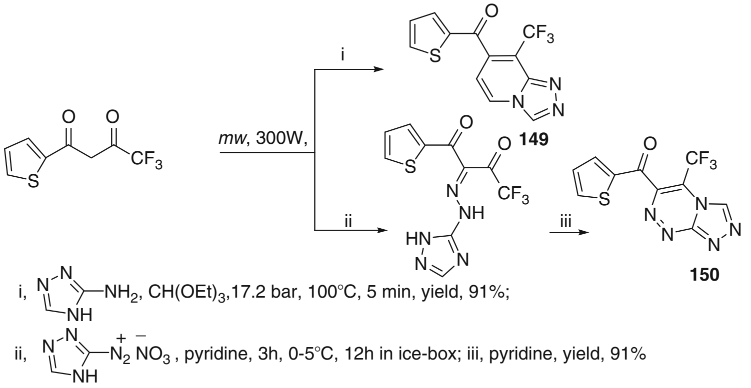
147

As it was shown by Golding et al., 4-(2,3,4,5,6-pentafluorophenyl)-1,2,4-triazoline-3,5-dione **148** belonging to perfluoroaryl-1,2,4-triazoles is an efficient reagent for trapping volatile organic compounds (VOCs) included in the list of the most important environmental pollutants [130].

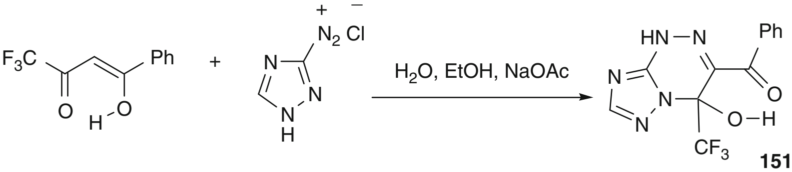


148

Shaaban showed the possibility to obtain under the microwave irradiation fused systems, 1,2,4-triazolo[1,5-a]pyrimidine **149** and 1,2,4-triazolo[3,4-c][1, 2, 4]triazine **150**, containing a trifluoromethyl group as a substituent in the six-membered ring [131].



Saloutin, Chupakhin et al. applied a related condensation involving 1,2,4-triazolyldiazonium resulting in the formation of 6-benzoyl-7-hydroxy-7-trifluoromethyl-4,7-dihydro[1,2,4]triazolo[5,1-c][1,2,4]triazine **151** (59 %) [132]. Rusinov et al. reported on another successful example of this reaction involving lithium β-diketonates and 3-amino-1,2,4-triazole and affording 7-fluoromethyl-1,2,4-triazolo[1,5-a]pyrimidine **152** [133].



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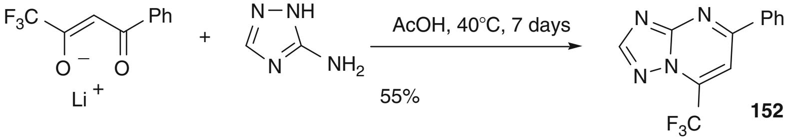
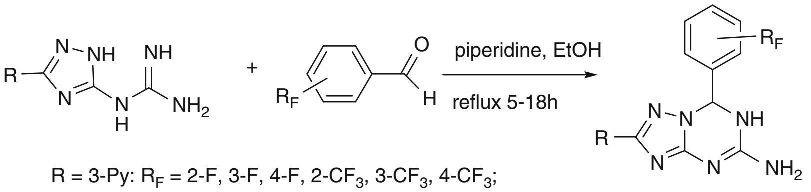


152

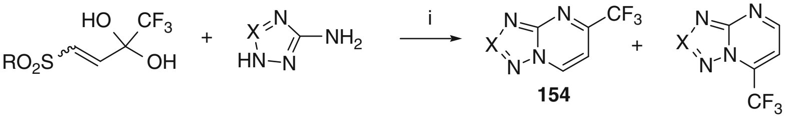
Dolzhenko et al. synthesized 12 new fluorinated 7-aryl-2-pyridyl-6,7-dihydro[1,2,4]triazolo[1,5-a][1,3,5]triazin-5-amines **153** via three-step procedure starting from (iso)nicotinic hydrazides [134].



R = 3-Py: R_F = 2-F, 3-F, 4-F, 2-CF_3, 3-CF_3, 4-CF_3;
R = 4-Py: R_F = 2-F, 3-F, 4-F, 2-CF_3, 3-CF_3, 4-CF_3

153 85-93%

Nenajdenko et al. obtained regioisomeric 5-CF_3 or 7-CF_3 triazolopyrimidines **154**, **155** by the reaction of 1,1,1-trifluoro-4-sulfonyl-but-3-ene-2,2-diol with 3-amino-1,2,4-triazole [135].

