

# Monofluorinated Heterocycles

Andrei A. Gakh

**Abstract** The chapter presents an overview of synthetic chemistry of ring-fluorinated heterocycles containing only one fluorine atom (monofluorinated heterocycles). Particular attention is given to modern nucleophilic and electrophilic fluorination methods, including catalytic reactions, chiral and microwave-assisted synthesis, carbene and hypervalent chemistry, utilization of ionic intermediates and ionic liquids, and others. One of the major emphases of the chapter is identification of the remaining “white spots” as opportunities for the future research effort.

**Keywords** Fluorination · Heterocycles

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## Abbreviations

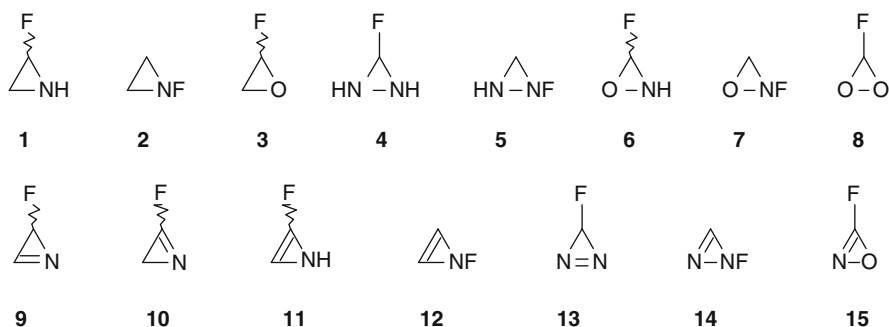
Accufluor®	1-Fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis-tetrafluoroborate
CEFOX	Cesium fluoroxysulphate
DAST	Diethylaminosulfur trifluoride
Deoxo-Fluor®	Bis(2-methoxyethyl)aminosulfur trifluoride
EMEF	<i>N</i> -Ethyl(hexamethylenetetraammonium) fluoride
NBS/Et <sub>3</sub> N•3HF	<i>N</i> -Bromsuccinimide/Et <sub>3</sub> N•3HF
NFSI	<i>N</i> -Fluorobenzenesulfonimide
“Proton sponge”/Et <sub>3</sub> N•3HF	1,8-Bis(dimethylamino)naphthalene/Et <sub>3</sub> N•3HF
Selectfluor®	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-tetrafluoroborate
TBAF (Bu <sub>4</sub> NF)	Tetrabutylammonium fluoride
TMAF (Me <sub>4</sub> NF)	Tetramethylammonium fluoride

## 1 Introduction

Ring-fluorinated heterocycles containing only one fluorine atom (monofluorinated heterocycles) constitute an important family of organic compounds with a wide array of applications ranging from drugs to multi-ton industrial intermediates [1, 2]. Although the first representatives of monofluorinated heterocycles, including 2-fluoropyridine [3], were synthesized almost 100 years ago, major developments in this field were made during the last two decades. Despite general recognition of their academic and practical importance, the family of monofluorinated heterocycles has significant gaps in synthetic methodology, availability, and basic physical–chemical data. It is expected that these gaps would eventually be filled. The main purpose of this review is not only to explore the field of synthetic chemistry of the monofluorinated heterocycles but also to identify the remaining gaps as opportunities for the future research effort.

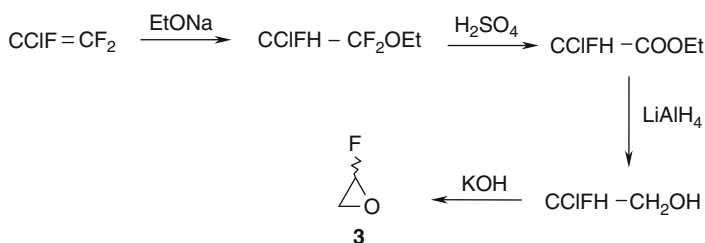
## 2 Three-Membered Monofluoroheterocycles

The monofluorinated derivatives are expected to be stable enough for isolation and characterization for almost all possible three-membered heterocycles, including marginally thermally stable 3-fluorodiazirine **13** [4]. In practice, however, many parent monofluorinated heterocycles **1–15** have not been reported yet, whereas their derivatives have been synthesized successfully. This is an unfortunate common feature for almost all of the three member-ring heterocycles presented below (Fig. 1).



