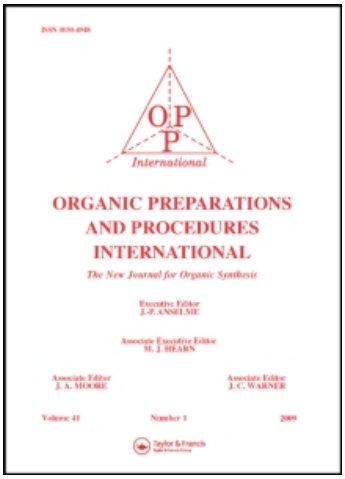

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THE SYNTHESIS OF FLUORINATED HETEROAROMATIC COMPOUNDS. PART 2. FIVE-MEMBERED RINGS WITH TWO HETEROATOMS. A REVIEW

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INTRODUCTION

Fluorinated heterocycles represent an important class of compounds, largely applied as agrochemicals, pharmaceuticals, fluoropolymers, fluorous catalysts and in new materials sciences.[1] Much effort has been devoted to developing efficient synthetic methodologies to target fluorinated compounds. Several reviews in the literature have been dedicated to this aspect of fluorinated heterocycles[2] and we refer to them for general information.

Our project of reviewing the synthesis of fluorinated heterocycles focused on aromatic five-membered heterocycles containing two or more heteroatoms. However, instead of considering *general methodologies* to obtain fluorinated targets, our approach has been devoted to addressing the most recent procedures for the *syntheses of each kind of fluorofunctionalized heterocycle*. The first part of our project, published in this series in 2005, discussed fluorinated five-membered heterocycles with more than two heteroatoms (oxadiazoles, thiadiazoles, triazoles, and tetrazoles) and contained general considerations and 200 citations to specific literature on this topic.[3] This second part is dedicated to the synthetic methodologies for fluorinated five-membered heterocycles with two heteroatoms, namely pyrazoles, imidazoles, isoxazoles, isothiazoles, oxazoles, and thiazoles. From a structural point of view, it is important to remember that in the case of *1H*-pyrazoles, C(3) and C(5) substituted derivatives are tautomeric forms. The same applies to C(4) and C(5) substituted derivatives of *1H*-imidazoles.

For five-membered heterocycles with two or more heteroatoms, the significant review by Elguero *et al.* (which appeared in this series in 1995)[4] discussed the synthesis, the reactivity, and some spectroscopic features of trifluoromethyl and perfluoroalkyl derivatives. Following our previous approach, our purpose is to present for each heterocycle an updated picture of the methodologies used to obtain both fluoroalkylated and ring-fluorinated targets.

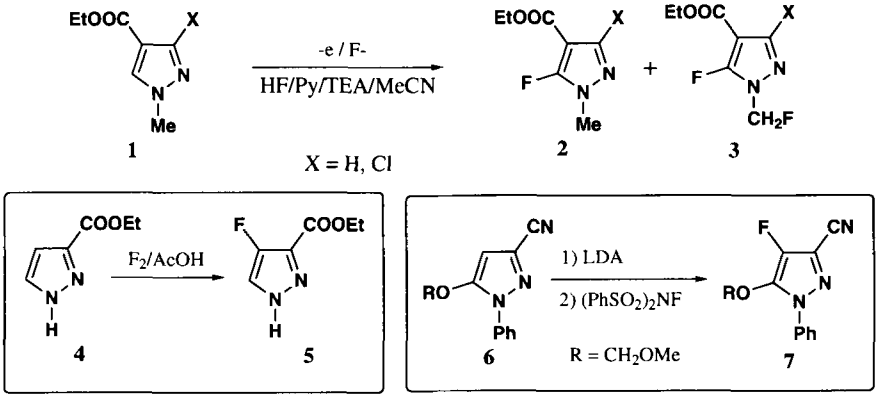
Only monocyclic aromatic substrates have been considered; dihydro or tetrahydro compounds will be discussed only when involved in syntheses of general interest. Each section

will initially discuss the synthesis of ring-fluorinated heterocycles (even when fluoroalkyl groups are present), followed by the methodologies for poly- or perfluoroalkyl systems. Experimental details, when available, will be cited only if of interest to clarify the involved processes. Particular attention was paid to the literature from the last two decades to the end of 2005. Previous papers will be cited only when of general interest or to clarify the synthetic approach.

I. PYRAZOLES[5]

1. Ring-fluorinated Pyrazoles

Several ring-fluorinated pyrazoles are known. MNDO[6] and *ab initio*[7] calculations have also been reported for a series of mono- and polyfluorinated compounds. Some ring-fluorinated pyrazoles have been synthesized following the *direct fluorination approach.* For example, the fluorination of **1** using the hydrogen fluoride-pyridine-triethylamine complex under electrolytic anodic oxidation, produced derivatives **2** and **3** (*Scheme 1*).[8] Other examples are fluorination of **4** (with F_2 in acetic acid) to obtain **5** (75%),[9] and the fluorination of 1-phenyl-2,3-dimethylpyrazolin-5-one (antipirine) (with F_2 in acetic acid or aqueous media) which essentially leads to the 4-fluoro derivative.[10] Fluorination of the lithium salt of the 3-cyanopyrazole **6** with the *N*-fluorobenzenesulfonimide produces the 4-fluoro compound **7**.[11]



Scheme 1

The introduction of a fluorine atom on the pyrazole ring has also been achieved by conventional methodology that consists of the photochemical decomposition of diazonium tetrafluoroborates in HBF_4. Even though yields are not always satisfactory, this method has been used to obtain: *i)* compounds **8** (R = H), **9**, and **10**;[12] *ii)* 3-fluoro-1-methyl- **8** (R = Me) and 4-fluoro-1-methylpyrazole **11** (R = Me);[13] *iii)* 5-fluoro-3,4-dimethylpyrazole **12**;[14] *iv)* 3,4- and 3,5-difluoropyrazoles **13** and **14** (*Fig. 1*).[15]

Additionally, ring-fluorinated pyrazoles can be prepared by typical heterocyclization reactions used in pyrazole syntheses. In this manner, pyrazoles containing both the fluorine and the fluoroalkyl groups have also been obtained. For example, 4-fluoropyrazoles **16** are formed

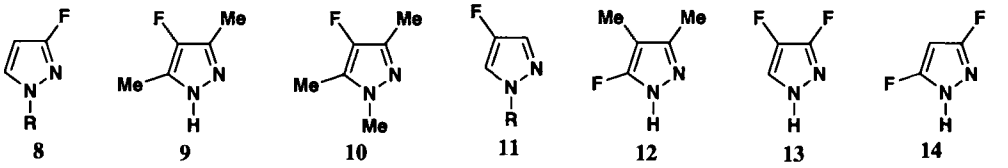
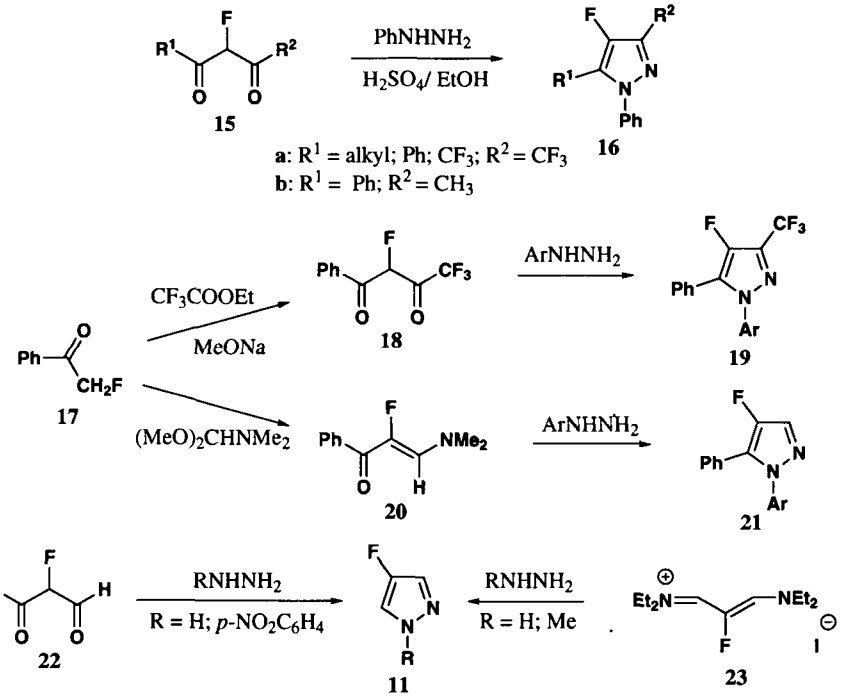


Fig. 1

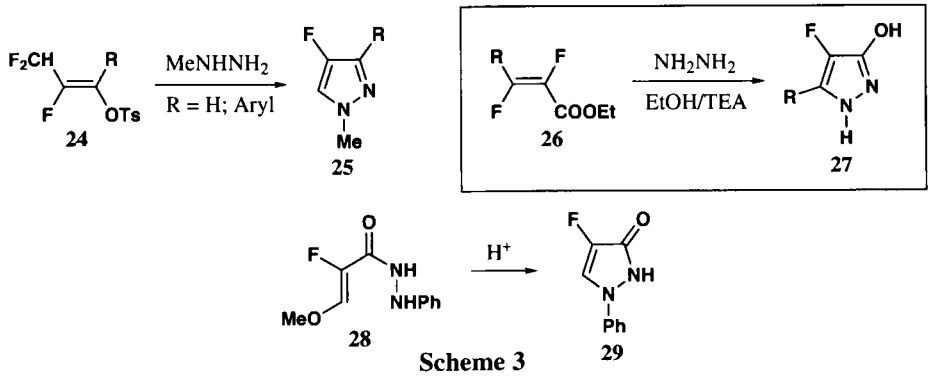
(72-85%) from 2-fluoro-1,3-diketones **15** (prepared by fluorination of the corresponding silyl enol ether with F_2/N_2) and phenylhydrazine.[16] Additional examples of this approach are the synthesis of **19** and **21** *(Scheme 2).*[17] Similarly, 4-fluoropyrazoles **11** (R = H, *p*-$NO_2C_6H_4$)) have been synthesized from fluoromalonic dialdehyde **22** (or its *bis*-dimethylacetal) and hydrazines;[18] moreover, compounds **11** (R = H, Me) were obtained in 57 and 90% yields, respectively, from *β*–fluorovinamidinium (1,5-diazapentadienium) salt **23** and hydrazine or methylhydrazine in MeCN.[19]



Scheme 2

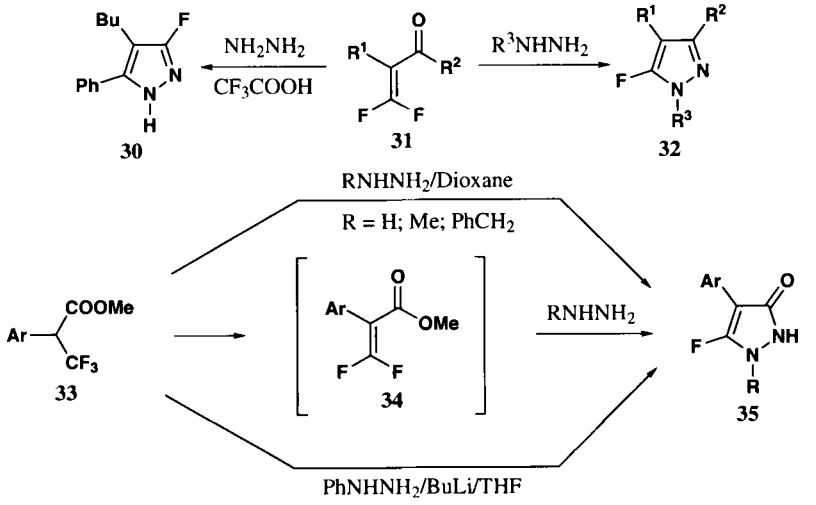
Other examples describing the synthesis of 4-fluoropyrazoles involve: *i)* the reaction of (*Z*)-2,3,3-trifluoro-1-propenyl-*p*-toluenesulfonates **24** and methylhydrazine in the presence of tetrabutylammonium fluoride leading to **25** (71-88%);[20] *ii)* the reaction of 3-substituted-*trans*-2,3-difluoro-2-acrylates **26** with hydrazine in the presence of bases affording 3(5)-hydroxy-4-fluoropyrazoles **27** (76-80%);[21] *iii)* the acid-induced ring-closure of the (*Z*)-acylhydrazine **28** into the 4-fluoro-1-phenylpyrazolin-3-one **29** (72%) (*Scheme 3*).[22]

In turn, 5-fluoropyrazoles **32** are prepared in excellent yields from 2,2-difluorovinylketones **31** with substituted hydrazines.[23] In the case of aliphatic hydrazines, the reaction is performed in aqueous ethanol under neutral conditions. In the case of aromatic hydrazines, the reaction is performed in THF in the presence of butyllithium (which enhances the nucleophilic character of the aryl substituted nitrogen of the reagent). Similarly, the reaction of representative **31** (R^1 = *n*-Bu; R^2 = Ph) with hydrazine monohydrate in the presence of trifluoroacetic acid produces the *1H*-3(5)-fluoropyrazole **30**.[23] 5-Fluoropyrazolin-3-ones **35** (X-ray data available for



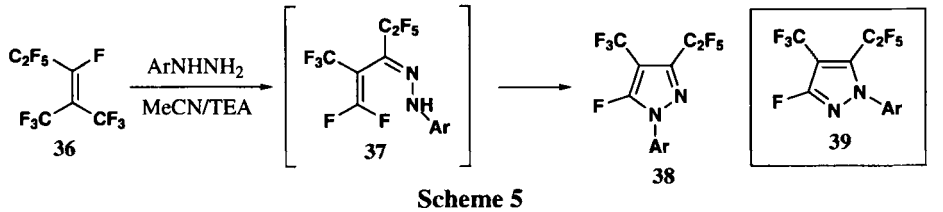
Scheme 3

35; Ar = Ph; R = Me) are similarly obtained (80-90%) by reacting 2-trifluoromethyl-2-arylacetates **33** with an excess of hydrazines.[24] The complete regioselectivity has been rationalized assuming a nucleophilic attack of the more nucleophilic nitrogen of the hydrazine, bearing the methyl (or benzyl) group, on the fluorinated vinyl carbon of the proposed intermediate **34** (*Scheme 4*). Accordingly, when the lithium salt of phenylhydrazine was used, the 5-fluoro compounds **35** (R = Ph) were formed (76-90%).[24]



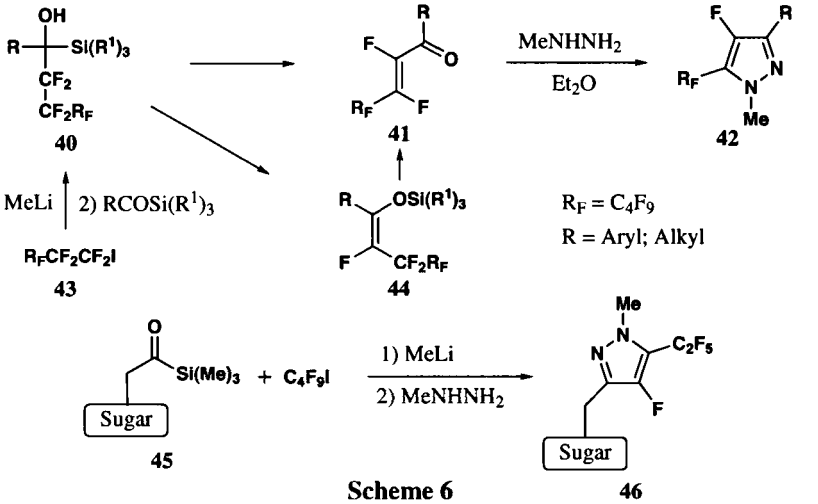
Scheme 4

Perfluorinated 2-pentene **36** represents a very useful synthon for the synthesis of pyrazoles bearing both a fluorine and a perfluoroalkyl group linked to the ring. The reaction of **36** with arylhydrazines in acetonitrile and in the presence of triethylamine (TEA) produced a mixture of 5-fluoropyrazoles **38** and 3-fluoropyrazoles **39** in various ratios depending on the reaction conditions (*Scheme 5*).[25] The formation of the 5-fluoro isomer **38** was rationalized through the intermediate **37**. For the formation of the 3-fluoro isomer, instead, the suggested initial base-catalyzed isomerization of **36** into the corresponding 1-pentene appears unlikely.[25] Other examples of ring-fluorinated pyrazoles prepared from the same substrate are reported.[26]



Scheme 5

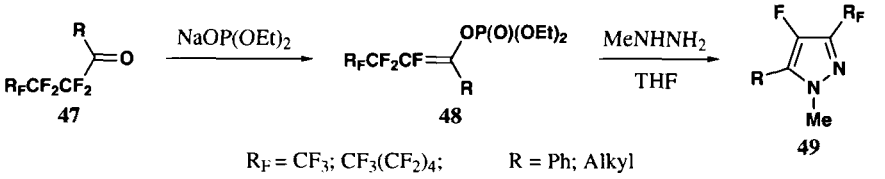
4-Fluoro-5-perfluoroalkylpyrazoles **42** have been reported (and their structure confirmed by NMR spectroscopy) by heterocyclization of perfluoroenones **41** (or their synthetic equivalents **40** and **44**) with methylhydrazine.[27] Only one regioisomer is formed, arising from a Michael-type attack of the more nucleophilic methylated nitrogen onto the perfluoroalkylated β-carbon of the enone.[27] [In a previous paper regarding the reaction of the (trimethylsilyl)perfluoroalkanol **40** (R = Ph; $R_F = C_4F_9$) with methylhydrazine, the formation of the corresponding 4-fluoro-3-perfluoroalkyl regioisomer had been claimed erroneously].[28] Enones **41** can be generated from 1-(trialkylsilyl)perfluoroalkanols precursors **40**[27,28] which, in turn are easily prepared from acylsilanes and perfluoroalkyl iodides **43** (*Scheme 6*). On this basis, one-pot procedures starting from acylsilanes are also possible and have been used to obtain fluorinated pyrazole rings linked to a carbohydrate moiety such as **46**.[27]



Scheme 6

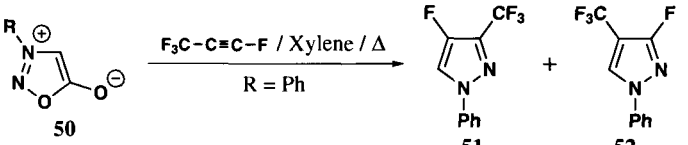
In the context of the above reaction, we note that 4-fluoro-3-perfluoroalkyl-pyrazoles **49** (80-90%) had previously been claimed (without any information to support the questionable regiochemistry) from the reaction of fluorinated enol phosphates **48** (structurally related to silylenol ethers **44**) with methylhydrazine (*Scheme 7*).[29]

Finally, cycloaddition reactions are also reported for the synthesis of ring-fluorinated pyrazoles. As an example, a mixture of 4-fluoro- and 3-fluoropyrazole (**51**, **52**) regioisomers (in 42 and 21% yields, respectively) is formed in the cycloaddition reaction of the *N*-phenylsydnone **50** (R = Ph) onto perfluoropropyne (*Scheme 8*).[30]



$R_F = CF_3$; $CF_3(CF_2)_4$; R = Ph; Alkyl

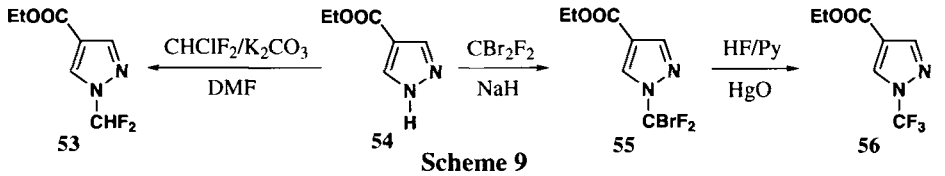
Scheme 7



Scheme 8

2. Fluoroalkylated Pyrazoles

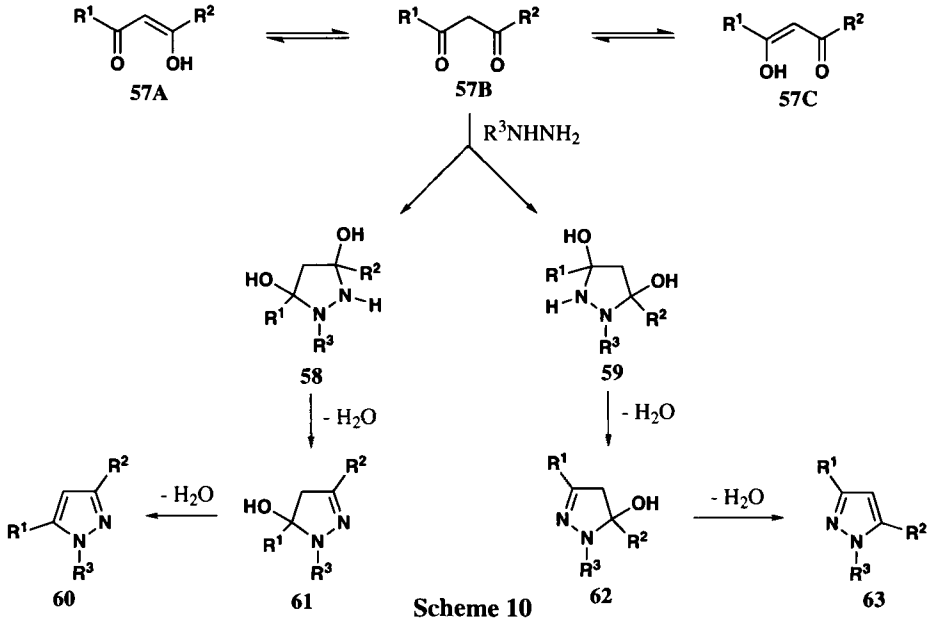
Polyfluoroalkyl or perfluoroalkyl pyrazoles generally arise from fluorinated open-chain precursors through common heterocyclization reactions leading to the pyrazole ring. These include cyclocondensation reactions of hydrazines with substrates such as β-dicarbonyls, α,β-unsaturated carbonyls, polyfluoroalkylcarbonyls, and congeners, and cycloaddition reactions of nitrilimines (or diazo compounds) with dipolarophiles. Some examples of modification of a preexisting functional group in the pyrazole ring include: *i)* fluorination of a 3,5-*bis*(trichloromethyl)pyrazole into the corresponding 3,5-*bis*(trifluoromethyl) derivative by using 1,3-dimethyl-2-imidazolidinone•HF complex as a fluorinating reagent;[31] and *ii)* transformation of a carboxy group into a trifluoromethyl group by using SF_4/HF fluorinating reagent.[32] The syntheses of *N*-difluoromethylpyrazole **53** and *N*-trifluoromethylpyrazole **56** have also been reported *(Scheme 9)*.[33]



Scheme 9

a) Syntheses from β-Dicarbonyl Compounds

The cyclocondensation reaction between β-dicarbonyl compounds and hydrazines is the main synthetic approach to pyrazoles.[5] The generally accepted mechanism for this reaction consists of an initial nucleophilic attack by the hydrazine on the more electrophilic site of the dicarbonyl. In the case of asymmetric reagents, the regiochemistry of such an attack will depend on the keto-enol equilibria of the dicarbonyl compound. 3,5-Dihydroxypyrazolidine **58** and **59** and 5-hydroxypyrazolines **61** and **62** have been suggested as the key intermediates (*Scheme 10*).[34,35] In the case of fluorinated compounds, a dihydroxypyrazolidine **58** ($R^1 = R^2 = CF_3$; $R^3 = H$) and a 5-hydroxypyrazoline **61** ($R^1 = CF_3$; $R^2 = Me$; $R^3 = H$) have been isolated and characterized.[36] Other examples of isolated 5-hydroxy-5-perfluoroalkylpyrazolines as intermediates in the synthesis of perfluoroalkylpyrazoles have been reported.[37] Additional references on this topic can be found in the course of this review.