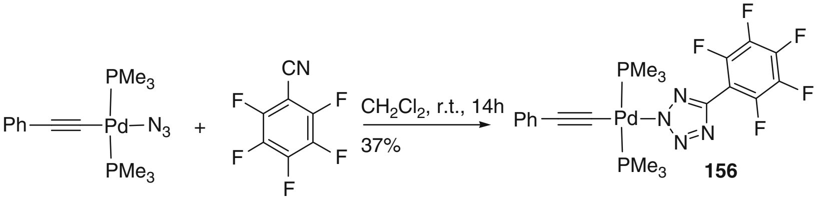


154 **155**

R = Ph, Me; i, reflux: H_2O, or AcOH, or MeCN, yield, 70-90%
X = HC, MeC, CF_3C, (1-Ad)C, *t*-BuC, PhC, 4-$MeOC_6H_4C$, 4-ClC_6H_4C, 2-BrC_6H_4C, MeO_2CC

4.3 Tetrazoles

Kim et al. showed that 1,3-dipolar cycloaddition of alkynyl Pd(II) azido complexes to perfluorobenzonitrile proceeded at room temperature affording the corresponding N-coordinated tetrazolato compound (*trans*-[Pd(C≡CPh)(N_4C-C_6F_5)($(PMe_3)_2$)]) **156** [136].



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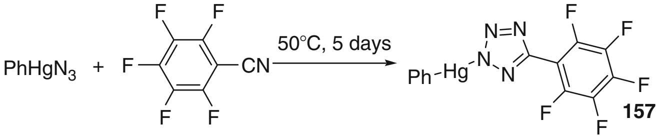
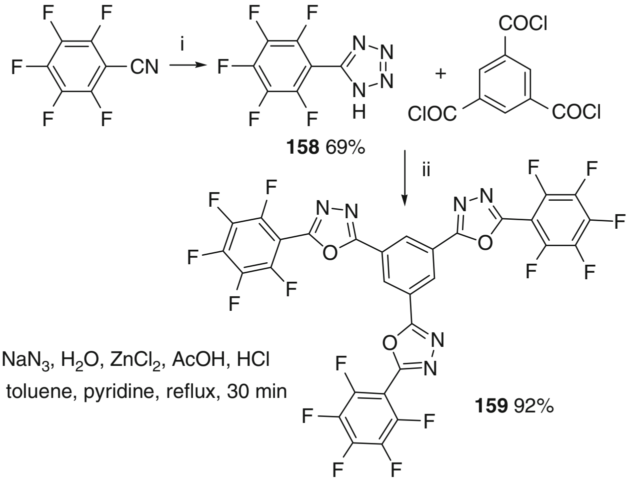
Klapötke et al. obtained recently by the intermolecular 1,3-dipolar cycloaddition of organomercury(II) azide to pentafluorocyanobenzene the corresponding (5-pentafluorophenyl-2H-tetrazol-2-yl)phenylmercury **157** (yield is unknown) [137].



157

The synthetic methods and photoluminescent properties of new dendrimers with an electron-deficient fluorinated starburst oxadiazole core were discussed in the publication of Chen, Fan et al. [138]. Here in the first, key stage the 1,3-dipolar cycloaddition occurred of 2,3,4,5,6-pentafluorobenzonitrile to NaN_3 along the known procedure (Demko-Sharpless) giving 5-(perfluorophenyl)-1H-tetrazole **158**. In the next stage 5-(perfluorophenyl)-1H-tetrazole was acylated by benzene-1,3,5-tricarbonyl trichloride to obtain 1,3,5-(5-perfluorophenyl-1,3,4-oxadiazol-2-yl)benzene **159**.

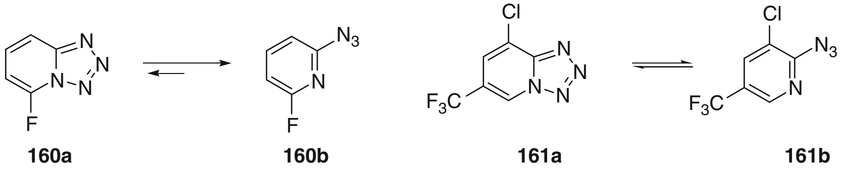


158 69%

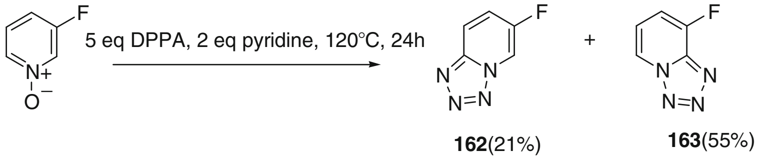
i, NaN_3, H_2O, $ZnCl_2$, AcOH, HCl
ii, toluene, pyridine, reflux, 30 min

159 92%

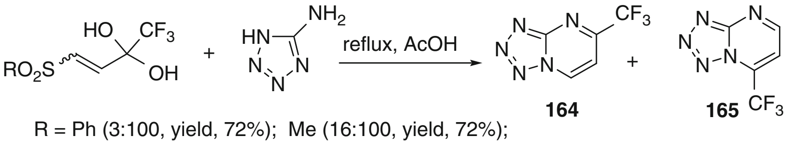
The fused tetrazoles are prone to ring-chain isomerism. Cmoch and Korczak investigated the azido-tetrazole equilibrium between two fluorine-containing tetrazoles: 6-fluorotetrazolopyridine **160** and 6-trifluoromethyl-8-chlorotetrazolopyridine **161** [139]. It turned out that the equilibrium in the case of compound **160** is completely shifted to the side of azide **160b**, whereas for compound **161** the NMR spectra showed the presence of both tetrazole **161a** and azide **161b** forms.