**Fig. 1** Three-membered monofluoroheterocycles

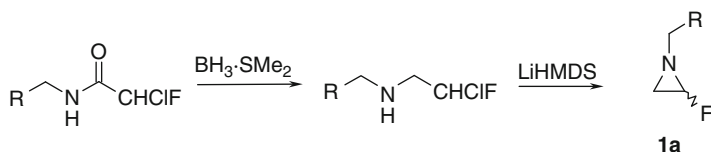
A reliable method of synthesis was reported only for the parent 2-fluorooxirane (**3**). It has been prepared in four steps from chlorotrifluoroethylene according to the procedure presented below (Scheme 1). The compound **3** is of theoretical interest as one of the smallest chiral compounds [5].



**Scheme 1** Synthesis of 2-fluorooxirane (**3**)

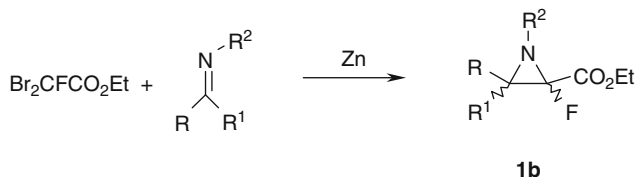
Parent 2-fluoroaziridine (**1**) is also chiral. The compound is expected to be stable, as well as its nonchiral *N*-fluoro isomer **2**. The derivatives of both compounds **1** and **2** are known and are of considerable academic interest due to their unusual geometry and substantial strain.

One of the recently reported syntheses of substituted 2-fluoroaziridines **1a** is based on ring closure of  $\beta$ -fluorinated  $\beta$ -chloroamines (Scheme 2). These  $\beta$ -fluorinated  $\beta$ -chloroamines can be prepared via reduction of corresponding chlorofluoroacetic acid amides [6].



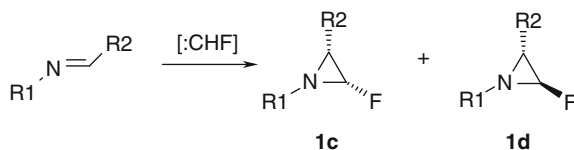
**Scheme 2** Synthesis of 2-fluoroaziridines **1a** from  $\beta$ -fluorinated  $\beta$ -chloroamines

Derivatives of 2-fluoroaziridine (**1**) can also be prepared via fluorocarbene addition to a C=N double bond. An example of this approach is presented below (Scheme 3). In this case, the ester of dibromofluoroacetic acid serves as a source of fluorocarbene-type intermediate, which is described in terms of “the Reformatsky-type aza-Darzens reaction” [7]. The reaction proceeds with reasonable stereoselectivity and produces a mixture of syn/anti products in better than 5:1 ratio. It is reported that the major syn isomers of **1b** are actually less thermodynamically stable than the minor anti-isomers [7].



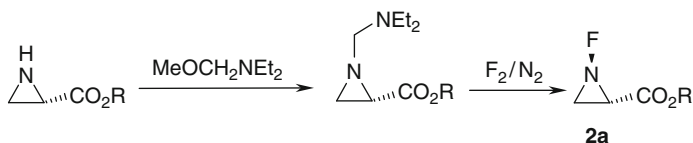
**Scheme 3** Synthesis of 2-fluoroaziridines **1b** from  $\beta$ -fluorinated  $\beta$ -chloroamines

The simplest fluorocarbene,  $\text{CHF}^\cdot$  (generated under ultrasound conditions from  $\text{CH}_2\text{FBr}_2$  and “activated” Pb in the presence of tetrabutylammonium bromide, TBAB) can be trapped by imines to yield 2-fluoroaziridines **1c** and **1d** (Scheme 4). The reaction likely proceeds via formation of azometine ylides [8].



