Synthesis of Fluorinated Pyridines

Anatoliy M. Shestopalov, Lyudmila A. Rodinovskaya, Valeri Yu. Mortikov, and Alexander E. Fedorov

Contents

Abstract Present review contains recent literature data published since 2009 for 2012 as till 2009 four reviews on this field have been published. The methods of synthesis of 2-, 3-, 4-fluoropyridines, di-, tri-, polyfluoropyridines, perfluoroalkylpyridines and also fluoropyridines fused with carbo-, heterocycles are presented. Methods for synthesis of F^{18} substituted pyridines for local radiotherapy of cancer and other biological active compounds are also presented.

A.M. Shestopalov (✉) • L.A. Rodinovskaya • V.Yu. Mortikov • A.E. Fedorov
N. D. Zelinsky Institute of Organic Chemistry Russian Academy of Sciences,
119991 Moscow, Russian Federation
e-mail: amshestopalov@gmail.com

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1 Introduction

The present review contains the literature published since 2009 for 2012. Till 2009 four reviews on this field have been published, completely [1, 2] or in part [3] devoted to methods syntheses C-F pyridines and perfluoroalkyl pyridines [2, 4]. To display full information about synthesis fluorinated pyridines in the present review earlier classical works also are included.

An arising interest towards fluoropyridines is explained by their interesting and unusual physical, chemical and biological properties owing to the presence of the strong electron-withdrawing substituent(s) in the aromatic ring. Fluoropyridines have reduced basicity and are usually less reactive than their chlorinated and brominated analogues. A selective synthesis of fluoropyridines remains a challenging problem. Here a synthetic methods for preparation of 2-, 3-, 4-fluoropyridines and di- and poly-fluoropyridines are reviewed along with some synthetic routes towards ^{18}F-substituted pyridines, which present a special interest as potential imaging agents for various biological applications.

In the search for new agricultural products having improved physical, biological, and environmental properties, one of the most generally useful chemical modifications is the introduction of fluorine atoms into lead structures. Fluorine-containing substituents are most commonly incorporated to carbocyclic aromatic rings, and a large number of compounds possessing fluorine-containing substituents on aryl rings have been commercialized as agricultural active ingredients [5, 6].

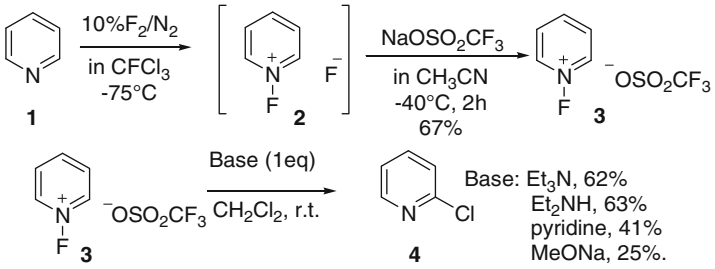
About 10 % of the total sales of pharmaceuticals currently used for the medical treatment are drugs containing fluorine atom. Over 50 years, many fluorinated medicinal and agrochemical candidates have been discovered and the interest toward development of fluorinated chemicals has been steadily increased. High availability of the fluorinated synthetic blocks and the effective fluorinating reagents, the widely reliable fluorination technology, and the accumulation of basic and advanced knowledge of the fluorine chemistry rapidly accelerated developments in this field [7].

2 Synthesis of 2-Fluoropyridines

2.1 N-Fluoropyridinium Salts. The Umemoto Reaction

The chemistry of the pyridine ring has been enriched by the development of many significant transformations. These reactions include addition, addition-elimination, elimination-addition, and ring-opening, as well as proton-abstraction reactions followed by nucleophilic substitution. The course of the reaction depends on the

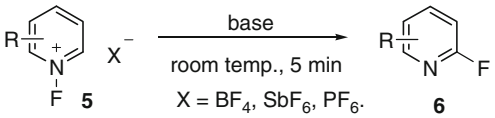
nature of the pyridine rings and bases employed [8]. New reactions involving *N*-fluoropyridinium salts **3** have now been added to the field of pyridine chemistry. In 1986, stable *N*-fluoropyridinium salts **3** were isolated and fully characterized by the T. Umemoto and his coworker [9–12]. These salts were synthesized by the counteranion replacement reaction of unstable pyridine-F_2 compounds [13] which violently decompose above -2 °C. The isolation of the stable salts followed shortly after Gakh's earlier report that the pyridine-F_2 compound, proposed as an JV-fluoropyridinium structure, reacted in situ with a trinitromethane salt to form 2-(trinitromethyl)pyridine in a 14 % yield [14]. The results of these efforts, including the discovery of the stable *N*-fluoropyridinium salts, have opened up a new area in pyridine chemistry [15, 16]. In 1987, the T. Umemoto and coworker reported novel base-induced reactions of the stable *N*-fluoropyridinium salts **3** [17] (Scheme 1).



1 **2** **3** **3** **4**

Scheme 1

N-Fluoropyridinium salts **5** are efficient precursors in the synthesis of substituted 2-fluoropyridines. They can be conveniently prepared in good yields by the reaction of the corresponding pyridine with F_2/N_2 at the presence of strong acid [17]. *N*-Fluoropyridinium tetrafluoroborates, hexafluoroantimonates or hexafluorophosphates (**5**, X=BF_4, SbF_6, PF_6) upon treatment with a base undergo an exothermic reaction to form selectively 2-fluoropyridines in moderate to high yield (Table 1) [18]. The reaction yields depend on the media's basicity and in a stronger degree on the presence of substituents in the pyridine ring. In addition, it was demonstrated that the yields of compounds **6** using ammonium fluoride as a base without a solvent were identical to the yields of **6** using Et_3N. Based on experimental data it was suggested that the fluorine substituent in products **6** arrives from counter anion (BF_4^-, SbF_6^- or PF_6^-) [18] (Scheme 2).



5 **6**

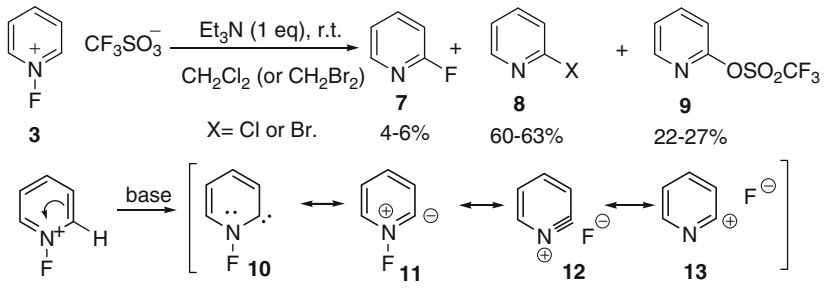
Scheme 2

Compounds **6** can be obtained in one-pot process by reacting the corresponding pyridines with F_2/N_2 mixture, followed by the subsequent treatment with Et_3N [18]. However, the yields of the fluorinated pyridines obtained by this protocol are significantly lower (22–35 %).

Table 1 Preparation of 2-fluoropyridine **6** from *N*-fluoropyridinium salts **5** [18]

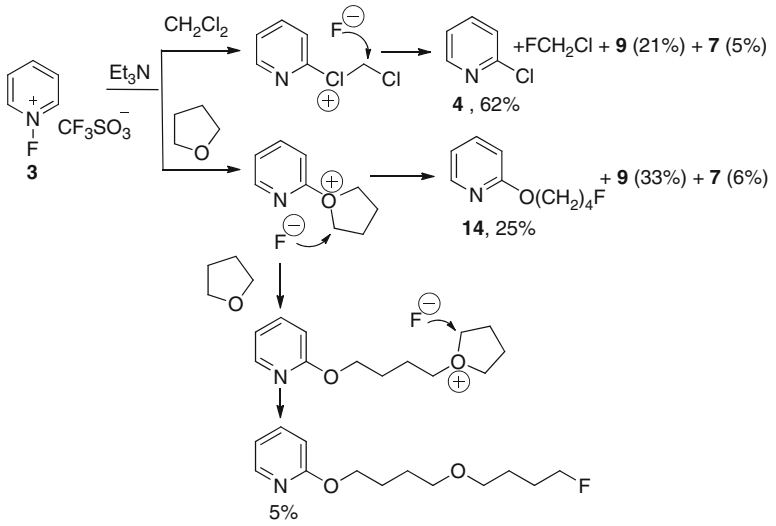
R	X	Base (equiv.)	Yield, %
H	BF_4	Et_3N (1)	66
H	BF_4	Et_3N (3)	73
H	BF_4	Et_3N (10	79
H	BF_4	*n*-$Bu^4N^+F^-$(2.6)	80
H	SbF_6	Et_3N (10)	78
H	BF_4	KF (9) (7 days, 40 °C)	26
H	PF_6	Et_3N (10)	74
4-Me	BF_4	Et_3N (10)	80
3,5-$(Me)_2$	BF_4	Et_3N (10)	87
3,5-$(Me)_2$	BF_4	Py (10)	30
4-*t*-Bu	BF_4	Et_3N (10)	91
2-MeO	BF_4	Et_3N (10)	75
2-MeO	BF_4	Py (10)	10
3,5-*bis*(CF_3)	BF_4	Et_3N (10)	99
3-CN	BF_4	Et_3N (10)	51
3-CN	BF_4	Py (10)	49
4-NO_2	BF_4	Et_3N (10)	21
4-NO_2	BF_4	Py (10)	31

The mechanism of this reaction was discussed in several publications [17, 18]. It was demonstrated that under workup with triethylamine in CH_2Cl_2 or CH_2Br_2 triflate salt **3** gives a mixture of three compounds: 2-fluoropyridine (7), 2-halopyridine **8**, and compound **9** [17] (Scheme 3). Similarly, it was demonstrated that salts **5** give 2-diethylaminopyridines, 2-phenylaminopyridines, or 2-(2-furyl and 3-furyl) pyridines when they are reacted with Et_2NH, benzene, or furan.

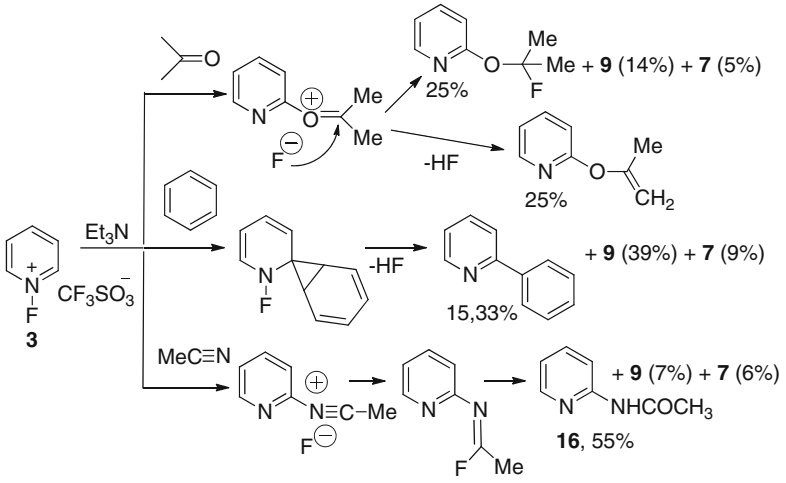


Scheme 3

It was proposed that under basic conditions salt **3** undergoes heterolytic C^2-H bond cleavage to form carbene **10↔11**, which in its turn eliminates F^- to give cation **12↔13**. A subsequent reaction of **12↔13** with nucleophiles or *n*-π-electron containing molecules gives above mentioned products. Some transformations of salt **3** leading to 2-substituted pyridines are shown below [17, 19] (Schemes 4 and 5).



Scheme 4

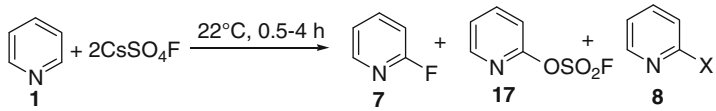


Scheme 5

Direct fluorination of pyridine also can be carried out using $CsSO_4F$ as a source of fluorine. It was shown that pyridine readily reacts with $CsSO_4F$ at room temperature producing a mixture of products (2-fluoro-, 2-fluorosulfonate- and 2-chloro- or 2-alkoxy-pyridines) (Table 2) [20] (Scheme 6).

Table 2 Products distribution in reaction between pyridine and $CsSO_4F$ [20]

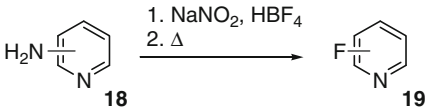
	Yield, %				Yield, %		
Solvent	**7**	**17**	**8**	Solvent	**7**	**17**	**8**
n-C_5H_{12}	56	44	–	$CHCl_3$	47	17	36; X = Cl
$(CH_3CH_2)_2O$	61	39	–	CH_2Cl_2	26	12	62; X = Cl
c-C_6H_{12}	70	30	–	$C(CH_3)_3OH$	64	18	18; X = $OC(CH_3)_3$
CCl_4	70	30	–	$CH(CH_3)_2OH$	22	7	71; X = $OCH(CH_3)_2$



Scheme 6

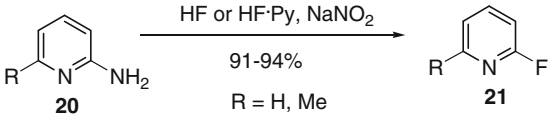
2.2 Synthesis of 2-Fluoropyridines from 2-Aminopyridines

One of the typical examples of the Baltz-Schiemann reaction is synthesis of fluoro-substituted pyridines **19** from aminopyridines **18** [21]. In this variation the Baltz-Schiemann reaction is most often used for the synthesis of 2-fluoropyridines [22]. On the first step a diazonium tetrafluoroborate is generated from 2-aminopyridine, $NaNO_2$ and solution of HF and BF_3 (HBF_4), while subsequent thermal decomposition of the diazonium salt leads to formation of 2-fluoropyridines (Scheme 7). In this part of the chapter examples of synthesis 2-fluoropyridines and illustrations of specific use Baltz-Schiemann reaction for preparation of biologically active derivatives of 2-fluoropyridines are described.



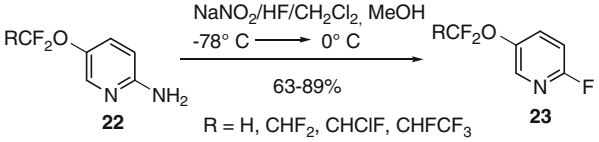
Scheme 7

The reaction has general character. It is applied for the synthesis of various 2-, 3- or 4-fluoropyridines and is full enough described in earlier reviews [1, 3, 4]. Practical use the Baltz-Schiemann reaction for preparation of pesticides or medicines is described in reviews [6, 7]. Several variations of the Baltz-Schiemann reaction allow synthesis of fluorinated pyridines in almost quantitative yields. For example, 2-fluoropyridines **21** were prepared in 91–94 % yields by diazotization of 2-aminopyridines **20** with sodium nitrite in anhydrous HF or HF-pyridine complex [23] (Scheme 8).



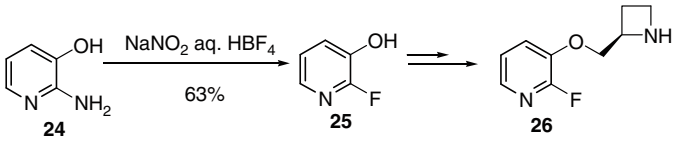
Scheme 8

Substituted 2-fluoro-5-fluoroalkoxypyridines (23) were prepared in good to high yields by diazotization of substituted 2-aminopyridines **22** with $NaNO_2$ in HF. Subsequently they were used as starting materials for the synthesis of some herbicides and insecticides [24] (Scheme 9).



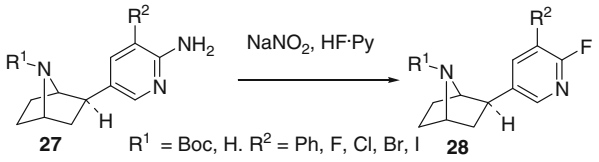
Scheme 9

3-Hydroxy-2-fluoropyridine (25) was prepared from 2-amino-3-hydroxypyridine (24) by diazotization with $NaNO_2$ in HBF_4 solution [25]. Next, compound **25** was used for the preparation of 2-fluoro-3-[2(S)-2-azetidinylmethoxy]pyridine (26), a closely related analog of the high affinity nicotinic ligand A-85380 (Scheme 10).