Keith (2006) developed an original one-stage solvent-free method of preparation of fluorine-containing tetrazolo[1,5-a]pyridines **162**, **163** forming in a plausible yield from the corresponding pyridine N-oxide and activated diphenylphosphorazidate (DPPA) in the presence of pyridine [140]. In this case the azido-tetrazole equilibrium is virtually totally shifted to the ring form.



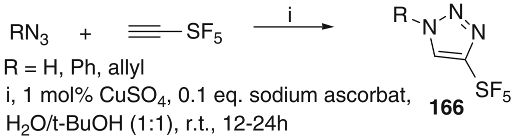
In the above cited paper [135] it was also reported that the reaction of 1,1,1-trifluoro-4-sulfonylbut-3-ene-2,2-diol with 5-aminotetrazole furnished regioisomeric 5-CF_3 or 7-CF_3 tetrazolopyrimidines **164**, **165**. It was also shown that the ratio of the regioisomers (at equal overall yield of the products) was governed by the nature of the substituent R in the 1,1,1-trifluoro-4- sulfonylbut-3-ene-2,2-diol.



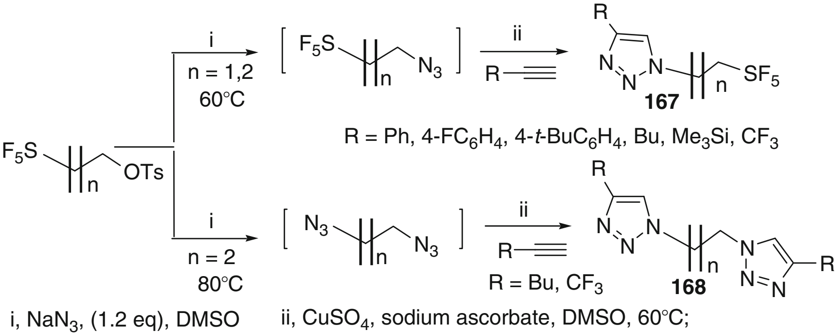
5 Other Types of Perfluorinated Substituents

5.1 *SF_5 Derivatives*

Pentafluorosulfanyl (SF_5) group is interesting as a stable moiety bearing simultaneously five fluorine atoms. In recent reviews [141, 142] it was stressed that this group is now widely applied in the organic synthesis and in industry. 1,2,3-Triazoles containing the SF_5 group attached to the endocyclic carbon atoms became recently more accessible. A number of publications describes the acceleration of the 1,3-dipolar cycloaddition with the use of the catalytic system based on Cu(I) generated *in situ* from $CuSO_4$ and sodium ascorbate. This procedure made it possible to obtain in relatively mild conditions a series of 1-R-4-pentafluorosulfanyl-1,2,3-triazoles **166** in "good yield" [62, 143].



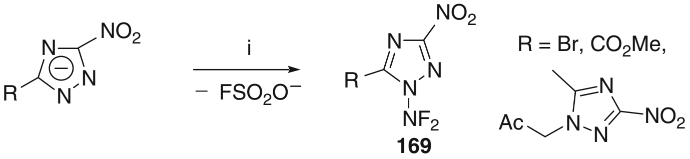
It should be noted that the recent advances in the chemistry of trifluoromethyl- and pentafluorosulfanyl derivatives of tri- and tetrazole favor the applied studies of these unique objects of the chemistry of the fluoro-containing heterocycles. Thus a significant attention is paid to 1,2,3-triazoles and tetrazoles containing a pentafluorosulfanyl group. The introduction of this group into the heterocycle provides a possibility to prepare energetic compounds of high density [142]. Shreeve et al. investigated the 1,3-dipolar cycloaddition of alkyl azides containing a terminal pentafluorosulfanyl group to substituted acetylenes [144].



In this case the yield of pentafluorosulfanylalkyl-4-R-1,2,3-triazoles **167** crucially depends on the ratio of the initial reagents and on the reaction temperature. At the excess of the sodium azide and at a high temperature the replacing azidation occurs of both the tosyl and the pentafluorosulfanyl groups giving the corresponding diazide and further bis-1,2,3-triazoles **168** in good yields [144].

5.2 NF_2 Derivatives

Tri- and tetrazoles containing an NF_2 group at the endocyclic nitrogen or carbon atoms belong to an exotic group of highly energetic compounds. The combination in the same molecule of the polynitrogen heterocyclic ring and the electron-acceptor difluoroamine group enhanced the energy potential of these molecules. The prospect of application of the difluoroamino derivatives of 1,2,4-triazole as components of energetic ionic liquids was estimated by the *ab initio* quantum-chemical calculations [21]. In the evaluation of the application prospects of the N-difluoroazoles their high sensitivity to explosive decomposition caused by various effects (impact, friction, electric discharge, fire beam) should be taken into consideration [94, 145, 146]. In an original article Shevelev et al. [147] reported on the preparation of NF_2 derivatives of 3-nitro-1,2,4-triazole **169** by the action of O-fluorosulfonyl-N,N-difluorohydroxylamine (F2NOSO2F) on NH-form of the corresponding 1,2,4-triazoles.



