Recent Trends in the Chemistry of Fluorinated Five and Six-Membered Heterocycles

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Received March 10, 2000

J. Heterocyclic Chem., **38**, 793 (2001).

Contents

1. Introduction.

Fluorine and/or perfluoroalkyl groups positioned strategically in heterocyclic systems, may modify the chemical properties, and biological activity [1-4]. A number of fluoro- and perfluoroalkyl substituted pharmaceuticals, agrochemicals, dyes, and polymers have been commercialized. As an important area of research, several reviews have been published which focus on methods for fluorination [5-7] and on the chemistry of particular classes of biologically active compounds which contain fluorine [1-6,8,9].

This review covers the recent literature up to the middle of 1999 and considers the synthesis and reactions of five- and six-membered fluorinated heterocyclic compounds.

1.1 Overview

The exchange of hydrogen by fluorine does not greatly alter the steric bulk of the molecule. This is because the fluorine atom has small a Van der Waals radius (1.35 Å), which is similar to that of hydrogen (1.20 Å). However, due to its high electronegativity, fluorine (4.0 versus 3.5 for oxygen) can have pronounced effects on the electron distribution in molecules, thus, affecting the basicity or acidity of neighboring groups, the dipole moment of the molecule and the overall reactivity and stability of neighboring functional groups [10].

The chemical reactivity of fluorinated compounds is due to: 1) the difference in carbon—fluorine (456/486 kJ/mol) and carbon–hydrogen bond energies (356/435 kJ/mol); 2) the difference in electronegativity between fluorine and hydrogen (4/2.1), which can gradually alter and even invert the reaction behaviour of adjacent centers; and 3) the ability to participate in hydrogen bonding as an electron pair donor [10,11]. The high carbon—fluorine bond energy hinders many metabolic transformations. For example, 5-fluorouracil, taken as a typical example inhibits the enzyme thymidylate synthase, which

catalyses methylation, and is an essential component of DNA synthesis. The difference in C–H/C-F bond energy, however, hinders *C*-methylation, which makes 5-fluorouracil and its analogs efficient cytotoxic agents [10-14].

The postulated difference between CH_3 and CF_3 groups is still a controversial issue [15]. The Van der Waal's radii of a trifluoromethyl group and of a methyl group are 2.7 Å/2 Å, whereas, the Van der Waals volumes are 42.6 Å/16.8 Å [11]. It has been suggested that there should be little or no effect on bond length when a methyl group attached to a carbon atom is replaced by a trifluoromethyl group [16]. Therefore, this transformation should result in minimal disruption to an enzyme–substrate complex [11,17].

2. Synthesis.

This discussion is divided into three sections depending on whether fluorine, or a polyfluoroalkyl group, are introduced into a heterocycle or whether the heterocycle is formed from fluorinated synthons.

2.1 Direct Introduction of Fluorine into Heterocyclic Systems.

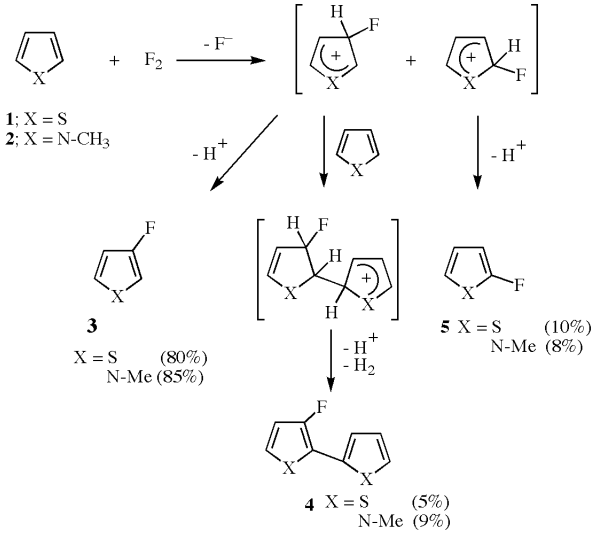
2.1.1 Electrophilic H/F Substitution.

A. Utility of Fluorine.

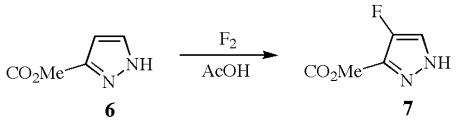
The introduction of a fluorine atom into heterocyclic systems can be achieved by using molecular fluorine. The great reactivity of elemental fluorine is attributed in part to the low dissociation energy of the F–F bond in the fluorine molecule (153 kJ/mol) [15,18]. Although F_2 can behave as a free-radical source of fluorine atom under different conditions it can also behave as an electrophile. Thus, Rozen and Gal have shown that F_2 diluted with N_2 can fluorinate electron–rich C—H bonds [19-21].

The reaction of fluorine with thiophene and *N*-methylpyrrole proceeds *via* a cationic intermediate [22,23] (Scheme 1).

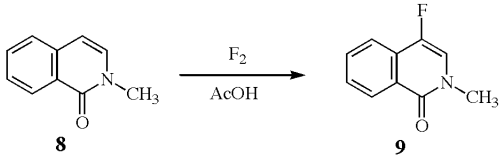
Scheme 1



In a related reaction, fluorination of 3-methoxycarbonylpyrazole (**6**) with fluorine in acetic acid at 20 °C led to the formation of 4-fluoro-3-carbomethoxypyrazole (**7**) in 75% yield [5,24].

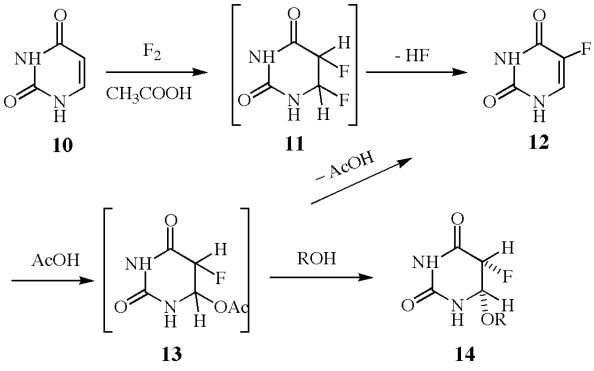


The isoquinoline ring system could not be fluorinated, but fluorination of the related 2-methylisoquinolinone (**8**) was successful [25]. In acetic acid, the 4-fluoro derivative **9** was isolated.



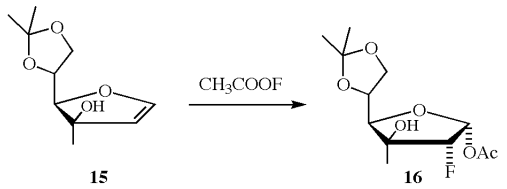
A nitrogen-diluted solution of fluorine reacted with pyrimidines for the synthesis of 5-fluorouracil and many other important biochemical derivatives [26-33]. In the synthesis of 5-fluorouracil, Cech and Holy [32] proposed that the reaction was initiated by *syn*-addition of fluorine across the double bond to give the difluoropyrimidine intermediate **11**, followed by hydrogen fluoride elimination to yield 5-fluorouracil (**12**). In acetic acid, an unstable acetoxy intermediate **13** is formed (Scheme 2). The addition of an alcohol gave the corresponding stable 5-fluoro-6-alkoxy-5,6-dihydrouracil derivative (**14**) [30].

Scheme 2

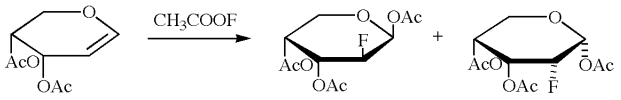


B. Utility of Acetyl Hypofluorites.

Although acetyl hypofluorite has explosive character it has been used to good effect in organic and polymer chemistry by Rozen *et al.* [34-36] CH_3COOF has recently been used to fluorinate 1,2-dideoxyhexenofuranoses **15** and hexenofuranoses **17** [37,38].