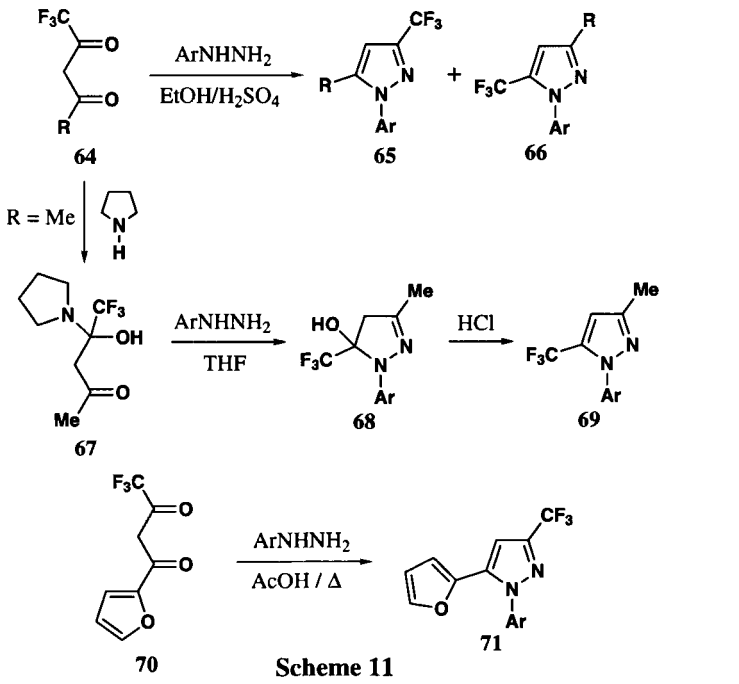
Scheme 10

A comprehensive overview has described reactions of fluorinated diketones (of general type CF_3COCH_2COR) with aryl- or hetarylhydrazines to yield a variety of trifluoromethylpyrazoles and 5-trifluoromethyl-5-hydroxypyrazolines **61** ($R^1 = CF_3$).[38] The observed results were rationalized with the support of semi-empirical calculations at the PM3 level, and this study proved that the regiochemistry of the reaction is kinetically controlled by the rate of dehydration of the two 3,5-dihydroxypyrazolidines **58** and **59**. In this context, it has also been assessed that the further dehydration of 5-hydroxy-5-trifluoromethylpyrazolines **61** ($R^1 = CF_3$) is inhibited by the presence of electron-withdrawing groups at the C(5) or N(1).[4,35,38] The electron-withdrawing CF_3 group (or in general, perfluoroalkyl group) at C(5) would in fact destabilize any cationic

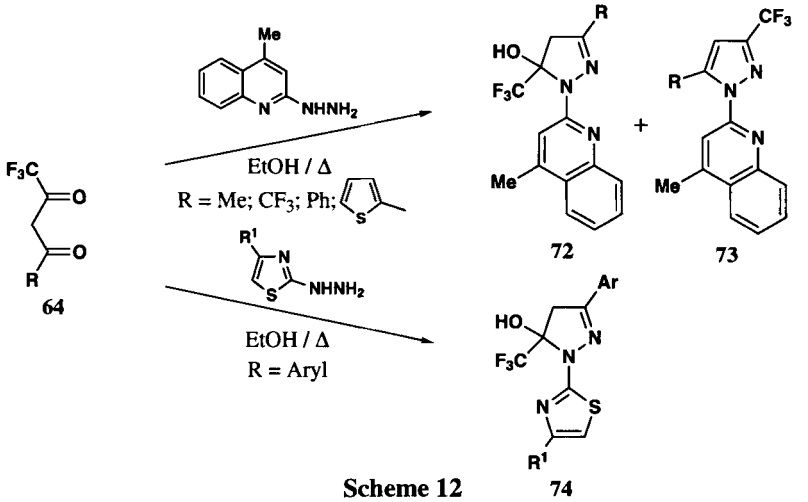
character in an E1-like mechanism. Inhibition of the dehydration process by decreasing the electron density at N(1) can be similarly rationalized,[39] and explains the differing results observed by using alkyl- or phenylhydrazines on one hand, and acylhydrazine, thiosemicarbazide, 2,4-dinitrophenylhydrazine or pentafluorophenylhydrazine, on the other. These considerations suggest care when comparing the regiochemistry of reactions performed in the presence of acids that catalyze the dehydration process.

Various papers report the synthesis of fluoroalkylated pyrazoles from fluorinated 1,3-dicarbonylic compounds. A series of β-diketones that contain one or two perfluoroalkyl groups react with hydrazines ($RNHNH_2$; R = H, Me, Ph, CH_2CH_2CN) in refluxing methanol containing hydrochloric acid to produce the corresponding pyrazole derivatives in 80-90% yield. Reactions with substituted hydrazines preferentially or exclusively lead to the pyrazole derivative bearing the perfluoroalkyl group at C(3).[40] However, in the reaction of perfluoroalkylmethyldiketones with phenylhydrazine, 5-R_F regioisomers are formed preferentially. Trifluoromethylpyrazoles are obtained from the reaction of a series of trifluoromethyl diketones **64** with arylhydrazines in $EtOH/H_2SO_4$. When small alkyl groups are present, significant amounts of both regioisomers **65** and **66** are obtained. On the other hand, when the diketone contains either bulky alkyl or aryl groups, the preferred regioisomer is the 3-trifluoromethylpyrazole **65**.[16b] The exclusive formation of 3-trifluoromethyl-4-fluoropyrazoles **16** ($R^2 = CF_3$; R^1 = Alkyl, Ph) is reported for the reaction of trifluoromethylated 2-fluoro-1,3-diketones **15** ($R^2 = CF_3$; R^1 = Alkyl, Ph) and phenylhydrazine (*Scheme 2*). Since these 2-substituted 1,3-diketones exist esclusively in the diketo form,[41] the observed regioselectivity was explained by the attack of the NH_2 end of the phenylhydrazine onto the more electrophilic carbonyl.[16] Other examples of 3-fluoroalkylpyrazoles obtained from arylfluoroalkyl-β-diketones have recently been reported.[17] The 3-trifluoromethyl-5-(2-furyl)pyrazoles **71** are obtained from the corresponding trifluoromethyl diketone **70** and arylhydrazines in acetic acid.[42] The opposite regioselectivity was observed in the exclusive formation of the 5-trifluoromethyl-5-hydroxypyrazolines **68** (59%) (easily dehydratable into **69**) by selective protection of the CF_3CO moiety with pyrrolidine (*Scheme 11*).[43]

Heteroarylhydrazines react with various trifluoromethyl-β-diketones **64** to form trifluoromethylated cyclic products.[44] 2-Hydrazinoquinoline produced either the 5-hydroxy-5-trifluoromethylpyrazolines **72** or a mixture of pyrazolines **72** (major component; ~ 60%) and 3-trifluoromethylpyrazoles **73** (~ 10%), depending on the R group of the diketone (*Scheme 12*).[44a] In turn, hydroxypyrazolines **72** undergo dehydration into the corresponding 5-trifluoromethylpyrazoles by treatment with H_2SO_4 in acetic acid. The reaction of the trifluoromethyl-β-diketone **64** (R = Me) with 4-hydrazinoquinoline under standard conditions mainly yielded an isolable hydrazone at the COMe moiety. Subsequent dehydration by treatment with H_2SO_4 in acetic acid produced the corresponding 5-trifluoromethylpyrazole.[44a] Similarly, cyclocondensation of 2-hydrazinothiazoles with some aryltrifluoromethyl-β-diketones **64** (R = Aryl) was claimed to yield the 5-hydroxy-5-trifluoromethyldihydropyrazoles **74**, whose dehydration into pyrazoles required



Scheme 11



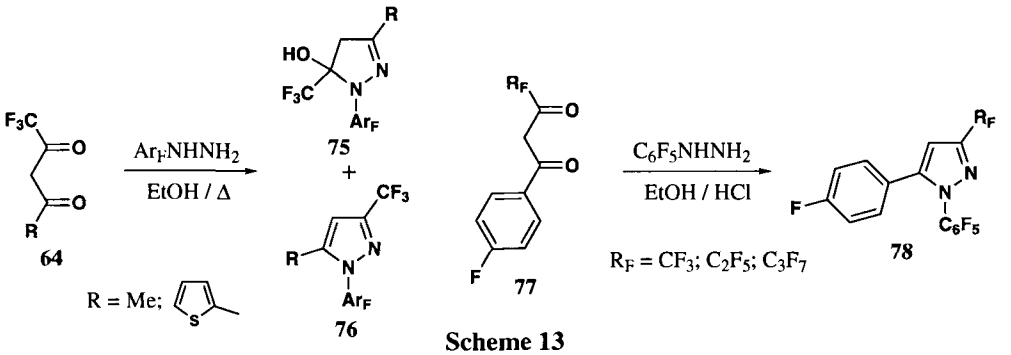
Scheme 12

refluxing in acetic anhydride.[44b] The regiochemistry of the reaction was determined from X-ray crystallography performed on a pyrazole derivative. Additional examples of reaction of aryl and heteroarylhydrazines with aryltrifluoromethyl-β-diketones **64** (R = Aryl), in neutral and acid conditions, have been reported very recently.[45]

The preferred formation of 5-hydroxy-5-trifluoromethyldihydropyrazoles **75** (49-60%) with respect to the 3-trifluoromethylpyrazoles **76** (5-13%) is also reported in the reaction of some diketones **64** with penta(poly)fluorophenylhydrazines in EtOH. The dehydration of **75** can be

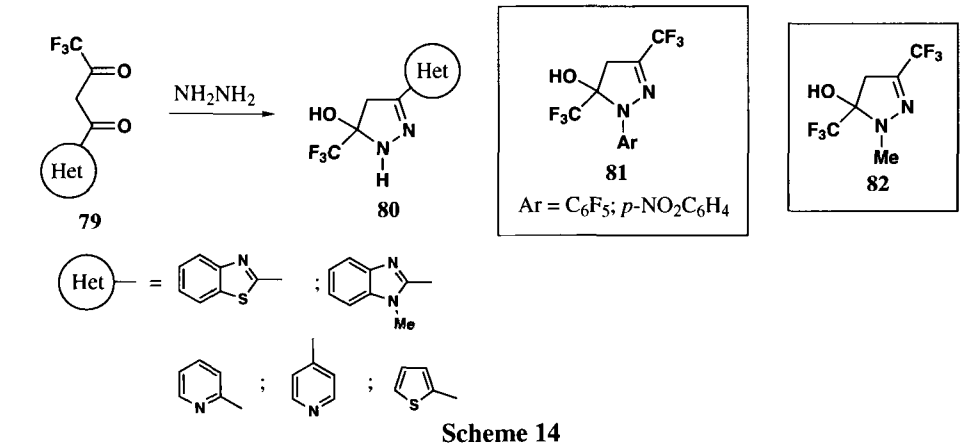
achieved with P_2O_5 in chloroform or with H_2SO_4 in acetic acid (*Scheme 13*).[46] In contrast, in the reaction of a series of perfluoroalkyl-1,3-diketones **77** with pentafluorophenylhydrazine in EtOH/HCl, the formation of 3-perfluoroalkylpyrazoles **78** (70-80%) has been claimed without support for the assigned regiochemistry.[47]

3-Hetaryl-5-hydroxy-5-trifluoromethyldihydropyrazoles **80** have been obtained from a series of (3-oxo-4,4,4-trifluorobutanoyl)heterocycles **79** reacted with hydrazine hydrate under



Scheme 13

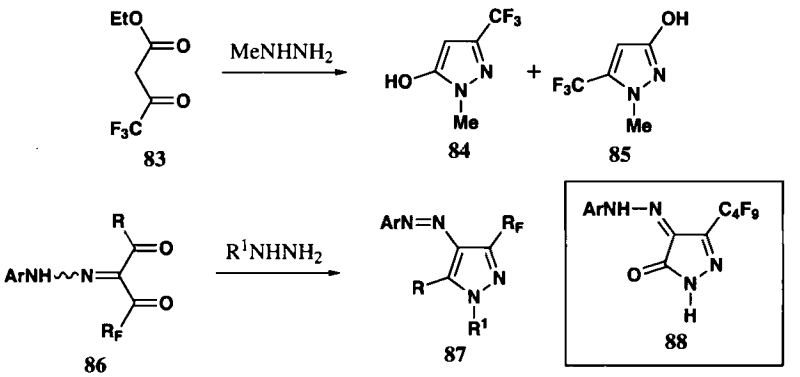
mild conditions (*Scheme 14*).[39] Moreover, the reaction of *bis*(trifluoromethyl) diketone **64** (R = CF_3) with *p*-nitrophenylhydrazine or pentafluorophenylhydrazine produced the corresponding 5-hydroxy-5-trifluoromethyl pyrazoline **81**.[39] The dehydration of these 5-hydroxypyrazolines into pyrazoles was shown to depend on structural features of the substrates. In this context, reinvestigation of the supposed formation of 3,5-*bis*(trifluoromethyl)pyrazoles from the reaction of *bis*(trifluoromethyl)diketone **64** (R = CF_3) and *N*-aryl or *N*-aroyl hydrazines in boiling ethanol[48] showed that the final products of the reaction were instead the corresponding 1-aryl- or 1-aroyl-3,5-*bis*(trifluoromethyl)-5-hydroxypyrazolines.[49] Reaction of the diketone **64** (R = CF_3) with methylhydrazine to give the 1-methyl-3,5-*bis*(trifluoro-methyl)-5-hydroxypyrazole **82** has been recently reported.[50]



Scheme 14

Other significant preparations from fluorinated β-diketones are: *i)* the synthesis of 3-pentafluorophenyl-5-methylpyrazoles from pentafluorobenzoylacetone and arylhydrazines;[51a] *ii)* the synthesis of *bis*(pyrazole)s (where the two pyrazole rings are linked by a perfluorinated chain at 5,5') by the reaction of hydrazine or arylhydrazine with *bis*-β-diketones, such as $RCOCH_2(CF_2)_nCOCH_2COR$.[51b]

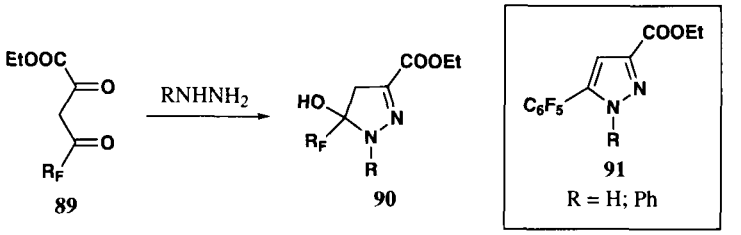
The use of a β-ketoester in the synthesis of fluoroalkylated pyrazoles is represented by the reaction of ethyl 4,4,4-trifluoroacetoacetate **83** with aqueous methylhydrazine to form both 5-hydroxy-3-(trifluoromethyl)pyrazole **84** (49%) and 3-hydroxy-5-(trifluoromethyl)pyrazole **85** (8%) (*Scheme 15*).[52] Other examples are the reaction of fluorinated β-ketoesters with phenylhydrazine (yielding phenylhydrazones that are isolated and cyclocondensed into 3-fluoroalkyl-5-hydroxypyrazoles),[53a] hydrazine,[53a] and benzylhydrazines.[53b] Polyfluorinated α-acetyl-β-ketoesters react with hydrazine to produce 4-alkoxycarbonylpyrazoles (45-50%).[54] Examples exploiting functionalized dicarbonyl compounds are: *i)* the reaction of 2-arylhydrazones of fluorinated 1,2,3-triketones **86** (R = Me, COOEt) with hydrazines to yield 4-arylazopyrazoles **87**;[55] and *ii)* the reaction of arylhydrazones of 2,3-diketoester **86** (R = OMe; $R_F = C_4F_9$) with hydrazine to yield pyrazolin-5-ones **88** (*Scheme 15*).[55] Additional examples of 2-(het)arylhydrazones of 1,2,3-triketones in the synthesis of 3-trifluoromethyl-4-arylazopyrazoles have been recently reported.[50]



$R_F = CF_3; H(CF_2)_2$ R = Me; COOEt R^1 = H; Ph

Scheme 15

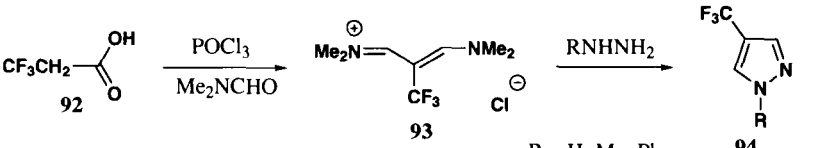
Ethyl polyfluoroacylpyruvates **89** react with hydrazine and phenylhydrazine at the β–dicarbonyl moiety leading to stable 3-alkoxycarbonyl-5-fluoroalkyl-5-hydroxypyrazolines **90** (*Scheme 16*).[56] In contrast, the copper chelates of fluorinated acylpyruvates and hydrazines produce the corresponding pyrazoles.[57] In turn, pentafluorobenzoylpyruvate **89** ($R_F = C_6F_5$) reacts with hydrazines to yield the 3-carboxyethyl-5-pentafluorophenylpyrazoles **91**.[58] Lithium salts of fluorinated β-diketones have been used as fluorine-containing synthons for the preparation of fluorinated pyrazoles.[59] A review article on the use of perfluorinated acyl(aroyl) pyruvates in the synthesis of fluorinated pyrazoles has been published recently and essentially reports results from the Russian school.[60]



$R_F = CF_3; C_4F_9; HCF_2$ R = H; Ph

Scheme 16

The trifluoromethylated vinamidinium salt **93**, prepared as illustrated (*Scheme 17*), can be considered the synthetic analogue of a β-dicarbonyl compound. Its reaction with hydrazines produces 4-trifluoromethylpyrazoles **94** (77-81%).[61]

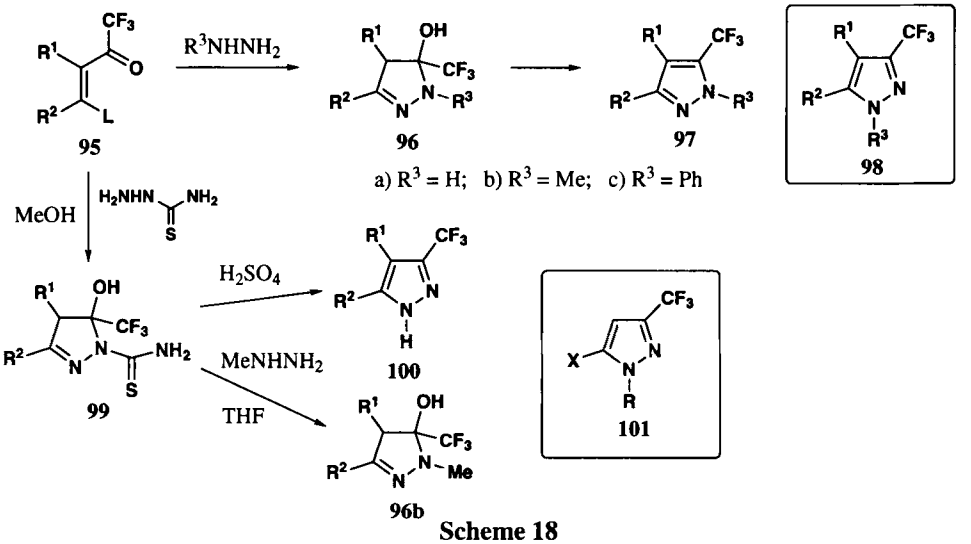


Scheme 17

b) Syntheses from α,β-Unsaturated Carbonyl Compounds

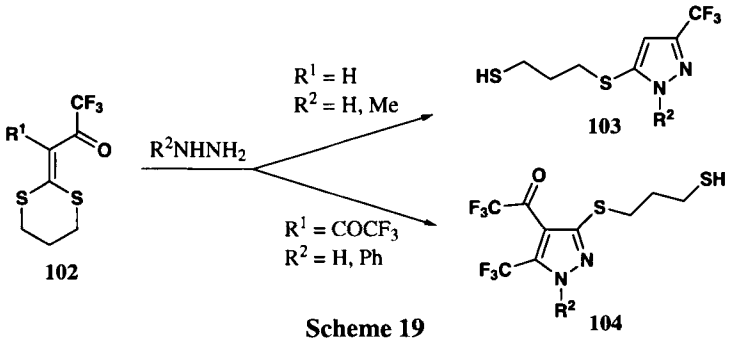
A series of fluoroalkyl pyrazoles have been obtained from α,β-unsaturated carbonyl compounds of the type **95**, where *L* represents a potential leaving-group (*Scheme 18*). Examples of this approach are reported for vinyl ethers **95** (L = OR) that react with hydrazine or methylhydrazine to directly afford 5-trifluoromethylpyrazoles **97** (65-98%).[62] The 5-hydroxy-5-trifluoromethylpyrazolines **96** (R^3 = Ph) were isolated from the reaction with phenylhydrazine (after refluxing for 4 h in ethanol) and were claimed to be resistant to dehydration.[62] A subsequent paper reports the formation of 1-phenyl-5-trifluoromethylpyrazole **97** ($R^1 = R^2 = H$; R^3 = Ph) from the corresponding vinyl ether **95** ($R^1 = R^2$ = H) and phenylhydrazine (by refluxing in ethanol for 24 h).[63] On the other hand, pyrazolines **99** (R^1 = H, Me, Aryl; R^2 = H, Me), isolated (73-96%) from the reaction of the corresponding vinyl ethers **95** (L = OR) with thiosemicarbazide, were transformed into the corresponding *1H*-pyrazoles **100** (57-75%) by treatment with H_2SO_4,[64] or into 1-methyl-5-hydroxy-5-trifluoromethylpyrazolines **96b** (68-90%) by treatment with methylhydrazine in THF (without mechanistic explanation, however) (*Scheme 18*).[65] The formation of 5-hydroxy-5-trifluoromethyl pyrazolines is also reported from the reaction of the vinyl ether **95** (L = OEt; $R^1 = R^2$ = H) with pentafluorophenylhydrazine or perfluoroalkanoylhydrazines.[63] The reaction of the same vinyl ether with methylhydrazine has been recently reinvestigated,[66] and some discrepancies in the previous report[62] have been corrected. In fact, the reaction of compound **95** (L = OEt; $R^1 = R^2$ = H) and methylhydrazine in refluxing ethanol yields both 3-trifluoromethylpyrazole **98** ($R^1 = R^2$ = H; R^3 = Me) (52%) and the 5-hydroxy-5-trifluoromethylpyrazoline **96** ($R^1 = R^2$ = H; R^3 = Me) (18%), the latter being converted to the corre-

sponding pyrazole **97** ($R^1 = R^2 = H$; $R^3 = Me$) by acid-catalyzed dehydration.[66a] Similar results were observed in the reaction of different vinyl ethers **95** (L = OMe; $R^1 = H$; $R^2 = Me$) and **95** (L = OEt; $R^1 = Me$; $R^2 = H$) with methylhydrazine.[67]