Scheme 10

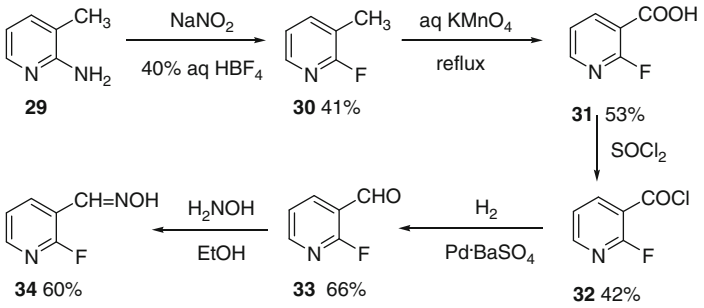
Synthesis of *exo*-2-(2′-fluorosubstituted 5′-pyridinyl)-7-azabicyclo[2.2.1]heptanes (28), novel nicotinic receptor antagonists, was based on diazotization reaction of corresponding 2-aminopyridines **27** using HF-pyridine complex [26–29] (Scheme 11). Classical examples of use of this reaction are resulted in earlier works [23–29]. Now the Baltz-Schiemann reaction continues to use for synthesis fluorinated pyridines.



Scheme 11

2-Amino-3-methylpyridine (29) has been used for synthesis fluorine-containing pyridine aldoximes of potential use for the treatment of organophosphorus nerve-agent poisoning [30]. The Baltz-Schiemann technique was used to convert 2-amino-3-methylpyridine into 2-fluoro-3-methylpyridine (30), subsequent permanganate oxidation of **30** provided acid **31**. Finally conversion of **31** to acyl chloride **32** and Rosenmund reduction resulted in carboxaldehyde **33**. Previously this technique was reported to give poor yields with heterocyclic acyl chlorides. The conversion of **32**

to carboxaldehyde **33** in good yield (66 %) demonstrated that fluoroheterocyclic compounds could undergo facile catalytic reduction by hydrogen in boiling xylene. Carboxaldehyde **33** reacted smoothly with hydroxylamine to provide oxime **34** in 60 % yield (Scheme 12). 2-Fluoropyridine-6-aldoxime was prepared similarly from 2-amino-6-methylpyridine (→ 2-fluoro-6-methylpyridine 39 % → -6-carboxylic acid 50 % → -6-carboxylic acid chloride 72 % → -6-carboxaldehyde 68 % → 6-oxime 71 %) [30].

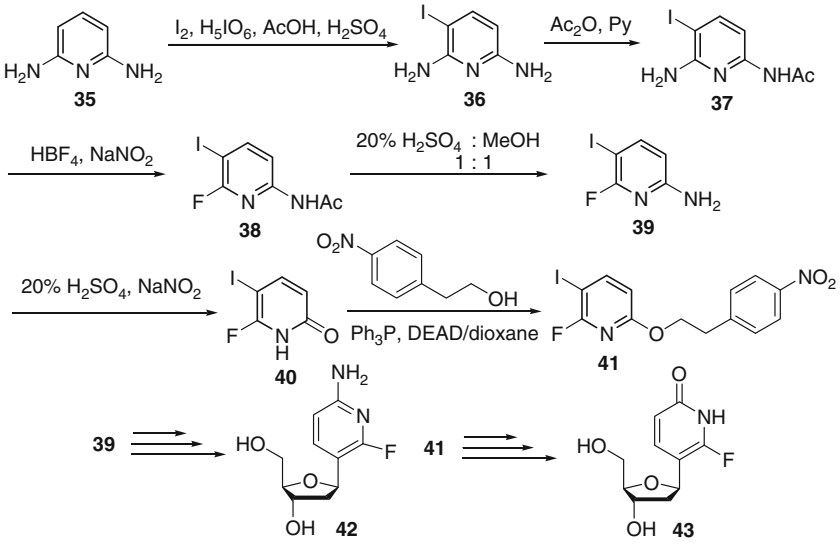


Scheme 12

Recently the Baltz-Schiemann reaction occupies important practical place for synthesis substituted 2-fluoropyridines as an inhibitor and modulators of various kinase [31–33] and other biologically active compounds [1, 2, 34, 35], including F^{18}-pyridines for radiotherapy of a cancer. Nucleoside analogues can be used to investigate a variety of enzyme substrate interactions, including polymerase dNTP recognition or protein-DNA targeting. They can also be incorporated into nucleic acid sequences using conventional synthesis protocols to explore the structural and functional aspects of DNA or RNA. In one class of DNA analogues fluorine replaces the carbonyls and methyl replaces the exocyclic amino groups in the nucleobase heterocycle yielding a hydrophobic isostere of the natural nucleoside with the desired molecular shape [36–38]. Substituted 2-fluoropyridines were recently used in the synthesis of pyridine C-nucleosides as analogues of the natural nucleosides dC and dU [39]. Commercially available 2,6-diaminopyridine (35) was used as the starting material for these synthesis. Compound **35** was fist transformed into the 2,6-diamino-3-iodopyridine (36) which was acylated and then converted into 6-amino-2-fluoro-3-iodopyridine (39), which was transformed into 6-(4-nitrophenyldimethoxy)-2-fluoro-3-iodopyridine (41). Both **39** and **41** were used for the synthesis of nucleosides **42** and **43** [39] (Scheme 13).

2.3 Nucleophilic Substitution in 2-Substituted Pyridines

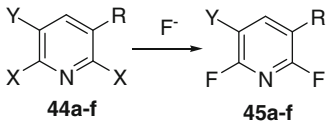
Pyridines containing leaving groups (Hal, R_3N^+, SO_2R, NO_2) in position 2 are often used as starting materials for preparation of 2-fluoropyridines in nucleophilic substitution reactions. Typical nucleophiles are fluorides of alkaline metals, hydrofluoric acid, tetrabutylammonium fluoride, and fluoroboric acid. Although this



Scheme 13

method allows preparation of 2-fluoropyridines in good yields, its main disadvantages include a set of special demands towards fluorine producing reagents, which, if not otherwise met, will significantly reduce the yield of the final products. In majority of all cases these reactions must be conducted in a dry aprotic solvents (DMSO, DMF, THF) with fluoride source introduced as a fine dry powder (normally due to its low solubility of fluorides in these solvents), since the hydration significantly reduces the nucleophilicity of fluoride anion. Dry environment for these reactions is dictated by a very high solvation ratio of the fluoride anion in water, which in its turn significantly increases its steric hindrance and reduces its nucleophilicity. However, in some cases high reactivity of the fluoride anion in water-organic solvent two-phase system can be maintained, for example, using crown ethers [40]. Recently it was shown that bulky *tert*-butanol as a solvent in nucleophilic substitution reactions gives only partially shielded solvates with fluoride anion and actually increases fluoride anion reactivity [40].

It was shown that 2-halopyridines **44** containing chlorine substituent in position 3, can be selectively converted into 2-fluoropyridines **45** by treatment with KF [41] (Scheme 14). The reactions were conducted at elevated temperature (100–200 °C) producing final pyridines **45** in 14–94 % yields (Table 3).

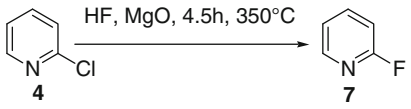


Scheme 14

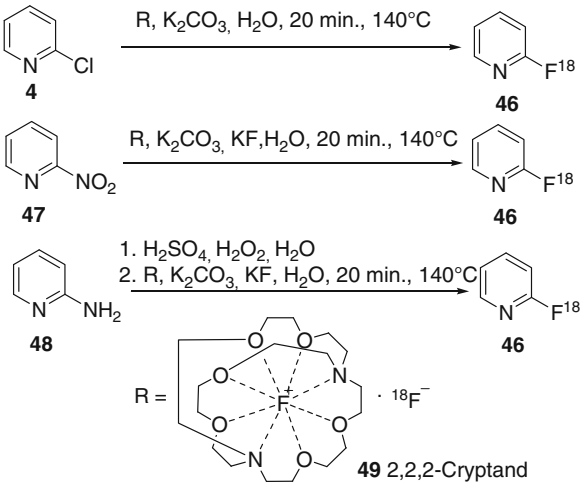
Table 3 Preparation of 2-fluoropyridine **45** [41]

Compound	X	Y	R	Temp. °C	Compound	Y	R	Yield %
44a	Cl	Cl	Cl	200	**45a**	Cl	Cl	76.6
44b	Cl	H	Cl	200	**45b**	H	Cl	72.4
44c	Cl	H	CH_3	200	**45c**	H	CH_3	33
44d	Cl	Cl	CH_3	200	**45d**	Cl	CH_3	69.4
44e	Cl	H	CF_3	200	**45e**	H	CF_3	83–94
44f	Br	H	NO_2	100	**45f**	H	NO_2	14

One-step synthesis 2-fluoropyridine (7) from 2-chloropyridine (4) in HF at temperature 350 °C with use as catalyst MgO is of interest for the industry [42] (Scheme 15). This method is the advanced of three-steps method [43]. For synthesis 2-F^{18}-pyridines (46) reactions of nucleophilic substitution of F-, NO_2- and NH_2-groups by F^{18} are used [44–46] (Scheme 16). The effective reagent – catalyst in synthesis 2-F^{18}-pyridines appeared 2,2,2-Cryptand (49) at the presence of which time of reaction is reduced up to 20 min. It is necessary to note, that 2-F^{18}-pyridines are used in radiobiology of a cancer, and half-life period of F^{18} is equal to 12 h.



Scheme 15

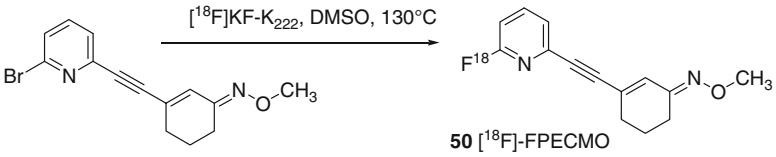


Scheme 16

Fluorination of pyridine by complex AlF_3 and CuF_2 at 450–500 °C forms a mixture of 2-fluoropyridine and 2,6-difluoropyridine in yields 32 and 11 % accordingly [47]. 3-Bromo-2-nitropyridine reacts with $Bu_4N^+F^-$ in DMF at 20 °C to form

2-fluoro-3-bromopyridine. Nucleophilic substitution proceeds highly regioselectively in the second position of pyridine [48]. 5-Amino-2-fluoropyridine used as an epilepsy medicine [49] was it is synthesized from 2-chloro-5-nitropyridine.

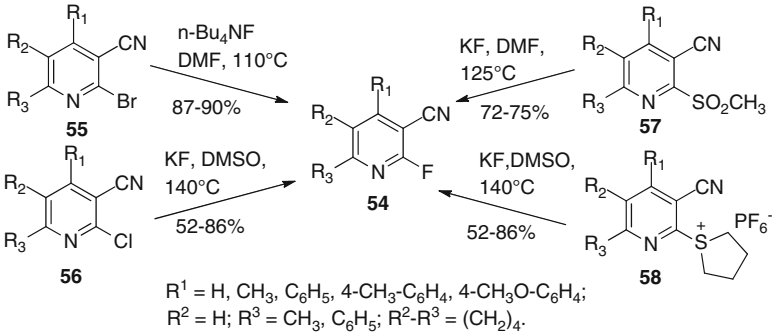
Fluorine-18 labeling and the pharmacological evaluation of a 2-fluoropyridine analog of ABP688, [^{18}F]-(E)-3-((6-fluoropyridin-2-yl)ethynyl)cyclohex-2-enone O-methyl oxime ([^{18}F]-FPECMO) (50), as a potential mGluR 5 imaging agent is described in the work [50]. Compound **50** was synthesized by reaction of nucleophilic substitution with use Kryptofix K_{222} (Scheme 17).



Scheme 17

3-Cyano-2-fluoropyridines are an important class of biologically active compounds that include potent kinase inhibitors, potassium channel inhibitors, and CNS active agents **51–53** (Fig. 1) [51–55]. In addition, fluorinated pyridines can be potentially used as labeling agents for various spectroscopic techniques such as positron emission tomography, X-ray photoelectron spectroscopy, and NMR spectroscopy.

Paper [56] describes the synthesis of 3-cyano-2-fluoropyridines (54) by nucleophilic substitution of 2-nucleofuge-containing substituted 3-cyanopyridines (Scheme 18). This method employs classic sources of nucleophilic fluoride such as KF and Bu_4NF in DMF or DMSO at higher temperatures. The use of chloride and bromide 2-nucleofuges affords 3-cyano-2-fluoropyridines in moderate to good yields. The 2-bromo substituted starting materials (55) present the advantage of being synthesized in one step in good yields, contrary to the 2-chloro-3-cyanopyridines (56) which are prepared in moderate yields. Readily available 3-cyanopyridine-2(1*H*)-thiones have also been C2-fluorinated in good yields via 3-cyano-2-methanesulfonylpyridines (57) and tetrahydrothiophenium (58) salt [56].



Scheme 18

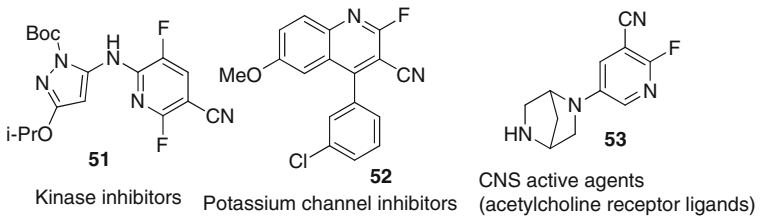
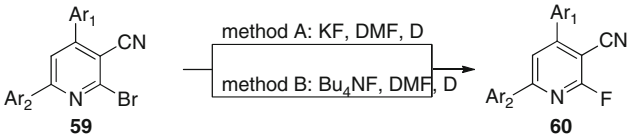


Fig. 1 Examples of biologically active fluorinated pyridines

Substituted 2-bromo-3-cyanopyridines (59) were successfully converted into substituted 3-cyano-2-fluoropyridines (60) (Scheme 19). A nucleophilic replacement of bromine with fluorine was achieved in heated DMF with dry KF (Method A) or with dry TBAF (Method B). The yields of 2-fluoropyridines **60** were 15–20 % higher for Method B [56].



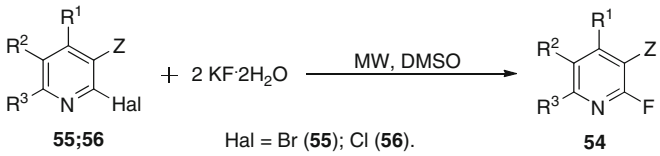
Ar^1	Ar^2	Yield (method A)	Yield (method B)
C_6H_5	C_6H_5	62	90
C_6H_5	4-F-C_6H_4	62	82
4-Cl-C_6H_4	C_6H_5	68	76
4-CH_3-C_6H_4	C_6H_5	76	87
4-CH_3O-C_6H_4	C_6H_5	76	90
2-C_4H_3S	C_6H_5	63	76

Scheme 19

Due to hydration significantly reduces the nucleophilicity of the fluoride anion [1, 56], these reactions are normally conducted in dry aprotic solvents (DMSO, DMF, THF) with the fluoride source introduced as a fine dry powder (due to its low solubility in these solvents). At the same time, reactions of 2- and 4-halopyridines with $KF{\cdot}2H_2O$ or reactions in aqueous solutions were shown to be very slow and incomplete. Although, considerable effort has gone into the development and optimization of anhydrous conditions for the preparation of fluorinated pyridines, to the best of our knowledge, there are no reports on these reactions in untreated reagent grade solvents or in aqueous medium.

Recently it has been shown a practical synthetic approach towards 3-cyano-2-fluoropyrines based on nucleophilic substitution of various leaving groups at the

2-postion of pyridine using "spray-dried" KF or Bu_4NF in dry DMF and DMSO [56]. The developed protocols offered good to high yields of the fluorinated pyridines, however, they suffered from relatively harsh conditions, prolonged reaction times, and the necessity to use anhydrous solvents and reagents. As such, 3-cyano-2-fluoropyridines (54) were obtained from pyridines **55, 56** by heating for 8 h at 140 °C (Scheme 20) (Table 3).



Scheme 20

Being based on fact that microwave irradiation can promote dehydration, nucleophilic substitution reaction using a series of substituted halogen azines under microwave irradiation using readily available $KF{\cdot}2H_2O$ in non-dry reagent-grade dimethylsulfoxide were investigated [57].