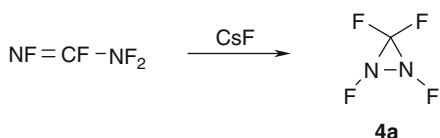
**Scheme 4** Synthesis of 2-fluoroaziridines **1c** and **1d**

N-fluorinated carboxyaziridines **2a** are also reported. These N-fluorinated heterocycles **2a** are of theoretical interest due to the exceptionally high configuration stability of the nitrogen atom (the barrier of interconversion sometimes exceeds 30 kcal/mol) [9]. One of the modern synthetic approaches entails stereoselective direct fluorination of the *N*-aminomethyl derivatives leading to **2a** (Scheme 5).



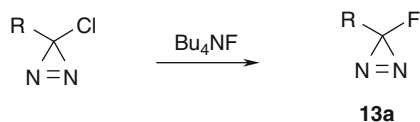
**Scheme 5** Synthesis of *N*-fluorocarboxyaziridines **2a**

Only polyfluorinated derivatives of fluorodiaziridines **4** and **5** were reported so far, including perfluorodiaziridine (**4a**), but the employed synthetic procedures are specific for polyfluorinated organic compounds and cannot be used for the preparation of the parent monofluorinated heterocycles **4** and **5** (Scheme 6) [10]. The same is true for fluorooxaziridines **6** and **7**.



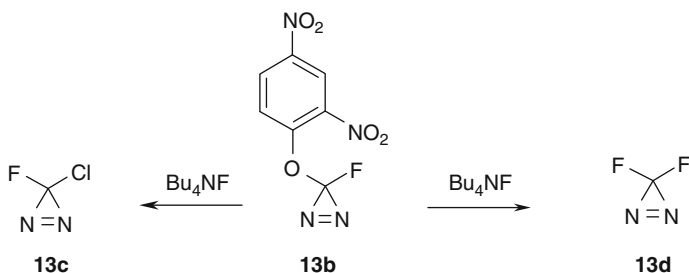
**Scheme 6** Preparation of perfluorodiaziridine (**4a**)

Unlike compounds **4–12** and **14–15**, the derivatives of monofluorinated diazirine **13** are well represented in the available literature and were a subject of extensive computational studies related to their stability in respect to the diazirine-diazo ring-opening process [4]. Several methods of synthesis were reported. One of them is based on nucleophilic fluorination of the corresponding 3-chloro derivatives of **13** using various sources of fluoride anion, such as  $\text{Bu}_4\text{NF}$  (Scheme 7) [11]. It was suggested that the reaction leading to fluorodiazirines **13a** might involve a diazirinium cation/anion pair. Indeed, some nucleophilic substitution reactions of 3-chlorodiazirines are first order reactions [12].



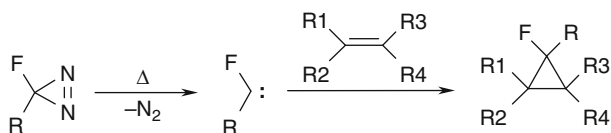
**Scheme 7** Nucleophilic fluorination of 3-chlorodiazirines

The 2,4-dinitrophenoxy group can also be used as the leaving group (e.g., compound **13b**) in the synthesis of fluorodiazirines **13c** and **13d**. This leaving group allows introduction not only of fluorine but also of chlorine using  $\text{Bu}_4\text{NCl}$  instead of  $\text{Bu}_4\text{NF}$  (Scheme 8) [13].