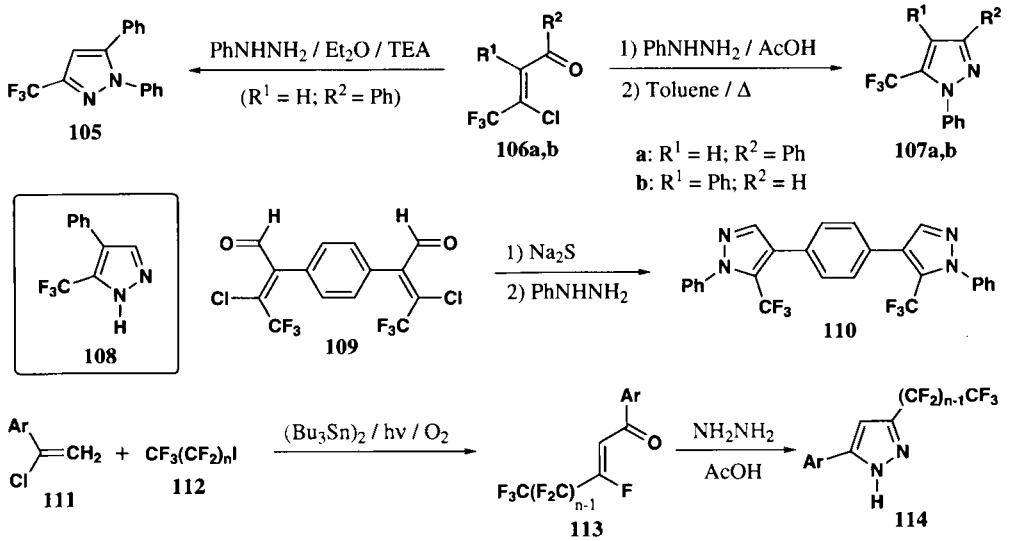
Scheme 18

Other examples belonging to this general scheme are the reaction of: *i)* diethoxy compound **95** ($L = R^2 = OEt$; $R^1 = H$) with hydrazine and methylhydrazine;[68] *ii)* enaminones **95** ($L = NMe_2$) and sulfides **95** (L = SR) with hydrazines;[69] *iii)* the enone **95** (L = Cl; $R^1 = H$; $R^2 =$ Ph) with phenylhydrazine in acetic acid by which both 5-trifluoromethyl- **97** ($R^1 = H$; $R^2 = R^3 =$ Ph) (as major component) and the 3-trifluoromethylpyrazole **98** ($R^1 = H$; $R^2 = R^3 = Ph$) are formed.[70] Dihalovinyl trifluoromethyl ketones **95** ($R^1 = H$; $R^2 = L = Cl$, Br) are claimed to react with alkylhydrazines to yield 5-halo-3-trifluoromethylpyrazoles **101** (X = Cl, Br; R = Me or Et) (56-85%) directly.[71] In the reaction of the dichlorovinyl compound with 2,4-dinitrophenylhydrazine, the arylhydrazone was isolated (62%) and then thermally cyclized in the presence of triethylamine (TEA) to the corresponding 3-trifluoromethyl-5-chloropyrazole **101** (X = Cl; R = 2,4-dinitrophenyl) (68%). Trifluoromethylpyrazoles **103** and **104** were obtained (45-75%) by reaction of fluorinated ketene dithioacetals **102** with hydrazines (*Scheme 19*).[72]



Scheme 19

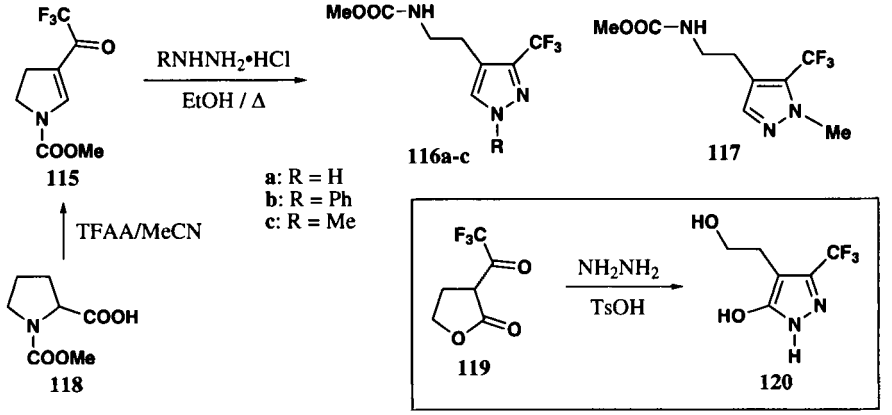
The formation of trifluoromethyl pyrazoles from trifluoromethyl enone **106a** or acrolein **106b** and phenylhydrazine has also been reported and was shown to depend on experimental conditions (although not described in great detail) (*Scheme 20*). The formation of 5-trifluoromethyl derivatives **107a,b** is explained through the involvement of the phenylhydrazones initially formed under acid catalysis.[73] Another example is the reaction of **106b** with hydrazine hydrate in the presence of TEA leading to 4-phenyl-3(5)-trifluoromethylpyrazole **108** (64%) or with phenylhydrazine (used on the *in situ* generated β-mercaptovinylaldehyde) by which trifluoromethylpyrazole **107b** (56%) was directly obtained.[74] Similarly, the formation of the *bis*(pyrazole) **110** (47%) from the corresponding precursor **109** is reported.[74] Structurally correlated perfluoroalkyl enones **113** (formed in the photolytic reaction of α-chlorostyrenes **111** with perfluoroalkyl iodides **112** in the presence of hexabutylditin under oxygen atmosphere) react with hydrazine to produce 3(5)-perfluoroalkylpyrazoles **114** (40-48%) (*Scheme 20*).[75]



Scheme 20

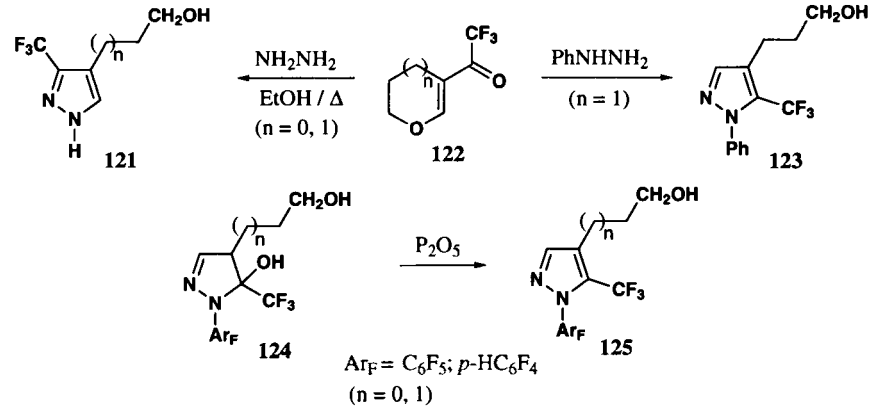
4-Trifluoroacetyl-2,3-dihydropyrrole **115**, easily accessible from *N*-methoxycarbonylproline **118** and trifluoroacetic acid anhydride,[76] is a useful synthon for the synthesis of trifluoromethylpyrazoles containing a β-aminoethyl side-chain. The reaction of **115** with hydrazine or phenylhydrazine hydrochlorides produced **116a,b** in about 90% yield.[77] In the case of the reaction with methylhydrazine, both the 3-trifluoromethyl pyrazole **116c** (52%) and its regioisomer **117** (31%) were obtained (*Scheme 21*). The reaction is rationalized through the initial formation of the carbinolamines at the $COCF_3$ moiety (isolated in neutral conditions) followed by ring closure – ring opening processes.[77] Similarly, the trifluoroacetyl-lactone **119** reacted with hydrazine [in the presence of *p*-toluenesulfonic acid (TsOH)] producing the pyrazole **120** (60%), supposedly through a hydrazone intermediate.[78]

The trifluoroacetyldihydrofuran **122** (n = 0) and dihydropyran **122** (n = 1), which can be considered as the cyclic analogues of vinyl ethers **95** (L = OR; *Scheme 18*), react with



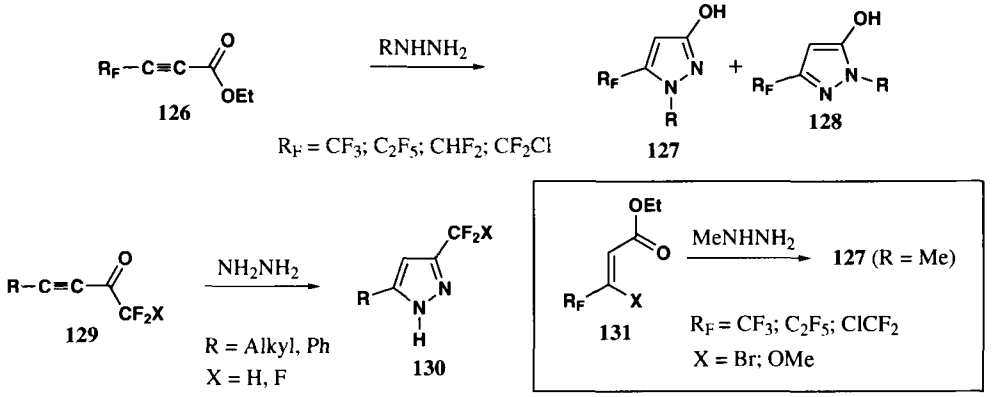
Scheme 21

hydrazine to give excellent yields of trifluoromethylpyrazoles **121** (*Scheme 22*).[79] At first glance, the reaction could be understood through the involvement of a carbinolamine of the trifluoroacetyl group. This result agrees with the report claiming the isolation of an hydrazone (80%) at the $COCF_3$ moiety from the reaction of the dihydropyran **122** (n = 1) with hydrazine.[80] However, later reports regarding the reaction of substrates **122** with substituted hydrazines suggest that the nucleophilic attack of the reagent should involve the β-carbon in a Michael-type reaction.[63] In fact, from the reaction of the dihydropyran **122** (n = 1) with phenylhydrazine the 1-phenyl-5-trifluoromethylpyrazole **123** (36%) was isolated. Moreover, from the reaction of dihydrofuran **122** (n = 0) and dihydropyran **122** (n = 1) with pentafluoro- or tetrafluorophenylhydrazine the 5-hydroxy-5-trifluoromethyl compounds **124** were isolated in about 46-71% yields.[63] In turn, dehydration of **124** into pyrazoles **125** can be achieved by treatment with P_2O_5 (*Scheme 22*).[63]



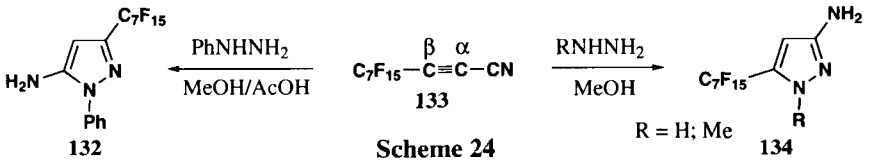
Scheme 22

Alkylhydrazines and fluorinated alkynoates **126** produced 1-alkyl-3-hydroxy-5-fluoroalkylpyrazoles **127** as the major regioisomeric product (*Scheme 23*). The regioisomeric ratio was found to be dependent on the experimental conditions, the hydrazine reagent, and the R_F group.[81] The 3(5)-fluoroalkylpyrazoles **130** (76-92%) were formed from the reaction of fluoroalkylacetylenes **129** and hydrazine through an isolated 5-hydroxy-5-fluoroalkyl intermediate.[82] Other examples of reactions of fluorinated ketoalkynes with hydrazine have been reported.[83] The reaction of α,β-unsaturated esters **131** with methylhydrazine yields 1-methyl-3-hydroxy compounds **127** (R = Me) preferentially (*Scheme 23*).[84]



Scheme 23

Perfluoroalkylpropynonitrile **133** has been used for the synthesis of amino-substituted perfluoroalkylpyrazoles (*Scheme 24*).[85] Thus, the reaction of **133** with hydrazine or methylhydrazine produces the 3(5)-amino compound **134** (R = H) or 3-amino-5-perfluoroalkylpyrazole **134** (R = Me), respectively (50-52%). In contrast, the reaction of **133** with phenylhydrazine yielded the 5-amino-3-perfluoroalkylpyrazole **132** (86%). An initial attack of the more nucleophilic nitrogen of the reagent at the β-carbon of the propynonitrile **133** explains the observed regioselectivity.[85]

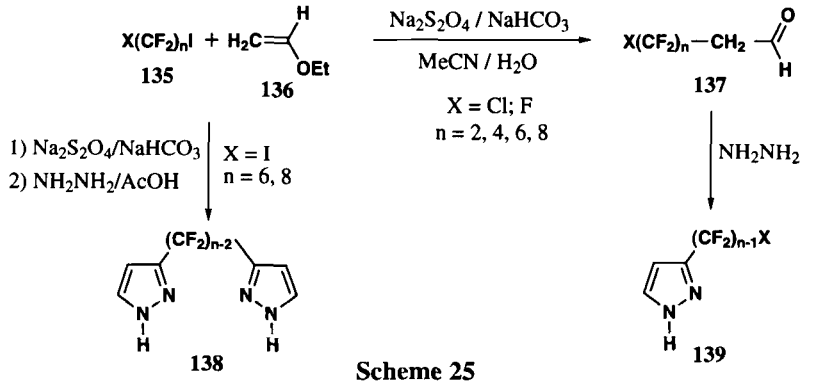


Scheme 24

(c) Syntheses from Polyfluoroalkylcarbonyls Compounds

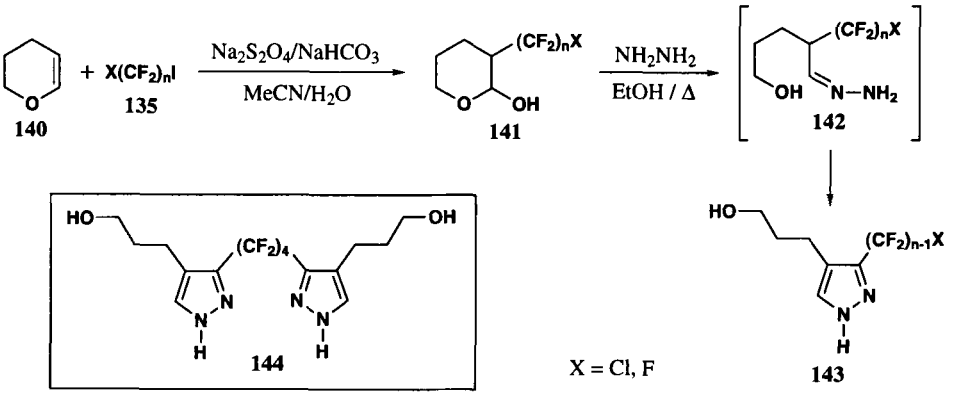
3(5)-Perfluoroalkylpyrazoles **139** have been prepared in excellent yields by reaction of various fluoroalkyl aldehydes **137** (easily accessible by reaction of fluoroalkyl iodides **135** with ethyl vinyl ether **136** in the presence of sodium dithionite and sodium hydrogen carbonate) with hydrazine acetate (NH_2NH_2•HOAc).[86] By the same methodology, starting from α,ω-diiodoper-

fluoroalkane **135** (X = I), *bis*(pyrazole)s **138** have also been obtained.[86] In a similar reaction, structurally related fluoroalkyl ketones and fluoroalkylacetates have been used in the synthesis of 3(5)-perfluoroalkyl substituted pyrazoles (*Scheme 25*).[87]



Scheme 25

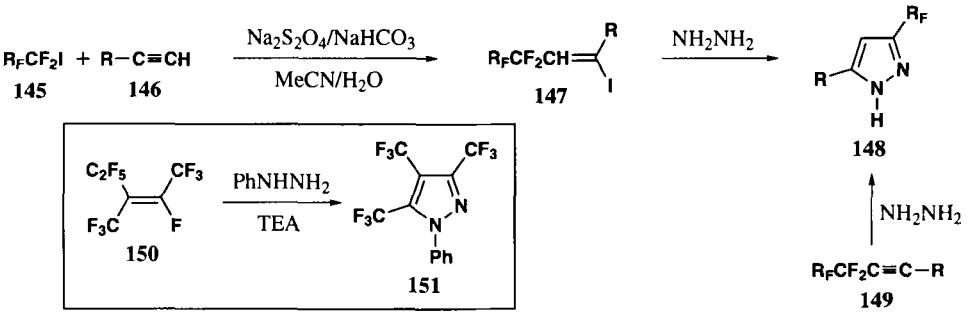
Similarly, perfluoroalkyl hemiacetals **141**, prepared from perfluoroalkyl iodides **135** and dihydropyran **140**, were succesfully used for the synthesis of 3-perfluoroalkylpyrazoles **143** (*Scheme 26*). Again, the use of the α,ω-diiodoperfluoroalkane **135** (X = I; n = 6) provided the *bis*(pyrazole) **144**.[87a]



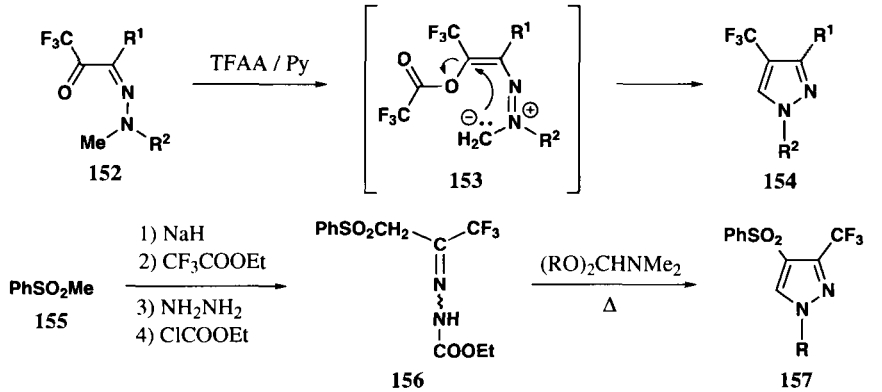
Scheme 26

Fluoroalkyl iodides **145** and alkynes **146**, under free radical reaction conditions, form adducts **147** that produced 3-perfluoroalkyl pyrazoles **148** (90%) upon reaction with an excess of hydrazine monohydrate (*Scheme 27*).[88] Alternatively, perfluoroalkyl-acetylenes **149** and hydrazine hydrate in ethanol produced 3,5-disubstituted pyrazoles **148** in almost quantitative yields.[89] Fluorinated acetylenic imines (the cross coupling products of fluorinated *N*-aryl imidoyl iodides with acetylenes) have also been used to synthesize 3-perfluoroalkylpyrazoles.[90] Perfluorinated 3-methyl-2-pentene **150** reacted with phenylhydrazine in the presence of TEA and produced the *tris*(trifluoromethyl)-1-phenylpyrazole **151** (84%).[91]

Finally, 4-trifluoromethyl-1-alkylpyrazoles **154** are prepared in good yields by trifluoroacetic anhydride-pyridine (TFAA/Py) induced cyclization of *C*-trifluoroacetyl-*N,N*-dialkylhydrazones **152** which is rationalized through the ylide-like intermediate **153** (*Scheme 28*).[92]



Scheme 27



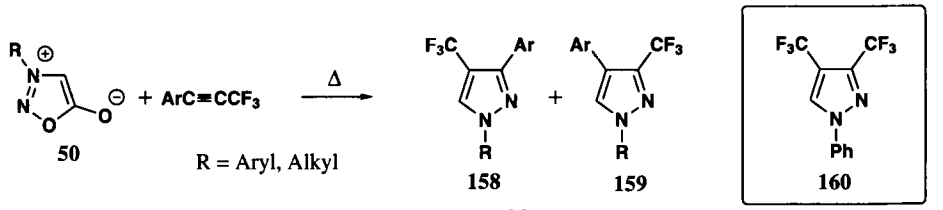
Scheme 28

3-Trifluoromethyl-4-phenylsulfonylpyrazoles **157** are reported (50-80%) by heterocyclization of hydrazones **156**, easily accessible from the sulfone **155** (*Scheme 28*).[93]

d) Syntheses from Cycloaddition Reactions

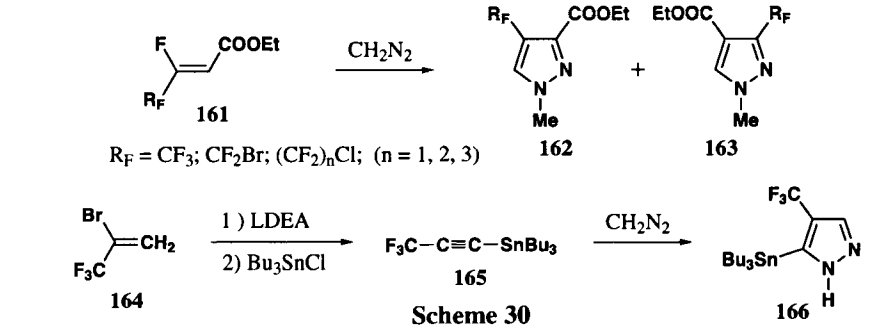
1,3-Dipolar cycloadditions of sydnones, diazoalkanes, and nitrilimines on acetylenic or ethylenic systems have been used for the synthesis of fluorinated pyrazoles. For example, trifluoromethylarylacetylenes (1-aryl-3,3,3-trifluoropropynes) reacted in highly boiling solvents with sydnones **50** (R = Aryl, Alkyl) with elevated regioselectivity to produce 4-trifluoromethylpyrazoles **158** together with small amounts of regioisomers **159** (*Scheme 29*).[94] Cycloaddition of the *N*-phenylsydnone **50** (R = Ph) onto perfluorobut-2-yne affording the 3,4-*bis*(trifluoromethyl)-1-phenylpyrazole **160** (70%) is also reported.[30]

Various examples using cycloadditions with diazomethane are reported.[95] For instance, fluoroacrylates **161** reacted with diazomethane to produce 4-fluoroalkyl- **162** and 3-fluoroalkylpyrazoles **163** (in a 9/1 ratio) in a total 80-90% yield (*Scheme 30*). In this case, the first formed 1*H*-pyrazole underwent a methylation with excess of diazomethane.[96] Cycloadditions