2-Bromo(chloro)-3-cyanopyridines (55, 56) were reacted with $KF{\cdot}2H_2O$ in DMSO in a sealed vessel using a focused microwave synthesis system (CEM Discover BenchMate) under continuous stirring [57]. The incubation time was 1.5–4 min with a fixed 300 W microwave irradiation power and a maximum temperature of 120 °C. Under such conditions the highest yields of the target compounds were achieved when the ratio of halogenazine to $KF{\cdot}2H_2O$ was 1:2 (Table 4).

Taking into account that nucleophilic substitution reactions of azines **55, 56** typically do not occur in untreated DMSO and $KF{\cdot}2H_2O$ under traditional heating, it is safe to assume that microwave irradiation promotes dissociation of KF and desolvation of the fluorine anion, which subsequently takes part in the nucleophilic substitution reaction, similarly to "spray-dried" KF in anhydrous DMSO (Fig. 2).

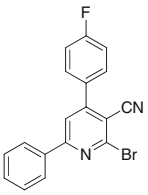
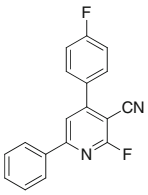
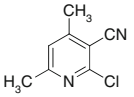
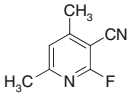
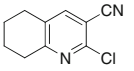
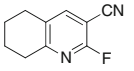
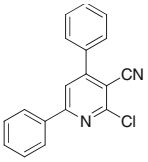
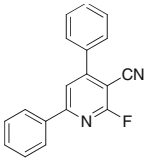
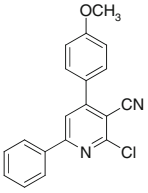
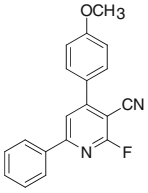
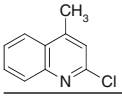
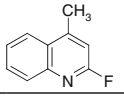
3 Synthesis of 3-Fluoropyridines

3.1 Synthesis of 3-Fluoropyridines from 3-Aminopyridines

The Baltz-Schiemann reaction is frequently used in synthesis substituted 3-fluoropyridine **58**–intermediate for synthesis of biologically active compounds [58–62]. In particular, compound **58** was used for synthesis of compound **59** active against atherosclerosis dyslipidemias [59, 60] (Scheme 21).

2,6-Dibromopyridine-3-diazonium tetrafluoroborate (60) was transformed at heating into 2,6-dibromo-3-fluoropyridines (61), which was used in synthesis inhibitors of Btk (Bruton's Tyrosine Kinaze) (62) [63] (Scheme 22).

Table 4 Structures of starting materials **55, 56** and yields of fluoroazines **54**

Starting material	Reaction product	Yield, %	
		"Spray-dried" KF, anhydrous DMSO, 140 °C, 8 h[56]	KF·2H$_2$O, DMSO, MW 300 W[57]
		–	68
		–	67
		75	78
		52	75
		86	77
		–	75
		–	62[c]

The modified method for the synthesis of 3-fluoropyridine (63) by heating of borofluoropyridines diazonium salts (64) or 3-(diisopropyltriazo)-pyridine (65) in perfluorohexane [64] was recently developed (Scheme 23).

The Baltz-Schiemann reaction was applied for the synthesis of 2-amino-5-fluoropyridine (67) which is a starting material for synthesis pyridothiadiazene 1,1-dioxides (68) acting as AMPA potentiators [65]. 2-Amino-5-fluoropyridine (67) was obtained from 2-amino-5-nitropyridine (66) by row of transformations: acetylation by acetic anhydride to protect a 2-amino group, hydrogenation of nitro group to the amine and then by Baltz-Schiemann reaction enter atom of fluorine and at a final stage removing protection of 2-amino group afforded **67** (Scheme 24).

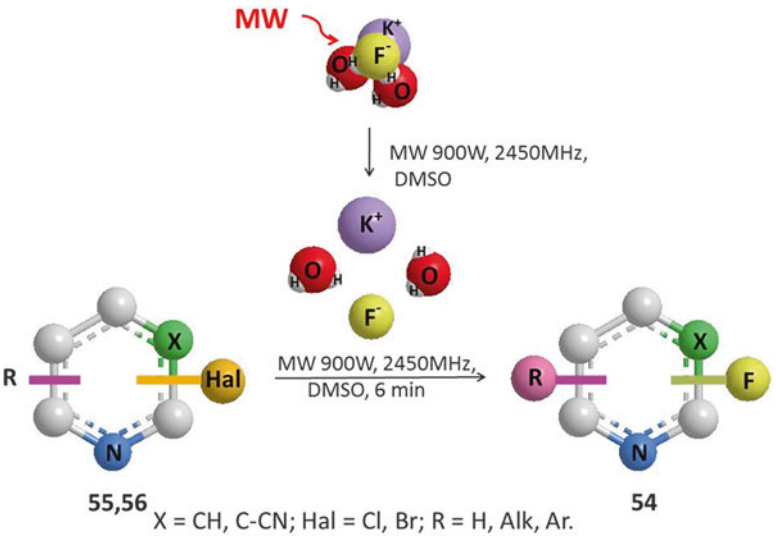
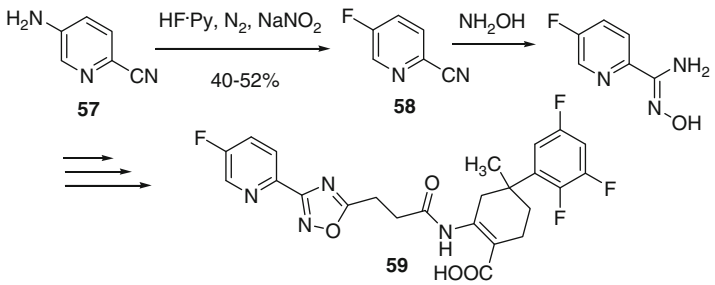
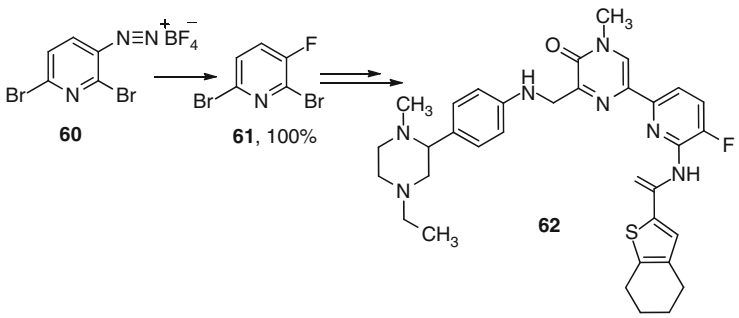


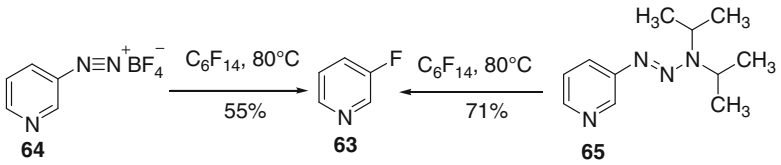
Fig. 2 Desolvation of F^- anion under microwave irradiation



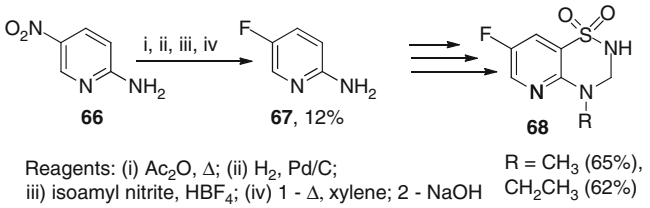
Scheme 21



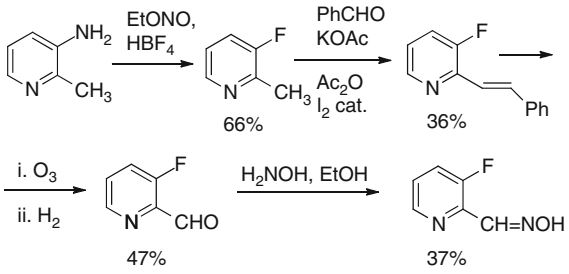
Scheme 22



Scheme 23



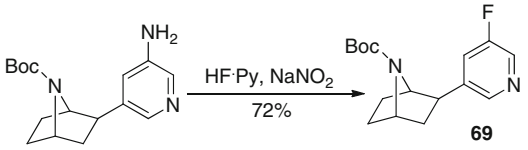
Scheme 24



Scheme 25

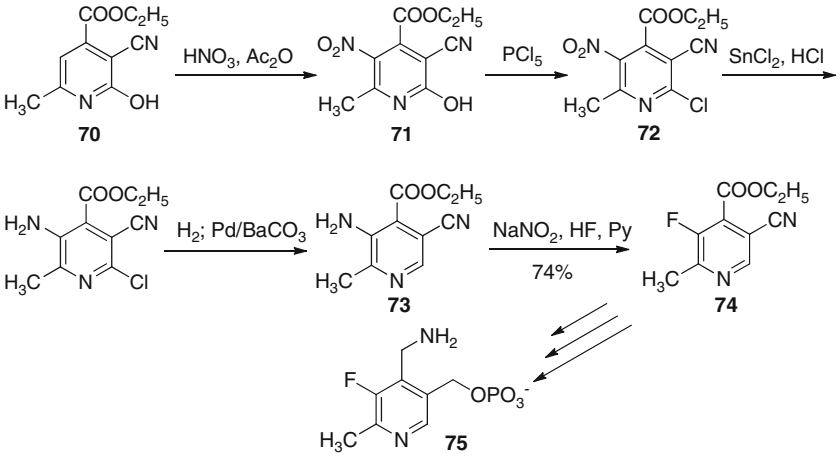
3-Fluropyridine-2-aldoxime was prepared similarly compound **34** from 3-amino-2-methylpyridine [30] (Scheme 25).

The Baltz-Schiemann reaction is the most often used method for the synthesis of 3-fluoropyridines. This method utilizes readily accessible 3-nitropyridies as the precursors; since they can be readily reduced into amines and then used in the Baltz-Schiemann reaction. In this section selected examples applied for the synthesis of practically important compounds are given. For example, the Baltz-Schiemann reaction was used for the synthesis of fluorosubstituted epibatidine analog **69** (epibatidine is a high affinity nonselective ligand for nicotinic cholinergic receptor (nAChRs)) [66] (Scheme 26).



Scheme 26

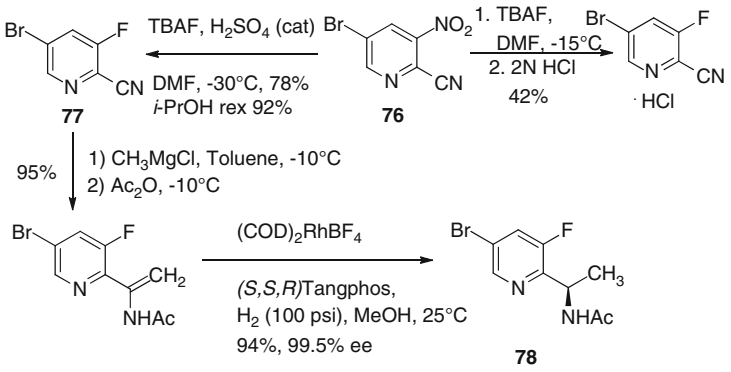
3-Deoxy-3-fluoropyridoxamine 5′-phosphate (75) (a coenzyme B_6 analog) was also synthesized using the Baltz-Schiemann reaction [67]. First substituted pyridine **70** was nitrated to form 3-nitropyridine **71**, which was subsequently treated with PCl_5 to form 2-chloro-5-nitropyridine **72**. It was then reduced in two steps to form 3-aminopyridine **73**, converted into 3-fluoropyridine **74** by the Baltz-Schiemann reaction, and afterwards was transformed into 3-deoxy-3-fluoropyridoxamine 5′-phosphate (F-PMP) (75) (Scheme 27).



Scheme 27

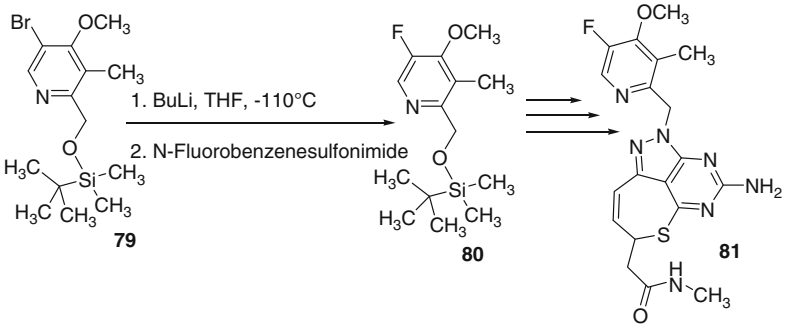
3.2 Substitution Reactions in the Synthesis of 3-Fluoropyridines

The nucleophilic substitution reactions leading to 3-fluoropyridines are rare. Although 2-amino (or buthylthio)-3-aminopyridines do not react with TBAF [68], the introduction of the electron-withdrawing group in position 2 of the pyridine ring in some cases makes possible such transformations. For example, 2-cyano-3-nitropyridine reacts with TBAF forming 2-cyano-3-fluoropyridine in 64 % yield [68]. Similar transformations were reported for 3-substituted-4-carbethoxypyridines, which also undergo nucleophilic substitution at the position 3 of pyridine ring [69]. Potent *Bradykinin B* was synthesized from bromopyridine **77**. This compound was obtained from 5-bromo-2-cyano-3-nitropyridine (76). At the reaction of nucleophilic substitution of NO_2-group the TBAF and H_2SO_4 as the catalyst were used. The further transformations result in compound **78** [70] (Scheme 28). The similar method of synthesis of compound **77** was used in synthesis of biologically active substances [71]. The nucleophilic substitution of NO_2-group by fluorine in compound **76** followed by addition of 2 N HCl results in muriatic 5-bromo-2-cyano-3-fluoropyridine [72].



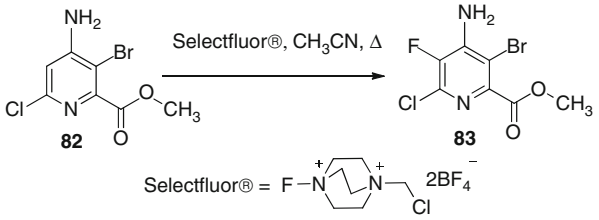
Scheme 28

The replacement of bromine into fluorine in compound **79** was performed in two-steps. Transmetallation with BuLi followed by fluorination of the organolithium compound with N-fluorobenzenesulfonimide resulted in 3-fluoropyridine **80**. It was used as a starting material for synthesis of substituted 6-thia-1,2,3,5-tetraazabenzoazulenes (81) – anticancer medicines [73] (Scheme 29).



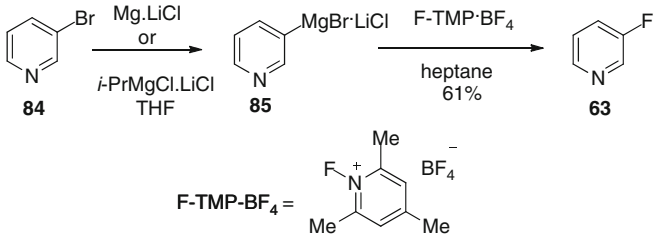
Scheme 29

High yield method for the preparation of substituted 3-fluoropyridines **83** with use Selectfluor® (1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo-[2.2.2] octane bis (tetrafluoroborate)) has been applied in synthesis of compounds possessing by herbicidal activity [74] (Scheme 30). This way allows to incorporate into a molecule atom of fluorine, not touching an amino group and halogens in initial compound **82**.



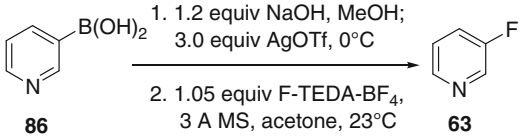
Scheme 30

N-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (F-TMP-BF_4) is also effective fluorinating reagent which have been used in synthesis 3-fluoropyridine (63) from Grignard mediated compound (85) [75] (Scheme 31).



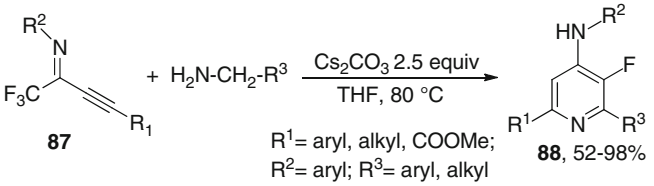
Scheme 31

Wide spectrum of fluorinated aromatic compounds has been synthesized by electrophilic fluorination of arylboronic acids. So 3-fluoropyridine (63) has been obtained from 3-pyridine boronic acids **86** and F-TEDA-BF_4 in 72 % yield [76] (Scheme 32).