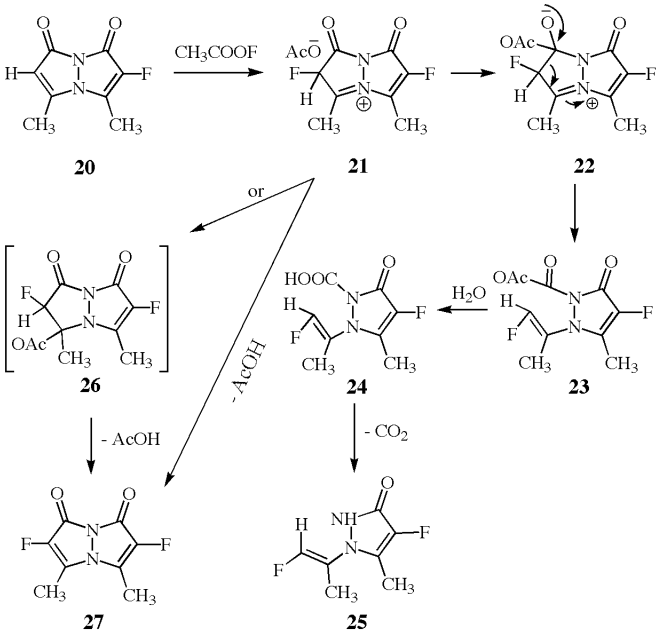
15 16



17 18 19

Fluorobimane **20** reacts with acetyl hypofluorite in a cold chloroform/nitromethane mixture to form (methyl, fluoro)-bimane **27** and a major pyrazolinone product **25**. The mechanism of this electrophilic fluorination was reported by Kosower *et al.* [39] (Scheme 3).

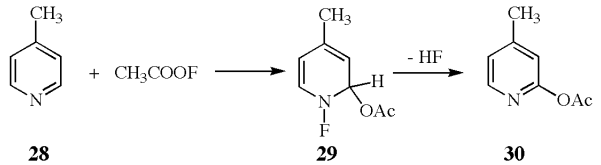
Scheme 3



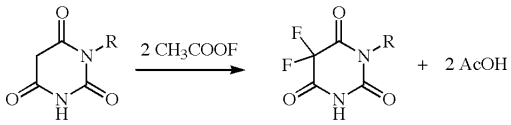
20 21 22 26 24 23 27 25

Pyridine substituted at the 4-position, such as 4-methylpyridine **28** reacts with AcOF to form 1-fluoro-2-acetoxy-4-methyl-1,2-dihydropyridine (**29**). The latter eliminates hydrogen fluoride at room temperature to give 2-acetoxy-4-methylpyridine (**30**) [40].

1-Alkyl-5,5-difluoropyrimidin-2,4,6-triones (**32**) could be prepared by treating pyrimidinone derivatives **31** with CH_3COOF at room temperature [41].



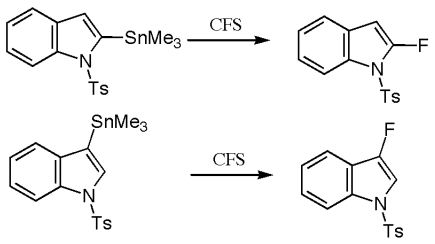
28 29 30



31 32

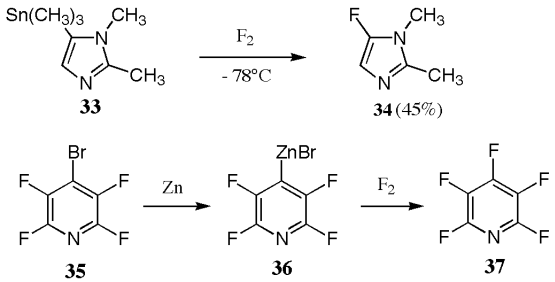
2.1.2 Electrophilic Displacement Reactions of Metallated Fragments.

The electrophilic fluorination of heteroarylstannanes with F_2, $CsSO_4F$ and $XeF_2/AgPF_6$ have been well-documented [42]. For example, 2-fluoroindoles and 3-fluoroindoles were obtained on reaction of the corresponding stannylated indole at room temperature in acetonitrile [42a].



The reaction of metallated heterocyclic species with molecular fluorine enables fluorination at low temperatures. This type of reaction seems promising (Scheme 4) [42,43].

Scheme 4



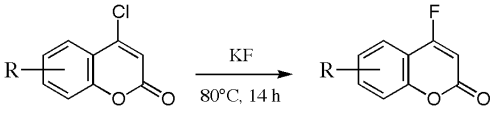
33 34 (45%) 35 36 37

2.1.3 Nucleophilic Displacement Reactions.

A. Utility of Alkali Metal Fluorides.

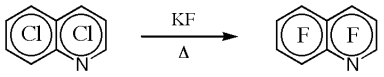
Introduction of fluorine into organic molecules *via* nucleophilic displacement reactions remains problematic since the fluoride ion often behaves as a base [6,44] rather than as the desired nucleophile. Halogen exchange reactions are of major importance in the synthesis of fluorinated heteroaromatic compounds.

4-Fluorocoumarins (**39**) are obtained by the reaction of KF with their chloro analogues [45].



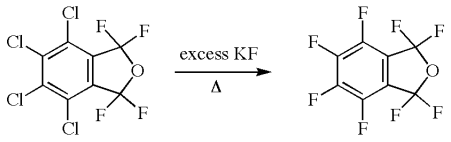
38 39

Reaction of KF with heptachloroquinoline (**40**) at elevated temperatures gave the expected heptafluoroquinoline (**41**) [46,47].



40 **41**

Finally, aromatic fluorinations using KF on polychlorinated substances have been investigated by Dmowski [48].

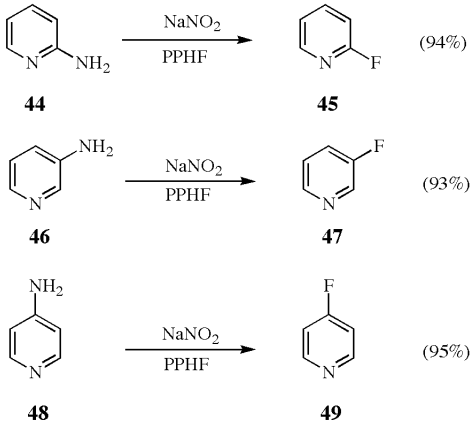


42 **43**

B. Utility of Polypyridinium Hydrogen Fluoride (PPHF).

Anhydrous hydrogen fluoride is one of the cheapest and most popular fluorinating agents but due to the potential hazards in handling and its low boiling point (19 °C) alternatives are required. This problem has been mitigated by using polypyridinium hydrogen fluoride (PPHF) which is pyridine: HF (3:7 w/w) [49]. Yoneda *et al.* [50] have demonstrated the efficiency of PPHF in the fluorination of pyridines (Scheme 5).

Scheme 5



44 **45**

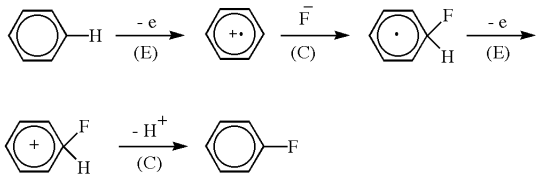
46 **47**

48 **49**

2.1.3 Anodic Electrochemical Fluorination.

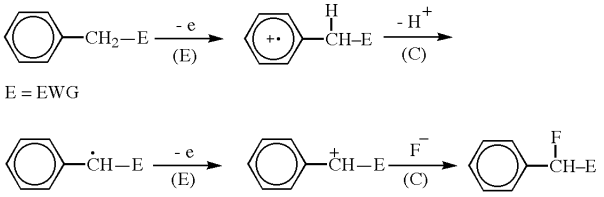
A wide variety of experimental evidence clearly points to an oxidation of the organic reactant leading to the formation of cation-radicals as the first step in a selective electrochemical fluorination reaction. It is generally agreed that the selective electrochemical fluorination proceeds *via* a ECEC mechanism (electrochemical reaction → chemical reaction → electrochemical reaction → chemical reaction). In the case of electrochemical substitution reaction, the first chemical step is fluoride attack and the second is proton release (Scheme 6) [51].