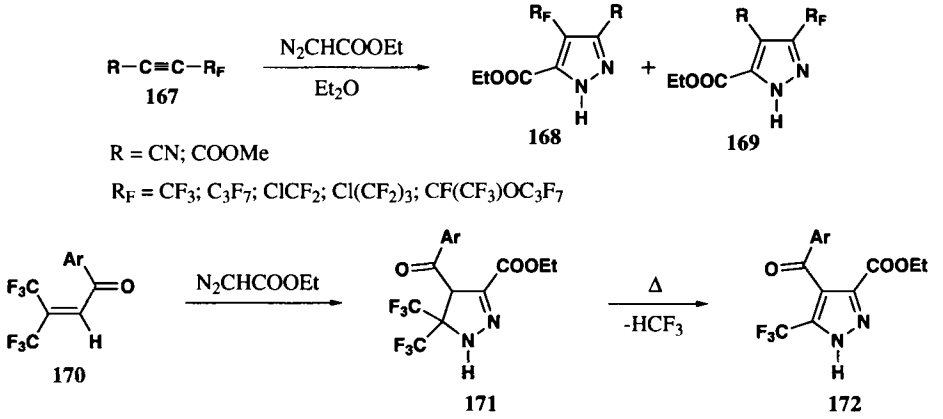
Scheme 29

between perfluoroalkenes and diazomethane leading to perfluoroalkyl-pyrazolines have also been reported.[97] Tributyl-(3,3,3-trifluoro-1-propynyl)-stannane **165**, readily prepared from 2-bromo-3,3,3-trifluoropropene **164**, and diazomethane exclusively yields the corresponding trifluoromethylpyrazole **166** (64-70%) (*Scheme 30*).[98] Furthermore, the tributylstannyl group allowed the regioselective introduction of various substituents on the pyrazole ring.[98]



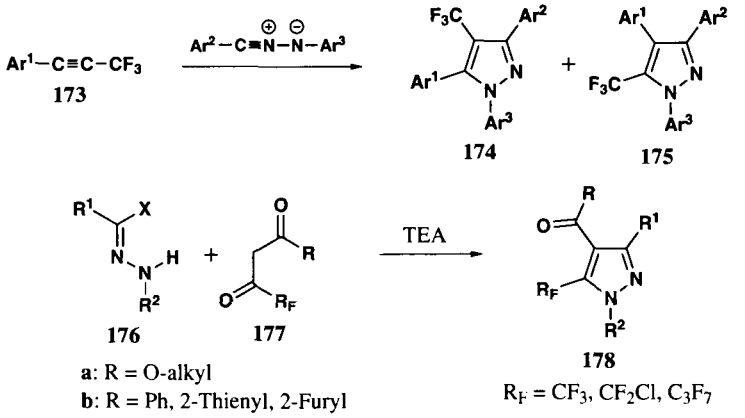
Scheme 30

Polyfluoroalkylpyrazoles **168** (major product) and **169** are formed in high yields by reaction of ethyl diazoacetate with polyfluoroalkyl alkynes **167** (*Scheme 31*).[99] On the other hand, hexafluorovinyl ketones **170** and ethyl diazoacetate lead to pyrazolines **171** (66-82%), which are transformed into the corresponding 4-aroylpyrazoles **172** (57-72%) by heating at 150°C in the presence of azo-*bis*(isobutyronitrile) (AIBN).[100]



Scheme 31

Finally, 4-trifluoromethylpyrazoles **174** (together with modest amounts of their regioisomers **175**) have been obtained, in good yields, from the cycloaddition reaction of trifluoromethylarylacetylenes **173** with nitrilimines (*Scheme 32*).[101] Hydrazonyl halides **176** react with fluorinated β-ketoesters **177a** or β-diketones **177b** (in their enolate form) exclusively producing



a: R = O-alkyl
b: R = Ph, 2-Thienyl, 2-Furyl

R_F = CF_3, CF_2Cl, C_3F_7

Scheme 32

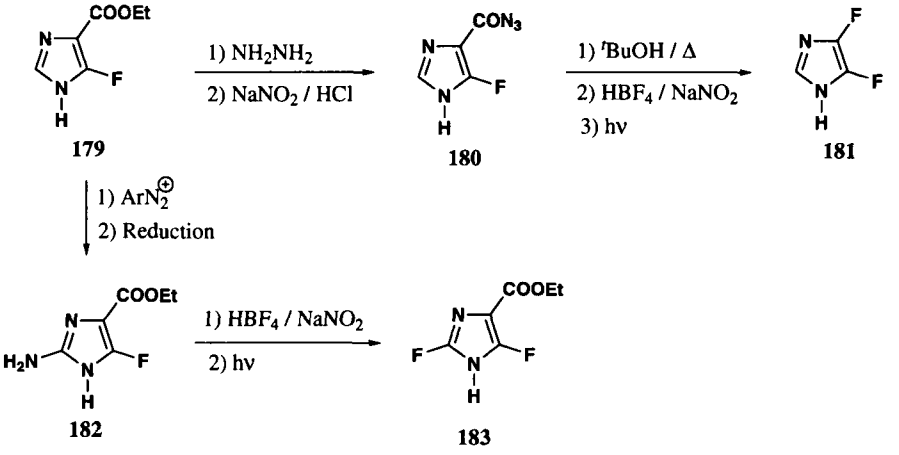
5-perfluoroalkypyrazoles **178** (74-86%) through the initially formed (although not isolated) 5-hydroxy-2-pyrazolines.[102] A cycloaddition reaction also occurs between hydrazonyl chlorides and trifluoroacetylacetonitrile.[103] *N*-Aryl-*C*-(trifluoromethyl)hydrazonyl halides react with β-diketones, β-ketoesters and congeners under alkaline conditions to produce the corresponding 3-trifluoromethyl-pyrazoles.[104]

II. IMIDAZOLES[105]

1. Ring-fluorinated Imidazoles

Several ring-fluorinated imidazoles are known. For a series of mono- and polyfluorinated compounds, MNDO calculations have also been reported.[6] A more recent theoretical study deals the 2,4,5-trifluoroimidazole as a proton carrier for water-free fuel cell membranes.[106]

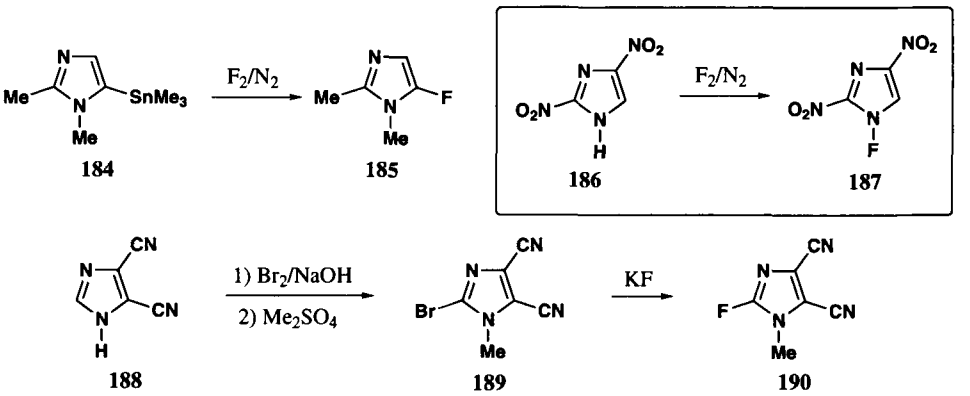
The general and historic methodology for introducing a fluorine atom directly onto the imidazole ring consists of the photochemical decomposition of imidazole diazonium fluoroborates. Obviously, this approach requires the presence of an amino group which will eventually be replaced by the fluorine. Common precursors of the aminoimidazoles can be the corresponding nitro-, azo-, or azidoimidazoles (from the corresponding carboxylic acid). Several ring-fluorinated imidazoles have been prepared with this methodology.[107] 2-Fluorohistidine and 2-fluorohistamine can be prepared by a similar procedure.[108] In some cases, the photochemical degradation of diazonium tetrafluoroborates has been performed directly on the imidazole portion of histidine in peptides such as thyroliberin.[109] A representative procedure is reported (*Scheme 33*) for 4,5-difluoroimidazole **181** (36%),[110] and ethyl 2,4(5)-difluoroimidazole-5(4)-carboxylate **183** (53%),[111] starting from the common precursor **179**.



179 180 181 182 183

Scheme 33

An example of electrophilic ring-fluorination is reported on stannylated *N*-methylimidazole **184** (*Scheme 34*). The formation of the fluorinated compound **185** was supported by NMR evidence only, since the reaction was not carried out on a preparative scale.[112] Fluorination of the 2,4-dinitroimidazole **186** produces the *N*-fluoro compound **187** (yields not reported) which was



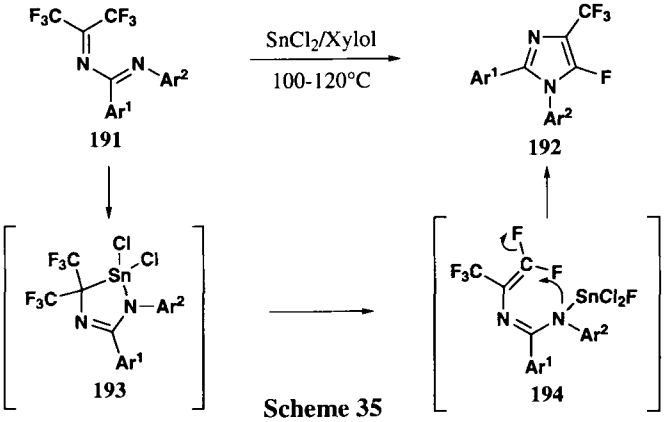
184 185 186 187 188 189 190

Scheme 34

claimed to act as a fluorinating reagent for polycyclic aromatic hydrocarbons (PAHs).[113] In fact, the electron-withdrawing effect of the two nitro groups weakens the *N-F* bond allowing the transfer of a fluorine atom to PAHs under mild conditions. An example of a transhalogenation reaction is reported for the fluorination of 2-bromo-1-methyl-4,5-dicyanoimidazole **189**[114] with KF in the presence of a catalytic amount of 18-crown-6 ether in diglyme, leading to the corresponding 2-fluoro derivative **190** (89%) (*Scheme 34*).[115]

A series of 5-fluoro-4-trifluoromethylimidazoles **192** has been prepared (58-65%) through cyclodefluorination of fluorinated amidines **191** mediated by tin(II) chloride.[116] This reaction, studied mostly by Burger's research group, is of general type, and the same kind of

heterocyclization takes place in the case of the corresponding carboxamides and thiocarboxamides allowing the synthesis of oxazole and thiazole derivatives, respectively (see later). The reaction sequence (*Scheme 35*) involves heterocyclic tin(IV) compounds of the type **193** as intermediates.[116] In a similar cyclization using germanium(II) chloride, the corresponding cyclic intermediate has been isolated and characterized by X-ray analysis.[117]



Scheme 35

2. Fluoroalkylated Imidazoles

a) Side-chain Fluorinated Imidazoles

For the synthesis of biologically important side-chain fluorinated imidazoles, the recent review by Dolensky *et al* should be consulted.[118] Fluoromethylimidazoles **195** and **196** and difluoromethylimidazoles **197** and **198** (*Fig. 2*) have been prepared by deoxyfluorination, with [*bis*(2-methoxyethyl)amino]sulfur trifluoride (*Deoxo-fluor*™), of the corresponding *N*-trityl protected (hydroxymethyl)imidazoles or formylimidazoles, respectively.[119]

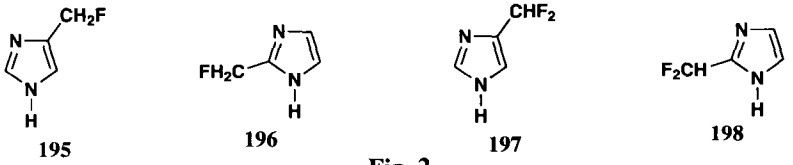
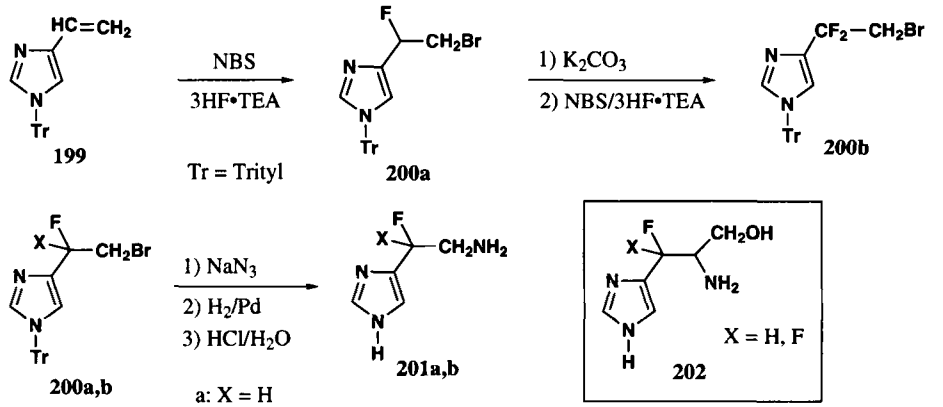


Fig. 2

A series of papers reports the synthesis of side-chain fluorinated hystamine and hystidine analogues containing one or two fluorine atoms at the carbon adjacent to the imidazole ring. β-Fluorohystamine **201a** had been prepared earlier by fluorodehydroxylation of β-hydroxyhistamine with SF_4 in HF.[120] A recent different approach consists of the "F-Br" addition to an *N*-trityl-protected 4-vinylimidazole **199**. The addition is achieved by treatment with *N*-bromosuccinimide (NBS), in the presence of a $TEA(HF)_3$ complex, and occurs with Markovnikov regioselectivity producing the bromofluoro compound **200a** (74%). Subsequent substitution with azide, and then reduction and removal of the trityl group provides β-fluorohystamine **201a** in its

dihydrochloride form.[121] (*Scheme 36*). Similarly, elimination of HBr from **200a**, followed by a second addition of "F-Br", produced **200b** from which the β,β-difluoro-hystamine **201b** was obtained.[121] The same approach has also been used for the synthesis of β-fluorourocanic acid and congeners,[122] as well as for β-fluoro- and β,β-difluorohystidinols **202**.[123]



Scheme 36

The reaction of imidazole with difluorochloromethane in alkaline medium produces the *N*-difluoromethyl substituted derivative **203** (R = H) (37%) (*Fig. 3*).[124] Similarly, 2-phenylimidazole produced the *N*-difluoromethyl derivative **203** (R = Ph) (75%), while 4(5)-phenylimidazole yielded a mixture of the two 4-phenyl- **204** (43%) and 5-phenyl- **205** (30%) regioisomers.[125] The difluoromethylation of 2-mercapto-4(5)-(4-nitrophenyl)imidazole occurred at both reaction sites.[126] Interestingly, a series of *N*-polyfluoroalkylimidazoles of the type **206** has been obtained by reaction of imidazole with polyfluorinated alkenes in the presence of base or KF.[127]

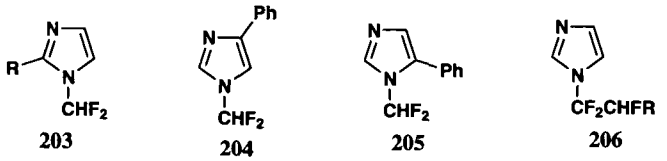
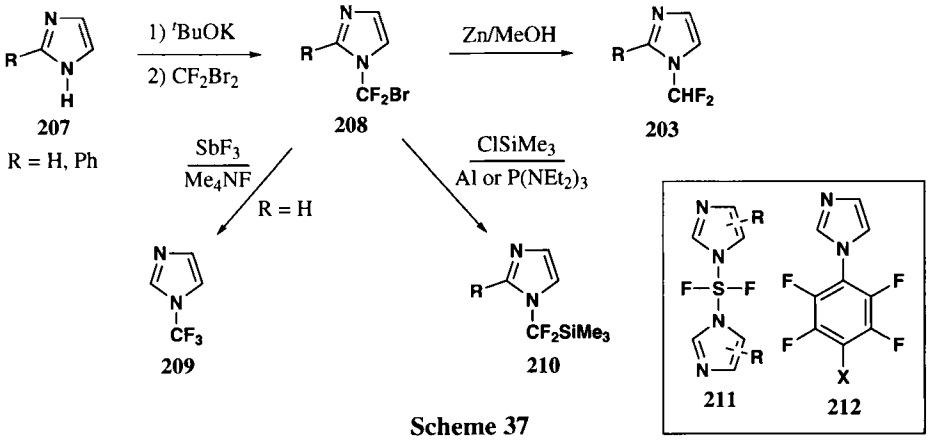


Fig. 3

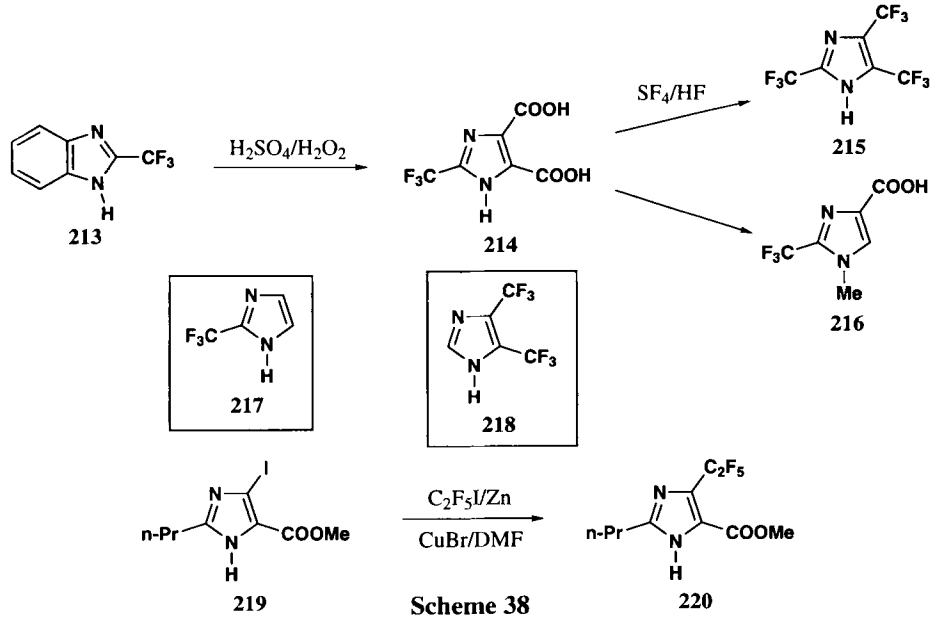
N-bromodifluoromethylimidazoles **208** are obtained from the reaction of potassium salts of imidazoles with dibromodifluoromethane.[128,129] Modification of the bromodifluoromethyl group in **208** can lead to difluoromethyl derivatives **203** (95%), to *N*-trifluoromethyl derivative **209** (30%), or to the silyl derivatives **210** (75-85%) (*Scheme 37*). The silyl derivatives **210** have been used as a reagent for a series of reactions with carbonylic compounds.[129] The *bis*(imidazolyl)sulfur difluorides of the general type **211** (prepared by using SF_4 on the 1-trimethylsilylimidazoles) have been patented as fluorinating reagents.[130] Nucleophilic substitution of pentafluorobenzenes with imidazole (in the presence of a base) produced *N*-tetrafluorophenylimidazoles **212** in high yields when X is an electron-withdrawing group (e. g., X = NO_2, CN, COOEt).[131]



Scheme 37

b) Perfluoroalkylation Reactions

The conversion of a carboxylic moiety into a trifluoromethyl group has also been applied in the imidazole series (*Scheme 38*). For instance, 2-trifluoromethyl-imidazole **217** and 2,4,5-*tris*(trifluoromethyl)imidazole **215** were obtained by fluorination with sulfur tetrafluoride

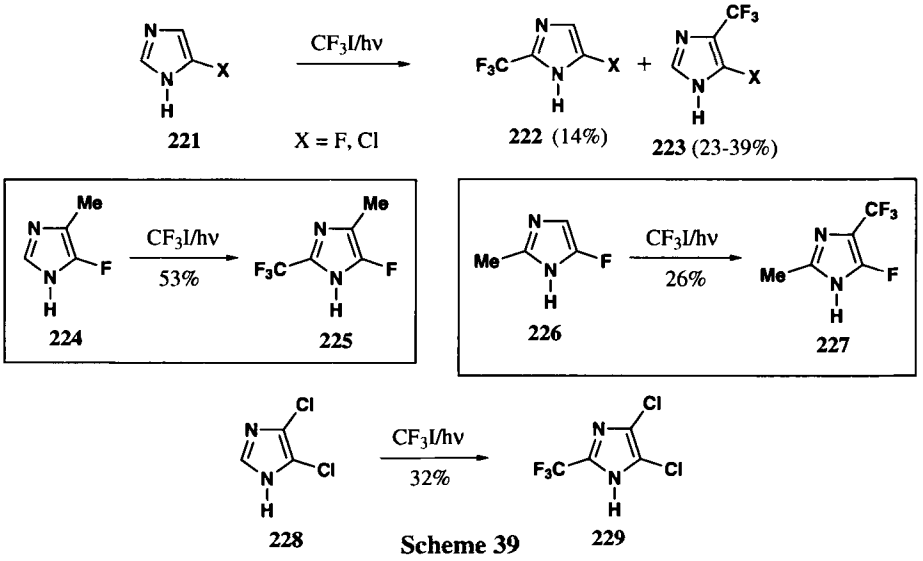


Scheme 38

of the corresponding imidazole 2-carboxylic acid and 2-trifluoromethyl-4,5-dicarboxylic acid **214** (easily accessible from oxidative cleavage of the commercially available 2-trifluoromethyl-benzimidazole **213**), respectively.[132] A series of functional group modifications allowed the transformation of **214** into **216**.[133] Similarly, the 4,5-*bis*(trifluoromethyl)imidazole **218** was obtained from the corresponding dicarboxylic acid and molybdenum hexafluoride.[134]

Besides the above modification reactions, the direct introduction of a trifluoromethyl, or more generally of a perfluoroalkyl group in the imidazole ring is well documented and is mainly used to obtain target compounds. The reaction can be performed under different experimental conditions and often involves photochemical, electrochemical or metal-catalyzed processes to generate the perfluoroalkylating reagent. A recent example of the reaction between a perfluoroalkylzinc or copper reagent with a iodoaromatic substrate is illustrated (*Scheme 38*) for the preparation of **220** (75-85%), a useful precursor in the synthesis of *angiotensin II* antagonists.[135]

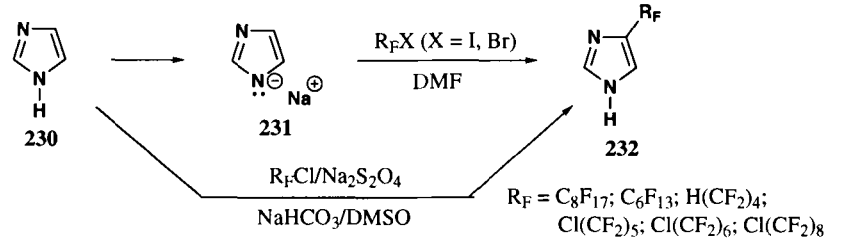
A general procedure for the perfluoroalkylation of the imidazole ring is based on the photo-induced dissociation of the *C-I* bond of a perfluoroalkyl iodide. Through a radical substitution route, either the C(4) or the C(2) of the imidazole ring can be perfluoroalkylated, the former generally being the preferred site. The reaction is rather slow with isolated yields of 4-R_F imidazoles ranging between 34 and 61% and those of the 2-R_F between 10 and 33%.[136] 1-Alkylimidazoles are trifluoromethylated mainly at the C(5), although some amount of 2- and 4-perfluoroalkykated products are observed. As expected, trifluoromethylation of arylimidazoles mainly involves the azole rather than the phenyl ring. For example, trifluoromethylation of 2-(4-methoxyphenyl)-imidazole leads to the corresponding 4-trifluoromethyl substituted imidazole (55%).[137] Recently, photochemical trifluoromethylation has been successfully carried out on substituted imidazoles carrying electron-withdrawing groups as in the illustrative examples (*Scheme 39*).[138] The photo-induced trifluoromethylation also takes place in the case of *N*-acylhistamines and *N*-acylhistidine esters leading to ring substitution at the C(2) (13-27%) or C(4) (23-34%).[137,139] Moreover, the direct photochemical trifluoromethylation of a histidine-containing tripeptide is also reported.[140]