i, F_2NOSO_2F, PTC: polyester PEG-400, $NaHCO_3$ aq, yield, 22-50%

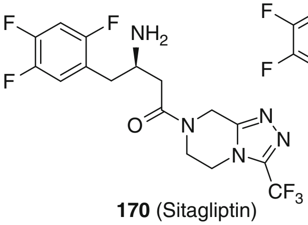
6 Applications

6.1 Medicine and Medicinal Chemistry

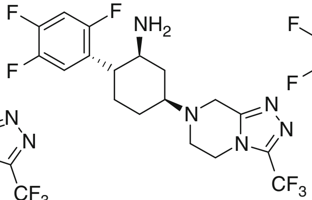
The medicinal applications of fluorinated tri- and tetrazoles grow steadily [148]. Some compounds containing in their molecular structure these heterocycles are included in the list of highly efficient modern drugs [149]. Many among fluorinated tri-and tetrazoles are regarded as promising antidiabetic, cardiological, fungicidal, antibacterial, and antiviral pharmaceuticals, drugs for the treatment of the central nervous system, etc. We give below some examples of these compounds exhibiting versatile kinds of biological activity.

6.1.1 Antidiabetics

Sitagliptin **170**, the first inhibitor of dipeptidyl peptidase IV (DPP-4) approved by the FDA for the treatment of type 2 diabetes, has a trifluorophenyl group linked to a β-amino butanoyl moiety coupled to a triazolopiperazine [150, 151]. Many publications appeared treating the problem of the synthesis of this compound and its derivatives. For instance, a scheme of asymmetric synthesis of the sitagliptin phosphate from the precursor, α,β-enamine amide, is given in [152]. A wide search for effective antidiabetic agents was performed among the homologues of this compound; therewith the varied structural parameter was the substituent in the phenyl ring [153] and also the substituents in the piperazine fragment [154]. Biftu et al. based on the data of XRD analysis and computer simulation proposed a structure and synthesized a new analogous compound **171** that also proved to be an efficient inhibitor of DPP-4 (IC50 = 21 nM), showed high activity *in vivo* and possessed a feasible pharmacokinetic profile [155]. Note an interesting study of Chen et al. who synthesized and tested the biological activity of a series of Sitagliptin analogs in whose molecules the fragment of 3-trifluoromethyl-1,2,4-triazolopiperidine was replaced by 4R-1,2,3-triazolopiperidine moiety. The highest biological activity was found in compound **172** [156].



170 (Sitagliptin)



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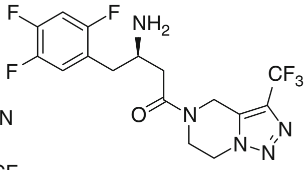

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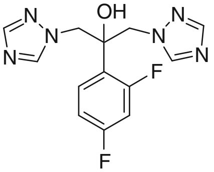
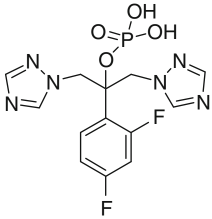
6.1.2 Fungicides

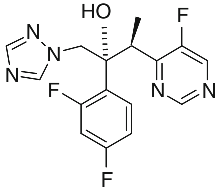
The following fluoroaryl derivatives of 1,2,4-triazole belong to the third generation fungicides: Fluconazole **173**, Fosfluconazole (prodrug) **174**, Voriconazole (UK 109496) **175**, Itraconazole **176** [4]. All these compounds are the inhibitors of the fungal cytochrome P450 enzyme 14α-demethylase. Recently results were published of the investigation of the fungicidal activity of the derivatives of 3-trifluoromethyl-1,2,4-triazole-5-thione: one among these substances, **177,** exhibited a high activity [157]. At present the research is carried out on the preparation of active pharmaceutical ingredients of new fungicides, Fluconazole analogs, containing alongside the 1,2,4-triazole ring fluoropyrimidine, tetrazole, and also the other heterocyclic fragments [158].



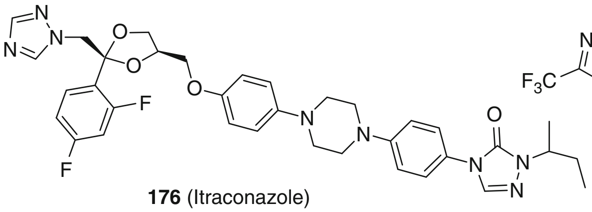
173 (Fluconazole)



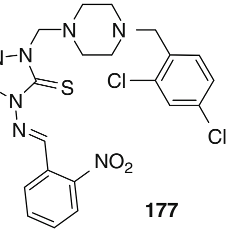
174 (Fosfluconazole)



175 (Voriconazole)



176 (Itraconazole)



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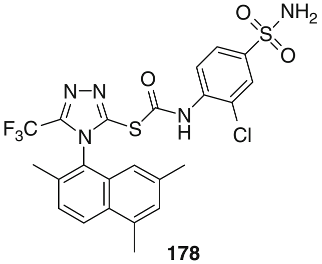
6.1.3 Antibacterials

Faidallah et al. showed that the derivatives of 3,5-di(trifluoromethyl)-1,2,4-triazolesulfonyl urea and thiourea exhibited a pronounced antimicrobial action [159]. McGeary et al. established a considerable inhibitory activity of 4-methyl-5-(trifluoromethyl)-4H-1,2,4-triazole-3-thiol and its derivatives with respect to β-lactamases [160].