**Scheme 8** Preparation of chlorofluorodiazirine **13c**

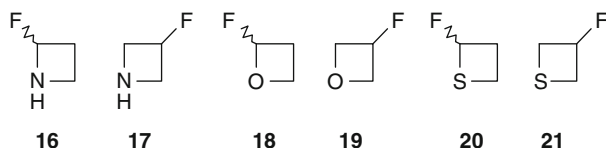
Perhaps one of the most valuable properties of monofluorodiazirines is their facile thermolysis leading to corresponding monofluorocabenenes via  $N_2$  elimination. Unlike their chloro- and bromo- analogs, monofluorocabenenes are stable enough to be captured with a variety of electron rich substrates, including double bonds [13]. The latter reaction yields monofluorocyclopropanes (Scheme 9) [13, 14].



**Scheme 9** Generation of monofluorocabenenes from monofluorodiazirines

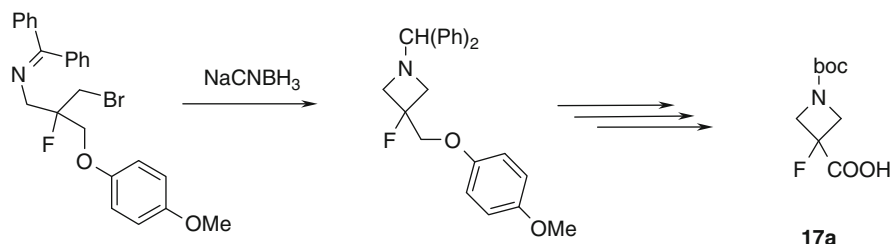
### 3 Four-Membered Monofluoroheterocycles

Four-membered monofluorinated heterocycles **16–21** are in general far more abundant than the three-membered ones, but this only applies to the easier-to-make 3-fluoroheterocycles **17**, **19**, and **21**. As expected, these small ring compounds also carry substantial strain due to the unfavorable stretching of their valence angles from the ideal tetrahedral arrangement to the almost square geometry. Some of the most common monofluorinated four-membered heterocycles are presented below (Fig. 2).



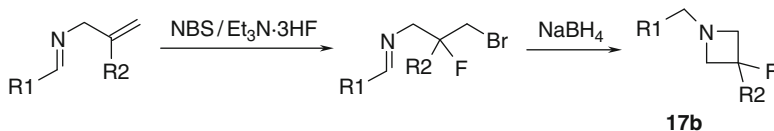
**Fig. 2** Four-membered monofluoroheterocycles

Unlike 2-fluoroazetidine (**16**), 3-fluoroazetidine (**17**) is now commercially available. Typical synthetic procedures for the synthesis of **17** derivatives are based on the cyclization of appropriate fluorinated aliphatic precursors. This methodology was successfully employed for the preparation of Boc-protected 3-fluoroazetidine-3-carboxylic acid (**17a**, Scheme 10) [15].



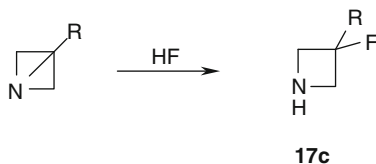
**Scheme 10** Preparation of Boc-protected 3-fluoroazetidine-3-carboxylic acid (**17a**)

A similar approach has been used for the synthesis of other 3-substituted 3-fluoroazetidines (**17b**) of biological interest. In this case, the introduction of the fluorine atom has been achieved via bromofluorination of a double bond with the NBS/Et<sub>3</sub>N•3HF system (Scheme 11) [16].



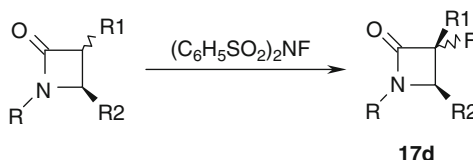
**Scheme 11** Synthesis of 3-substituted 3-fluoroazetidines **17b** via bromofluorination

Other known methods for the synthesis of 3-fluoroazetidines **17c** include direct fluorination of azetidines [17] and the reaction of 1-azabicyclo[n.1.0]alkanes with liquid HF or the pyridine•10HF complex (Scheme 12) [18].