Scheme 39

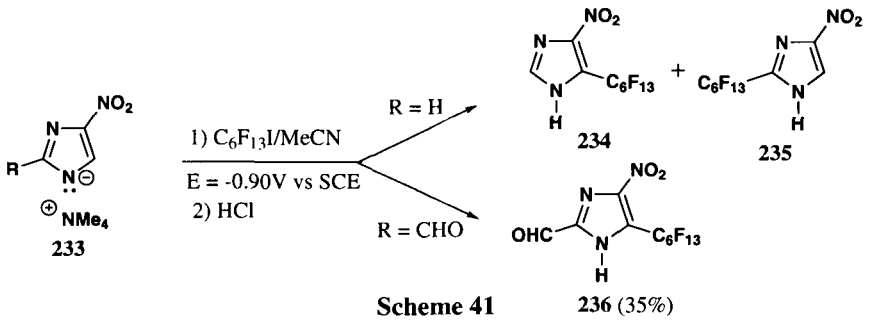
High yields of 4(5)-fluoroalkylimidazoles **232** (52-86%) were obtained by the regioselective reaction of the imidazole anion (sodium imidazolide) **231** (acting as an electron-donor

species) with fluoroalkyl iodides or bromides in DMF under laboratory light, and results have been rationalized by assuming an $S_{RN}1$ mechanism (*Scheme 40*).[141] The 4(5)-fluoroalkylimidazoles **232** (63-67%) were also formed in the reaction of imidazole **230** with R_FCl in the presence of sodium dithionite in DMSO.[142]



Scheme 40

Perfluoroalkylation of imidazoles is also conveniently realized by electrochemically induced $S_{RN}1$ substitutions. For instance, electrochemical reduction of perfluoroalkyl halides

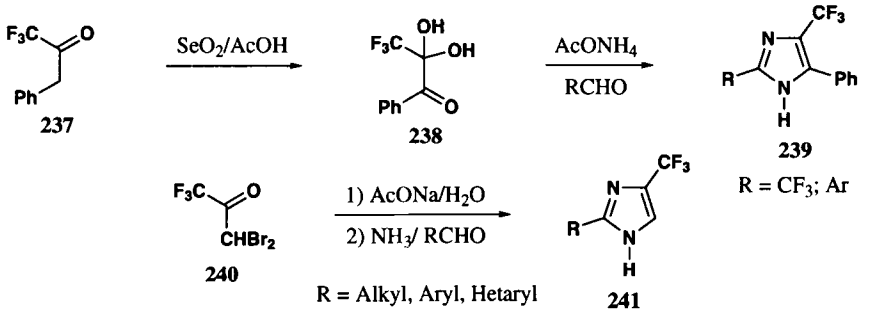


Scheme 41

(CF_3Br, *n*-C_4F_9I, *n*-$C_6F_{13}I$) in the presence of differently substituted imidazoles yielded the corresponding perfluoroalkylated compounds.[143,144] Representative examples of preparative scale electrolysis, where imidazole tetramethylammonium salts **233** are used in the presence of 4-nitropyridine *N*-oxide, are illustrated (*Scheme 41*).[144] Note that, in the case of **233** (R = H), perfluoroalkylation reaction takes place either at C(5) or at C(2), and a mixture of the corresponding **234** and **235** (in a 2:1 ratio) is formed in 65% combined yields.

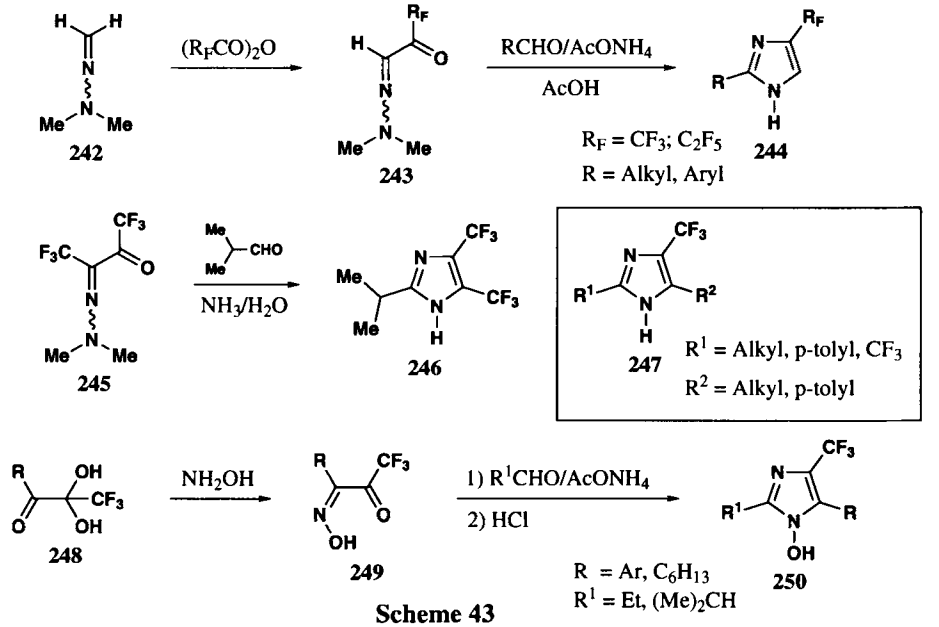
c) Syntheses from Heterocyclization Reactions

The synthesis of 4(5)-trifluoromethylimidazoles **239** (R = Ar) (15-47%) and 2,4(5)-*bis*(trifluoromethyl)imidazole **239** (R = CF_3) (46%) has been achieved through the classical cyclocondensation reaction of α-dicarbonyls with ammonia and aldehydes (*Scheme 42*).[145] Similarly, 4(5)-trifluoromethylimidazoles **241** can be prepared from 3,3-dibromo-1,1,1-trifluoroacetone **240** (after its hydrolysis with sodium acetate).[146]



Scheme 42

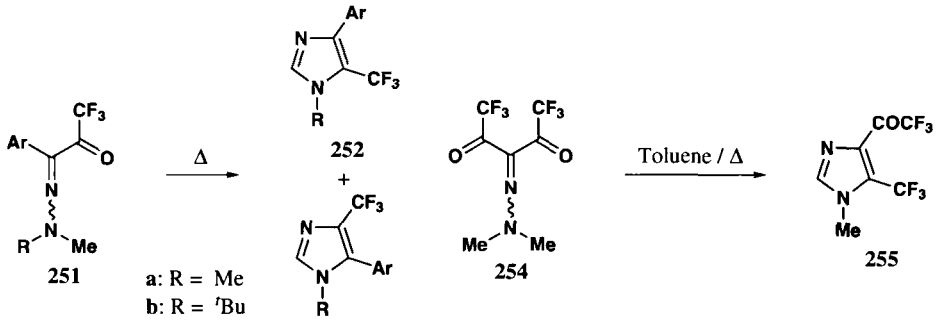
In an analogous synthetic approach, fluorinated *N,N*-dimethylhydrazones **243**, easily prepared from formaldehyde dimethylhydrazone **242** and trifluoroacetic or pentafluoropropionic anhydrides, were considered as the synthetic equivalent of fluorinated ketoaldehydes. Their reaction with aldehydes in the presence of ammonium acetate in acetic acid produced the corresponding 4(5)-perfluoroalkylimidazoles **244** (61-68%) (*Scheme 43*).[147] (Note that *ab initio* calculations showed that the 4-trifluoromethyl tautomer is more stable than the 5-trifluoromethyl one).[147] Additional examples of this approach have been reported.[148] The fluorinated *N,N*-dimethylhydrazone **245**, obtained by trifluoroacetylation of trifluoroacetaldehyde dimethylhydrazone, has been used as a perfluorobiacetyl analogue in the synthesis of the 4,5-*bis*(trifluoromethyl)imidazole **246** (35%).[148a] The 4-(trifluoromethyl)imidazoles **247** are similarly obtained by using 1,1,1-trifluoro-2,3-alkandiones **248** prepared from various trifluoroacetylated aldehyde dialkylhydrazones.[148b] Finally, 1,1,1-trifluoroalkane-2,3-dione-3-oximes **249** reacted with aldehydes in the presence of



Scheme 43

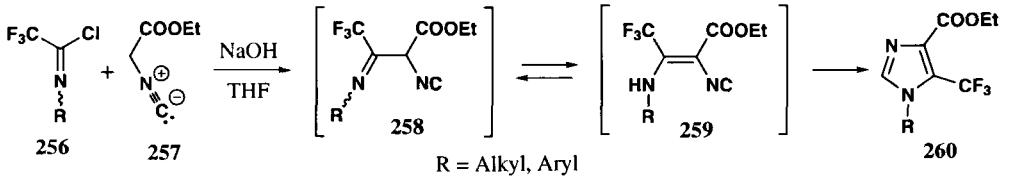
ammonium acetate and, after treatment with HCl, produced *N*-hydroxy-4-trifluoromethylimidazoles **250** (60-72%) (*Scheme 43*).[149]

A thermally-induced cyclization of trifluoroacetylated arylaldehyde *N,N*-dialkylhydrazones **251** is claimed to yield trifluoromethyl substituted imidazole regioisomers **252** and **253** in different ratios depending on experimental conditions (*Scheme 44*).[150] For instance, compounds **251a,b** in refluxing toluene mainly produced 5-trifluoromethylimidazoles **252a,b** in good yields.[150] Similarly, dimethylhydrazone **254** is converted into **255** (78%). On the other hand, thermal cyclization of **251a** in the presence of silica gel lead to the regioisomeric 4-trifluoromethylimidazoles **253a** as the major product.[150] The influence of various parameters on this reactivity has been considered but no explanation of the obtained results is reported.[151,152]



Scheme 44

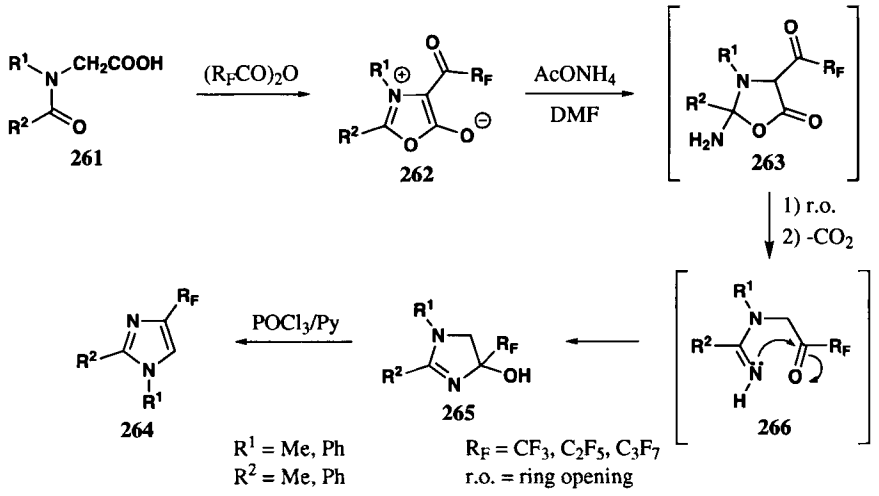
Following a cycloaddition model, the synthesis of 5-trifluoromethylimidazoles **260** could be achieved, with high regioselectivity and in 59-85% yields, by the base-induced reaction of ethyl isocyanoacetate with trifluoroacetimidoyl chlorides **256** (*Scheme 45*).[153]



R = Alkyl, Aryl

Scheme 45

4-Perfluoroalkylimidazoles **264** can be conveniently synthesized from the mesoionic 4-perfluoroacyl-1,3-oxazolium-5-olates **262**, that are easily prepared from *N*-acyl-*N*-alkylglycines **261** and perfluoroalkanoyl anhydrides (*Scheme 46*).[154] The reaction of **262** with ammonium acetate in DMF yields hydroxyimidazolines **265** (78-98%) through the regioselective attack of ammonia on the C(2) of the oxazole nucleus. Subsequent dehydration of **265** by treatment with $POCl_3$ and pyridine yielded compounds **264** (88-99%).[154] On the other hand, the reaction of mesoionic 1,3-oxazolium-5-olates **262** ($R_F = CF_3$) with amidines mainly lead to 5-perfluoroacyl-imidazoles.[155]



Scheme 46

Finally, the classical photochemical rearrangement of pyrazoles into imidazoles has to be mentioned, even though this approach is not appropriate for a preparative scale synthesis. The reaction follows the conventional pathways typical of five-membered heterocycles.[156] In the reported example, trifluoromethyl substituted 1-methylimidazoles (*Fig. 4*) are formed by photoinduced ring-atoms transposition of trifluoromethyl substituted 1-methylpyrazoles following different routes, depending on the substrate.[157]

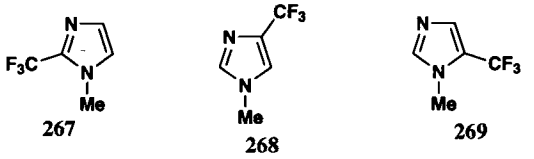
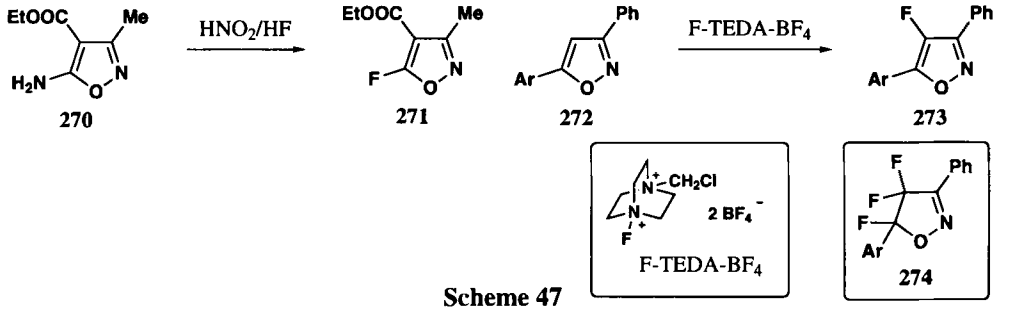


Fig. 4

III. ISOXAZOLES[158]

1. Ring-fluorinated Isoxazoles

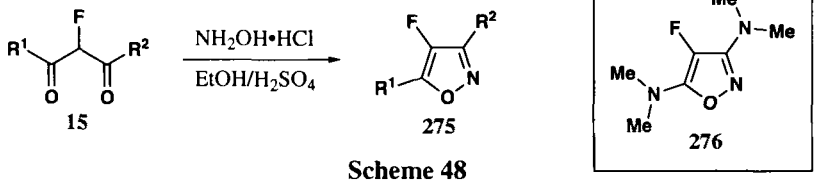
An example of ring-fluorinated isoxazoles prepared by conventional modification of an amino group is the 5-fluoroisoxazole **271** (40%) (*Scheme 47*).[159] Alternatively, the availability of various electrophilic fluorinating reagents[160] allows one to realize a direct annular fluorination.



Scheme 47

For instance, transfer-fluorination reactions of 3,5-diarylisoxazoles **272** by using the "N-F" reagent "F-TEDA-BF_4"[161] produced the corresponding 4-fluoroisoxazoles **273** in 28-39% of yields (*Scheme 47*).[162] When an electron-withdrawing substituent was present in the 5-aryl moiety, higher temperatures were required and, in this case, trifluoroisoxazolines **274** were isolated as a by-product.

Besides these examples, 4-fluoroisoxazoles are obtained by using the reaction between α-fluoro-β–dicarbonyl compounds and hydroxylamine (*Scheme 48*). For example, 4-fluoroisoxazole **275** (R^1 = R^2 = Ph) is formed in 33% yield from the reaction of fluorinated diketone **15** (R^1



Scheme 48

= R^2 = Ph) with hydroxylamine hydrochloride in ethanol and in the presence of sulfuric acid.[16] In the case of the unsymmetrical diketone **15** (R^1 = Me; R^2 = CF_3) only the 3-trifluoromethyl-4-fluoro-5-methylisoxazole **275** (R^1 = Me; R^2 = CF_3) was claimed as a result of an attack of the nucleophilic reagent on the more electrophilic carbonyl of the non-enolized substrate.[16] Similarly, the synthesis of 3,5-*bis*(dimethylamino)-4-fluoroisoxazole **276** from a suitably fluorinated 1,3-dielectrophilic substrate has been reported.[163]

2. Fluoroalkylated Isoxazoles

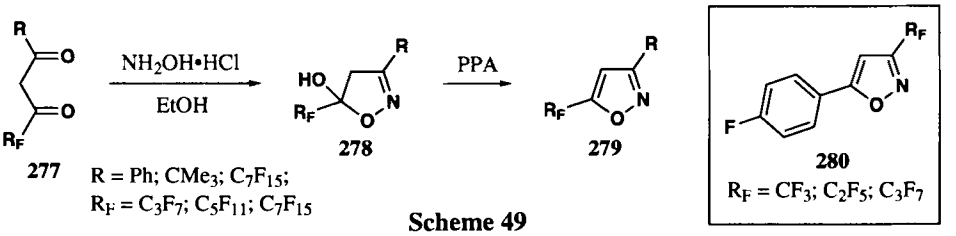
General approaches towards fluoroalkylated or perfluoroalkylated isoxazoles take advantage of common methodologies for building the isoxazole heterocycle from open-chain precursors: *i)* the cyclocondensation reactions of 1,3-dielectrophilic compounds with hydroxylamine; and *ii)* the cycloaddition reactions of 1,3-dipolar reagents (such as nitrile oxides) to suitable dipolarophiles. An example consisting of a modification of a functional group linked to the isoxazole ring is the fluorination of the 5-trichloromethylisoxazole with hydrogen fluoride or antimony trifluoride which produces a mixture of side-chain mono or polyfluorinated compounds.[164]

a) Syntheses from β-Dicarbonyl Compounds

It is well known that the reaction of β-dicarbonyls with hydroxylamine is a general synthetic approach to 3,5-disubstituted isoxazoles. As already cited in the pyrazole series, the widely accepted mechanism consists of a nucleophilic attack by the nitrogen end of the hydroxylamine on the more electrophilic site of the dicarbonyl compound. The resulting carbinolamine will undergo cyclization/dehydration steps into the 5-hydroxyisoxazoline, which can eliminate another molecule of water in the rearomatization step yielding the final isoxazole.[34] In the case of asymmetric diketones, the reactivity of the electrophilic centers, and hence the final regiochem-

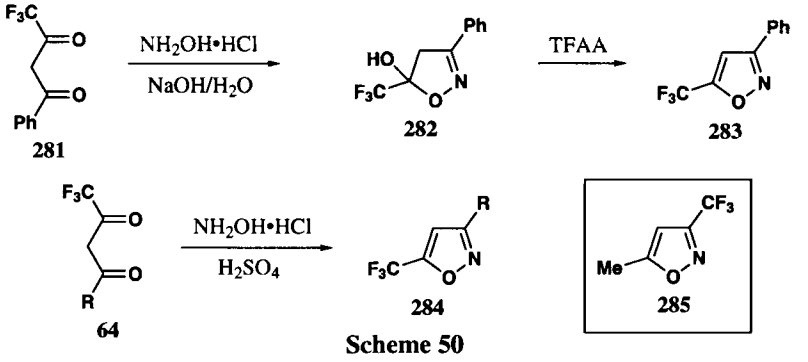
istry, is affected and/or controlled by the keto-enolic tautomeric equilibria which in turn are also determined both by the reaction medium and by the presence of the fluorinated moiety.[41] Moreover, as already observed in the pyrazole series, the resistance to dehydration of the 5-hydroxy-5-perfluoroalkyl-2-isoxazolines allows them to be isolated.

Historical examples exploiting this approach are the reaction of diketones **277** with hydroxylamine hydrochloride producing the 5-hydroxy-5-perfluoroalkyl-isoxazolines **278** (83-94%) (*Scheme 49*).[165] The latter were then dehydrated with polyphosphoric acid (PPA) at 180-200°C to produce the corresponding isoxazoles **279** in 75-90% yield. Other examples claim the synthesis of 3-perfluoroalkyl-5-arylisoxazoles **280** from diketones and hydroxylamine hydrochloride in pyridine,[166] although the reported regiochemistry can be questioned.