Scheme 6



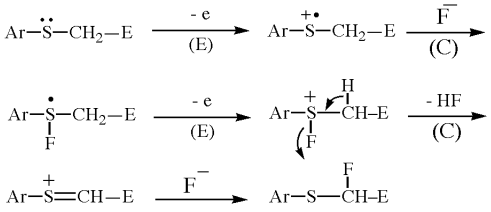
In the case of side chain fluorination, proton release is possibly the first chemical step (Scheme 7) [52].

Scheme 7



Fuchigami *et al.* [52] have proposed a novel mechanism in the case of active methylene group attached to sulfur (Scheme 8) [53-55].

Scheme 8

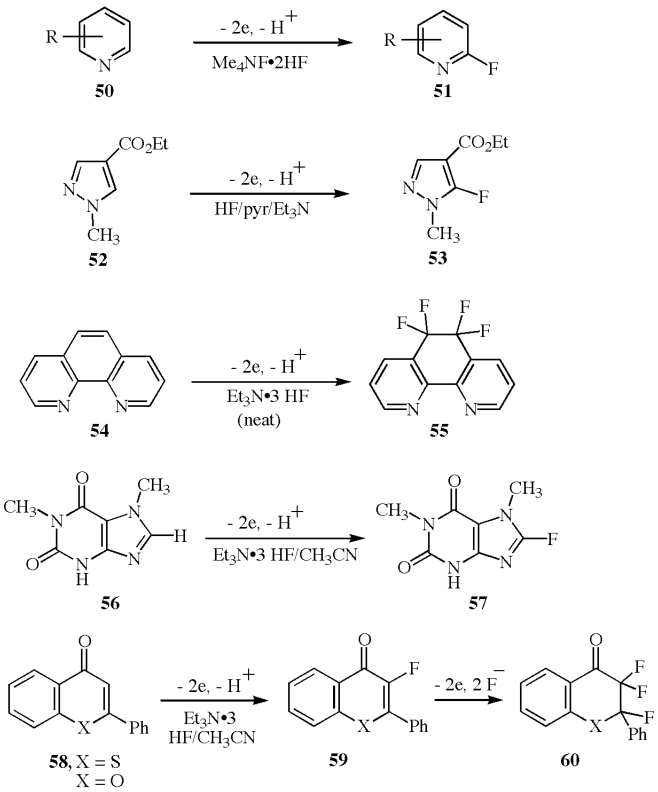


Examples of electrofluorination are shown in Scheme 9 [56-67].

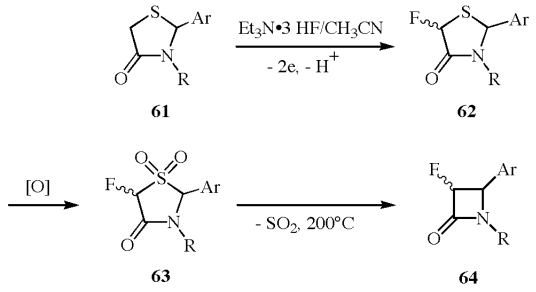
Monofluoro-β-lactams **64** could be prepared *via* the anodic fluorination of 2-aryl-4-thiazolidinones **61** (Scheme 10) [68–70].

2-Fluorothieno[2,3-*b*]pyridines **69** were prepared by the anodic monofluorination of 2-pyridylsulfides **65** to yield the α-fluoromethylpyridyl sulfides **66**. The latter were cyclised readily in a basic medium to give the thienopyridineimine **67**. Compound **67** in the presence of ethanol forms the intermediate **68** which, in turn, aromatised *via* loss of diethylcarbonate (Scheme 11) [71-74].

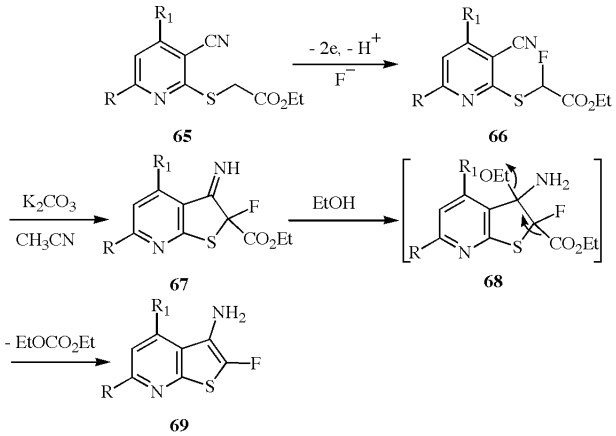
Scheme 9



Scheme 10



Scheme 11

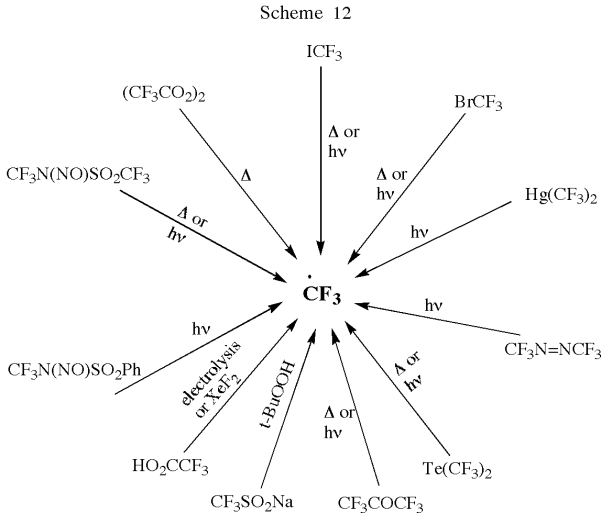


2.2 Introduction of a Polyfluoroalkyl Group.

2.2.1 Introduction of a Trifluoromethyl Groups as Radical Species.

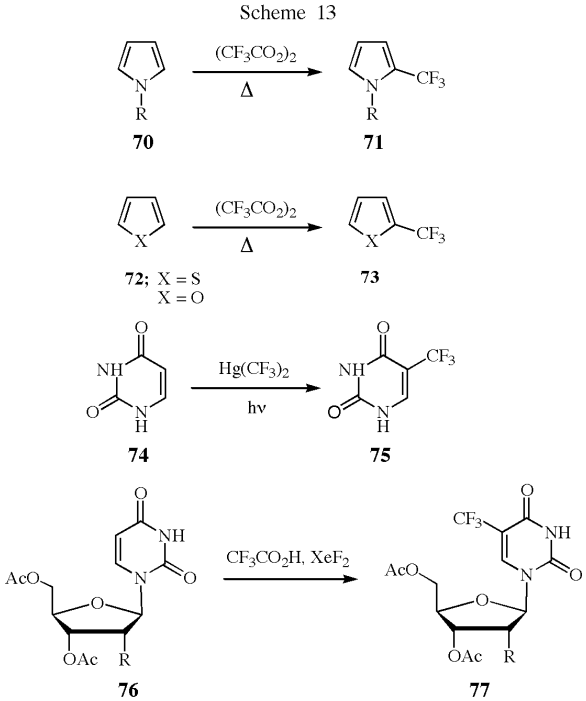
Trifluoromethyl radicals have been generated thermally from bis-(trifluoromethyl)tellurium [75], iodotrifluoromethane [76], bromotrifluoromethane, hexafluoroacetone, and *N*-trifluoromethyl-*N*-nitrosotrifluoromethylsulfonamide [77]. The methods available for preparing trifluoromethyl radicals are summarized in scheme (12) [75-81].