Scheme 32

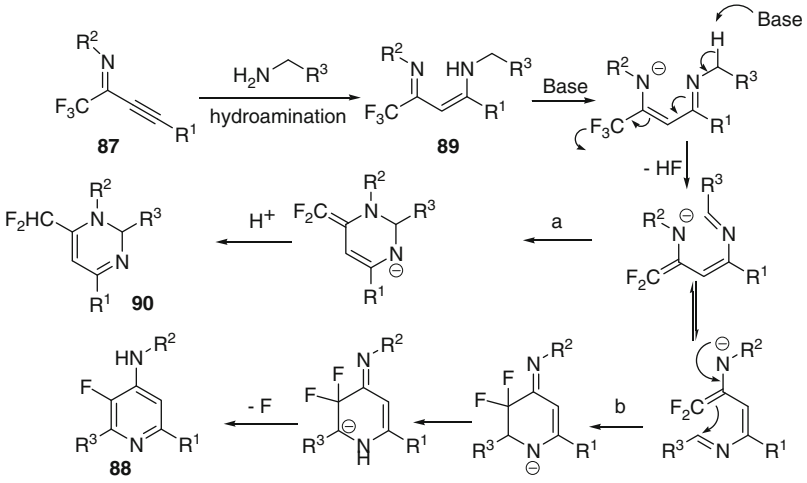
A new strategy for the synthesis of poly-substituted pyridines **88** based on C-F bond breaking of the anionically activated fluoroalkyl group **87** is described (Scheme 33). A series of 2,6-disubstituted 4-amino pyridines were prepared through this domino process in high yields under noble metal-free conditions, making this method a supplement to pyridine synthesis [77].



Scheme 33

A possible mechanism of this transformation includes hydroamination of alkynylimine with amine to form the intermediate vinylogous amidine **89** (Scheme 34), which undergoes deprotonation and dehydrofluorination to generate an anion and

an imine coexisting in one molecule. When the reaction is carried out at a low temperature with a soluble base (path a), the in situ generated amide nucleophile attacks imine immediately without isomerization to form dihydropyrimidine **90** through a kinetically controlled pathway. Raising the reaction temperature (path b), however, makes the carbon nucleophilic addition become an option, rendering a 1,2-dihydropyridine ring under thermodynamic control, which finalizes the pyridine ring after proton migration, β-F elimination, and isomerization, and an insoluble base can effectively inhibit the kinetic pathway.



Scheme 34

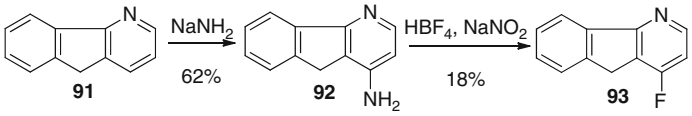
4 Synthesis of 4-Fluoropyridines

In general, the reactivity of the pyridine ring in nucleophilic substitution reaction decreases in the row C2 > C4 > C3. Consequently, more synthetic routes are reported for 4-fluoropyridines compared to 3-fluoropyridines. Pyridines can form cationic complexes with electrophiles resulting in activation of heterocyclic ring towards nucleophilic substitution. On the other hand, pyridines have significantly reduced reactivity towards electrophiles and typically undergo electrophilic substitution reactions in the presence of strong Lewis acids selectively in the position 3 [78].

4.1 Baltz-Schiemann Reaction in the Synthesis of 4-Fluoropyridines

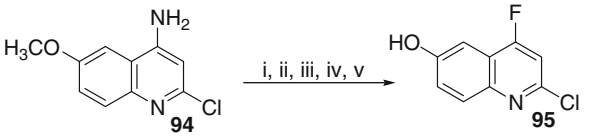
The Baltz-Schiemann reaction can also be used for the synthesis of 4-fluoropyridine derivatives [21, 22, 26–29]. For example, it was successfully applied to the synthesis of 4-fluoroazafluorene [79]. First, 1-amino-4-azafluorene (92) was synthesized

by amination of 4-azafluorene (91) using the Chichibabin reaction and then was converted into 1-fluoro-4-azafluoren (93) in 18 % yield (Scheme 35).



Scheme 35

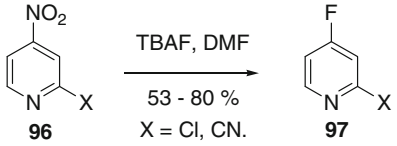
6-Hydroxy-2-chloro-4-fluoroquinolones (95) have been synthesized by Baltz-Schiemann reaction for creation of novel quinolone compounds applied as S-nitrosoglutathione reductase (GSNOR) inhibitors [80] (Scheme 36). 4-Fluoropyridinone synthesized by Baltz-Schiemann reaction from 2-chloro-4-fluoropyridine, it is used in synthesis 4-fluorocytisine [81].



Scheme 36

4.2 Substitution Reaction in the Synthesis of 4-Fluoropyridines

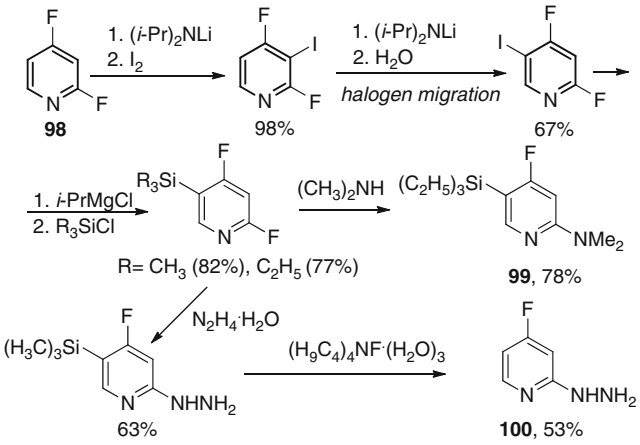
Usually 4-fluoropyridines are synthesized from their nucleofuge-containing precursors by the nucleophilic substitution reaction. For example, 4-nitropyridines **96** react with TBAF in DMF with the formation of substituted 4-fluoropyridines **97** [68] (Scheme 37). This reaction is highly regioselective despite of the presence of relatively good leaving group (Cl or CN) in position 2 of pyridine.



Scheme 37

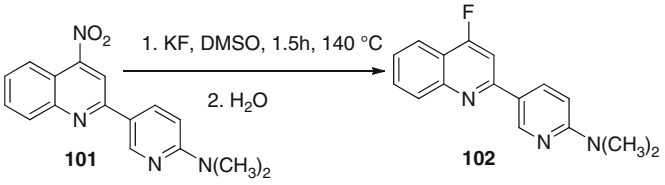
Radiolabeled 4-[^{18}F]fluoropyridine can be synthesized by no-carrier-added nucleophilic aromatic substitution with K[^{18}F]F-K_{222} [82]. In another instances, the nucleophilic substitution reaction was also employed for the synthesis of steroids containing 4-fluoropyridine motif [83, 84], and for the synthesis of 4-fluoropyridines annulated with pyrrole (azoindoles) [85, 86]. Substantial difference in the reactivity

of the pyridinium ring toward nucleophilic substitution in 5-iodo-2,4-difluorpyridine was effectively used for the preparation of 4-fluoropyridines **99, 100** using difluoropyridine **98** as starting material [87] (Scheme 38).



Scheme 38

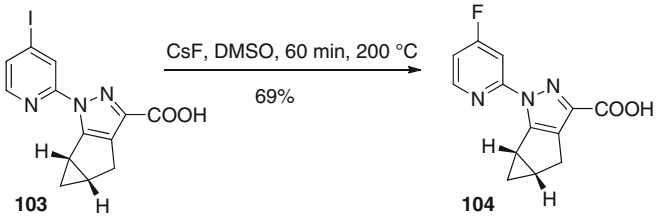
Unsubstituted 4-fluoropyridine has been synthesized by reaction of 4-nitropyridine with Bu_4NF at heating in DMSO [88]. Nucleophilic substitution of NO_2-group in quinolone **101** proceeds with use KF in DMSO at 140 °C (1.5 h) with formation substituted 4-fluoroquinolone **102** in 37 % yield [89] (Scheme 39).



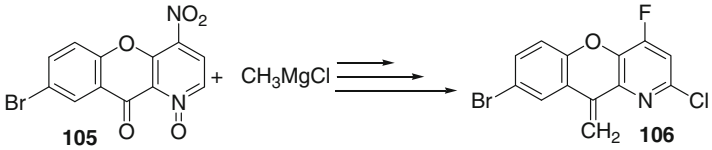
Scheme 39

New anesthetic compound – tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c] pyrazole (104) has been prepared by reaction iodopyridine **103** with CsF in DMSO without change of stereochemistry at rather hard conditions (60 min. at 200 °C) [90] (Scheme 40). Compounds **104** are modulators of receptors of cannabinoids and can be used against a cancer and Alzheimer's and Parkinson's diseases [90].

Compound **106** was obtained by multistep approach including nucleophilic substitution of NO_2 group by F (using Bu_4NF as fluorination agent) in **105** (Scheme 41). Compound **106** is used in synthesis of new drugs against Alzheimer's



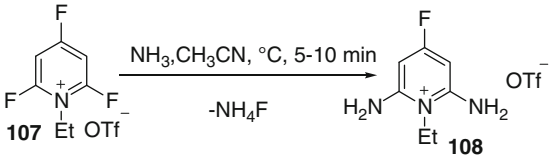
Scheme 40



Scheme 41

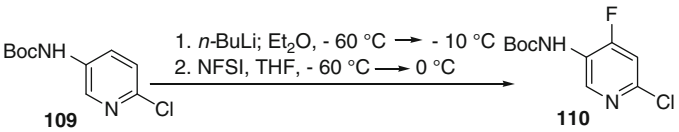
disease, schizophrenia and others [91]. The reaction of nucleophilic substitution used for synthesis of 4-fluoro(pyridines)quinolones as starting materials to obtain new biologically active compounds [89, 92, 93]. It is possible to note, that in various conditions for this reaction have been published, however as a whole this method became classical, that is evidently displayed in reviews [1–4], and also in book of Fainzil'berg and Furin [94].

Monofluoropyridines were obtained also from polyfluoropyridines, using reactions of nucleophilic substitution. N-Ethyl-2,6-diamino-4-fluoropyridinium triflate (108) was synthesized from N-ethyl-2,4,6-trifluoropyridinium triflate (107) by interaction anhydrous ammonia gas in MeCN at 0 °C during 5–10 min. in 72 % yield [95] (Scheme 42). Compound **108** is used for synthesis biologically active 8-fluoro-4-ethyl-4H-bis[1,2,3]dithiazolo[4,5-b:5′,4′-e]pyridine-3-yl [95].



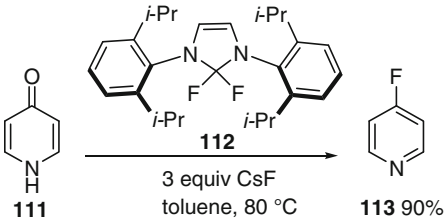
Scheme 42

Substituted 4-fluoropyridine **110** was synthesized from 2-chloro-5-tert-butylcarbonylaminopyridine (109). Treatment of **109** (Scheme 43) with *n*-BuLi followed by quenching with *N*-fluorobenzenesulfonimide (NFSI) gave the desired fluoropyridine **110** in 60 % yield [96]. Compound **110** is used in synthesis a potent, orally active, brain penetrant inhibitor of phosphodiesterase 5 (PDE5).



Scheme 43

New effective deoxyfluorination reagent – N,N-diaryl-2,2-difluoroimidazol (112) was applied for synthesis of fluorinated pyridines from corresponding hydroxypyridines [97]. Fluorination of pyrine-4(1H)-one (111) with compound **112** in toluene at the presence of 3 equivalents of CsF at 80 °C lead to 4-fluoropyridine (113) [98] (Scheme 44). Similarly 3-fluoro- and 2-fluoropyridines were obtained in 84 and 50 % yields accordingly.



Scheme 44

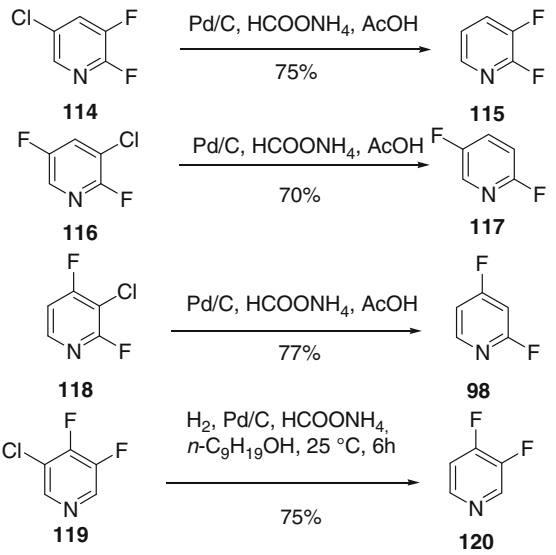
5 Synthesis of Di- and Polyfluoropyridines

In many cases, di- and polyfluoropyridines can be prepared using the same reactions for preparation of monofluorinated analogues. The degree of fluorination in some case can be controlled, however often it leads to mixtures of polyfluorinated compounds. Some polyfluoropyridines can be reduced back to di- or monofluoropyridines, which can be successfully used for a selective synthesis of these compounds.

5.1 Synthesis of Difluoropyridines

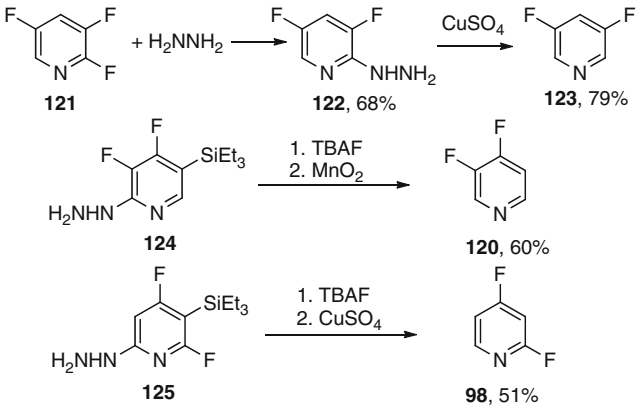
Pentafluoro- and tetrafluoropyridines, which are usually prepared from pentachloropyridine using Halex process, can be used as the starting materials for the synthesis of difluoropyridines [99]. For example, it was demonstrated that pentafluoropyridine can be utilized in the synthesis of substituted 3,5-difluoropyridines, which were investigated as new antithrombotic drugs [100, 101]. However, one of the most commonly used reaction for the synthesis of difluoropyridines is a selective reduction of polyhalogenated pyridines [99]. For example, chlorodifluoropyridines **114, 116, 118** can be reduced to the corresponding difluoropyridines **115, 117** and **98** using palladium on carbon/ammonium formate in 80 % acetic acid. The described reaction is highly

selective and only chlorine atom is getting reduced. Similarly, a catalytic hydrogenation of 3-chloro-4,5-difluoropyridine (119) provided mixture of 3,4-difluoropyridine (120) along with small amount of 3-fluoropyridine (ratio 95:3) [99] (Scheme 45).



Scheme 45

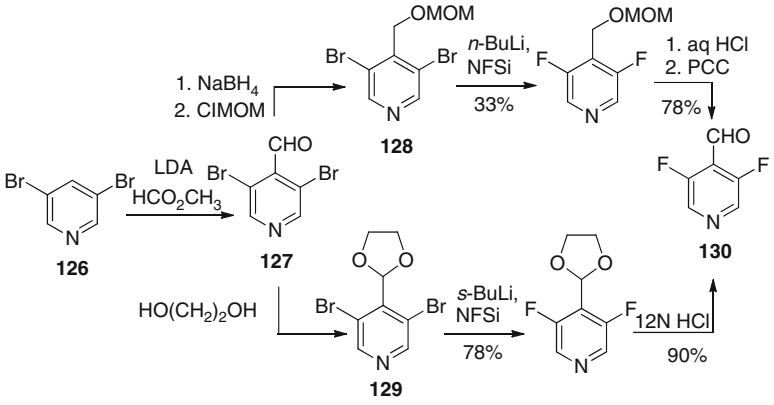
Other possible synthetic route leading to difluoropyridines such as **123, 120** and **98** is based on the reductive deamination of difluoropyridinehydrazines in the presence of $CuSO_4$ or MnO_2 combined with the removal of SiR_3 group [99] (Scheme 46).