Scheme 49

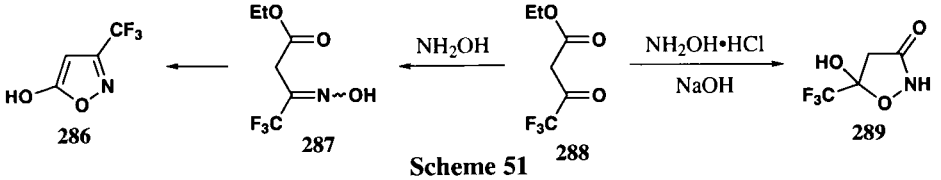
The reaction of the diketone **281** with hydroxylamine is reported to produce the 5-hydroxy-5-trifluoromethylisoxazoline **282** (91%) (*Scheme 50*).[167] Subsequent dehydration of **282** to the isoxazole **283** (91%) is then achieved by reflux in trifluoroacetic acid (TFAA). The same reaction was repeated more recently[168] disproving the previously reported formation of an oxime leading to the 3-trifluoromethyl regioisomer.[169] Very recently the reaction of hydroxylamine with



Scheme 50

various aryl trifluoromethyl-*β*-diketones leading to 5-hydroxy-5-trifluoromethyl-isoxazolines and their dehydration to 5-trifluoromethylisoxazoles has been overviewed.[170] The preparation of the 3,5-*bis*(trifluoromethyl)isoxazole **284** (R = CF_3) (83%) from the corresponding diketone **64** (R = CF_3) and hydroxylamine in the presence of sulfuric acid has been reported,[16b] whereas the unsymmetrical methyl-trifluoromethyl diketone **64** (R = Me) produces a mixture of both **284** (R = Me) and **285** (in 2:1 ratio) in 73% overall yield (*Scheme 50*).[16b]

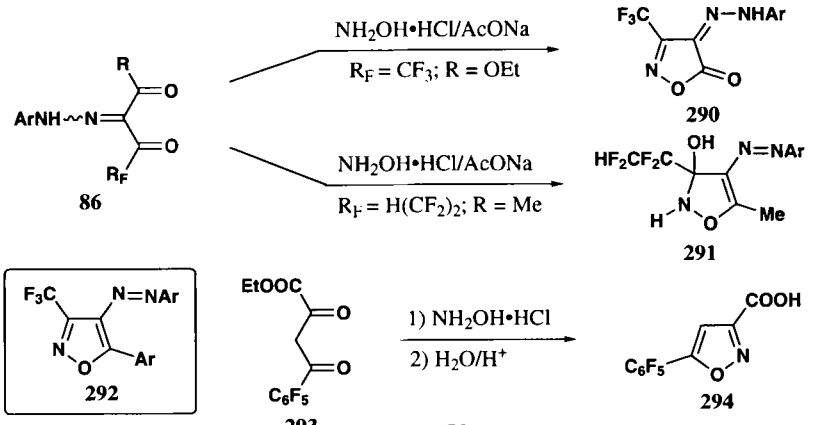
The 5-hydroxy-5-trifluoromethylisoxazolidin-3-one **289** is formed (56%) from the reaction of ethyl trifluoroacetylacetate **288** with hydroxylamine in alkaline media (*Scheme 51*).[171] Even though the assigned structure has been supported by X-ray diffraction data, the proposed mechanism involving the initial attack of the oxygen end of hydroxylamine on the trifluoroacetyl carbonyl may be questioned. However, this result conflicts with a previous (uncited) patent



Scheme 51

describing the reaction of **288** with hydroxylamine free-base leading to a mixture of the 3-trifluoromethyl-5-hydroxy derivative **286** (isolated as sodium salt after final treatment with EtONa) and the oxime **287** which has also been isolated and cyclized into the isoxazole after treatment with a base (*Scheme 51*).[172]

The reaction of the 2-arylhydrazono-2,3-diketoester **86** (R_F = CF_3; R = OMe) with hydroxylamine produces the corresponding isoxazolin-5-one **290**. Similar reaction on the 2-arylhydrazono-1,2,3-triketone **86** [R_F = $H(CF_2)_2$; R = Me] gives the 3-hydroxyisoxazoline **291** which is claimed to be stable to dehydration (*Scheme 52*).[55] The synthesis of 3-trifluoromethyl-4-arylazo-5-arylisoxazoles **292** has been also reported;[173] however, a recent reinvestigation questioned the



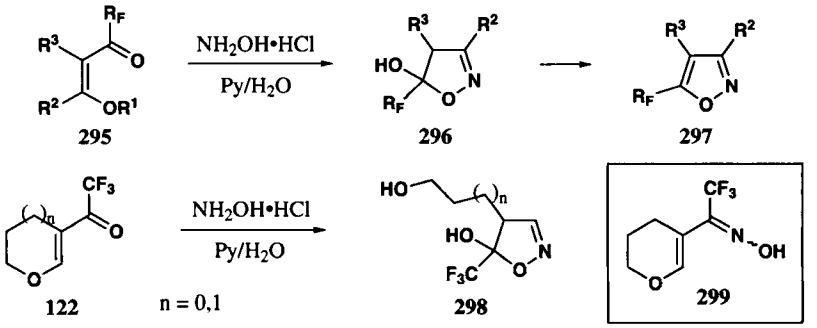
Scheme 52

assigned regiochemistry, the correct product structure being that of the 5-trifluoromethyl-3-aryl regioisomers.[170] Ethyl pentafluorobenzoyl-pyruvate **293** and its copper salt, react with hydroxylamine to afford 5-pentafluorophenylisoxazole **294** as the final product (*Scheme 52*).[58]

b) Syntheses from α,β-Unsaturated Carbonyl Compounds

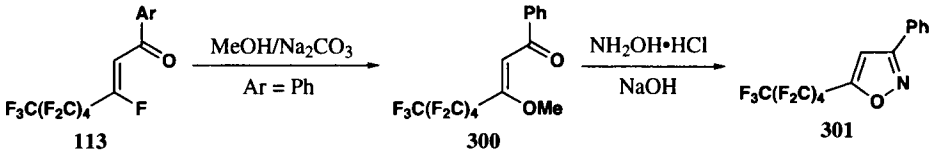
Fluorinated enol ethers **295** (R_F = CF_3) react with hydroxylamine hydrochloride in the presence of pyridine to yield the 5-hydroxy-5-(trifluoromethyl)isoxazolines **296** (R_F = CF_3) (68-

80%) through a nucleophilic attack of the reagent at the β-carbon atom (*Scheme 53*).[174] The same reaction is claimed in the case of cyclic enol ethers **122**, from which formation of isoxazolines **298** (60-90%) is reported.[174] This result appears in conflict with the isolation of an oxime at the $COCF_3$ moiety such as **299**[80] (see also the Pyrazole Section).



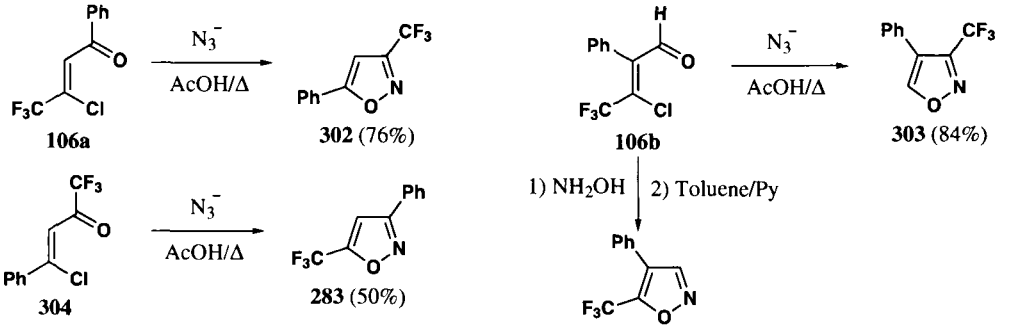
Scheme 53

Similarly, enol ethers **295** (R_F = CF_3; R^1 = Me; R^2 = Ar; R^3 = H) yielded the corresponding isoxazolines **296** or isoxazoles **297** that could be also directly obtained by using an excess of hydrochloric acid.[175] An additional example leading to a 5-hydroxy-5-trifluoromethylisoxazoline **296**, which could be dehydrated with P_2O_5 into the corresponding 5-trifluoromethylisoxazole, has been reported.[176] The 5-hydroxy-isoxazolines **296** (R_F = CF_3, C_2F_5; R^2 = OEt, R^3 = H) were obtained (80-88%) from the corresponding diethoxyenones **295** (R_1 = Et; R_2 = OEt) and hydroxylamine hydrochloride in H_2O/Py.[68] In a similar reaction, perfluoroalkyl enone **300**, prepared by solvolysis of **113** (Ar = Ph) yielded the 5-perfluoroalkylisoxazole **301** (40%) (*Scheme 54*).[75]



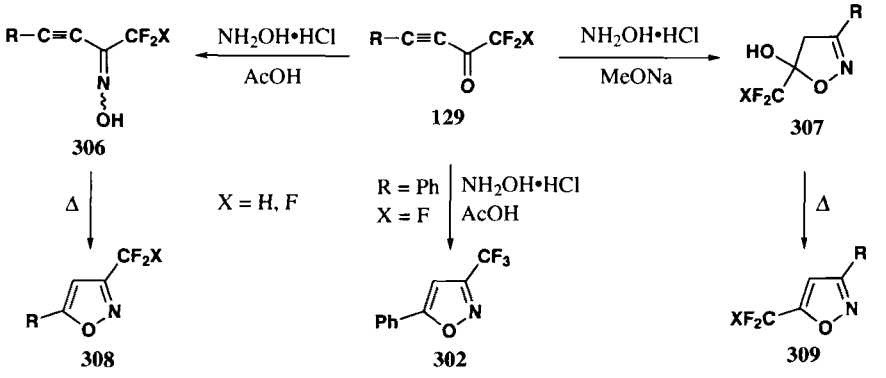
Scheme 54

Trifluoromethyl compounds **106a**, **106b**, and **304** have been reported as starting substrates for the synthesis of trifluoromethyl isoxazoles, although scarse experimental details were furnished (see also the Pyrazole Section). The reaction with sodium azide in acetic acid produced isoxazoles directly, through decomposition of the initial formed azides (*Scheme 55*).[73] The same reaction was recently used for the preparation of regioisomers **302** and **283**.[168] In the case of acrolein **106b**, the isoxazole **305** arises from cyclocondensation of the corresponding oxime (*Scheme 55*).[73]



Scheme 55

The reaction of fluorinated α,β-ynones **129** (R = Alkyl; X = H, F) with hydroxylamine represents an example of regiochemistry controlled by acidic or basic reaction conditions (*Scheme 56*). The reaction between **129** and hydroxylamine hydrochloride in acetic acid produces the oxime **306** which can be cyclized by refluxing in benzene with azeotropic removal

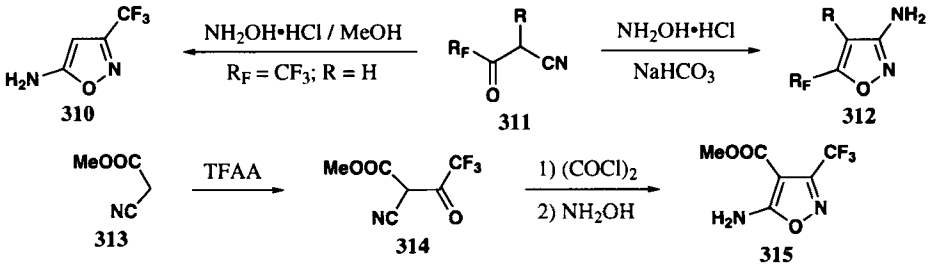


Scheme 56

of water, to yield the 3-polyfluoroalkyl regioisomer **308** (80%).[82] In contrast, when the reagent was used in the presence of MeONa, the resulting isoxazoline **307** provided the 5-fluoroalkyl regioisomer **309**.[82] This methodology has also been used to obtain a target 5-substituted 3-trifluoromethyl-isoxazole.[177] The preparation of the 3-trifluoromethyl-5-phenylisoxazole **302** by condensation of fluorinated ynone **129** (R = Ph; X = F) with hydroxylamine hydrochloride was also reported.[168]

The reaction of fluorinated β-ketonitriles **311** and hydroxylamine was reported for the synthesis of amino-substituted perfluoroalkylisoxazoles, which are useful precursors of herbicides, fungicides, bactericides, and drugs. However, in this case also a rather incomplete description is given in patent literature.[172] In fact, the reaction of trifluoroacetylacetonitrile **311** (R = H; $R_F = CF_3$) with hydroxylamine hydrochloride in methanol at reflux is reported to furnish the 5-

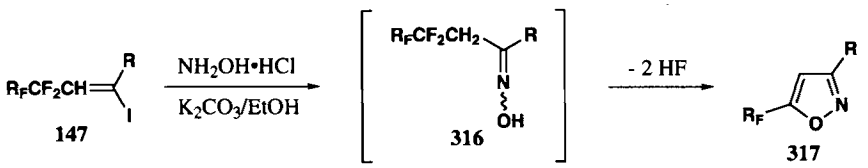
amino-3-trifluoromethylisoxazole **310** (53%).[172] In contrast, the reaction of a series of β-ketonitriles **311** with hydroxylamine free-base (from the hydrochloride and sodium bicarbonate), is reported to furnish the 3-amino-5-perfluoroalkyl regioisomer. The representative **312** ($R_F = CF_3$; R = Me) was obtained in 32% yield,[178] methyl 5-amino-3-(trifluoromethyl)isoxazole-4-carboxylate **315** (34% final yield) is also obtained in a three-step one-pot synthesis from the reaction of methylcyanocetate **313** and trifluoroacetic anhydride (TFAA) as illustrated (*Scheme 57*).[179]



Scheme 57

c) Syntheses from Perfluoroalkylcarbonyl Compounds

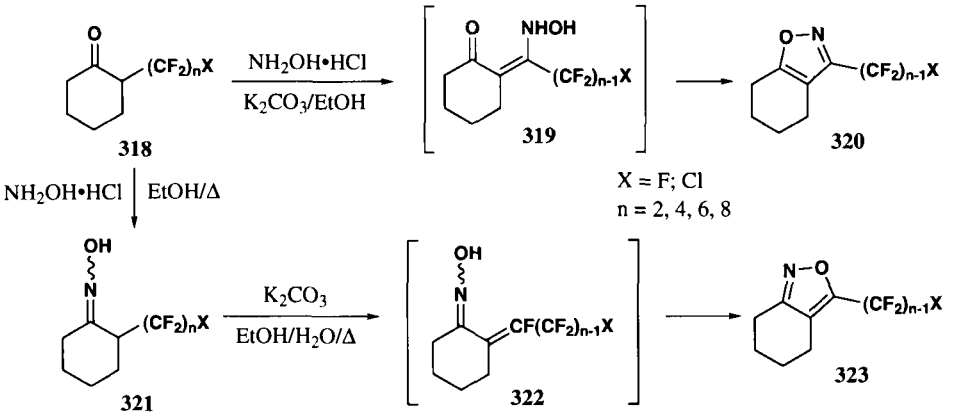
Both *E* and *Z* isomers of 1-polyfluoroalkyl-2-iodoalkenes **147** [see their use in the synthesis of perfluoroalkyl pyrazoles (*Scheme 27*)], react with hydroxylamine hydrochloride in the presence of potassium carbonate affording 5-polyfluoroalkyl isoxazoles **317** (80-96%) through the oxime intermediate **316** (*Scheme 58*).[88b,180]



$R_F = CF_3$; C_3F_7; $ClCF_2$; ClC_3F_6

Scheme 58

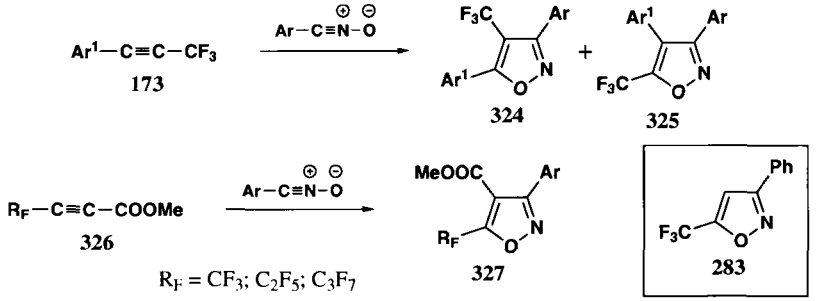
The reaction of per(poly)fluoroalkyl cyclohexanones **318** with hydroxylamine allows the regiospecific synthesis of per(poly)fluoroalkylisoxazoles **320** and **323** (*Scheme 59*). When the reaction was carried out in the presence of potassium carbonate, fluoroalkylisoxazoles **320** were obtained (75-90%).[181] The formation of this regioisomer is rationalized through the Michael-type addition of hydroxylamine onto the initially formed α,β-unsaturated carbonyl compound derived from **318**. In contrast, the reaction with hydroxylamine hydrochloride proceeds through the oxime intermediate **321** from which isomeric isoxazoles **323** are formed (45-50%) after treatment with K_2CO_3.[181]



Scheme 59

d) Syntheses from Cycloaddition Reactions

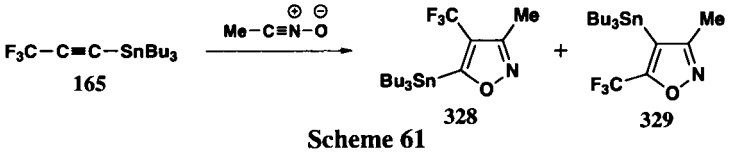
In the cycloaddition reaction of nitrile oxides with alkynes or suitable alkenes as dipolarophiles, the fluorinated moiety can be part of either one or both the reagents involved in the cycloaddition. Aromatic nitrile oxides, which can be obtained *in situ* from the corresponding hydroximoyl chlorides in the presence of triethylamine (TEA), react with various substituted 1-aryl-3,3,3-trifluoropropynes **173** to give the 4-trifluoromethylisoxazoles **324** together with small amounts of the regioisomer **325** (*Scheme 60*).[182] The yields range between 17-88% as a function



Scheme 60

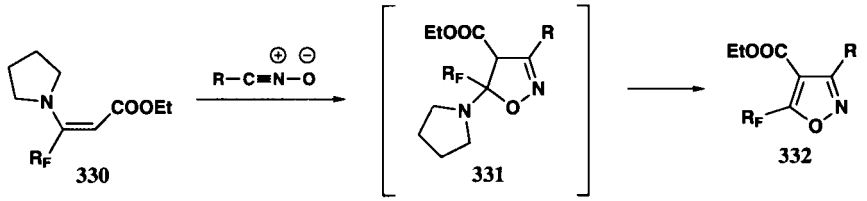
of the aryl substituent, and the observed regioselectivity has been explained in terms of HOMO-dipole/LUMO-dipolarophile control.[182] High yields (~90%) of 5-perfluoroalkylisoxazoles **327** as the preferred regioisomer have been reported from the cycloaddition of aromatic nitrile oxides and methyl perfluoro-2-alkynoates **326**.[183] Similarly, the 5-trifluoromethyl-3-phenylisoxazole **283** is obtained (19%) by the cycloaddition reaction of benzonitrile oxide with 3,3,3-trifluoropropyne.[169] Other examples of cycloaddition reactions of aliphatic or aromatic nitrile oxides with fluorinated monosubstituted alkenes (to yield Δ^2-isoxazolines) or alkynes are reported.[184]

The cycloaddition of acetonitrile oxide to tributyl(3,3,3-trifluoro-1-propynyl)stannane **165** produced the corresponding trifluoromethylated tributylstannyl-isoxazoles **328** and **329** as an unresolved mixture (86:14 ratio) in 77% combined yield (*Scheme 61*).[98a] Cross-coupling arylation of this mixture into separable 5-aryl substituted (from **328**) and 4-aryl substituted (from **329**) isoxazoles can be accomplished.[98a] Perfluoroalkylated isoxazoles from the reaction of benzaldoxime and fluorinated alkynes in the two-phase medium $CHCl_3/NaOCl_{(aq)}$ are also reported.[185]



Scheme 61

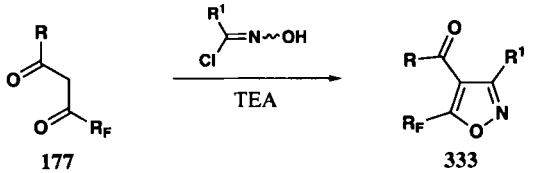
The 5-perfluoroalkyl isoxazoles **332** are regiospecifically prepared from the reaction of nitrile oxides (generated from the reaction of nitroalkanes with TEA/$POCl_3$) with (*Z*)-3-perfluoroalkyl-3-pyrrolidinoacrylates **330** (*Scheme 62*).[186] In this case, the regiochemistry is governed by the pyrrolidine group which will also act as a leaving group in the final step. Although the observed conversion is not excellent (35-60%, depending on the R_F group), isolated yields, based on the conversions, are high (69-92%).[186]



R_F = CF_3; CF_2Br; $(CF_2)_3Cl$ R = Me; Et; Ph

Scheme 62

Similarly to what is observed in the pyrazole series, β-ketoesters and β-diketones can also participate in cycloadditions with nitrile oxides. For example, the reaction of hydroximoyl chlorides with fluorinated β-ketoesters **177a** or β-diketones **177b** in the presence of triethylamine yielded 5-perfluoroalkylisoxazoles **333**. The reaction involved a cycloaddition of the *in situ* formed nitrile oxide with the enolic form of the dicarbonyl compound, followed by spontaneous dehydration (*Scheme 63*).[102,187] In the case of other fluorinated β-diketones, a different

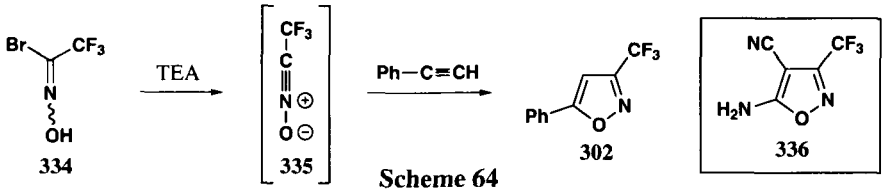


a: R = OMe, OEt;
b: R = Ph, 2-Thienyl; R_F = CF_3; CF_2Cl; C_3F_7

Scheme 63

regiochemistry for the cyloaddition may result, depending on the prevailing enolate species present in the reaction medium.[102,187]

Some cycloaddition reactions where fluorinated nitrile oxides have been used as 1,3-dipolar reagents have also been reported. For example, trifluoroacetonitrile oxide **335** [from hydroximoyl bromide etherate **334** and triethylamine (TEA)] reacts with phenylacetylene to give excellent yields of 5-phenyl-3-(trifluoromethyl)isoxazole **302** (*Scheme 64*).[188] Other examples of

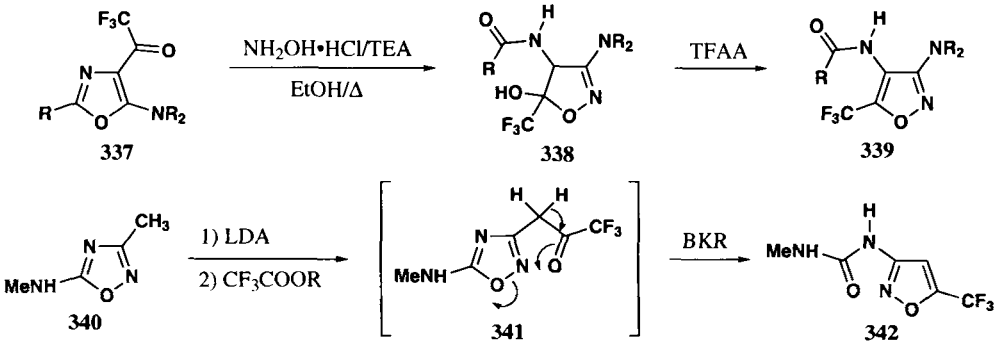


Scheme 64

this approach have also been described.[188,189] Reactions involving polyfluoroalkyl substituted nitrile oxides and β-diketones or β-ketoesters are also reported.[104a] Trifluoroacetylhydroximoyl bromide etherate reacts with malononitrile in the presence of sodium methoxide to give the expected 5-aminoisoxazole **336** (45%).[190] A similar reaction performed with methyl cyanoacetate produces methyl 5-amino-3-(trifluoromethyl)isoxazole-4-carboxylate **315** (81%).[191]

e) Miscellaneous

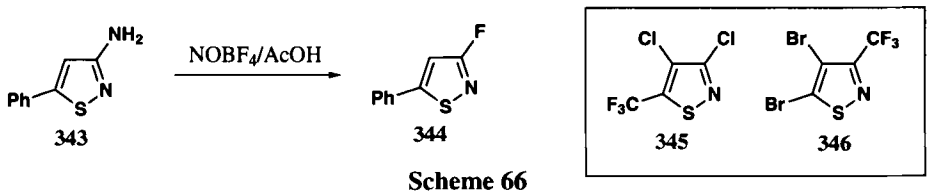
Ring-rearrangement reactions of suitably substituted heterocycles are also reported for the synthesis of fluorinated isoxazoles. An ANRORC-like rearrangement[192] of the oxazole **337** reacting with hydroxylamine leads to the 5-trifluoromethylisoxazoles **339** through the ring-opening ring-closure process and subsequent dehydration of first-formed isoxazolines **338** (*Scheme 65*).[193] For the ureidoisoxazole **342** (38%), an intriguing synthesis is reported[194] through a Boulton-Katritzky rearrangement (BKR)[195] of the enolate form of the 1,2,4-oxadiazole **341** arising from **340** (*Scheme 65*). In this case, the driving-force of the reaction can be recognized in the higher thermodynamic stability of the isoxazole ring compared to the oxadiazole heterocycle.[195,196]



Scheme 65

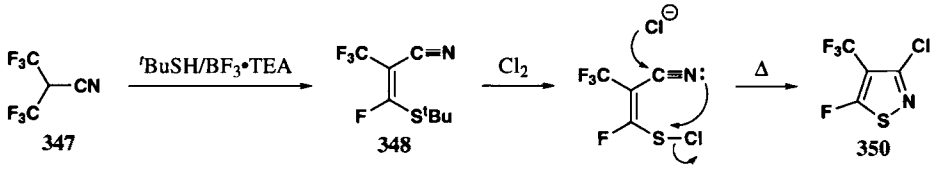
IV. ISOTHIAZOLES[197]