Scheme 12



Pyrroles and *N*-alkylpyrroles [82-84], 2-substituted imidazoles [85], thiophene [86], furan [86], uracil [82], and 2-deoxyuridine [77,87], all react with trifluoromethyl radicals

Scheme 13

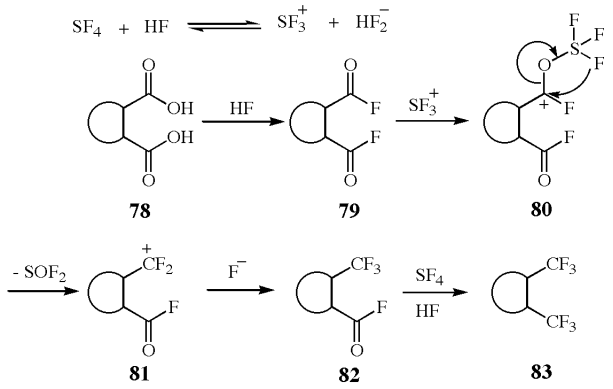


to give just one product. It is believed that the trifluoromethyl radicals, in this reaction is behaving as an electrophile (Scheme 13).

2.2.2 Transformation of Carboxylic Groups into Trifluoromethyl Groups.

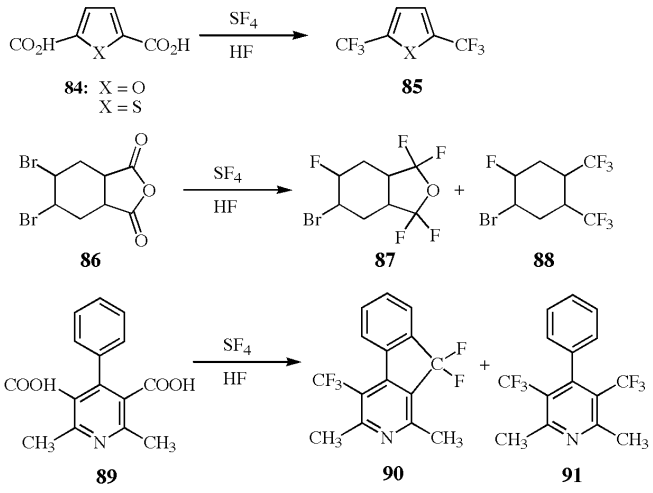
Sulfur tetrafluoride in the presence of hydrogen fluoride is capable of converting carbonyl and carboxylic groups into trifluoromethyl groups [88-91]. The mechanism of this conversion is shown in Scheme 14 [91].

Scheme 14



The following trifluoromethyl substituted heterocycles have been prepared *via* the same route [92-94] usually under forcing conditions (Scheme 15).

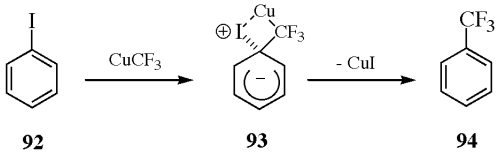
Scheme 15



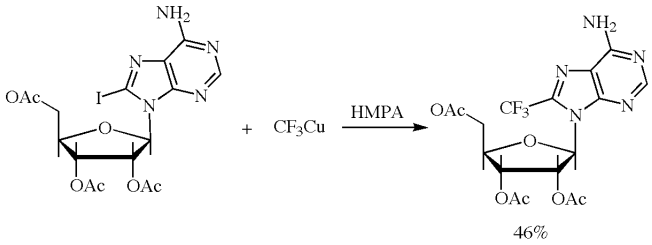
2.2.3 Introduction of Trifluoromethyl Groups *via* Trifluoromethyl Copper.

Trifluoromethyl iodides react with aromatic and heteroaromatic halides in the presence of copper to give trifluoroalkyl-substituent compounds. The reactive species in this reaction was shown to be $CuCF_3$ *via in situ* metathesis of (trifluoromethyl)cadmium and zinc reagents with soluble copper salts (Scheme 16) [84,95,96].

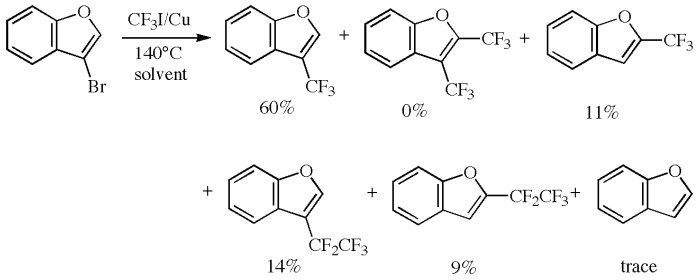
Scheme 16



This method has been applied to pyrimidine and purine nucleosides [97].



In some cases the reaction is more complex than simple coupling to give the trifluoromethylated product. For example, 3-bromobenzofuran produces at least seven products with CF_3I/Cu. The amount of each product is dependent on the solvent employed [98]. The pentafluoroethyl products were postulated to arise from decomposition of trifluoromethylcopper to form pentafluoromethylcopper. The formation of the 2-substituted benzofurans was explained by addition of the trifluoromethyl anion to the delocalized double bond between the 2- and 3-position, followed by migration of hydride ion and elimination of the bromide anion.



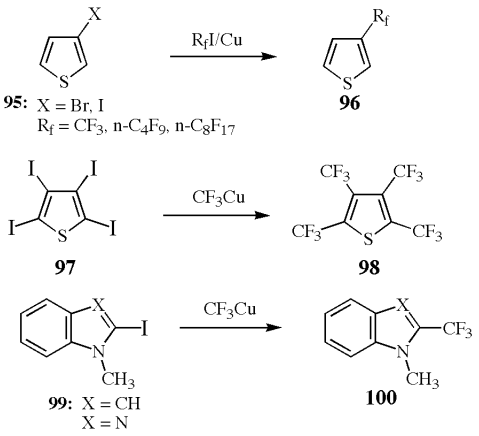
Likewise, the following perfluoroalkyl-substituted heterocycles were obtained (Scheme 17) [98-101].

2.3 Introduction of Fluorine and Perfluoroalkyl Groups into Heterocycles *via* Cyclocondensation Reactions.

2.3.1 [3+2] Cyclocondensation Reactions.

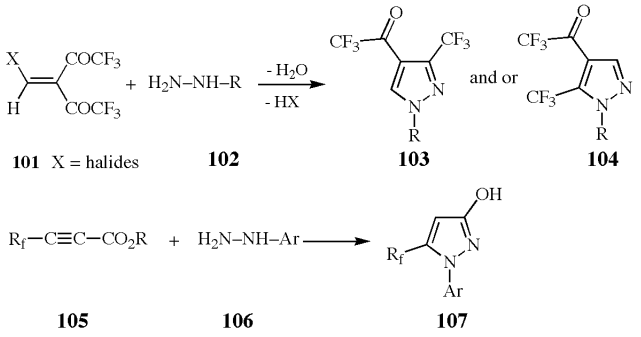
A. Condensation Reactions of 1,2-Dinucleophiles with Fluorine-Containing 1,3-Dielectrophilic Building Blocks.

Scheme 17

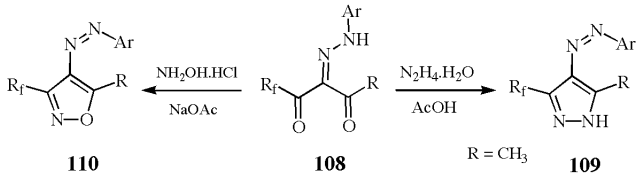


A large number of fluoro-containing 1,3-bis-electrophilic building blocks are known. Partially fluorinated penta-2,4-diones [102-105]; methyl 2-cyano-2-fluoroacetate [106,107]; 3-perfluoroalkylpropiolates [108], *etc.* react with 1,2-dinucleophiles, like hydrazines and hydroxylamines, to give pyrazoles and isoxazoles, respectively (Scheme 18) [102–108].