Scheme 46

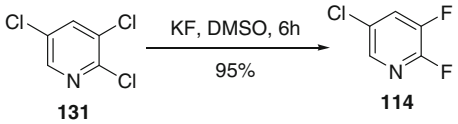
3,4-Difluoropyridine (**120**, 79 %) can be synthesized by the nucleophilic substitution of chlorine in 4-chloro-3-fluoropyridine with KF [99], while, 2,5-difluoropyridine (**117**, 75 %) can be prepared by deamination reaction of 2-hydrazino-3,6-difluropyridine in the presence of NaOH [99].

An interesting example is synthesis of 3,5-difluoropyridine **130** [102]. This compound was prepared from 3,5-dibromo-4-formylpyridine (127) by electrophilic fluorination of its protected forms **128** or **129** by *N*-fluoro-benzenesulfonimide (NFSI) (Scheme 47).



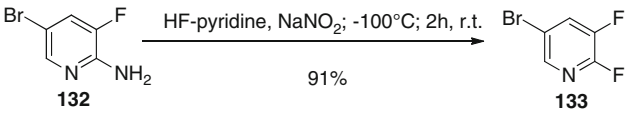
Scheme 47

As it was mentioned, substituted difluoropyridines can be used for the synthesis of monofluorinated pyridines. For example, varied difluoropyridines were converted into monofluoropyridyl-carboxylic acids [103, 104] and hydrazines [79, 105] by the reaction with the corresponding nucleophilic reagents. Reactions of nucleophilic substitution in dichloro-, trichloro- and also trifluoro-or tetrafluoropyridines by waterless KF, Bu_4NF and others nucleophilic reagent most are frequently used for synthesis difluoropyridines. For example, the reaction of 2,3,5-trichloropyridine (131) with KF in DMF proceeds during 6 h at 150 °C to give 5-chloro-2,3-difluoropyridine (114) in 95 % yield [106] (Scheme 48). Similarly compound **114** was obtained using Bu_4NBr in a mixture with KF in 42 % yield [107].



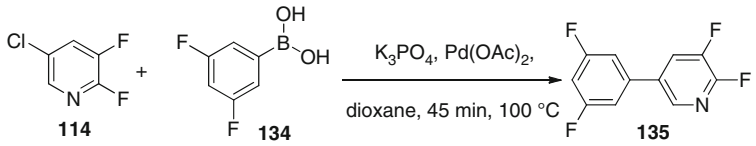
Scheme 48

5-Bromo-2,3-difluoropyridine (133) it is synthesized by Baltz-Schiemann reaction from 2-amino-5-bromo-3-fluoropyridine (132) [108] (Scheme 49).



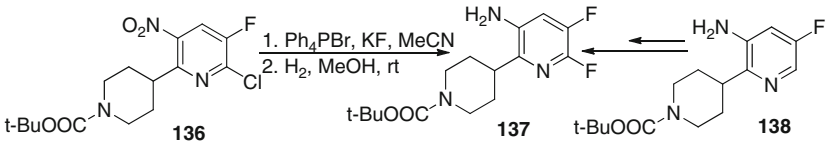
Scheme 49

Reaction of compound **114** with boronic acid **134** resulted in a derivative 2,3-difluoropyridine **135**, used as HGF (Hepatocyde Growth Factor) modulators [109] (Scheme 50).



Scheme 50

Substituted 2,3-difluoropyridine **137** was prepared from 3-fluoropyridine precursor **136** using nucleophilic substitution with KF [110] (Scheme 51). Compound **137** was obtained similarly from substituted 3-fluoropyridine **138** by multistep sequence including chlorination, protection amino group, nucleophilic substitution with KF and removal of protective acyl groups [111] (Scheme 51). Compound **137** is used for synthesis of insecticides [110, 111].



Scheme 51

4- or 5-halosubstituted 2,3-difluoropyridines are widely used for synthesis of biologically active compounds [108, 112–115]. These reactions of nucleophilic substitution are highly regioselective. Various heterocycles containing 2,3-difluoropyridine group **139–143** were synthesized by this method (Fig. 3).

Various polyfluoropyridines have found application in synthesis hardly available difluoropyridines fused with others heterocycles [116]. Reaction of pentafluoropyridine (144) with 2-amino-3-picoline (145) under basic conditions in acetonitrile at reflux or under microwave heating gave only one product – dipyridoimidazole **146** (Scheme 52).

Reaction of 2-amino-3-picoline (145) with 4-phenylsulfonyl-tetrafluoropyridine (147) was less selective than the reactions described above and three major

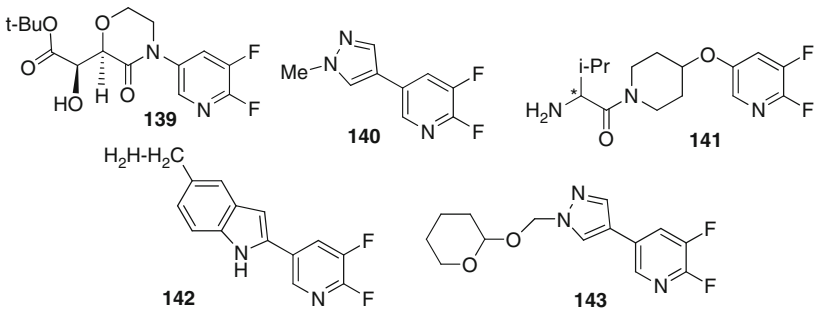
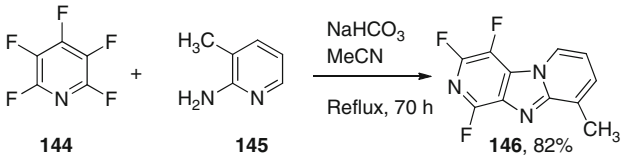
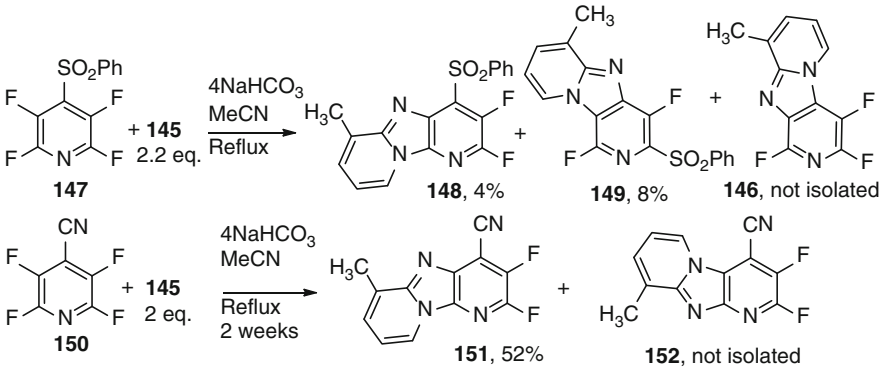


Fig. 3 Derivatives of 2,3-difluoropyridine



Scheme 52

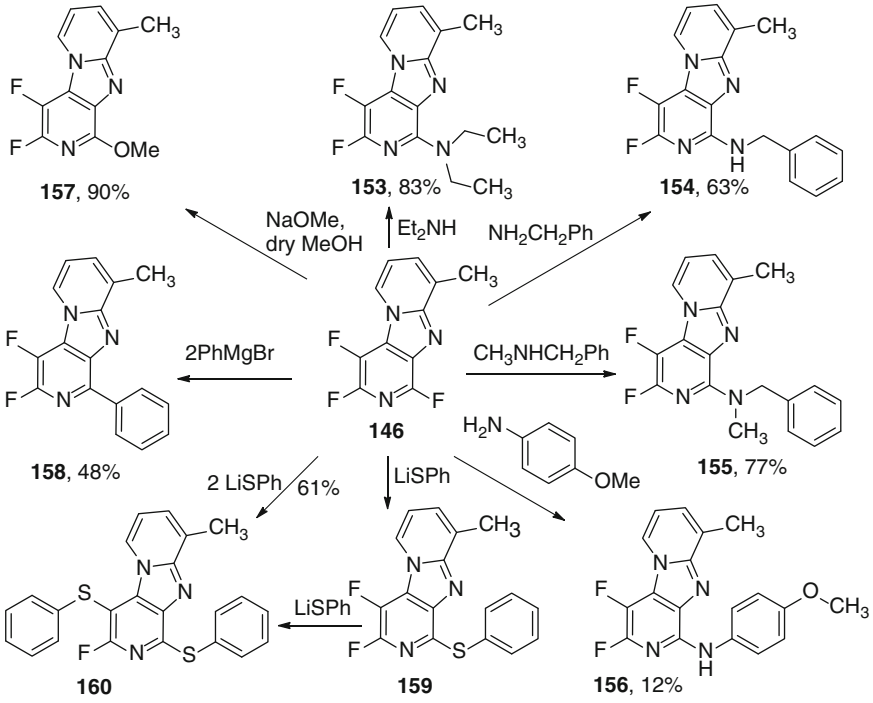
products, **148**, **149** and **146**, were synthesized accordingly ^{19}F NMR. Interaction of 4-cyano-tetrafluoropyridine (150) with 2-amino-3-methylpyridine (145) also resulted in formation a mixture of isomers of dipyridoimidazoles **151, 152** [116] (Scheme 53).



Scheme 53

Various substituted difliorodipyridoimidazoles **153–158** have been synthesized on the basis of obtained dipyridoimidazole **146** [116]. All reactions of **146** with nucleophiles gave products arising from selective displacement of fluorine located at the C-1 position. Reaction with only one equivalent of lithium benzenethiolate

gave the disubstituted derivative **160** as the major product (44 %) arising from displacement of fluorine atoms located at the C-1 and C-4 positions, with only a small amount of the monosubstituted product **159** (2 %). Subsequently, reaction of **146** with two equivalents of lithium benzenethiolate gave high yields of **160** [116] (Scheme 54).

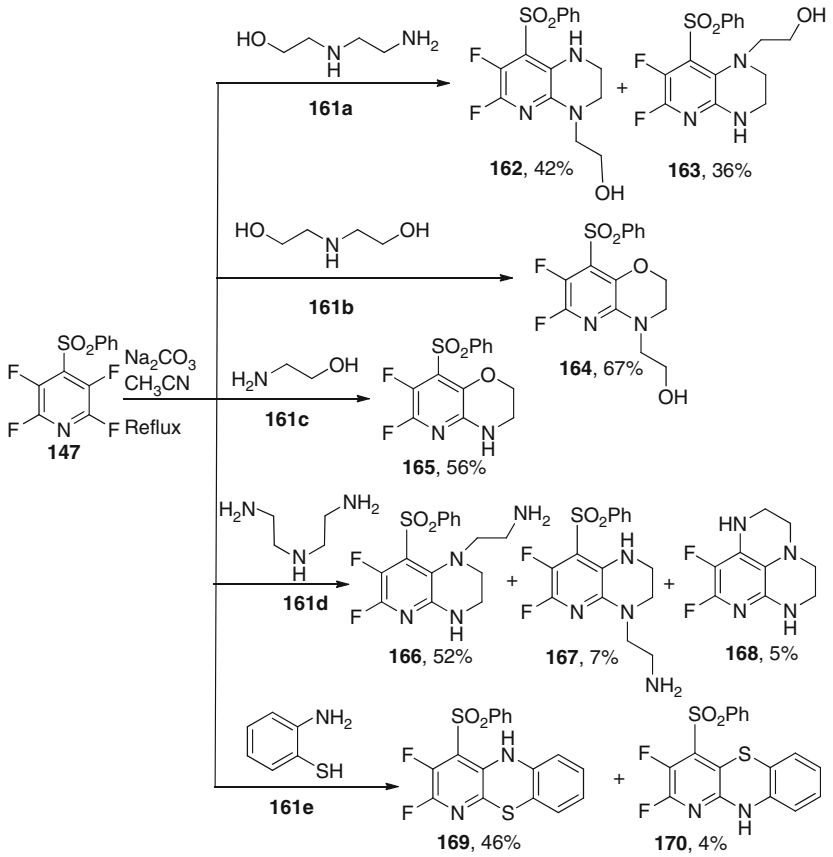


Scheme 54

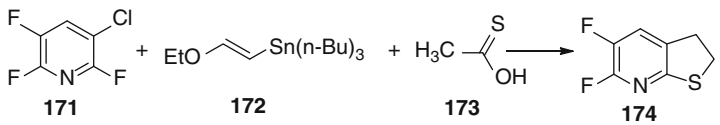
4-Phenylsulfonyl tetrafluoropyridine (147) was used successfully for synthesis difluoropyridines fused with hydrogenated pyridines **162–170** [117]. Synthesis of such compounds is based on reaction double (threefold) nucleophilic substitution of atoms of fluorine (sulfonyl groups) with 1,4-dinucleophiles (161) (Scheme 55).

By reaction of 5-chloro-2,3,6-trifluoropyridine (171) with vinylstannane **172** and monothioacetic acids (173) 5,6-difluoro-2,3-dihydrothieno[2,3-b]pyridine (174) was obtained and used as precursor for synthesis of anticancer drugs [118] (Scheme 56).

Examples of synthesis substituted 2,6-difluoropyridines are not numerous (Scheme 57). 3-Chloro-2,6-difluoropyridine (176) was obtained by interaction 2,3,6- trichloropyridine (175) with KF in sulfolane in 89 % yield [119]. 4-Bromo-2,6-difluoropyridine (178) it is synthesized from symmetric trifluoropyridine (177) [120]. Reaction of 2,6-dichloropyridine (179) with KF at heating in sulfolane at



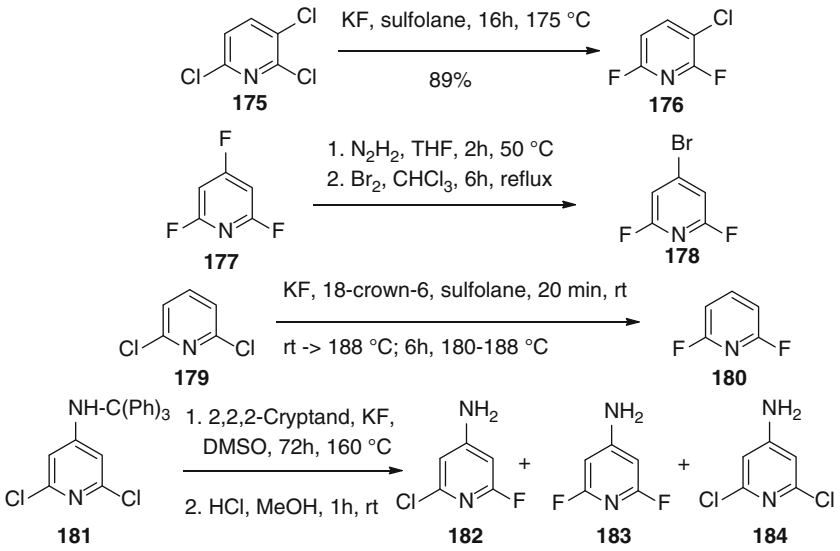
Scheme 55



Scheme 56

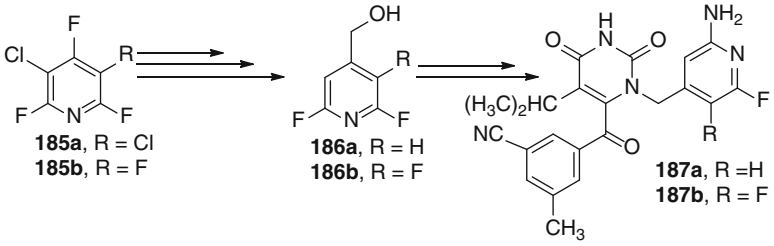
presence of 18-crown-6 give 2,6-difluoropyridine (180) in 78 % yield [121]. Heating of 2,6-dichloro-4-triphenylmethylaminopyridine (181) with 2,2,2-cryptand, KF in DMSO during 72 h give a mixture of compounds **182–184** [122].