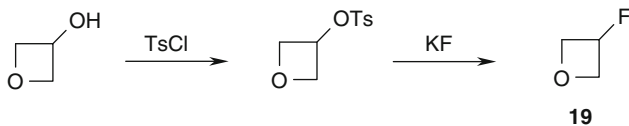
**Scheme 12** Synthesis of 3-substituted 3-fluoroazetidines **17c** via 1-azabicyclo[n.1.0]alkanes

Stereoselective electrophilic fluorination of substituted azetidinones ( $\beta$ -lactams) with *N*-fluorobenzenesulfonimide (NFSI) can be used for the synthesis of 3-fluoroazetidinones **17d** (Scheme 13). These compounds are of interest for the development of carbapenem antibiotics [19].



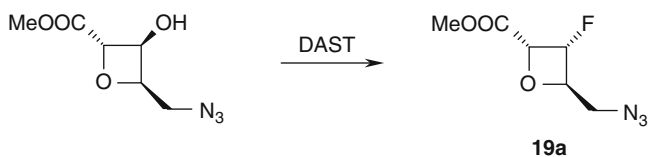
**Scheme 13** Stereoselective electrophilic fluorination of  $\beta$ -lactams

Similar to 2-fluoroazetidine (**16**) and 3-fluoroazetidine (**17**), derivatives of 3-fluoroazetidine (**17**) are better known and more studied than 2-fluoroazetidine (**16**). Parent 3-fluoroazetidine (**17**) can be easily prepared from 3-oxetol tosylate and KF (Scheme 14) [20].



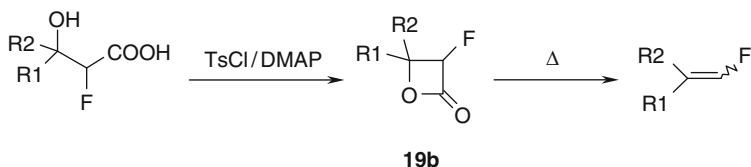
**Scheme 14** Synthesis of 3-fluorooxetane (**19**)

Alternatively, 3-oxetanols can be directly converted to 3-fluorooxetanes **19a** using DAST as a fluorinating agent (Scheme 15). This method was used for the preparation of 3-fluorooxetane  $\delta$ -amino acids [21].



**Scheme 15** DAST fluorination

Keto-derivatives of 3-fluorooxetane (fluorinated  $\beta$ -lactones **19b**) are also known. They can be prepared via cyclization of  $\alpha$ -fluoro- $\beta$ -hydroxycarboxylic acids. In some cases, corresponding 1-fluoroalkenes were also detected in the reaction mixture. These 1-fluoroalkenes are the primary thermal decomposition products of the fluorinated  $\beta$ -lactones **19b** ( $\text{CO}_2$  elimination, Scheme 16) [22].



**Scheme 16** Synthesis and thermal decomposition of fluorinated  $\beta$ -lactones **19b**

A derivative of 2-fluorothietane (**20**) was recently prepared and successfully used in a glycosidation reaction leading to the S-analog of the natural antibiotic Oxetanocin A. The synthesis of this 2-fluorothietane derivative **20a** was performed using direct fluorination of substituted thietane with DAST or Deoxo-Fluor® in 2-position (Scheme 17) [23].