Scheme 18

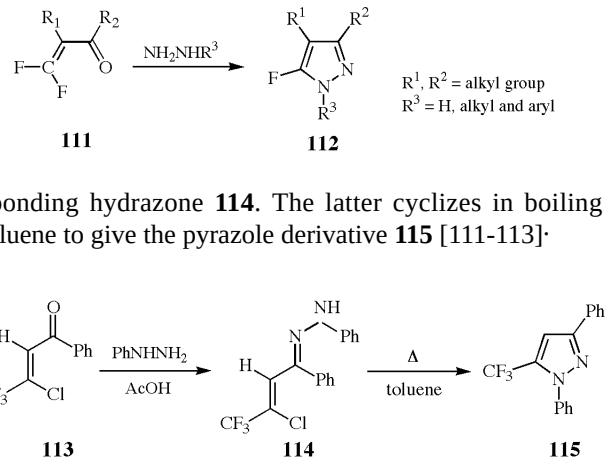


Arylhydrazones **108** react with hydrazine hydrate in acetic acid to form the substituted pyrazoles **109**. Interaction of **108** with hydroxylamine hydrochloride in the presence of sodium acetate results in the formation of substituted isoxazole **110** [109].

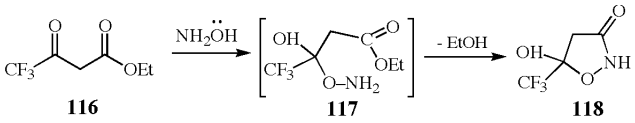


2,2-Difluorovinyl ketones **111** react with monosubstituted hydrazines to afford 5-fluoropyrazoles **112** [110].

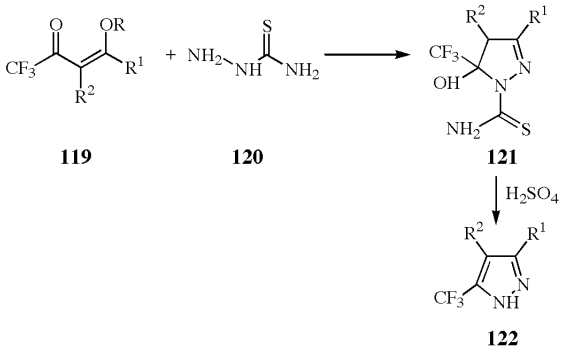
The β-Chloro-β-trifluoromethylenone **113** reacts with phenylhydrazine, in an acidic medium, to afford the corresponding hydrazone **114**. The latter cyclizes in boiling toluene to give the pyrazole derivative **115** [111-113].



The condensation of hydroxylamine with fluoroketoester **116**, in a basic medium, affords the corresponding 5-hydroxy-5-trifluoromethylisoxazolin-3-one **118** [114].



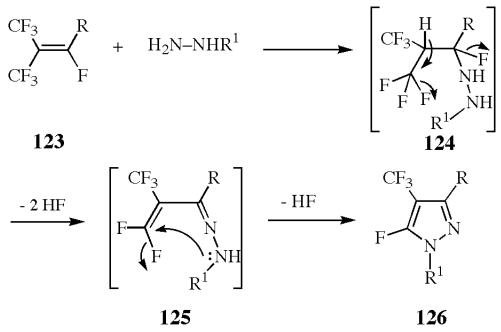
A series of pyrazole-1-thiocarboxamide derivatives **121** and *N*-H pyrazole derivatives **122** can be obtained by treating β-alkoxyvinyl trifluoromethyl ketones **119** with thiosemicarbazide **120** [115-117].



The reaction of 1,1-bis(trifluoromethyl)-2-fluoro olefins with (1,2 nn) compounds is of preparative and mechanistic interest, because this type of olefin does not represent a 1,3-dielectrophilic (1,3 ee) species. The second electrophilic center is generated during the reaction (Scheme 19). The single fluorine bonded to C(5) can be exchanged by a wide variety of nucleophiles [118].

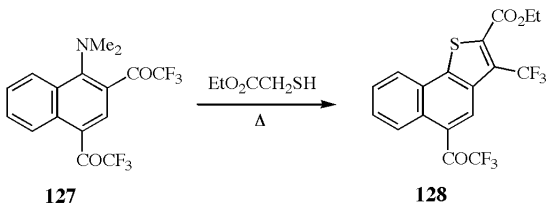
Aromatic compounds having substituents with an electrophilic center adjacent to the position of nucleophilic substitution reactions *e.g.*, *N*,*N*-dimethyl-2,4-bis(trifluoro-

Scheme 19



acetyl)-1-naphthylamine are (1,3 ee) building blocks. They react with (1,2 nn) species, like ethyl thioglycolate, benzylmercaptan [119], amino acid esters [120,121], hydrazines, and hydroxylamines [122], to yield trifluoromethyl-substituted naphthothiophenes, benzindoles, benzindazoles, and naphthoisoxazoles, respectively (Scheme 20).

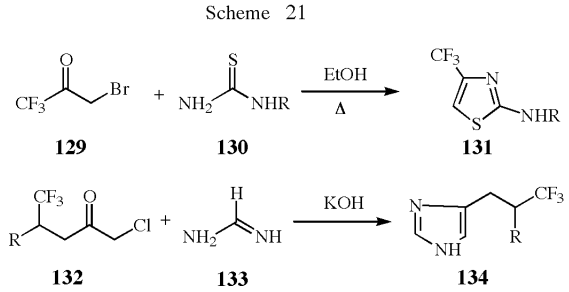
Scheme 20



B. Condensation Reactions of 1,3-Dinucleophiles with Fluoro-Containing 1,2-Dielectrophilic Building Blocks.

1,3-Dinucleophiles such as thioamides, thiourea and amidines react with 3-bromo-1,1,1-trifluoro-2-propanone [124], and 1-chloro-5,5,5-trifluoro-2-pentanone derivatives [126] to give trifluoromethyl-substituted thiazoles [124,125] and imidazoles [127,128] (Scheme 21).

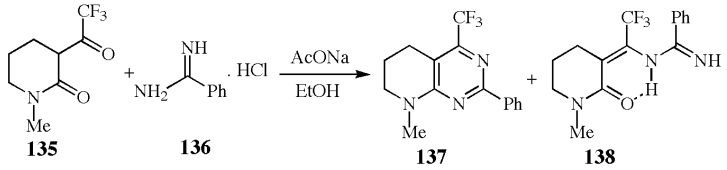
Scheme 21



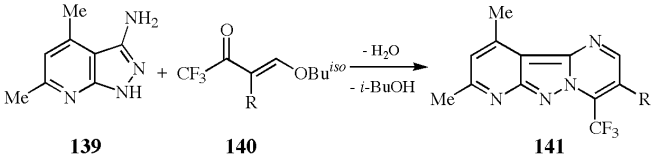
C. Condensation Reactions of 1,3-Dinucleophiles with Fluoro-Containing 1,3-Dielectrophilic Building Blocks.

Fluoro-substituted six-membered heterocycles are available *via* reaction of cyclic trifluoromethylated 1,3-diketone **135** with benzamidine hydrochloride **136** to give trifluoromethylated pyrimidine **137** [129]. Intermediate **138** was also obtained.

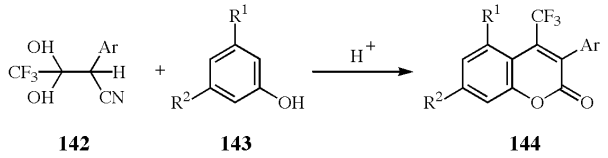
Scheme 22



The reaction of 3-amino-4,6-dimethyl-1*H*-pyrazolo-[3,4-*b*]pyridine **139** with 1,1,1-trifluoro-4-(isobutoxyl)-3-buten-2-ones **140** gave 4-(trifluoromethyl)pyrido-[2',3':3,4]pyrazolo[1,5-*a*]pyrimidine in a 90% yield [130].