Synthesis of substituted 2,6-difluoropyridine – starting materials for generation of potential medicines, is based on use of polyhalogenated pyridines in reactions of nucleophilic substitution. Compound **185a** was transformed successively to



Scheme 57

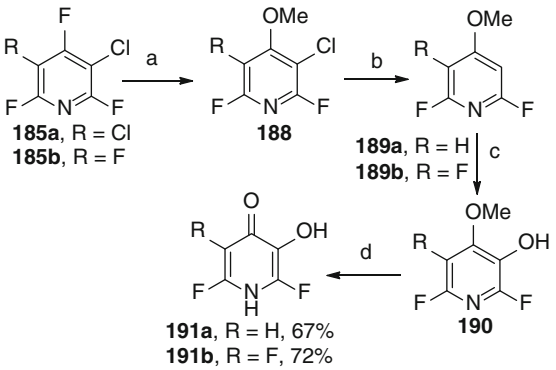
substituted 2,6-difluoro-4-hydroxymethylpyridine (**186a**), which was used in synthesis of HIV-1 non-nucleoside reverse transcriptase inhibitor **187a** [123] (Scheme 58).



Scheme 58

A range of fluorinated 3-hydroxypyridin-4-ones having fluorine or fluorinated substituent attached at 2- or 5- position of the pyridine ring has been synthesized in order to improve biological properties of 3-hydroxypyridin-4-ones. The syntheses of di- and trifluoro-3-hydroxypyridin-4-ones (**191a**) and (**191b**) started from the pentahalo substituted pyridines **185**. Treatment of the commercially available 3,5-dichloro-2,4,6-trifluoropyridine (**185a**) or 3-chloro-2,4,5,6-tetrafluoropyridine (**185b**) with 1 equivalents of sodium methoxide yielded **188** in good yield. Treatment of **188** with 10 % Pd/C at the presence of ammonium formate at 50 °C for 10 h gave

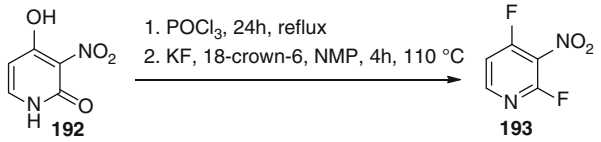
compounds **189** in high yields. Subsequent lithiation, electrophilic substitution, and oxidation as outlined above, introduced a hydroxyl group to afford compound **190**. The 4-methyl protecting group was removed to produce **191a** and **191b**, respectively [124] (Scheme 59).



(a) NaOMe; (b) Pd/C, $HCOONH_4$; (c) (i) LDA in THF at –75 °C for 0.5 h, (ii) $B(OMe)_3$ at –75 °C for 2 h, (iii) CH_3CO_3H at 0 °C for 1 h; (d) BBr_3, overnight

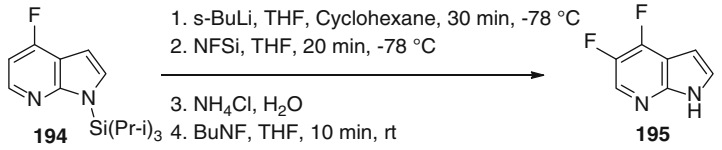
Scheme 59

2,4-Difluoro-3-nitropyridine (**193**) was used for synthesis antibacterial agents. **193** was prepared from 4-hydroxy-3-nitropyridine-2(1H)-on (**192**) by sequential processing with $POCl_3$ and then with KF [125] (Scheme 60).



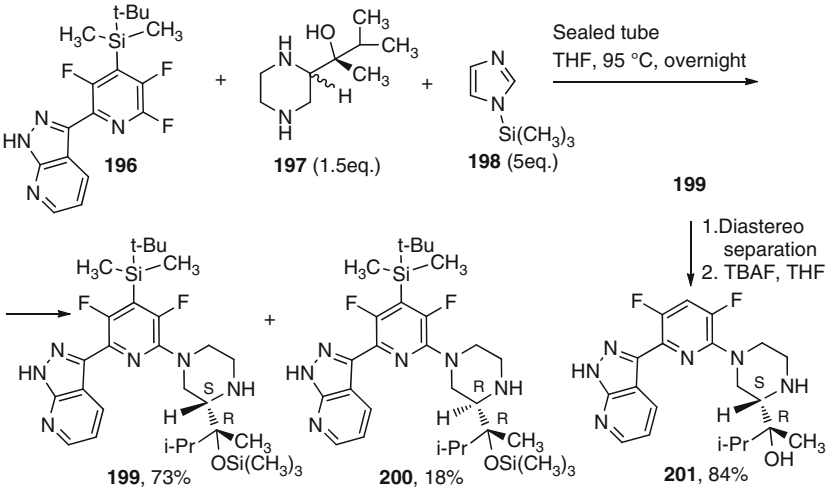
Scheme 60

Sequential reactions of N-substituted 4-fluoroindole **194** with s-BuLi, NFSI and then with Bu_4NF led to 4,5-difluoroindole **195** in 60 % yield. Compound **195** was used as a starting material for synthesis of kinase inhibitors [126] (Scheme 61).



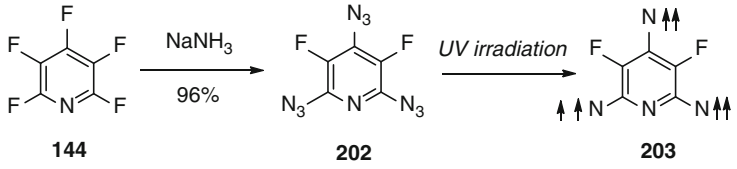
Scheme 61

Pyrazolopyridine kinase inhibitors, containing 3,5-difluoropyridine fragment **201** were prepared by multistep synthesis. Three-component reaction of trifluoropyridylpyridopyrazole (**196**), 3-methyl-2-(piperazin-2-yl)butan-2-ol (**197**) and 1-trimethylsilylimidazole (198) proceeded with formation of a mixture isomers **199** (R, S) and **200** (R, R). The reaction of isomer **199** (R, S) with TBAF in THF gives target compound **201** having (R, S) configuration [127] (Scheme 62).



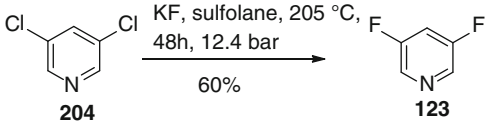
Scheme 62

3,5-Difluoro-2,4,6-triazidopyridine (**202**) has been synthesized by reaction of nucleophylic substitution from pentafluoropyridine (144) and sodium azide [128, 129]. The 3,5-difluoro-2,4,6-trinitren (**203**) has been obtained further from this compound and investigated by IR-spectroscopy [128, 129] (Scheme 63).



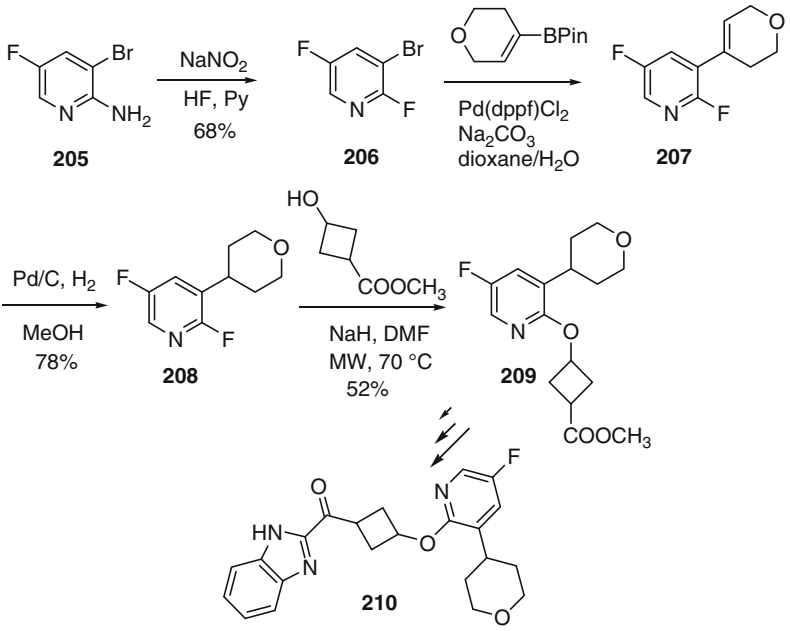
Scheme 63

Nucleophilic substitution of 3,5-dichloropyridine (**204**) with KF led to 3,5-difluoropyridine (123) [130] (Scheme 64).



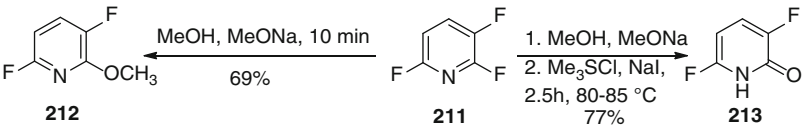
Scheme 64

Substituted 2,5-difluoropyridines **206** are obtained from the corresponding aminopyridines **205** by Baltz-Schiemann reaction, which are used in various areas of organic synthesis, including synthesis of biologically active compounds [108, 131–133]. For example, by few steps reaction 2-amino-3-bromo-5-fluoropyridine (**205**) was converted to biologically active compounds (**210**) by few steps [133] (Scheme 65).



Scheme 65

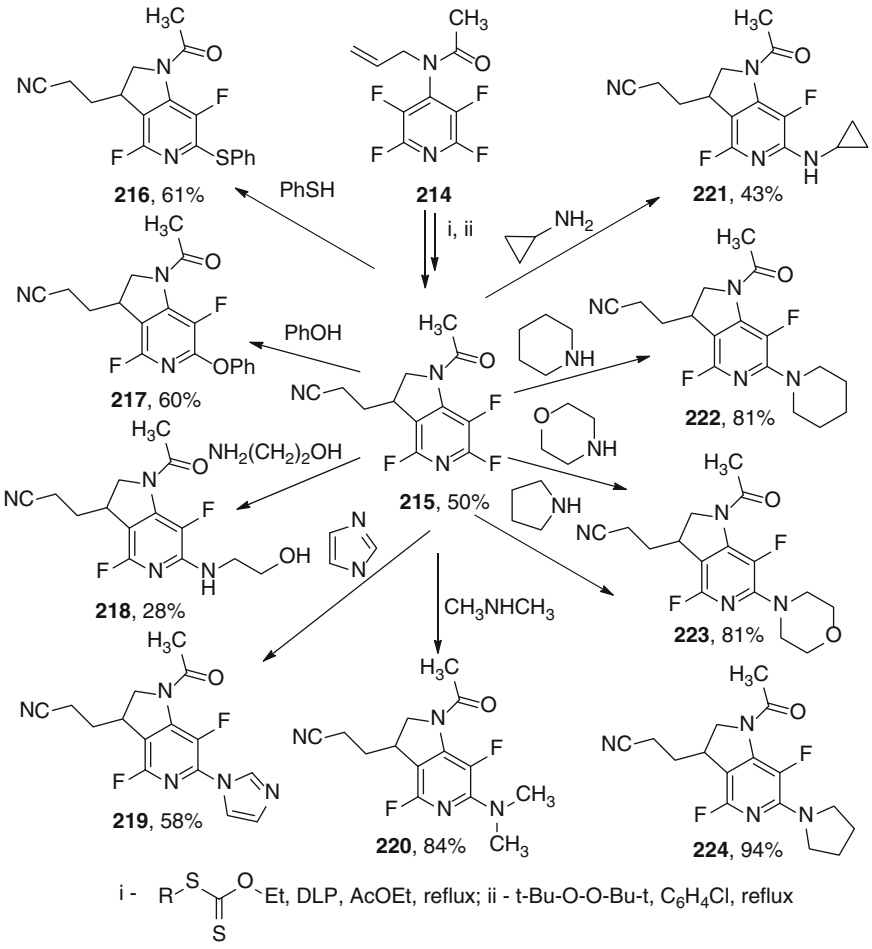
2,3,6-Trifluoropyridines were used for synthesis of substituted 2,5-difluoropyridines. The atom of fluorine which is taking place in the position 2, is most nucleophilic. Therefore, reactions with nucleophilic reagent proceeded highly regioselectively. 3,6-Difluoro-2-methoxypyridine (**212**) has been obtained from 2,3,6-trifluoropyridine (**211**) in methanol at presence MeONa [134–136] (Scheme 66). Pyridine (**212**) was applied in synthesis of antiviral compounds [134].



Scheme 66

3,6-Difluoropyridine-2(1*H*)-one (**213**) has been obtained by reaction of **121** with MeONa in MeOH followed by treatment with Me_3SiCl and NaI in MeCN [136, 137] (Scheme 66).

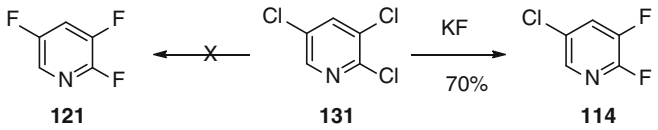
Trifluoroazoindoline **215** has been widely used in reaction of nucleophilic substitution for synthesis substituted difluoroazoindolines **216–224**. The starting compound **215** has been obtained from tetrafluoropyridine **214** by two steps (Scheme 67). It is interesting to note, that pyrrole ring formation at the second step of process proceeds under action of peroxide and explained by the radical mechanism. Nucleophilic substitution with various N-, O- and S-nucleophiles proceeded regioselectively with replacement of atom F in the second position as well as in the previous cases [138].



Scheme 67

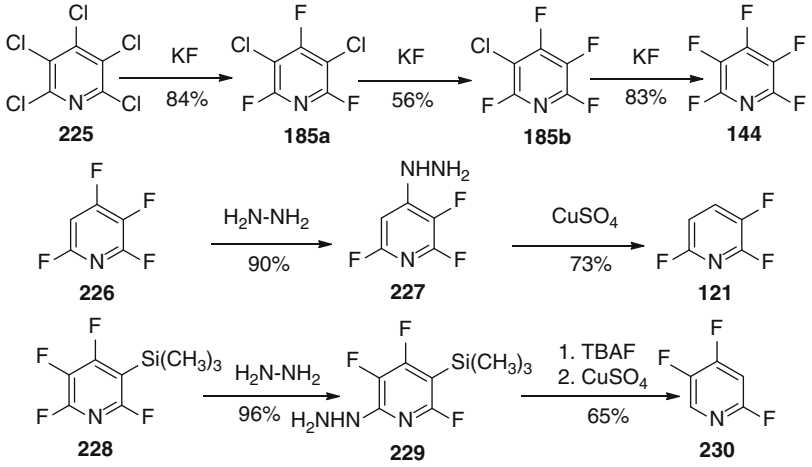
5.2 *Synthesis of Trifluoropyridines and Polyfluoropyridines*

Usually trifluoropyridines are prepared by the reduction or nucleophilic substitution of perhalogenated pyridines [99]. However, the reaction of the corresponding 2,3,5-trichloropyridine (131) with KF (in sulfolane, dimethylpropyleneurea, 220 °C, 16 h) resulted in only partial fluorination and formation of 2,3-difluoro-5-chloropyridine (114) [99]. Attempts to prepare 2,3,5-trifluoropyridine (121) from the corresponding trichloropyridine were unsuccessful (Scheme 68).



Scheme 68

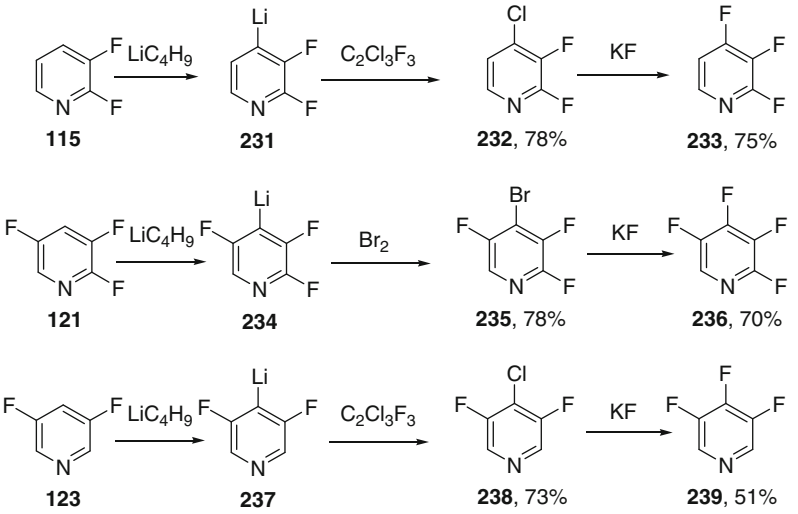
Pentachloropyridine (**225**) was used as the starting material in the reaction with KF, first producing dichlorotrifluoropyridine (**185a**). At higher temperature, this compound was converted into 3-chlorotetrafluoropyridine (**185b**) and then pentafluoropyridine (144) [99]. Tetrafluoropyridines **226, 228** were used in the reduction reactions for the selective synthesis of 2,3,6-trifluoropyridine (121) or 2,4,5-trifluoropridine (**230**) [99] (Scheme 69).