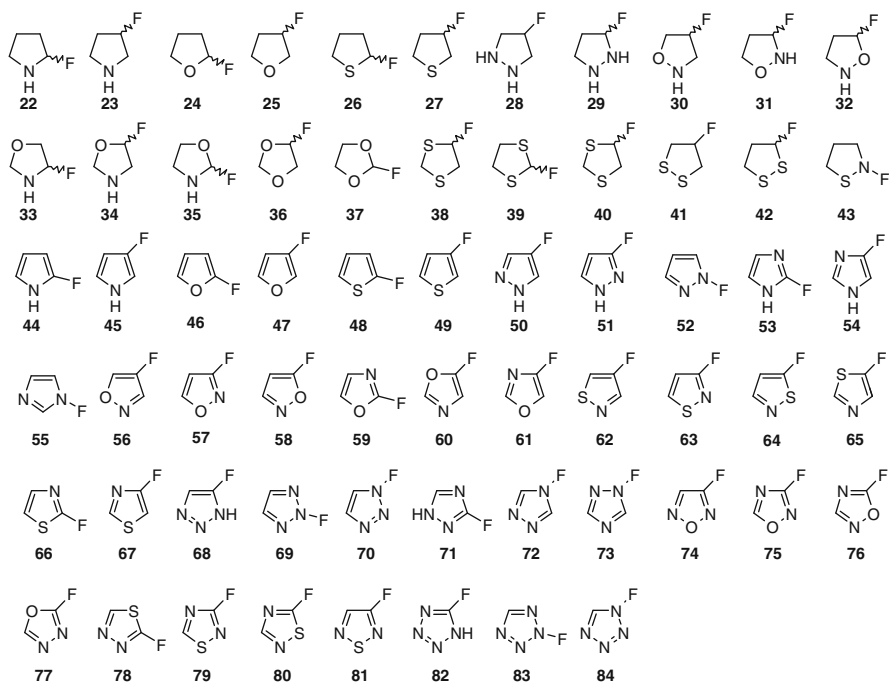




**Scheme 17** Synthesis of the 2-fluorothietane derivative **20a**

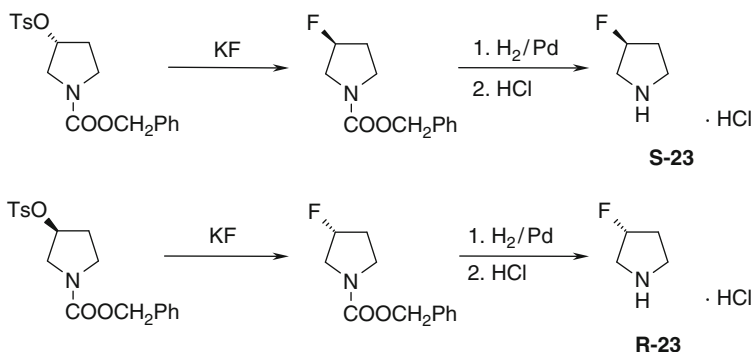
## 4 Five-Membered Monofluoroheterocycles

Synthesis and reactions of five-membered monofluoroheterocycles are frequently reported in the literature. Some of the popular fluorinated heterocycles of this class are presented below (Fig. 3).



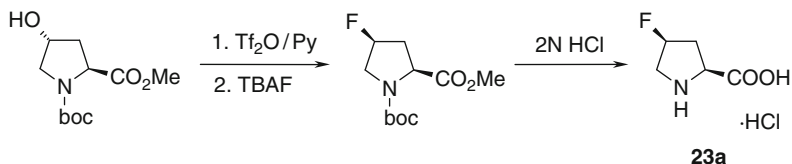
**Fig. 3** Five-membered monofluoroheterocycles

Unlike 2-fluoropyrrolidine (**22**), both stereoisomers of the parent 3-fluoropyrrolidine (**23**) are now available commercially. They can be prepared from corresponding enantiomerically pure 3-tosylates using KF as a nucleophilic fluorinating agent (Scheme 18) [24]. Alternatively, stereoselective fluorination of 3-hydroxypyrrolidines can be accomplished with DAST [25].