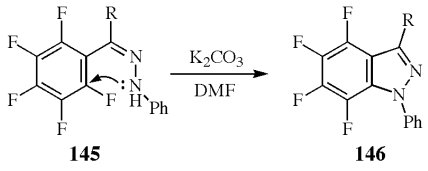
A series of fluorinated benzopyran-2-ones **144** could be prepared by reaction of butyronitrile derivatives **142** with phenols **143** [131].



D. 1,5-Cyclocondensation Reactions.

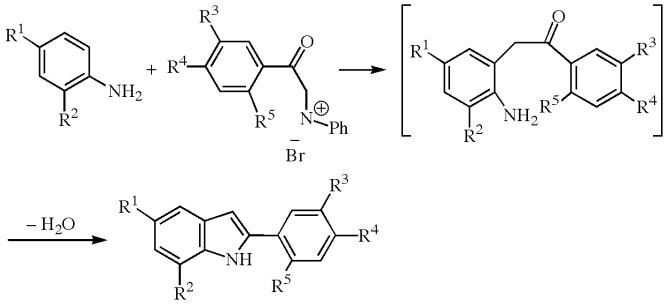
In certain cases the open-chain products of [3+2] and [4+1] condensation reactions can be isolated, and the ring closure can be done in a second step.

Phenylhydrazones of perfluorobenzaldehyde and 2,3,4,5,6-pentafluoroacetophenone cyclize on heating in the presence of potassium carbonate to give 4,5,6,7-tetrafluoroindazoles [132].



N,*N*-Dialkylhydrazones, obtained from aliphatic and aromatic aldehydes, can be transformed into trifluoromethyl-substituted pyrazoles after *C*-trifluoroacetylation with trifluoroacetic anhydride (Scheme 23) [133-138a].

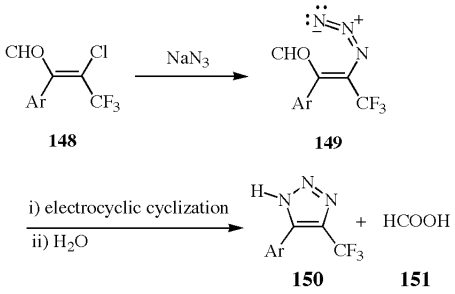
Bansal and co-workers [138b] have prepared several fluorinated indoles by the reaction of substituted anilines with fluorinated pyridinium salts.



E. Miscellaneous.

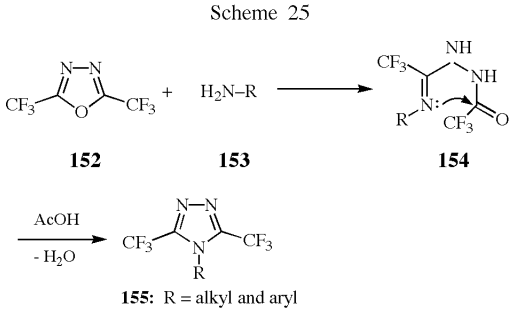
β-Chloro-β-perfluoroalkyl substituted acroleins **148** react with sodium azide to give fluorinated triazoles **150**. Compound **149** simply undergoes an electrocyclic closure to a 5-membered ring, which then undergoes nucleophilic attack of the aldehyde by H_2O to deformylate the cyclic intermediate. The mechanism of the reaction is shown in Scheme 24 [139].

Scheme 24



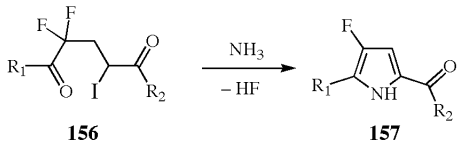
2,5-Bis-(trifluoromethyl)-1,3,4-oxadiazole **152** undergoes ring cleavage on treatment with amines to give the hydrazine derivatives **154**. Compounds **154** cyclized in boiling acetic acid to afford the *N*-substituted 1,2,4-triazole derivatives [140,141].

Scheme 25



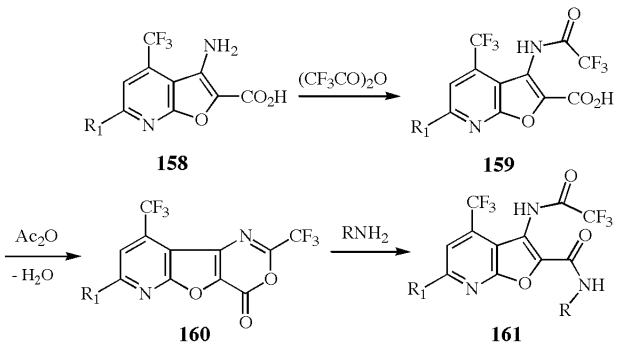
155: R = alkyl and aryl

Fluoropyrrole derivatives **157** are synthesized by the reaction of α,α-difluoro-γ-iodoketones **156** with ammonium hydroxide at room temperature [142].



A general synthetic route to fluorinated 1,3-oxazine derivatives such as **160** using cyclic α,β-enamino acids **158** and trifluoroacetic anhydride has been reported by Venkataratnam *et al.* [143–146]. Treatment of **160** with amines leads to a variety of fluorinated furopyridines **161** (Scheme 26).

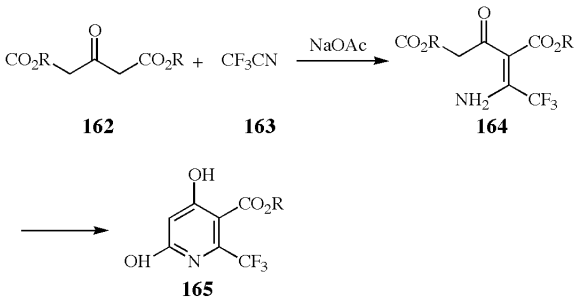
Scheme 26



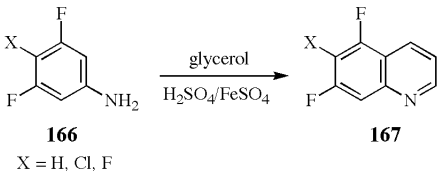
The reaction of active methylene reagents, such as **162**, with trifluoroacetonitrile **163** in the presence of sodium acetate gives β-enamino ester derivatives **164**. The latter cyclized in a basic medium to give the fluorinated pyridine derivatives **165** [147–149].

3,5-Difluoroanilines **166** react with glycerol in a Skraup condensation to produce the corresponding fluorinated quinolines **167** in high yields [150].

Scheme 27



The reaction of 3-amino-5-trifluoromethyl-1,2,4-triazole **168** with acetylacetone derivatives **169** afforded triazolo[1,5-*a*]-pyrimidine **170** [151].



166 X = H, Cl, F **167**

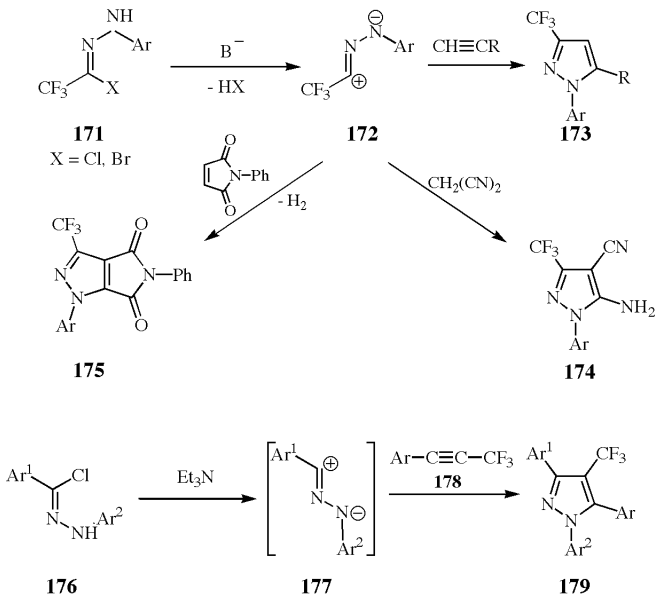
2.4 Introduction of Fluorine and Perfluoroalkyl Groups into Heterocycles *via* Cycloaddition Reactions [152].