6.1.4 Antiviral Agents

Girardet et al. synthesized and investigated the anti-HIV-1 activity of the derivatives of 3-trifluoromethyl-1,2,4-triazole-5-thiol **178** [161]. The anti-HIV action of compound **178** proved to be comparable with that of the efficient protease inhibitor Efavirenz. The authors of the article noted that the compound exhibited single-digit nanomolar activity against the Y188L mutant, with no cytotoxicity.



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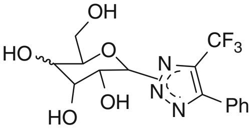
Known publications were cited in [162] concerning the structures of 1,2,3-triazole analogs of nucleosides containing a polyfluoroalkyl substituent in the heterocyclic core **179–181**.



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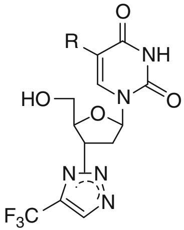

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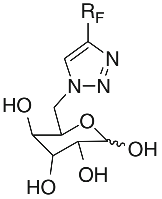
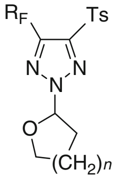


181

Nucleoside mimetics, N^2-substituted derivatives of 4-tosyl-5-polyfluoroalkyl-1,2,3-triazoles containing fragments of 3-chlorotetrahydrofuran, 3-chloro-tetrahydropyran, tetrahydropyran, dihydrofuran, dihydropyran, or acyclic substituents, were also studied **182–186** [162]. It was demonstrated that some among the studied compounds exhibit a pronounced anti-Epstein-Barr virus (EBV) activity.



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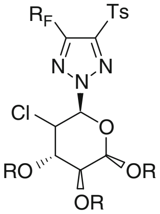

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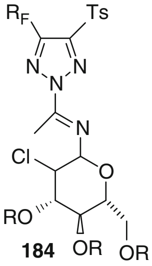

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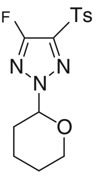

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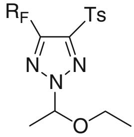
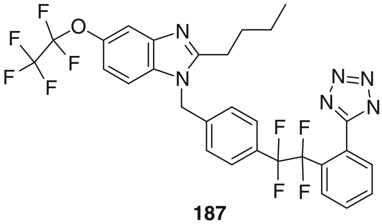


186

n = 1,2 $R_F = CF_2, C_3F_7$, R=H, Ac

6.1.5 Hypotensive Drugs

Angiotensin II receptor antagonist like Losartan and its analogs retain strong positions on the pharmaceutical market of the hypotensive drugs [158]. Yagupolskii et al. have synthesized two fluorine-containing Losartan analogs with fluoroalkyl substituents **187–189**, whose pharmacological activity is expected to be high [163].



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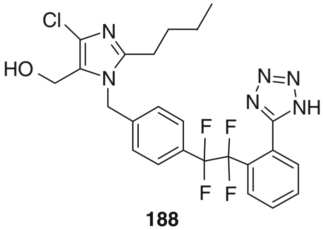

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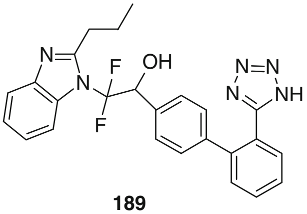

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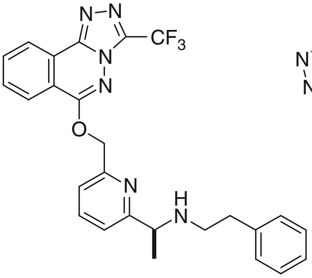
6.1.6 CNS Therapy

Lebsack et al. produced a series of 1,2,3-triazolo[3,4-a]phthalazine derivatives, in particular, containing a trifluoromethyl substituent in the fused 1,2,4-triazole ring **190**, as high-affinity ligands to the $\alpha_2\delta$-1 subunit of voltage gated calcium channel [164]. These compounds are interesting as anticonvulsant drugs. The work of Williams et al. [165] consisted in the synthesis and the study of the biological activity of new antidepressants, 3-styryl[4.5]-spiroether and [4.5]-spiroether neurokinin-1 (NK1) antagonists **191**, **192**, containing in the molecular structure trifluoromethyltetrazol-1-yl fragment. The research concerning the pursuit of promising neurokinin-1 (NK1) antagonists, containing fluorinated tri- and tetrazoles is continued [166].