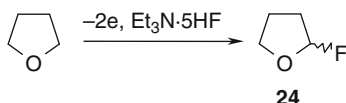
**Scheme 18** Synthesis of *R*- and *S*-3-fluoropyrrolidines

Substituted 3-fluoropyrrolidines are extensively studied, primarily in the form of 2-carboxy derivatives (fluorinated prolines), which are valuable nonnatural amino acids capable of improving the conformational stability of collagen [26, 27]. A practical synthesis of the 4-fluoroproline diastereomer (**23a**) from 4-hydroxyproline was recently reported (Scheme 19) [27].



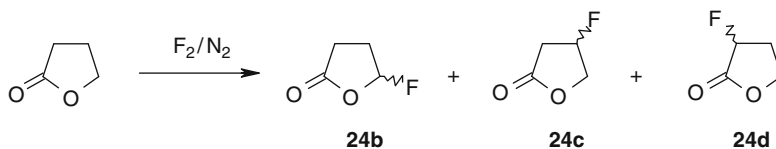
**Scheme 19** Synthesis of 4-fluoroproline (**23a**)

Parent 2-fluorotetrahydrofuran (2-fluorooxolan, **24**) was prepared by the anode oxidation of THF using  $\text{Et}_3\text{N} \cdot 5\text{HF}$  as a fluorine source (Scheme 20). The synthesis can be performed in solvent-free conditions [28].



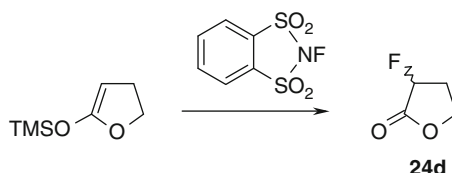
**Scheme 20** Synthesis of 2-fluorotetrahydrofuran (**24**)

Direct fluorination of  $\gamma$ -butyrolactone leads to a mixture of predominantly monofluorinated  $\gamma$ -butyrolactones **24b**, **24c**, and **24d** (Scheme 21). Regioselectivity of the fluorination process can be improved by adding NaF as a HF scavenger [29].



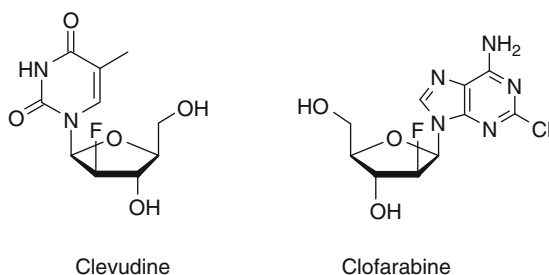
**Scheme 21** Direct fluorination of  $\gamma$ -butyrolactone

Regioselective electrophilic fluorination of  $\gamma$ -butyrolactone can be accomplished using *N*-fluoro-*o*-benzenedisulfonimide via silyl enol ether (Scheme 22) [30].



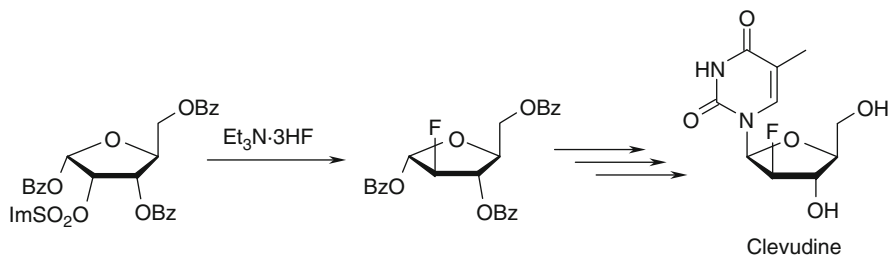
**Scheme 22** Electrophilic fluorination of  $\gamma$ -butyrolactone silyl enol ether

Polyhydroxy derivatives of 3-fluorooxolane (**25**) are a very important class of heterocycles, which are primarily found among fluorinated carbohydrates and nucleosides. Several important drugs contain a fluorinated oxolan fragment (Fig. 4). Among them are the Hepatitis B drug Clevudine (L-FMAU, 1-[(2*S*,3*R*,4*S*,5*S*)-3-fluoro-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-methylpyrimidine-2,4-dione) [31] and the leukemia drug Clofarabine (5-(6-amino-2-chloro-purin-9-yl)-4-fluoro-2-(hydroxymethyl)oxolan-3-ol) [32].