A. [3+2] Cycloaddition Reactions.

Trifluoromethyl-substituted nitrile imines **172**, generated from *N*-aryltrifluoroacetohydrazonoyl halides **171**, have been added as

1,3-dipoles to yield trifluoromethyl pyrazoles (Scheme 28) [152–154].

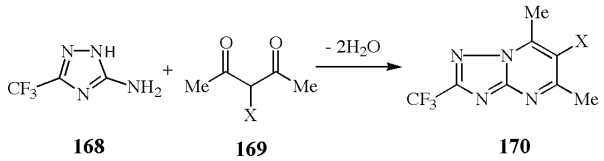
Scheme 28



171 X = Cl, Br **172** **173** **175** **174**

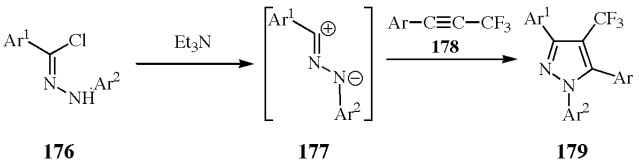
176 **177** **179**

Likewise, trifluoromethylpyrazoles (**179**) are synthesized from nitrilimines **177** and 1-aryl-3,3,3-trifluoro-1-propynes [155].



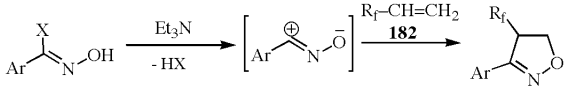
168 **169** **170**

Nitrile oxides **181**, generated *in situ* from hydroximoylchlorides **180** react with fluorinated olefins **182** to give isoxazoline derivatives **183** [156-158].



176 **177** **179**

[3+2] Cycloaddition of 2-aryl-5-azido-3-trifluoromethylthiazoles **184** to dimethyl acetylenedicarboxylate (**185**), occurs even at room temperature, and affords thiazolyl-1,2,3-triazole derivatives **186** [158,159].

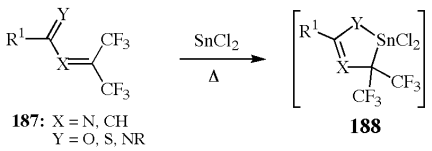


180 X = Cl, Br **181** **183**

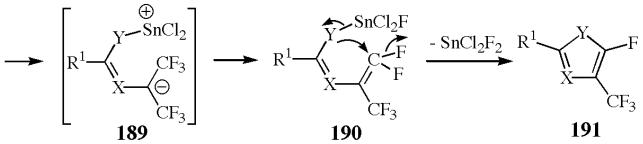
B. [4+1] Cycloaddition Reactions.

The synthesis of fluorinated five-membered heterocyclic compounds **191** from the reaction of bis(trifluoromethyl)-substituted hetero-1,3-dienes **187** with tin(II) chloride was first described by Burger *et al.* [160-166]. Scheme 29 shows the mechanism that they proposed [160]. The tin heterocyclic intermediate **188** is the key step of this reaction.

Scheme 29

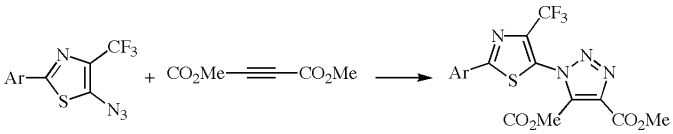


187: X = N, CH Y = O, S, NR **188**



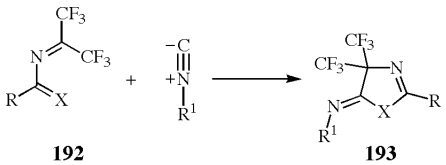
189 **190** **191** X = N, CH Y = O, S, NR

Isonitriles add to bis(trifluoromethyl)-substituted hetero-1,3-dienes **192** to give a variety of five-membered heterocycles **193** [167].



184 **185** **186**

Similarly, compound **192** (X = O) reacts with alkynes to give isoxazoles **194** and 1,3-oxazines **195** [168].



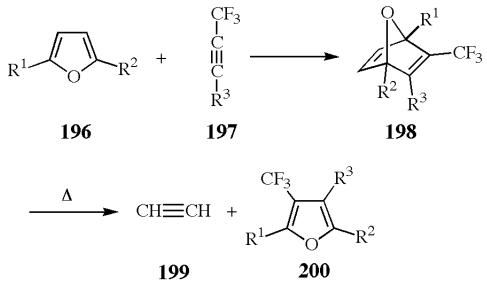
192 **193**

X = O, S, N–R

C. [4+2] Diels-Alder Reactions.

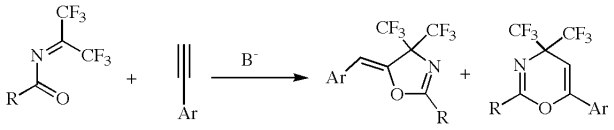
Perfluoroalkyl-substituted acetylenes, such as **197** react with furans **196** to give the Diels-Alder adducts **198**. The latter undergo thermal retro-Diels-Alder reaction to give the 3-trifluoromethylfuran **200** in a high yield (Scheme 30) [169-176].

Scheme 30



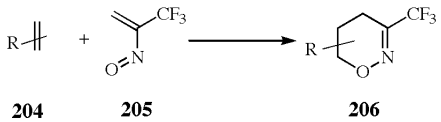
196 **197** **198** **199** **200**

3-Chloro-4-fluorothiophene-1,1-dioxide **201** dimerizes with loss of sulfur dioxide and hydrogen chloride to give 5-chloro-3,6-difluorobenzothiophene 1,1-dioxide **203** *via* Diels-Alder adduct **202** [177].



192 (X = O) **194** **195**

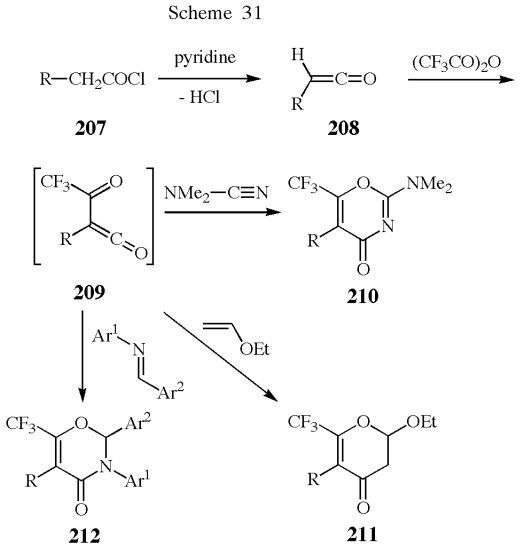
A large variety of trifluoromethyl-substituted 1,2-oxazines **206** could be prepared *via* the cycloaddition reaction of 3,3,3-trifluoro-2-nitroso-1-propene **205** with olefins [178].



204 **205** **206**

Various trifluoromethylated heterocycles can be prepared from carboxylic acid chlorides **207** by reaction with pyridine and trifluoroacetic acid anhydride followed by trapping the trifluoroacetyl ketene intermediate **209** with a variety of dienophiles. The reaction mechanism is given in Scheme 31 [179-181].

Scheme 31

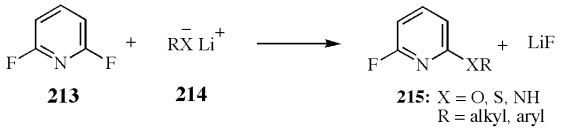


207 **208** **209** **210** **212** **211**

3. Chemical Reactions.

3.1 Nucleophilic Substitution Reactions.

Nucleophilic displacement reactions involving fluoroheterocyclic compounds and various nucleophiles have been reported [182-188]. For example, 2,6-difluoropyridine derivative **213** reacts with lithiated amines [184], alcohols [185], phenols [182] and thiophenols [182] to give a series of 2-substituted pyridines **215** [182].