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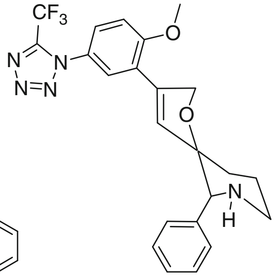

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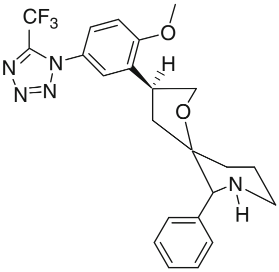

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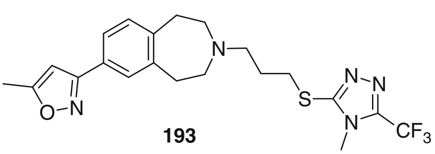
1,2,4-Triazol-3-yl-thiopropyl-tetrahydrobenzazepine **193** whose structure includes a nonfused 1,2,4-triazole-3-trifluoromethyl-5-thiol fragment separated by an alkyl bridge from the benzazepine framework was found to be a potent and selective dopamine D_3 receptor antagonist [167]. Sugane et al. established the high biological activity *in vitro* of new glycine transporter 1 (GlyT1) inhibitors 3-biphenyl-4-yl-4-(2-fluorophenyl)-5-R-4H-1,2,4-triazole, in particular, of compound **194** [168].



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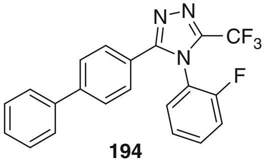

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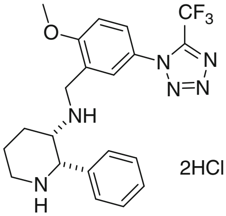
Below two structural formulas of potent, orally active, long-acting morpholine acetal human NK-1 receptor antagonists **195**, **196**, are given. These compounds are tested as efficient drugs for the treatment of the Alzheimer disease [169]. The fluorine-containing biaryl-triazolopyridine **197** is tried as a potent and selective p38α inhibitor for stress relief [170].



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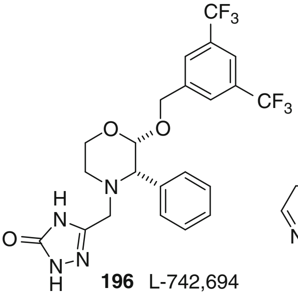
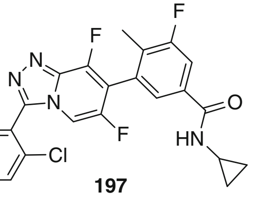


196 L-742,694



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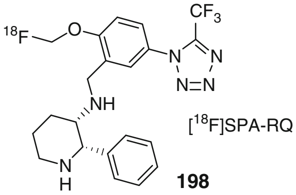
6.1.7 Imaging Agents

One of the modern ways of CNS disorders diagnostics depends on the development of new radiolabeled NK1 receptor antagonists. Some examples of fluorine-18 labeling compounds are known [171, 172], effective radioligands for imaging brain neurokinin type-1 (NK1) receptors in clinical research and drug discovery with positron emission tomography, like [^{18}F]SPA-RQ **198**.



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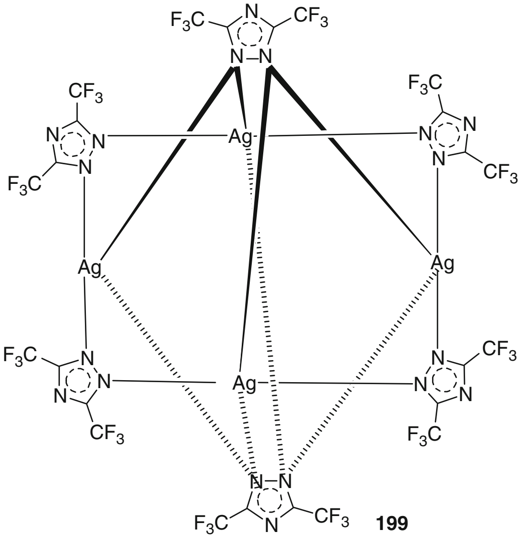
6.2 *Light-Emitting Diodes*

Some complex compounds of fluorinated tri- and tetrazoles possess interesting photo- and electroluminescent properties. We have given above formulas of **93**, **94,** representatives of a new series of charge neutral Os (II) pyridyl 3-trifluoromethyl- 1,2,4-triazolate complexes with either bis(diphenylphosphino)methane or cis-1,2-bis(diphenylphosphino)ethene chelates. Their structural, electrochemical, photophysical properties and thermodynamic relationship were established [89, 90]. It was demonstrated that such coordination compounds can be used in the production of highly efficient white [173], blue [174], orange, and red organic light-emitting diodes (LEDs) [175].

The photo- and electroluminescence properties of a series of novel, heteroleptic, *mer*-cyclometallated iridium complexes have been fine-tuned from green to blue by changing the substituents on the 3-trifluoromethyl-1,2,4-triazolylpyridyl ring of the ligand [176, 177]. Chi, Chou, Wu et al. synthesized Ir(III) emissive complexes with 5-pyridyl-3-trifluoromethyl-1,2,4-triazole ligand which might be used in white OLEDs technologies [178].