The introduction of fluorine or a fluorinated group in the isothiazole heterocycle is reported both through modification of functional groups (already linked to the heterocyclic ring) and by heterocyclization of fluorinated open-chain precursors. An example of the first approach is the synthesis of 3-fluoro-5-phenyl derivative **344** (41%) from the 3-amino compound **343** through the corresponding diazonium tetrafluoroborate (*Scheme 66*).[198] In turn, trifluoromethylisothiazoles **345** and **346** are reported by fluorination of the corresponding isothiazole carboxylic acids with SF_4/HF as fluorinating reagent.[199]



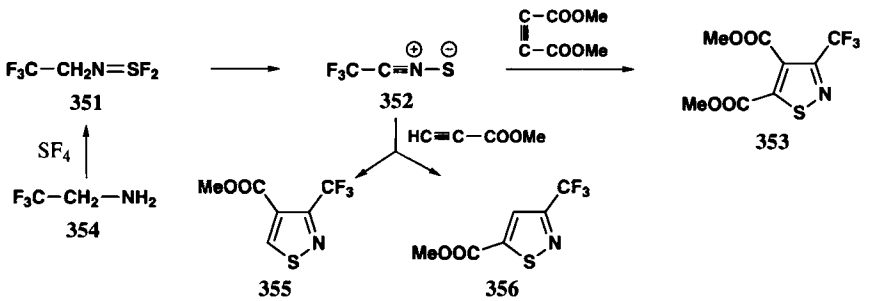
Scheme 66

Heterocyclization reactions of fluorinated open-chain intermediates can be considered as the fluorinated counterpart of the general synthetic methods developed for isothiazoles. An interesting example is the thermally-induced intramolecular cyclization of the sulfenyl chloride **349** (which was obtained by chlorination of the *E/Z* isomers of the sulfide **348**)[200] into the 5-fluoro-4-(trifluoromethyl)isothiazole **350** (54%) (*Scheme 67*).[201] This reaction can be considered to belong to the general oxidative cyclization of *β*-mercaptoacrylonitriles.[197b,202]



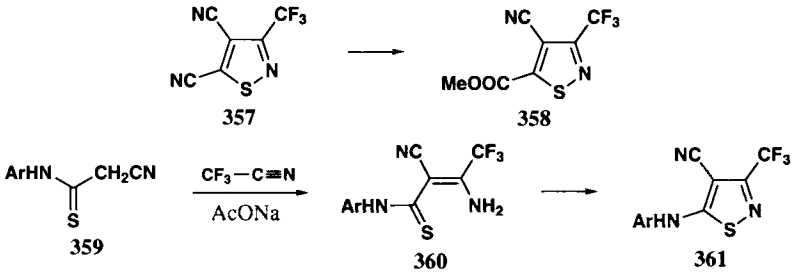
Scheme 67

3-Trifluoromethylisothiazoles are obtained (in low yields) by a 1,3-dipolar cycloaddition of trifluoroacetonitrile *N*-sulfide **352** (which is formed by thermal elimination of HF from iminosulfur difluoride **351**) with activated acetylenes such as dimethyl acetylendicarboxylate or methyl propiolate (*Scheme 68*). In the latter case, a mixture of two regioisomers **355** and **356** (in 1:5 ratio) was obtained.[203]



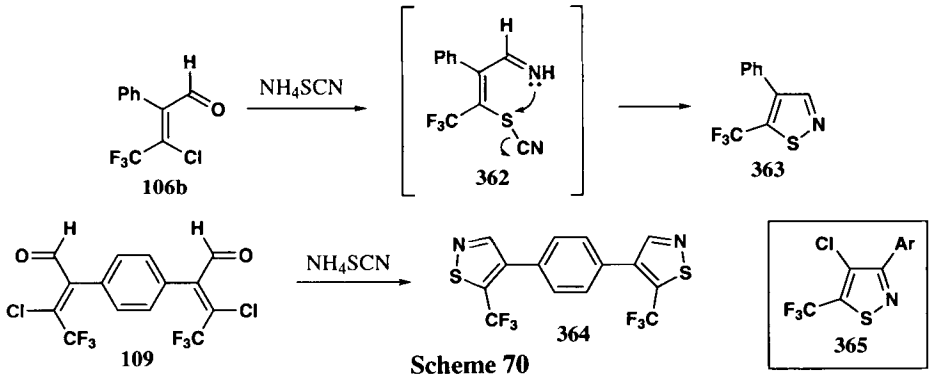
Scheme 68

The synthesis of 4,5-dicyano-3-trifluoromethylisothiazole **357** has been reported in a patent but experimental details are not available.[204] In turn, the dicyano compound **357** can be selectively transformed into the ester **358**, a useful precursor for introducing the trifluoromethylated isothiazole moiety toward target molecules.[204] The synthesis of a series of 3-trifluoromethylisothiazoles **361** from oxidative cyclization of aminoacrylic acid thioamides **360** (*Scheme 69*), and their use as pesticides and herbicides, has been also reported in a patent.[205]



Scheme 69

The formation of 5-trifluoromethylisothiazole **363** (56%) is claimed from the reaction of β-chloro-β-trifluoromethylvinylaldehyde **106b** with ammonium thiocyanate (NH_4SCN) (*Scheme 70*).[74] Although no suggestions are discussed on the mechanism, one might assume that the reaction involves the cyclization of intermediates such as **362**. Similarly, the formation of *bis*(isothiazole) **364** from the corresponding precursor **109** is reported (48%).[74] The synthesis of 5-trifluoromethylisothiazoles **365** as herbicides is also patented.[206]



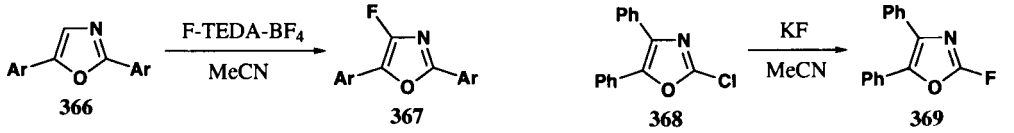
Scheme 70

V. OXAZOLES[207]

1. Ring-fluorinated Oxazoles

Ring-fluorinated oxazoles are prepared both by direct fluorination and by substitution reaction with KF. To the best of our knowledge, there is no report in the literature about the introduction of fluorine onto the oxazole ring *via* diazonium salts. The 4-fluoro-2,5-diaryloxazoles **367**, cited in a recent patent[208] as components in liquid crystalline mixtures, are synthesized

by direct fluorination of the corresponding 2,5-diaryloxazoles (*Scheme* 71) with the "N-F" reagent "F-TEDA-BF_4"[161] (see *Scheme 47*). The same patent reports also 5-fluoro-2,4-disubstituted oxazoles, but no experimental details are mentioned for their preparation.[208] The synthesis

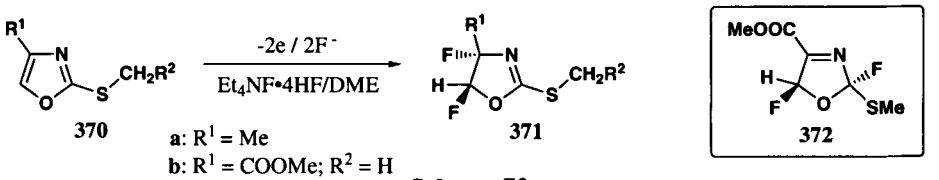


366 367 368 369

Scheme 71

of 2-fluoro-4,5-diphenyloxazole **369** (56%), which is used in the derivatization of amino acids and thiols for fluorescence and chemiluminescence analyses, is reported from 2-chloro derivative **368** through the displacement of chlorine with KF in the presence of 18-crown-6/acetonitrile complex (*Scheme 71*).[209]

The electrochemical fluorination of the oxazole ring has been reported for some 2-alkylthio substituted substrates **370**: fluorination of 4-methyloxazoles **370a** produced the corresponding 4,5-difluoro-4-methyl-2-oxazolines **371a** (50-63% isolated yields) (*Scheme 72*);[210] on the other hand, fluorination of the 4-carboxymethyloxazole **370b** yielded a mixture of the 4,5-difluoro-2-oxazoline **371b** (51%) and the 2,5-difluoro-3-oxazoline **372** (18%).[210] The suggested



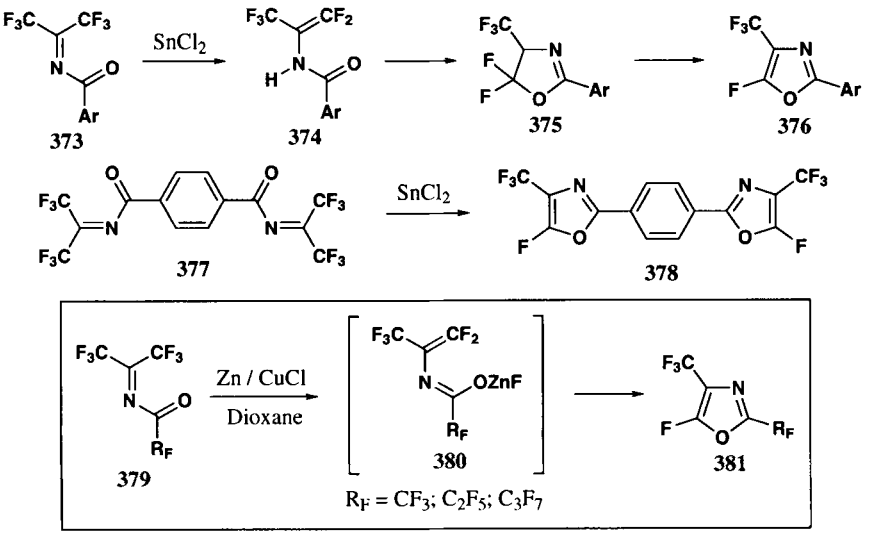
370 371 372

a: R^1 = Me
b: R^1 = COOMe; R^2 = H

Scheme 72

mechanism for this anodic fluorination implies an initial one-electron oxidation of the sulfide generating a radical cation (at the sulfur atom) from which different species, leading to final products, originate.[210] (See also the electrochemical fluorination of similar substrates in the thiazole series).

A general way to obtain 5-fluorooxazoles **376** considers cyclodefluorination of fluorinated *N*-acylimines **373**.[116] This type of cyclization, also observed in the imidazole and thiazole series, is typically achieved in the presence of $SnCl_2$ and proceeds through intermediates of the type **374** and **375** (*Scheme 73*).[116] This methodology has also been exploited for the synthesis of fluorinated *bis*(oxazole) **378**[116d,211] used for the construction of poly(aryl-ether-oxazole)s with trifluoromethyl side-groups.[212] Similar procedures, including an interesting example of ultrasound-induced cyclization in the presence of Zn, have also been reported[213,214] and perfluorinated oxazoles **381** (27-60%) have been prepared by heating perfluoroacylimines **379** with zinc in dioxane,[215] or in the presence of a monovalent copper salt catalyst (CuCl, CuBr) and dicyclohexyl-18-crown-6.[216] A single electron-transfer step and the formation of the imidate **380** has been suggested (*Scheme 73*).[216]

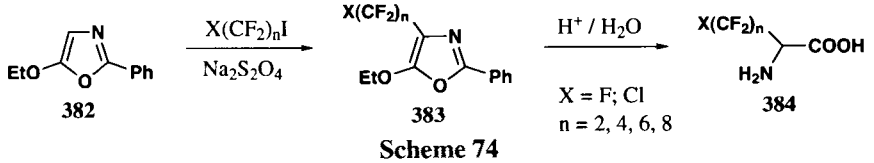


Scheme 73

The 5-fluoro-4-trifluoromethyloxazoles **376** have been used to introduce a trifluoromethyl oxazole moiety on to several nucleophiles by exploiting the reactivity of the C(5)-fluoro moiety towards nucleophilic substitution.[217] Similar fluorine-displacement reactions have also been reported in the case of perfluorinated oxazoles **381**.[216b] [An interesting reactivity is reported for the nucleophilic substitution of 5-fluoro-4-trifluoromethyloxazole **376** (Ar = Ph) with benzylic or β,γ-unsaturated alcohols in the presence of a base. The initially formed benzyl or allyl ether undergoes rearrangement into 4-benzyl- (or allyl-) oxazolin-5-ones which are useful precursors of trifluoromethylated open-chain products].[218]

2. Fluoroalkylated Oxazoles

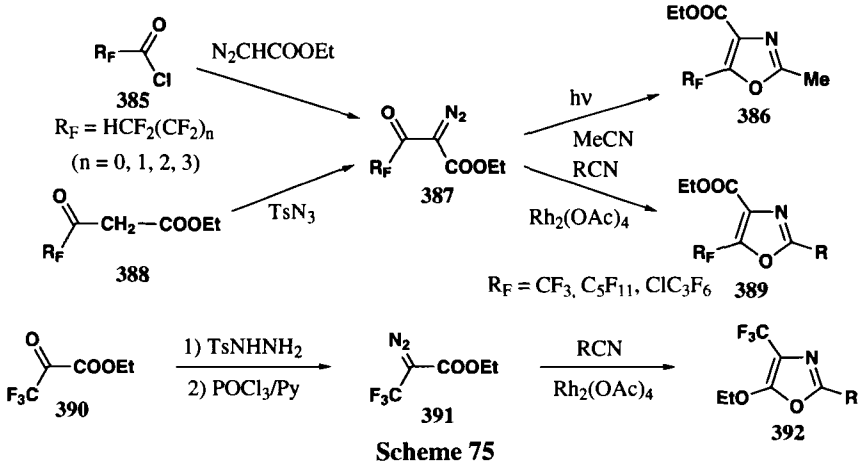
The direct introduction of a polyfluoroalkyl group onto C(4) of the oxazole ring is reported for the 5-ethoxy-2-phenyloxazole **382** using a polyfluoroalkyl iodide in the presence of sodium dithionite ($Na_2S_2O_4$) (*Scheme 74*).[219] It is noteworhy that the resulting polyfluoroalkylated oxazole **383** is used as an intermediate for the synthesis of polyfluoroalkyl glycines **384** through acid hydrolysis.[219] A perfluoroalkylation of substituted oxazoles using perfluoroacylperoxides is patented, but no experimental details are available.[220]



Scheme 74

Generally, fluoroalkyl oxazoles are obtained by heterocyclization reactions of fluorinated open-chain precursors. A simple [3+2] cycloaddition of acylcarbenes with nitriles provides

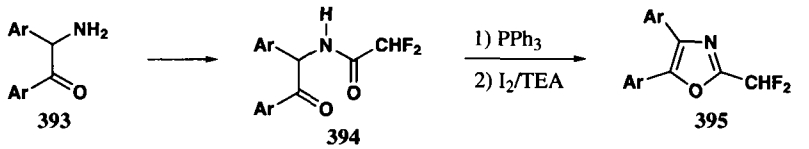
a general method for the synthesis of oxazoles (*Scheme 75*). In this context, fluorinated oxazoles **386** are prepared by irradiation of fluorinated α-diazo-carbonyl compounds **387** in acetonitrile.[221] These were also obtained through a diazo transfer reaction between ethyl fluoroalkylacetoacetate **388** and perfluoroalkanesulfonyl azide or tosyl azide (TsN_3).[222] A different



Scheme 75

approach providing a series of 5-fluoroalkyl substituted oxazoles **389**, in fair to good yields, considers the rhodium acetate mediated cycloaddition between nitriles and α-diazo carbonyl compounds **387**.[222] A similar reaction had been reported for the synthesis of 4-trifluoromethyl-5-ethoxyoxazoles **392** (82-90%) (*Scheme 75*).[223] By using ethyl cyanoformate, the reaction produces the oxazole **392** (R = COOEt), from which hydrolysis and decarboxylation finally lead to the oxazole **392** (R = H).[223b]

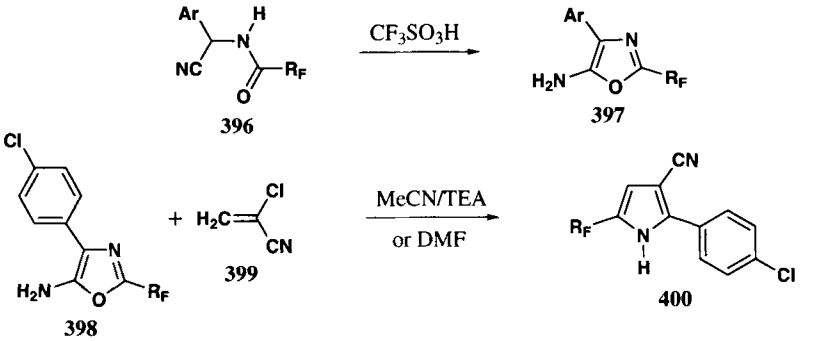
A patented synthesis of 2-difluoromethyl-4,5-diaryloxazoles **395**, useful for the preparation of cyclooxygenase inhibitors, is realized from α-aminoketones **393** (*Scheme 76*).[224]



Scheme 76

The 5-amino-2-perfluoroalkyloxazoles **397** have been reported in a series of patents on the preparation of insecticidal fluorinated aryl pyrroles. The reaction involves the acid catalyzed heterocyclization of a perfluoroacylamino nitriles **396** precursor in the presence of various reagents such as trifluoroacetic acid, trifluoromethanesulfonic acid (yielding the corresponding oxazol-5-yl ammonium salts), or acyl chlorides (yielding acylamino derivatives). The obtained oxazoles are then used for the preparation of perfluoroalkyl pyrroles through a cycloaddition reaction with activated olefins (such as **399**) performed in DMF or in MeCN in the presence of triethylamine (TEA).[225] An example of this procedure is illustrated for representative perfluo-

roalkylpyrrole **400** (*Scheme 77*).[225b] In this context, it is worth mentioning that perfluoroalkanoylaminonitriles **396** have also been cyclized into the corresponding 2-perfluoroalkyloxazolin-5-ones **402** in aqueous acid conditions.[226] These compounds can also be obtained through the general methodology involving the heterocyclization of α-aminoacids **401** (or their derivatives) with perfluoroacylating reagents.[227]

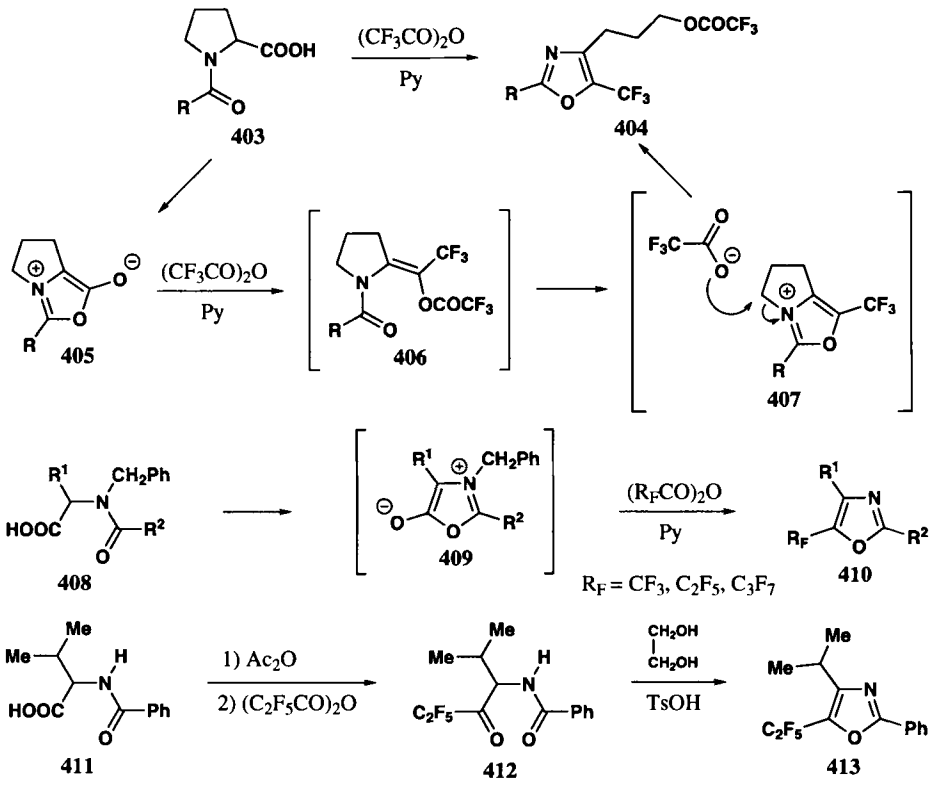


Scheme 77

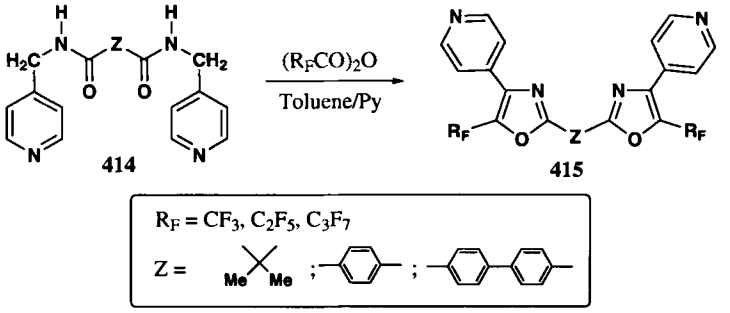
Kawase and coworkers, reported the synthesis of 5-trifluoromethyloxazoles **404** by the reaction of *N*-acylprolines **403** with trifluoroacetic anhydride in the presence of pyridine (*Scheme 78*).[228] The process is explained through a Dakin-West[229] reaction involving mesoionic 1,3-oxazolin-5-olates **405**. The reaction can also be performed on *N*-acyl-*N*-benzyl-α-amino acids **408** by treatment with trifluoroacetic or perfluorocarboxylic anhydride in the presence of pyridine *via* the initially formed mesoionic intermediates **409** to afford high yields of 5-trifluoromethyl- or 5-perfluoroalkyloxazoles **410**.[228b,230] The 5-pentafluoroethyloxazole **413** (49%) is obtained by dehydration of α-benzoylaminoketone **412**, which in its turn, is obtained from *N*-benzoylvaline **411** through a Dakin-West reaction as the key-step for the introduction of the fluoroalkyl group.[231]

A synthetic strategy, related to the one used for 4-(4'-pyridyl)-oxazoles,[232] is applied for the synthesis of a series of 4,4'-*bis*(pyridyl)-5,5'-*bis*(perfluoroalkyl)-2,2'-*bis*(oxazole)s **415**.[233] Acylation of 4-aminomethylpyridine with different bidentate acylating reagents lead to a series of *N,N'-bis*(4-pyridylmethylen)diamides **414** with different alkyl or aryl spacers Z (as indicated for some examples in the *Scheme 79*). Subsequent treatment of diamides **414** with perfluoroalkyl anhydrides in the presence of pyridine produced the *bis*(oxazole)s **415** in poor to excellent yields (20-98%).[233]