213 **214** **215:** X = O, S, NH; R = alkyl, aryl

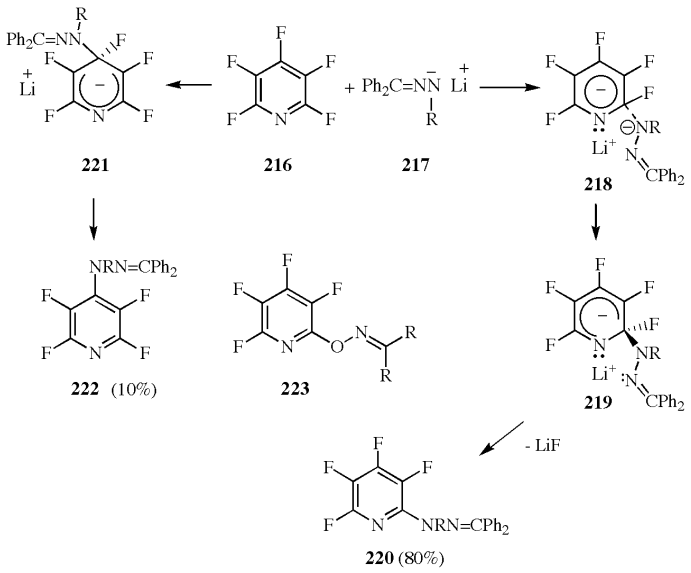
Treatment of the pentafluoropyridine **216** with the lithiated hydrazones **217** gives 2-pyridylhydrazones **220** in a good yield (80%). Scheme 32 shows the mechanism suggested by Tipping *et al.* [186]. The differences in 2- and 4-substitution ratios arise directly from the chelation stability in intermediate **219** [186]. Similarly, a series of pyridyl derivatives **223** could be prepared [184,185-188].

The reaction of trifluoro-1,3,5-triazine **224** with *N*,*N*-dimethylaniline **225** in acetonitrile gives aryltriazine derivative **227** *via* the intermediate **226** [189].

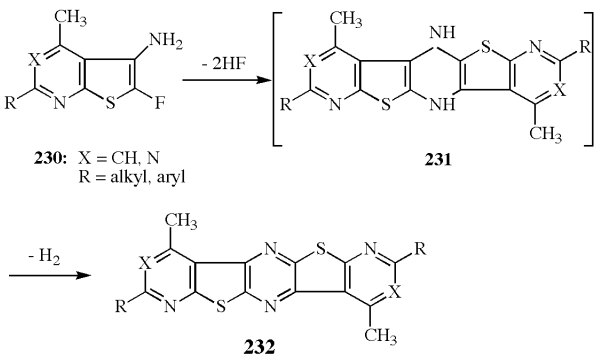
1,2,4,5,7,8-Hexafluordibenzo[1,4]dioxin **229** was synthesized from 2,3,5,6-tetrafluorophenol **228** in the presence of sodium *tert*-butoxide. The X-ray structure analysis has been performed [190].

It has been reported [72,191] that, at 100 °C, 2-fluorothienoazines **230** undergoes self–condensation to the dimeric cyclic compound **232** (Scheme 33). This interesting reaction also occurs slowly during the storage of the

Scheme 32



Scheme 33

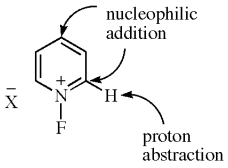


monomer **230** even at –70 °C. The highly π-conjugated system in **232** is the driving force for such dimerizations.

3.2 Reactions of *N*-Fluoropyridinium Salts.

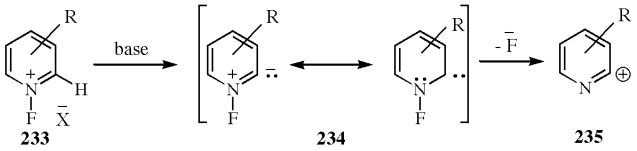
The *N*-fluoropyridinium cation is a multicenter electrophile with several potential sites for reactions with nucleophiles or bases (Scheme 34) [192-200].

Scheme 34



Many reactions of *N*-fluoropyridinium salts containing an unsubstituted position 2 and/or 6 have been explained in terms of the base-mediated generation of the intermediate **235** (Scheme 35) [200].

Scheme 35



Reactions of *N*-fluoropyridinium salts with the suggested intermediate **235** are illustrated in scheme 36. Examples include syntheses of amides **237**, 2-phenylpyridine **238**, furylpyridine **239**, and ether **241** in the presence of triethyl amine [201-203]. Finally, it has been postulated that diazocarbonyl compounds **242** are both bases and nucleophiles in the novel synthesis of 2-substituted pyridines **244** (Scheme 36) [204].

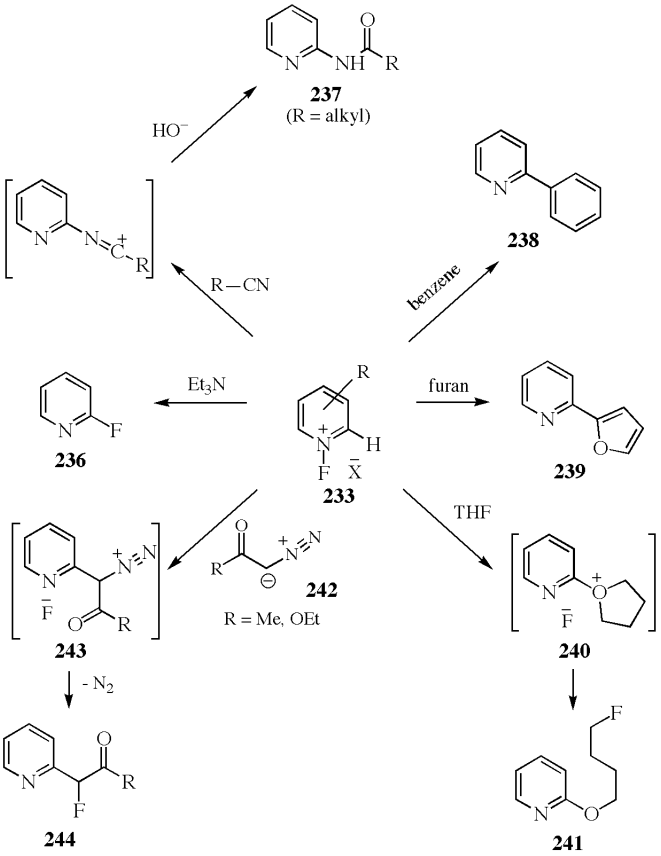
4. Conclusion and Prospects.

There has been a rapid growth in research on fluorinated heterocyclics. This, trend will continue in the future not only because of the compounds biological properties, but also, because of their industrial applications [205]. Through this review, it is hoped that an understanding of the potential of fluorinating agents in the synthesis of fluorinated heterocycles, biologically active compounds and medicinals will result. The recent flood of papers and patents on the biologically active fluorinated heterocyclic compounds [7-9,61,62,206-208] testify to its great potential. Finally, it is hoped that this review will fill an existing literature gap by providing a concise overview of the subject.

Acknowledgments.

I am deeply indebted to the Alexander von Humboldt stiftung for granting me a research fellowship (1998-1999). I would also like to thank my host Prof. Dr. D. Döpp in

Scheme 36



Duisburg University, Germany for kind hospitality and supplying some original references included in this article. I would also thank Prof. Dr. T. Fuchigami, Tokyo Insitiute of Technology, 4259 Nagatsuta, Yokohama 227, Japan for offering some of original references of his research.

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