6.3 *Sorbents, Ion Liquids, and Surfactants*

Omary et al. have demonstrated that fluorous metallorganic frameworks (FMOFs) **199**, **200** are highly hydrophobic porous materials with a high capacity and affinity to C_6-C_8 hydrocarbons of oil components [179]. FMOFs exhibits reversible adsorption with a high capacity for *n*-hexane, cyclohexane, benzene, toluene, and *p*-xylene, with no detectable water adsorption even at near 100 % relative humidity drastically outperforming activated carbon and zeolite porous materials. The results suggest great promise for FMOFs in applications like removal of organic pollutants from oil spills or ambient humid air, hydrocarbon storage and transportation, water purification, *etc.* under practical working conditions



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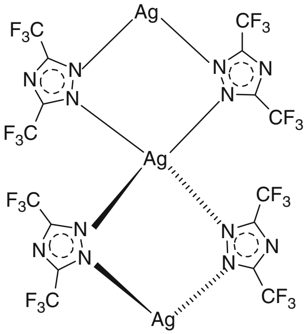

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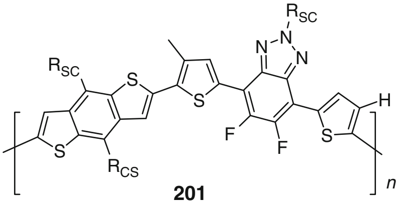
Read et al. synthesized surface-active derivatives of 1,2,3-triazole **49**, **50** containing at the nitrogen atom perfluoroalkyl (lipophilic) substituents, and at the carbon atom perfluoroalkoxy or alkoxy (hydrophilic) groups. It is significant that the surfactant properties of these compounds can be purposefully regulated varying the length of the fluoroalkyl chain [49, 50].

The ionic liquids formed by the 1,2,4-triazolium cation and dinitramide anion as well as charge-diffuse tetrazolium cation with a variety of substituents coupled with various (usually oxygen containing) anions have been studied by *ab initio* quantum chemistry calculations [21, 180].

6.4 Ion and Electron Conductors

We cited above the study of Boskurt et al. who synthesized 5-(perfluoroheptyl)-3H-1,2,3-triazole-4-carboxylate **65** [69]. They also reported on the effect of the proton conductivity observed in the solutions of organic electrolytes with the additives of this fluoroalkylated 1,2,3-triazole. Recent research advances on conjugated polymers for photovoltaic devices have focused on creating low band gap materials, but a suitable band gap is only one of many performance criteria required for a successful conjugated polymer [181]. This work focuses on the design of two medium band gap copolymers for the use in photovoltaic cells which are designed to possess a high hole mobility, low highest occupied molecular orbital and lowest unoccupied molecular orbital energy levels. The resulting fluorinated polymer **201** is a viable candidate for the use in highly efficient tandem cells. It also highlights other performance criteria which contribute to high photovoltaic efficiency, besides a low band gap.



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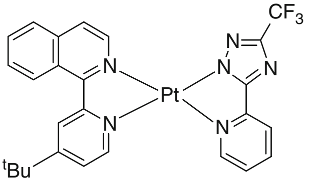
6.5 Ligands

Some fluorine-containing tri- and tetrazoles behave as polidentate ligands and form stable complex compounds with various metal ions. The coordination compounds of Os(II), Ir(III), Ga(III), In(III), Ag(I), Sn(IV) with 5-pyridyl-2-yl-3-trifluoromethyl-1,2,4-triazole ligands we have already mentioned.



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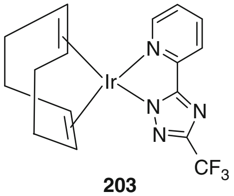

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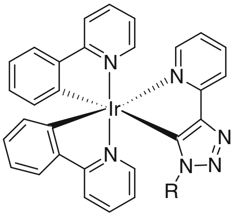

R = C_6F_5

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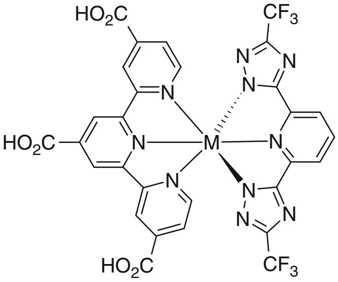


M = Os(II), Ru(II)

205

Let us cite some other characteristic examples. Thus, based on 5-(6-methylpyridin-2-yl)-3-trifluoromethyl-1,2,4-triazole ligand platinum(II) complexes **202** were synthesized with spatially encumbered chelates, and their photophysical properties were also studied [182]. Compound **202** was found to be weakly emissive in both