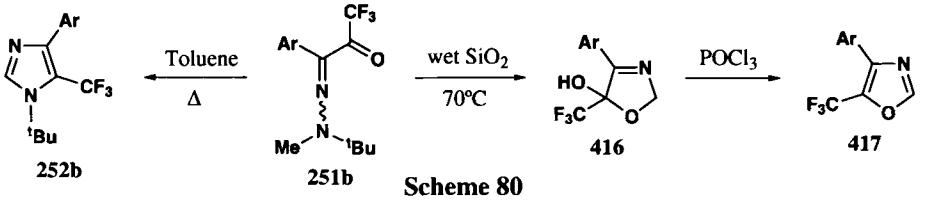
The synthesis of 5-hydroxy-5-trifluoromethyl-3-oxazolines **416** (43-67%) is reported through a rather unusual (and unexplained) thermally induced reaction of *N*-*t*-butyl-*N*-methylhydrazones **251b** adsorbed on wet silica gel (*Scheme 80*).[234,235] Subsequent treatment of **416** with



Scheme 78



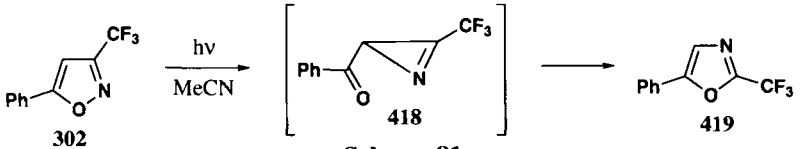
Scheme 79



Scheme 80

$POCl_3$/pyridine produced the 5-trifluoromethyloxazoles **417** in high yields. In this rearrangement, the bulkiness of the *t*-butyl group as well as the wet SiO_2 used is claimed to play a determining role. On the other hand, the same compounds **251b** in refluxing toluene lead to imidazoles **252b**.[150,152]

Recently, a photoinduced ring-rearrangement reaction leading to 2-trifluoromethyloxazole **419** has been reported. Irradiation of the 3-trifluoromethyl-isoxazole **302** in acetonitrile produces **419** (60%) on a preparative scale (*Scheme 81*).[236] The rearrangement follows the classical *ring contraction-ring expansion* route (well documented in the isoxazole series) involving an azirine species intermediate.[156]

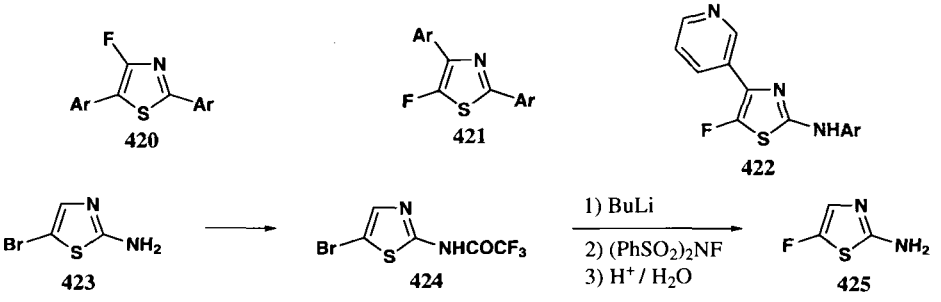


Scheme 81

VI. THIAZOLES[237]

1. Ring-fluorinated Thiazoles

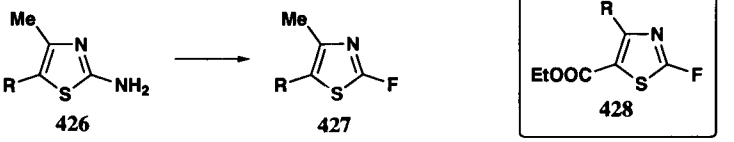
Different methodologies are reported for the synthesis of ring-fluorinated thiazoles. Some 4-fluoro-2,5-diarylthiazoles **420** (*Scheme 82*) have been cited in a patent regarding the



Scheme 82

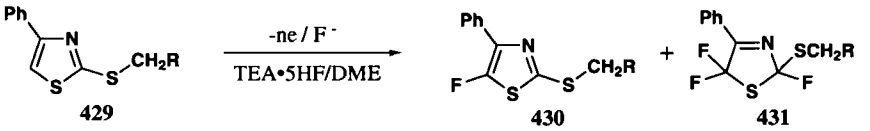
properties of liquid-crystalline mixtures, and their synthesis is reported[208] through direct fluorination of 2,5-diarylthiazoles with "F-TEDA-BF_4"[161] reagent (see *Scheme 47*). The 5-fluoro-2,4-diarylthiazoles **421** are also cited, but no experimental information is reported for their preparation.[208] Direct fluorination by using the above reagent in DMF has also been employed for the synthesis of 5-fluoro-2-arylamino derivative **422** (40%) (*Scheme 82*).[238] An interesting annular fluorination occurs in the synthesis of 2-amino-5-fluorothiazole **425**, which is used to introduce the thiazole moiety in various target compounds. The synthetic sequence starts with the protection of the bromothiazole **423** which is then lithiated and fluorinated by using *N*-fluorobenzensulfonimide (*Scheme 82*).[239]

Besides the direct fluorination leading to 4-fluoro- or 5-fluorothiazoles, fluorodeamination reactions using either diazonium tetrafluoroborate[240] or sodium nitrite in poly-HF-pyridine[241] are reported for the synthesis of 2-fluorothiazoles **427** and **428**, respectively (*Scheme 83*).



Scheme 83

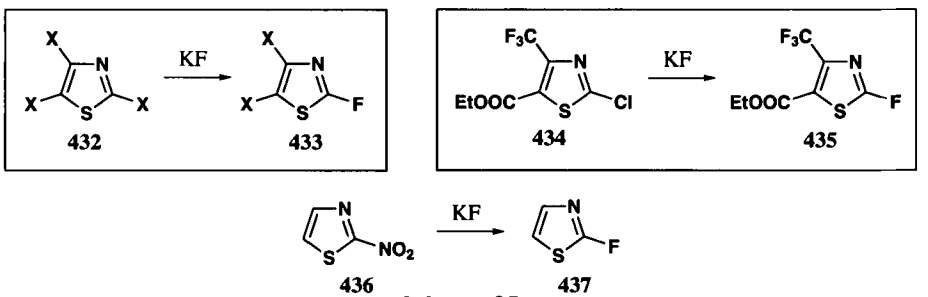
Electrochemical fluorination of 2-thiazolyl sulfides **429**, by using TEA·5HF as a fluorine source and a supporting electrolyte, was successfully carried out to provide the corresponding 5-fluorothiazoles **430** (20%) and 2,5,5-trifluorothiazolines **431** (50%) (*Scheme 84*).[242] In the case of **429** (R = CN), besides the expected 5-fluoro derivative **430** (R = CN; 20%), the



Scheme 84

side-chain monofluorinated thiazole at the CH_2 moiety (60%) was also isolated. The product selectivity depends on the structure of the side-chain substituent, which affects the redox potential of the substrate. As observed in the oxazole series (where only polyfluorinated oxazolines were formed)[210] the reaction is explained by a conventional one-electron oxidation of the starting sulfide to generate a radical-cation (at the sulfur atom) from which different species, leading to the final products, will arise.[242]

Ring-fluorinated thiazoles can also be prepared by aromatic nucleophilic substitution (*Scheme 85*). In a series of polyhalogenated thiazoles, e.g. **432** (X = Cl), fluorination with potassium fluoride in tetramethylenesulfone at 130°C yielded 2-fluorothiazoles **433**.[243] Other examples

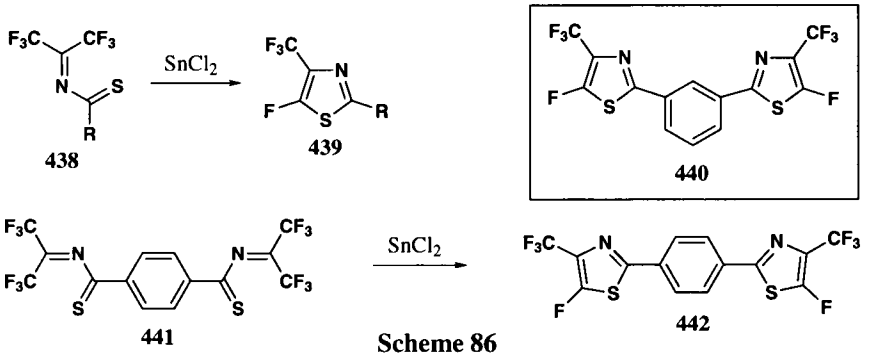


Scheme 85

are the formation of 2-fluorothylthiazole **435** (38%) from reaction of the corresponding 2-chloro compound **434** with KF in the presence of 18-crown-6 in acetonitrile,[244] and the fluorodenitration

of 2-nitrothiazole **436** into the 2-fluorothiazole **437** (20%) by treatment with KF in *N*-methyl-2-pyrrolidone at 110°C.[245] A series of patented polyfluorinated thiazoles originate through transhalogenation reactions of the corresponding polychlorinated precursor using HF (fluorination at the side-chain) or KF (annular fluorination).[246]

Ring-fluorinated thiazoles are also acquired through heterocyclization reactions of suitable open-chain precursors. As anticipated from the imidazole and oxazole series, fluorinated *N*-thioacylimines **438** have been successfully used for the synthesis of 5-fluoro-4-trifluoromethylthiazoles **439** (*Scheme 86*).[116] This methodology has been extended to the synthesis of fluorinated



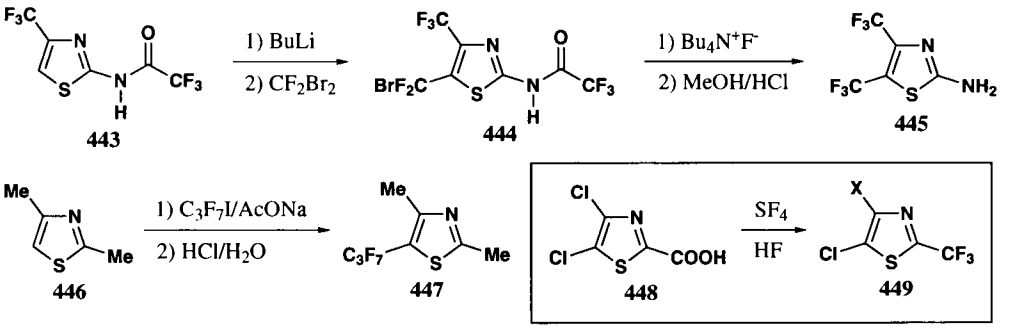
438 439 440 441 442

Scheme 86

bis(thiazole)s **440** and **442**, which are used for the construction of poly(arylether-thiazole)s containing trifluoromethyl pendants.[247] A representative synthesis of the monomer **442** involves the cyclization of **441** arising from the reaction of terephthalic acid dithioamide and hexafluoroacetone (*Scheme 86*).

2. Fluoroalkylated Thiazoles

Dibromodifluoromethane reacts with the thiazole **443** (in the presence of *n*-BuLi) yielding the corresponding 5-(bromodifluoromethyl)thiazole **444** (80%).[248] In turn, compound **444** was converted into the 2-amino-4,5-*bis*(trifluoromethyl)thiazole **445** (53%) by using tetrabutylammonium fluoride followed by final hydrolysis (*Scheme 87*).[248] As for the direct introduction of perfluoroalkyl groups on the thiazole ring, a historic example describes the reaction of

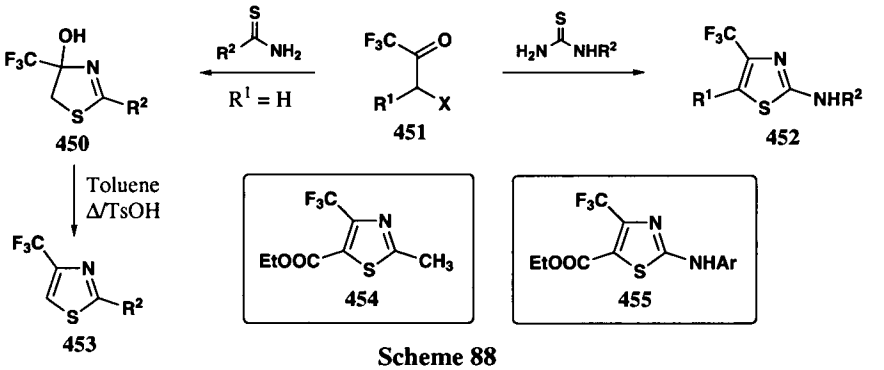


443 444 445 446 447 448 449

Scheme 87

2,4-dimethylthiazole **446** with perfluoropropyl iodide in the presence of sodium acetate at 190-200°C to produce the corresponding 5-perfluoropropyl derivative **447** (55%).[249] A later patent reports the perfluoroalkylation of thiazoles with perfluorinated acylperoxides; however, no experimental details are available.[220] Similarly to other azoles, trifluoromethylthiazoles are obtained from the corresponding thiazolecarboxylic acids by treatment with SF_4/HF as a fluorinating reagent.[250] Fluorination of 2-carboxy-4,5-dichlorothiazole **448** with sulfur tetrafluoride mainly produced the 2-trifluoromethyl compound **449** (X = Cl) (90%), together with amounts of the 2-trifluoromethyl-4-fluoro derivative **449** (X = F) (*Scheme 87*).[243]

Besides the examples above, the synthesis of perfluoroalkylthiazoles is generally realized by heterocyclization reactions of perfluorinated open-chain precursors through the usual synthetic methodologies for the thiazole ring.[237] In this context, the most widely used methodology is represented by the Hantzsch synthesis, which is the cyclization of α-halocarbonyl compounds with a reactant containing the N-C-S fragment. Commonly used reagents for this purpose are thioureas or thioamides, the latter being occasionally prepared *in situ* by sulfuration of the corresponding amides. Several examples of this approach have been reported [240b,248,251] after the historic synthesis of 2-amino-4-trifluoromethylthiazole **452** (R^1 = R^2 = H) and its 5-carboxyethyl derivative **452** (R^1 = COOEt; R^2 = H) (*Scheme 88*).[252]

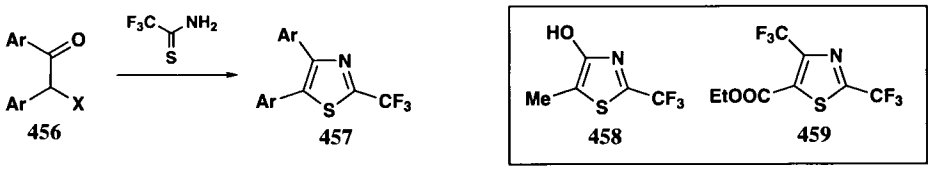


Scheme 88

Interestingly, in the case of the reaction of the bromoketone **451** (X = Br; R^1 = H) with thioamides, 4-hydroxy-4-trifluoromethylthiazolines **450** were isolated. As already observed in the pyrazole and isoxazole series, the stability of these thiazoline derivatives is due to the electronic effect of the trifluoromethyl group linked to an sp^3 carbon atom. In turn, thiazolines **450** were transformed into thiazoles **453** by refluxing in toluene in the presence of *p*-toluenesulfonic acid.[253] Improved procedures for the high-yield synthesis of 4-trifluoromethyl-5-carboxyethylthiazole **454** from the reaction of ethyl 2-chloro-4,4,4-trifluoroacetylacetate **451** (X = Cl; R^1 = COOEt) with thioacetamide in MeCN have been reported.[254] Recently, the synthesis of 2-arylamino-4-trifluoromethylthiazoles **455** (85-97%) from the reaction of arylthioureas with the trifluoromethylated chlorocarbonyl compound **451** (X = Cl; R^1 = COOEt) has been reported for

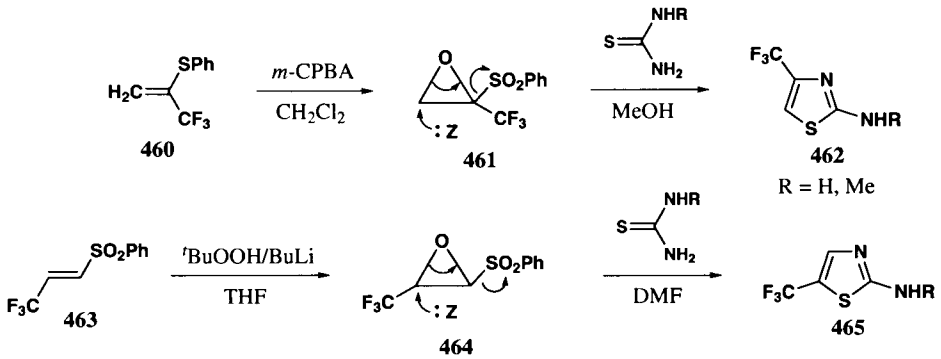
the preparation of pharmaceutically interesting molecules.[255] Similarly, cyclocondensation of the bromo-β-diketone **451** (X = Br; R^1 = COPh) with thiourea yields 2-amino-5-benzoyl-4-(trifluoromethyl)thiazole (84%), which can be diazotized and coupled with phenolic substrates.[256]

Syntheses involving fluorinated thioamides reacting with α-halocarboyl compounds are also reported (*Scheme 89*). An example is represented by the preparation of 2-trifluoromethyl compounds **457** (28-34%) where the thioamide is prepared *in situ* from trifluoroacetamide and P_2S_5.[257] Similarly, the reaction of trifluorothioacetamide with ethyl α-bromo-propionate gave the 2-trifluoromethyl-4-hydroxy-5-methylthiazole **458**, which is a useful intermediate for the preparation of thiazole derivatives with fungicidal activity.[258] In this context, the synthesis of 2,4-*bis*(trifluoromethyl)-5-carbethoxythiazole **459** (precursor for agricultural fungicides) from the reaction of trifluorothioacetamide with the trifluoromethylated chlorocarbonyl compound **451** (X = Cl; R^1 = COOEt) has also been reported.[259]



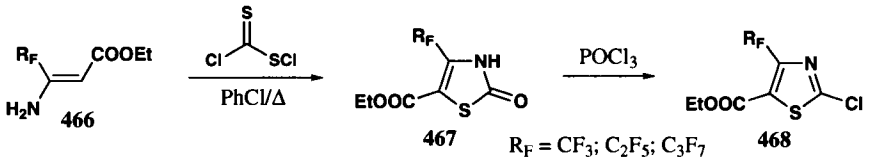
Scheme 89

Trifluoromethylepoxysulfones **461** and **464** are used as α-haloketone equivalents in the synthesis of trifluoromethylthiazoles. The reaction of **461** [prepared by oxidation of the vinylthioether **460** with *m*-chloroperbenzoic acid (*m*-CPBA)] with thioureas gives the 4-trifluoromethylthiazoles **462** (91-99%) (*Scheme 90*, where Z indicates the sulfurated nucleophile).[260] On the other hand, the reaction of the oxirane **464** (prepared by oxidation of the vinylsulfone **463** with ^{t}BuOOH in the presence of BuLi) with the same thioureas in DMF produces the 5-trifluoromethylthiazole regioisomers **465** (30-38%).[260]



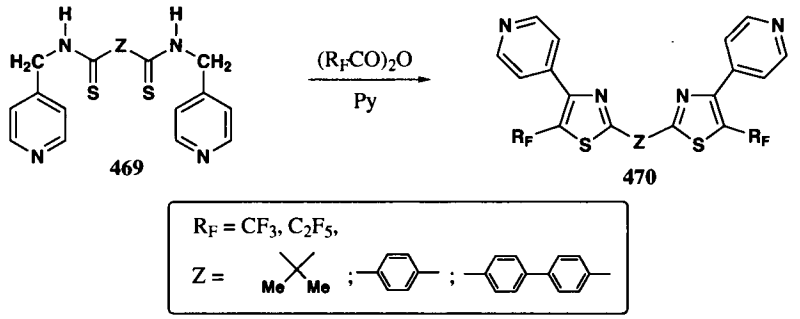
Scheme 90

A thiazole cyclization occurs in the reaction of fluorinated 3-amino-acrylates **466** (easily accessible from ethyl acetylacetate and perfluoronitriles) with chlorocarbonylsulfenyl chloride, leading to 4-perfluoroalkyl-2-oxo-5-thiazoles **467** (41-55%) (*Scheme 91*). Their subsequent reaction with $POCl_3$ produced 4-perfluoroalkyl-2-chlorothiazoles **468** (69-92%).[244] [Note that the reactivity of functional groups at C(2) and C(5) in compounds **468** allows the introduction of the fluorinated thiazole moiety into target molecules]. A recent application of this thiazole cyclization has been reported.[261] This synthesis of fluoroalkyl thiazole derivatives has also been object of several patents.[262]



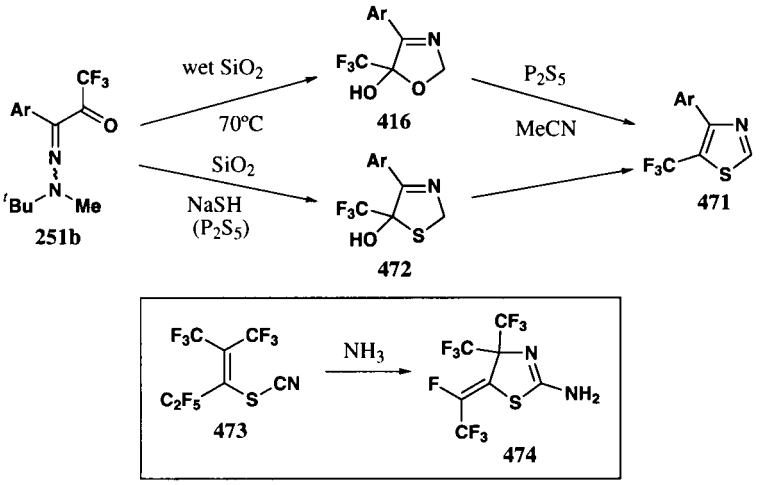
Scheme 91

On the basis of the synthetic approach already described in the oxazole series (see *Scheme 79*), the synthesis of 4,4'-*bis*(pyridyl)-5,5'-*bis*(perfluoroalkyl)-2,2'-*bis*(thiazole)s having the general formula **470** is reported to take place (in modest yields) from symmetrical dithioamides **469** (prepared by sulfuration of the corresponding diamides with Lawesson's reagent) by reaction with perfluoroalkanoic acid anhydrides (*Scheme 92*).[233]



Scheme 92

The formation of 5-trifluoromethylthiazoles **471** is claimed[235] to occur by sulfuration of the oxazolines **416** obtained from thermally induced cyclization of *t*-butyl-(methyl)hydrazones **251b**. The same trifluoromethylthiazoles **471** (18-36%) or 5-hydroxy-5-trifluoromethylthiazolines **472** (23-59%) were directly obtained from hydrazones **251b** and sulfurating reagents in a one-pot procedure (*Scheme 93*).[152,235,263] In turn, thiazolines **472** can easily be dehydrated into thiazoles **471**. Finally, a thiazole cyclization takes place by reaction of perfluorinated pentene-3-thiocyanate **473** with ammonia, yielding fluorinated 2-aminothiazoline **474** as the more stable *E*-isomer (*Scheme 93*).[264]



Scheme 93

VII. CONCLUDING REMARKS

The synthesis of fluorinated five-membered heterocycles containing two or more heteroatoms represents a challenging research area, especially when the achievement of a particular target is essential for the development of new materials with specific properties. This second review although not exhaustive, satisfactorily completes the original goals of summarizing and reorganizing the last two decades of literature on the synthesis of fluorinated azoles. It is hoped that these two reviews will be helpful in the planning of straightforward synthetic strategies for specific heterocyclic targets.

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