Scheme 69

Various tri- and tetrafluoropyridines **233, 236** and **239** have been synthesized from the corresponding di- and trifluoropyridines **115**, **121, 123.** The starting material was first lithiated by *n*-BuLi and transformed into chlorofluoropyridines **232**,

238 and bromofluoropyridine **238** by the reaction with $C_2Cl_3F_3$ or Br_2. The last step of the synthesis is based on Halex exchange reaction using spray-dried KF in anhydrous DMSO to give corresponding polyfluorinated pyridines **233**, **236**, **239** [99] (Scheme 70).

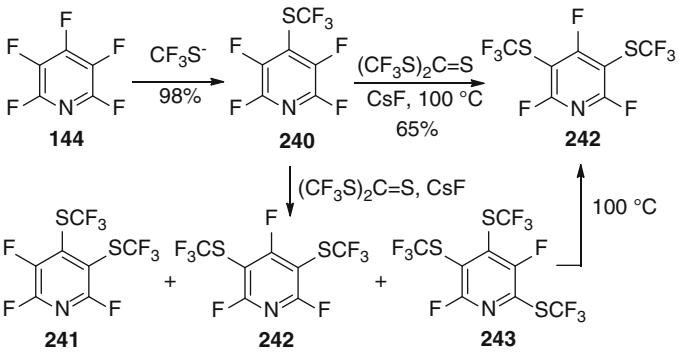


Scheme 70

Mixtures of polyfluorinated pyridines can be obtained from the corresponding pyridines by fluorination with tetrafluorocobaltates (III) [139], this reaction has a low selectivity. For example, the reaction mixture derived from the reaction of pyridine with $KCoF_4$ at 220 °C is reported to contain more than seven fluoropyridines, two fluoro-2-azahexenes, three azahexadienes, and two fluoro-N-methylpyrrolidines. Four fluorinated products were isolated from a fluorination of pyridine by CoF_3 at 150 °C: a 2-azahexene, two *N*-methylpyrrolidines and 4*H*-nona-fluoropiperidine [140].

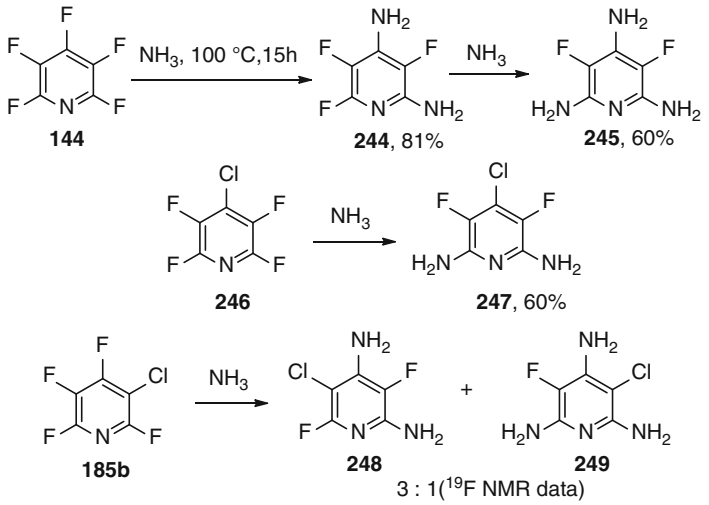
2,3,5,6-Tetrafluoro-4-trifluoromethylthiopyridine (**240**) was prepared in high yield by the reaction of pentafluoropyridine (144) with the CF_3S^- anion, generated from $F_2C{=}S$ or its trimer, and cesium fluoride at –15 °C [139] (Scheme 71). When the trimer was used as a precursor of the CF_3S^- anion compound **240** reacted further at 20 °C to give a mixture of polysubstituted pyridines **241–243** in the ratio of 4.5: 2: 1, respectively. When the reaction mixture was then heated at 100 °C both compounds **241** and **243** were fully converted into compound **242**. Compound **242** was the only product (65 %) of the reaction which was carried out at 100–110 °C [141] (Scheme 71).

Pentafluoropyridine (144) was applied for the synthesis 2,4-diamino-3,5,6-trifluoropyridine (**244**) [142]. Thus double nucleophilic substitution of fluorine atoms in 2 and 4 positions of the pyridine **144** occurred to give **244**. The same



Scheme 71

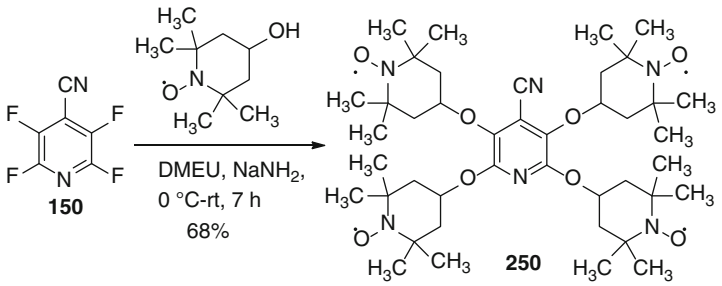
reaction of nucleophilic substitution with 4-chloro-2,3,5,6-tetrafluoropyridine (**246**) or 3-chloro-2,4,5,6-tetrafluoropyridine (**185b**) results to diamino-difluoropyridines **247** or mixture of isomers of diaminodifluoropyridine **248** and triaminofluoropyridine **249** [142] (Scheme 72).



Scheme 72

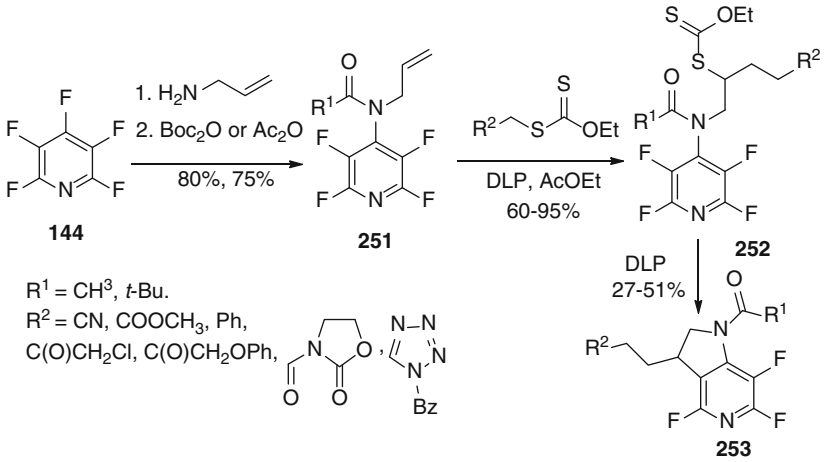
The scope and limitation of the synthesis of polynitroxides (**250**) by nucleophilic substitution of electron-deficient fluorinated pyridines was described [143] (Scheme 73). The method provided a facile route to the formation of polynitroxides exhibiting strong electron exchange between nitroxide groups.

The tendency perfluoropyridines to nucleophilic substitution is widely used in synthesis fluorinated and fused pyridines. In most cases the first nucleophilic



Scheme 73

substitution proceeds at 4 or 2 positions, sometimes at once 2,4-disubstituted trifluoropyridine is formed. Selective double substitution is used for synthesis fluoroazoindoles **253,** through intermediate **251, 252** [144] (Scheme 74).



Scheme 74

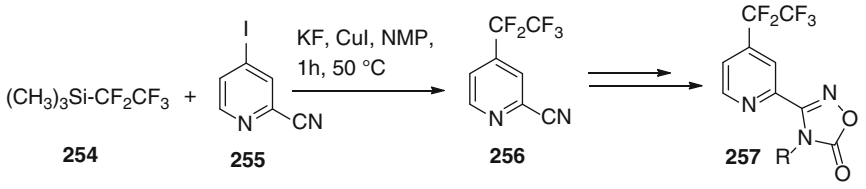
Various compounds benzothieno(furano)pyridines [145], 4-cyclopentadienylpyridines [146], 4-phenoxypyridines [147], 4-acetylenepyridines [148], furano[2,3-b]pyridines [149], 4-aminopyridines [150], bistetrafluoro-4,4′-pyridine [151] and others practically important pyridines [152–155] were obtained by the reaction of nucleophilic substitution.

6 Synthesis of Perfluoroalkylpyridines

Perfluoroalkylpyridines have reliably come in synthetic practice. These compounds are components of molecules applied as medicines, pesticides, dyes and other practically important compounds [1–3, 21].

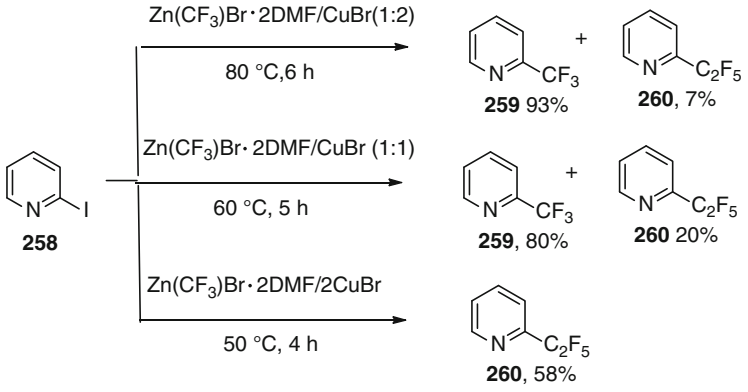
6.1 Substitution Reaction

Various perfluoroalkylhalides, perfluoroalkylsilanes and also fluorinated organometallic compounds were used most frequently for reactions of substitution. Pentafluoroethyltrimethylsilane **(254)** reacts selectively with 2-cyano-4-iodopyrydine (**255**) at presence KF and CuI in NMP to form substituted 4-pentafluoroethylpyridine (**256**) which is used for synthesis of pesticides **257** [156] (Scheme 75).



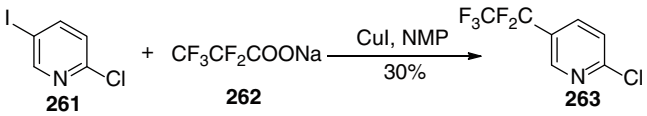
Scheme 75

2-Trifluoromethylpyridine (**259**) and 2-pentafluoroethylpyridine (**260**) were obtained by the reaction of 2-iodopyridine (**258**) and tri- and pentafluoroethylcooper at heating in DMF Trifluoromethylcopper and pentafluoroethylcopper are prepared conveniently via the reaction of the solid complex $Zn(CF_3)Br{\cdot}2DMF$ with copper(I) bromide in N,N-dimethylformamide (Scheme 76). The maintenance of trifluoromethyl- and pentafluoroethyl derivatives was determined by ^{19}F NMR spectroscopy in both the mixtures [157].



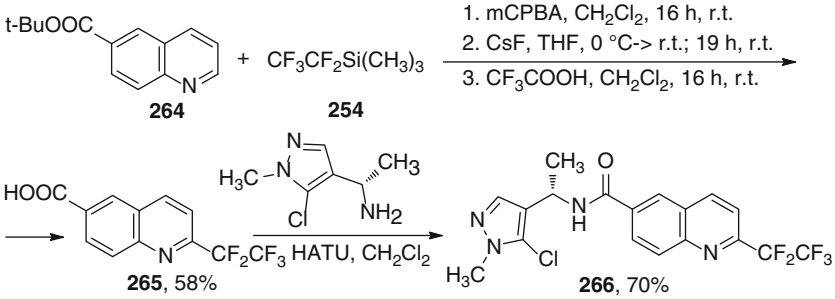
Scheme 76

Reaction of 2-chloro-5-iodopyridine **(261)** and sodium pentafluoropropionate (**262**) at presence CuI in NMP resulted in 2-chloro-5-pentafluoroethylpyridine (**263**) in 30 % yield [158] (Scheme 77).



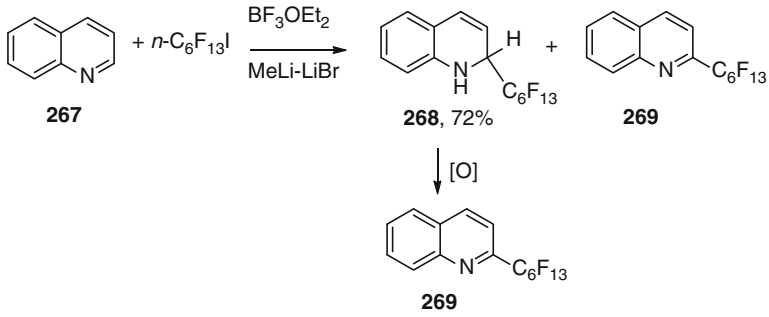
Scheme 77

Pentafluoroethylquinoline **265** was obtained by the reaction of pentafluoroethyltrimethylsilane **(254)** with substituted quinoline **264** [159]. Compound **265** was a precursor for the synthesis of **266** as VR1 receptor for treating pain, inflammation and other diseases (Scheme 78).



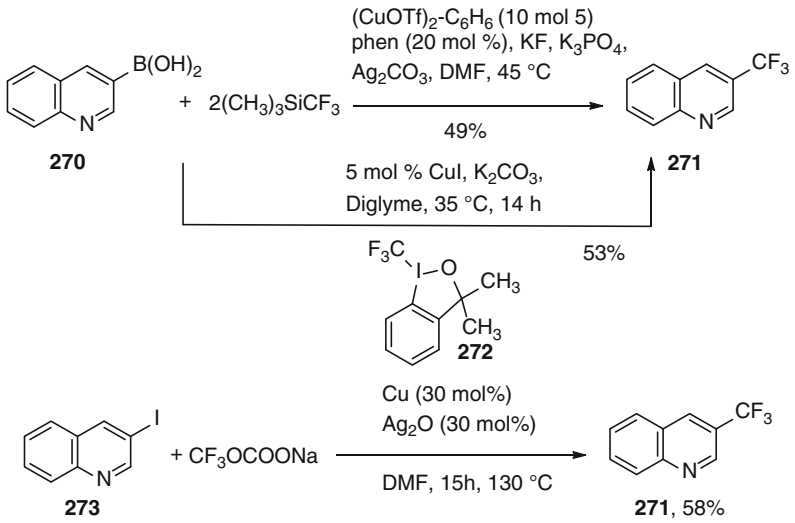
Scheme 78

2-Perfluorohexyl-1,2-dihydroquinoline (**268**) was obtained in 72 % yield together with trace amounts of 2-(periluorohexyl)quinoline (**269**), the latter being formed by the autoxidation of **268**. The perfluoroalkylation was improved up to 90 % yield by using 2 equiv. each of pertluorohexyl iodide, boron trifluoride, and methyllithium-lithium bromide. The autoxidation of dihydroquinoline **268** was complete in chloroform after 2 days and **269** was obtained quantitatively [160] (Scheme 79).



Scheme 79

Some articles have described synthesis of 3-trifluoromethylquinoline (**271**) [161–165]. Catalytic oxidative trifluoromethylation of 3-qunolineboronic acid **(270)** resulted in 3-trifluoromethylquinoline in 49 % yield [161]. Use Togni's reagent **(272)** in reaction with boronic acids **270** resulted in increase yield of **271** up to 53 % [162]. 3-Trifluoromethylquinoline was also obtained by reaction of boronic acids **270** with CF_3I [163] or with trifluoromethyl sulfonium salts [164] in 87 % yield. Interaction of 3-iodoquinoline (**273**) with sodium trifluoromethyl formate at presence Cu and Ag_2O also led to compound **271** [165] (Scheme 80).