Table 1 1,2,4-triazolium salts as catalysts of enantioselective reactions

Catalysts	Reaction (synthesis)	References
142	Macrocyclization of α,γ-dialdehydes	[123]
	Nucleophilic carbyne-catalyzed redox azidation of epoxyaldehydes	[124]
144	Synthesis of *trans*-γ-lactams; the most efficient *trans*-γ-lactam synthesis has been achieved using cyclohexyl-substituted carbyne precursor	[129]
145	The asymmetric intermolecular Stetter reaction was investigated	[125]
147	Enantioselective N-heterocyclic carbene-catalyzed Michael addition reactions to α,β-unsaturated aldehydes by redox oxidation	[126]
	Asymmetric intramolecular Stetter reaction	[127]

fluid and solid states at room temperature. Exotic coordination compounds are also known prepared from the mentioned bidentate ligands and the isoelectronic system Ir(I) **203** with distorted square-planar geometry [183]. Here the lowest absorption band consists of increased triplet dπ → π transitions of Ir (I) atom. Later Swager et al. obtained heteroleptic tris-cyclometallated Ir(III) complexes **204** based on 2-(1-perfluorophenyl-1,2,3-triazol-4-yl)pyridine [110]. Complex compounds **205** formed by two tridentate ligands coordinated to Os(II) or Ru(II) interesting as components of dye-sensitized solar cells (DSCs), were recently prepared by Chou et al. [184].

6.6 Organic Catalysis

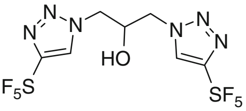
Chiral N-pentafluorophenyl 1,2,4-triazolium salts (triazolium bicyclic catalysts) had been found to significantly influence reaction yields and enantiomeric ratios. The examples of the application of triazolium bicyclic catalysts **142, 144, 145, 147** whose structures we have already mentioned are listed in Table 1.

6.7 Energetic Compounds

The burning of the energetic compositions containing organofluorine derivatives affords products with relatively small molecular mass which favors the operating characteristics. Owing to these and many other useful properties the fluorine-containing heterocyclic compounds, first of all tri- and tetrazoles, are traditionally attractive energetic substances.

Klapotke et al. described the energetic properties of sodium 5-trifluoromethyltetrazolate, sodium 5-pentafluoroethyltetrazolate, and sodium 5-heptafluoropropyltetrazolate [185]. Based on DSC-thermograms the authors concluded that the 5-perfluoroalkyltetrazole salts are thermally and thermodynamically stable energy-rich substances. It was also indicated that the sodium salts of 5-perfluoroalkyltetrazoles showed relatively low sensitivity to impact and friction. The other publications of this scientific team reported on the calcium salts of 5-perfluoroalkylated tetrazoles as components of ternary mixtures with magnesium and Viton [186], and also on pyrolants containing magnesium and guanidinium 5-(perfluoropropyl)-5H-tetrazolate and ammonium 5-(perfluoropropyl)-H-tetrazolate [187] The subject of the energy-rich salts formed from nitro-1,2,4-triazol-5-one, 5-nitroaminotetrazole, and other nitro-substituted azoles, among them energetic polymer salts from 1-vinyl-1,2,4-triazole derivatives, was treated in a series of Shreeve et al. publications that we cited before [62, 86–88, 94]. The data on enthalpy of formation, density, detonation velocity (calculated value), and on the other parameters were published making it possible to regard these salts as interesting components of explosive compositions. As promising components of explosive compositions trifluoromethyl- or pentafluorosulfanyl-substituted poly-1,2,3-triazole compounds should be mentioned. Below are given the formulas of some representative of pentafluorosulfanyl derivatives of tri- and tetrazoles **206**–**210**. It is noteworthy that the introduction of the SF_5 group into the 1,2,3-triazole ring results in energetic compounds of high density (1.83–1.90 g/cm^3) [142, 188], the most important quality for the energy-rich compounds and materials.

Let us turn again to the pioneering publication of Shevelev et al. [147] that has announced the synthesis of N-difluoroazoles, the representatives of the new series of N-substituted azole. Focusing our attention on NF_2 derivative of 3-nitro-1,2,3-triazole containing the NF_2 group **211**, it may be stated that this extraordinary molecule may be regarded as a precursor of the hypothetic substance possessing exclusively high detonation parameters. Presumably, due to the high sensitivity to the mechanical treatment (impact, friction) similar compounds are very dangerous in handling.



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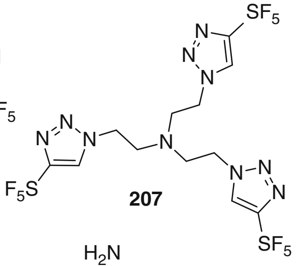

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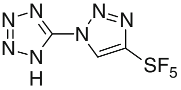

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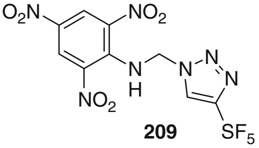

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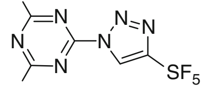

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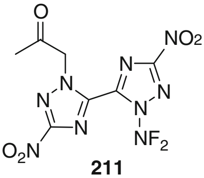

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7 Conclusions

The analysis of the literature published within the last decade easily demonstrates the essential intensification of applied research in the field of fluorinated derivatives of tri- and tetrazoles. The especially intensive development is observed in the directions of creating new biologically active substances based on the mentioned compounds, light-emitting diodes, polymer materials, sorbents, catalysts of chemical processes. The appearance of original and refinement of the known approaches to the synthesis of fluorine-containing tri- and tetrazoles is a natural response to these demands. It is easy to forecast in the near future a significant success in this field of the chemistry of fluorine-containing heterocyclic compounds.

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