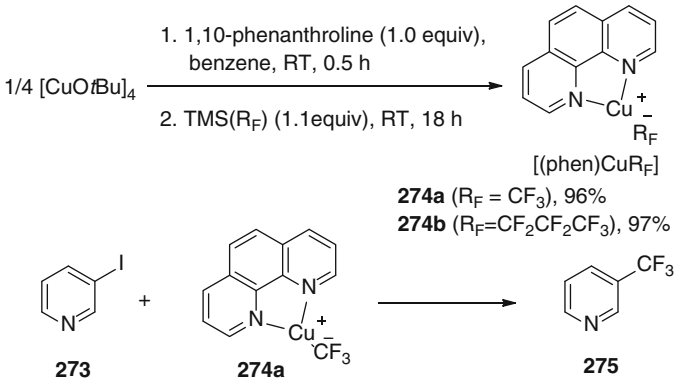


Scheme 80

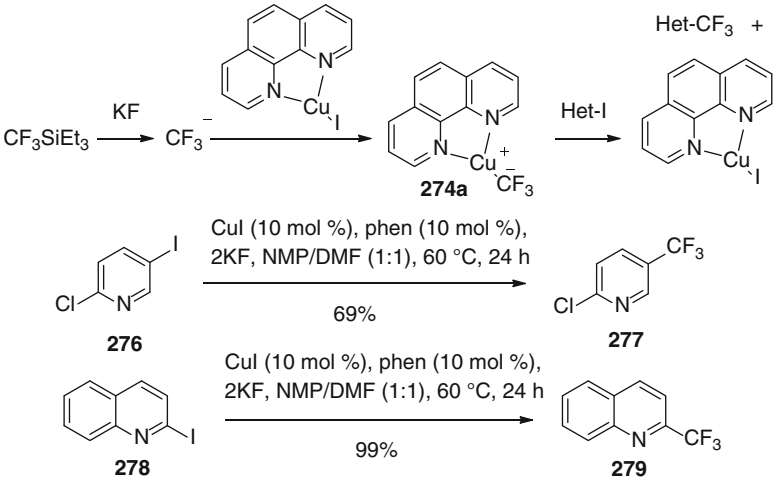
Convenient reagents for incorporation of perfluoroalkyl groups in a molecule of pyridine are 1,10-phenanthroline-ligated (perfluoroalkyl) copper (I) complexes **274** [166], which were obtained by reaction of copper 1,10-phenanthroline complex with Ruppert reagent and its C_2F_5-analog. The 1,10-phenanthroline complex **(274a)** has been used in reaction with 3-iodopyridine **(273)** for synthesis 3-trifluoromethylpyridine **(275)** [167, 168] (Scheme 81).

Cu(I)-diamine complexes were found to catalyze the trifluoromethylation of other heterocycles. In the presence of a small amount of CuX (X = Cl, Br, I) and 1,10-phenanthroline, the cross-coupling reactions of iodoazines with trifluoromethylsilanes proceeded smoothly to afford trifluoromethylated azines in good yields [169]. For example, trifluoromethylazines **277, 279** have been synthesized in good yields [169] by such method from iodoazines **276, 278** (Scheme 82).

The corresponding trichloromethylazines **280** are frequently used for synthesis trifluoromethylazines **281** (pyridine, quinoline, phenantroline and others.). SbF_3, SbF_5, liquid HF or their mixtures can be used for chlorine-fluorine replacement

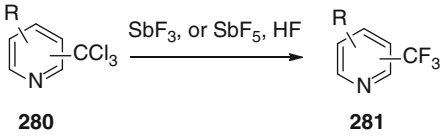


Scheme 81



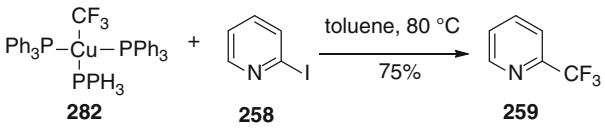
Scheme 82

[170–173] (Scheme 83). Trifluoromethylazines **281** are formed by this method usually in good yield.



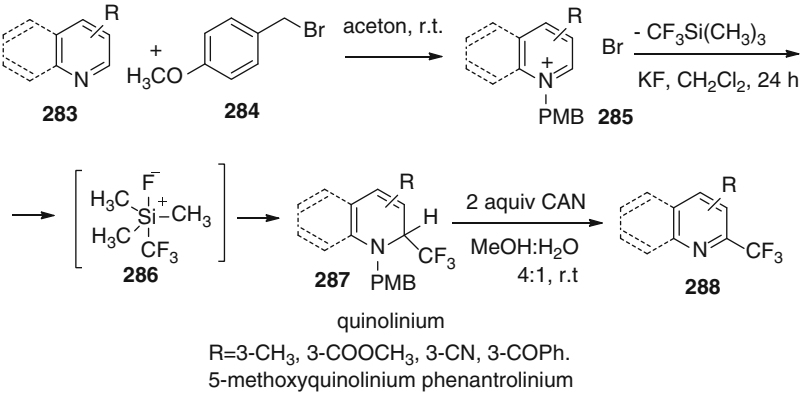
Scheme 83

Interaction of complex **282** obtained from copper difluoride, trifluoromethyltrimethylsilane and three moles of PPh_3 with 2-iodopyridine (**258**) led to 2-trifluoromethylpyridine (**259**) in 75 % yield [174] (Scheme 84).



Scheme 84

Ample opportunities are opened with synthesis of trifluoromethylated azines via oxidative nucleophilic substitution of hydrogen by trifluoromethyl carbanions [175]. This pathway to the synthesis of trifluoromethylazines includes reaction of quaternization of azines **283** by p-methoxybenzylbromide (PMB) (**284**) to obtain salts **285**. Further KF is added to reaction mixture of salt **285** and $CF_3Si(CH_3)_3$ to generate anion **286**. Regioselective trifluoromethylation results in formation of 1,2-dihydropyridines **287** which then have been oxidized by action CAN to get appropriate trifluoromethylazines **288** (Table 4) [175] (Scheme 85). Regioselectivity of the reactions is determined by the nature of substituent at pyridine's cycle. So in case of an ether of nicotinic acid and 3-benzoylpyridine the mixture of 2-and 6-trifluoromethylpyridines are formed (Table 5).

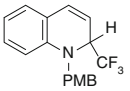
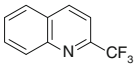
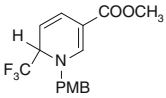
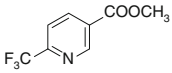
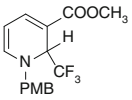
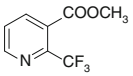
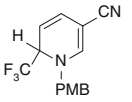
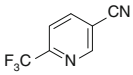
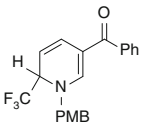
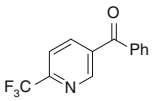
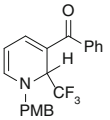
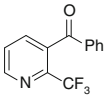
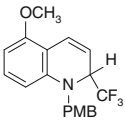
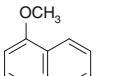


Scheme 85

6.2 *Synthesis of Perfluoroalkylpyridines Based on Cyclization Reactions*

Reactions of cyclization are widely used for synthesis hardly available multifunctional perfluoroalkylpyridines [2, 3, 176]. As a rule, these reactions proceed regioselectively and in good yields. A perfluorocarbonyls, 1,3-dicarbonyls, α,β-unsaturated carbonyl compounds and enamines are basic raw material for this synthesis [2, 3, 176]. For example, condensation of trifluoromethyl substituted 1,3-dicarbonyl compounds **289** with cyanacetamide (**290**) proceeds highly regioselectively to form substituted 4-trifluoromethylpyridine-2(1H)-ones (**291**) [2, 3, 176–179]. 1,3-Dicarbonyl

Table 5 Aromatization of 2-Trifluoromethyl-1,2-dihydroazines **287**

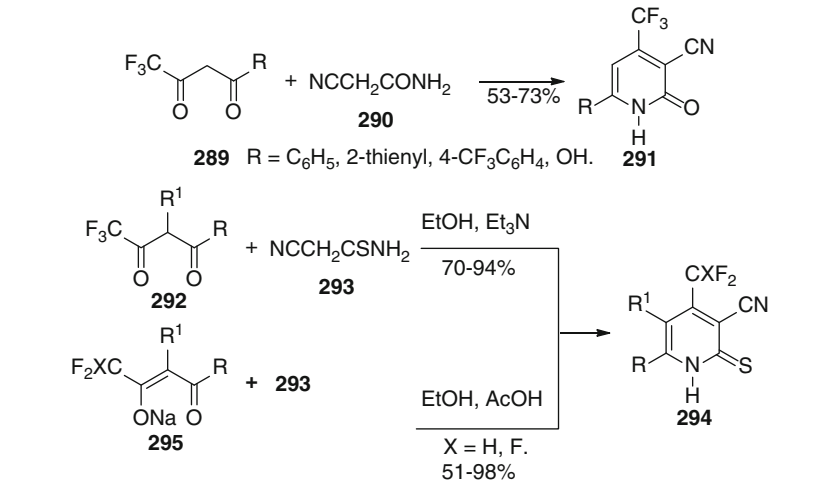
Substrate **287**	Product **288** (yield)		Overall yield for three steps	Total yield of two isomers
		(77 %)	59 %	
		(79 %)	32 %	46 %
		(47 %)	14 %	
		(62 %)[a]	18 %	
		(91 %)	40 %	62 %
		(60 %)	22 %	
		(90 %)	68 %	

[a]DDQ was used it stead of CAN (2.2 equiv. of DDQ, CH_2Cl_2, 0 °C to rt)

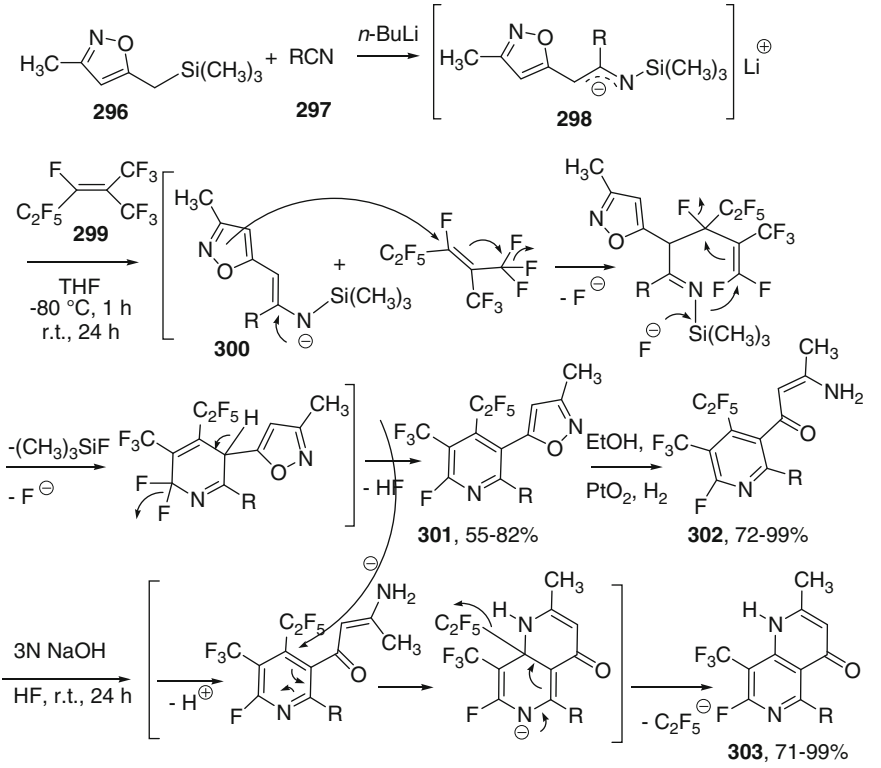
compounds **292** and cyanthioacetamide **(293)** are used for synthesis substituted 4-trifluoromethylpyridine-2(1H)-thiones **294** [180–182]. More simple and convenient way of synthesis of compounds **294** is based on use of sodium salt of 1,3-dicarbonyl compounds **295** and cyanthioacetamide **(293)** [183]. Thus isolation and purification of 1,3-diketones **292** is not required. As a whole, synthesis of 4-three(di)fluoromethylpyridine-2(1H)-thiones **294** from sodium salts **295** and **293** proceeded highly regioselective in good yields (Scheme 86).

New method for synthesis 7-fluoro-8-(trifluoromethyl)-1H-1,6-naphthyridines **(303)** is based on intermolecular cyclization of N-silyl-1-azaallyl anion **(298)** with perfluoroalkylethylenes **299** [184] (Scheme 87).

Reaction of aniline **(304)** and ethyl trifluoroacetoacetate **(305)** resulted in formation of 4-trifluoromethylquinolin-2-one **(306)** from which 2-brom-4-trifluoromethylquinoline **(307)** was synthesized further. Reaction of compound **307** with pyridines **308** at the presence of a palladium complex as the catalyst resulted in quinoline ligands **309** [185] (Scheme 88).

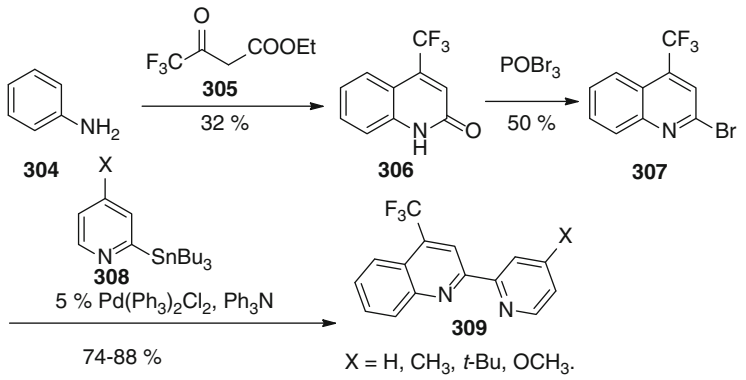


Scheme 86



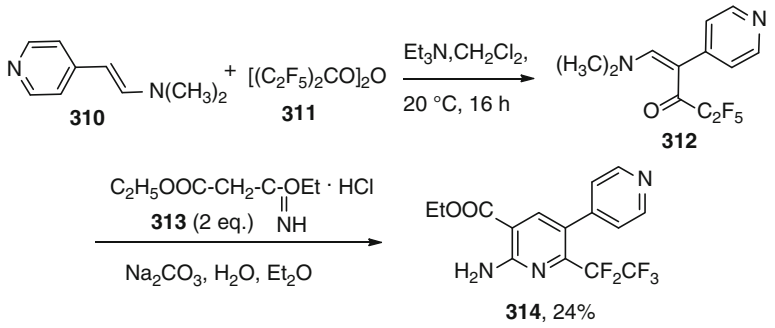
R = 4-CH_3-C_6H_4, 4-CH_3O-C_6H_4, 4-$(CH_3)_2N$-C_6H_4, 4-Cl-C_6H_4, 4-CF_3-C_6H_4, 2-Py, 4-Py, Et, CH_3-O-CH_2-.

Scheme 87



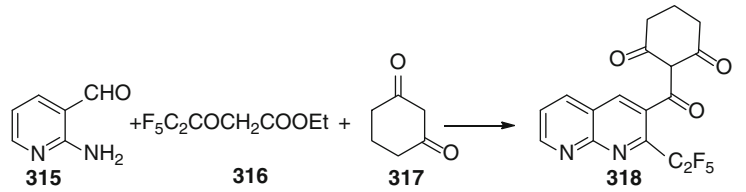
Scheme 88

Reaction of enamine **310** with pentafluoropropionic anhydride **(311)** gives compound **312**. The condensation of **312** with two moles of diethyl iminomalonate hydrochloride **(313)** led to substituted perfluoroalkylpyridine **314**, which further is used in synthesis inhibitors of phosphoesterase [186] (Scheme 89).



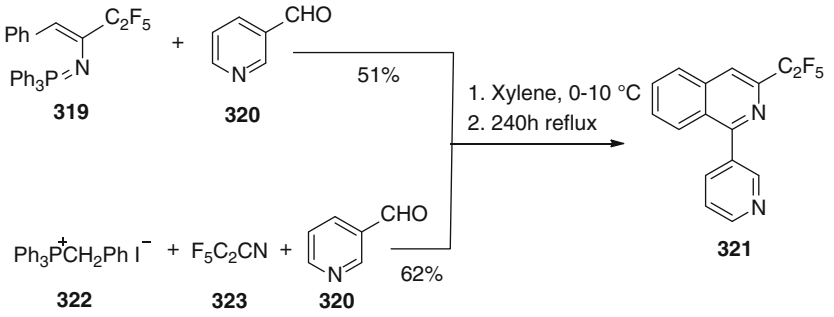
Scheme 89

Perfluoroalkyl [1, 8]-naphtiridine (**318**) with herbicidal effect was synthesized by reaction of 2-amino-3-formylpyridine (**315**), 1,3-dicarbonyl compound **316** and 1,3-cyclohexanedione (**317**) [187] (Scheme 90).



Scheme 90

Substituted 3-perfluoroethylisoquinoline **(321)** was obtained by interaction of compound **319** and pyridine-3-carbaldehyde (**320**). Compound **321** has been obtained also by three-component condensation directly from salt **322**, pentafluoroacetonitrile (**323**) and pyridine-3-carbaldehyde (**320**) [188]. These reactions proceed with formation of two cycles at hard conditions (reflux in xylene for a long time) (Scheme 91).



Scheme 91

The methods of synthesis of fluorine-containing pyridines described in the given review specify growing interest to chemistry of these compounds that is caused by the big practical importance of fluorinated azines.

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