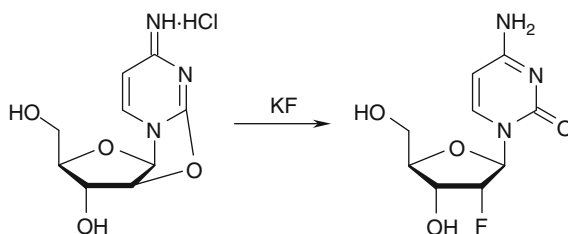
**Fig. 4** Clevudine and Clofarabine

Synthesis of these monofluorinated nucleosides can be accomplished via coupling of fluorinated ribofuranose derivatives with appropriate nucleoside bases. One practical method to synthesize Clevudine involves fluorination of 1,3,5-tri-*O*-benzoyl-2-*O*-imidazolylsulfonyl- $\alpha$ -L-ribofuranose with  $\text{Et}_3\text{N}\cdot 3\text{HF}$  [33]. The nucleophilic substitution reaction is facilitated by the use of the potent imidazolyl-sulfonyl leaving group (Scheme 23).



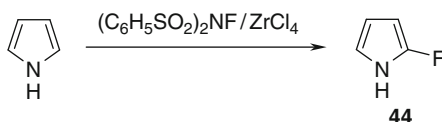
**Scheme 23** Synthesis of Clevudine

The introduction of fluorine into a ribose ring can also be accomplished in appropriately activated nucleosides, but the synthetic utility of this approach is somewhat limited by the availability of parent nucleosides with a proper stereoconfiguration of the leaving groups. In some cases, a base itself can act as a leaving group (anhydro-nucleoside approach). An example of this route is presented below (Scheme 24) [34].



**Scheme 24** Fluorination via anhydro-nucleoside approach

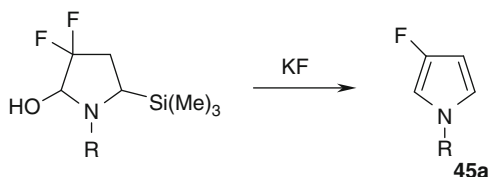
Both 2- and 3-fluoropyrroles (**44** and **45**) as well as their derivatives are valuable precursors in the synthesis of fluorinated porphyrins [35]. Parent 2-fluoropyrrole (**44**) has been synthesized and fully characterized only recently. The compound was produced using a “soft” Lewis acid-catalyzed fluorination reaction of pyrrole with NFSI (Scheme 25) [36].



**Scheme 25** Synthesis of 2-fluoropyrrole (**44**)

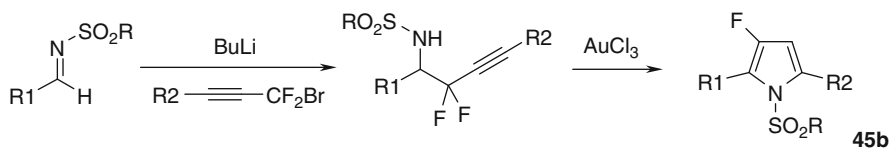
Attempts to develop an efficient method of synthesis of 3-fluoropyrrole (**45**) have been met with limited success [35]. Derivatives of 3-fluoropyrrole can be

produced using several well-established methods, including the Shiemann-type photochemical fluorination via diazonium salts [37]. An efficient method for the synthesis of 3-fluoropyrrole derivatives **45a** was reported recently (Scheme 26) [38]. The method is based on KF-induced dehydrofluorination and aromatization of substituted 3,3-difluoropyrrolidines.



**Scheme 26** Synthesis of 3-fluoropyrrole derivatives **45a**

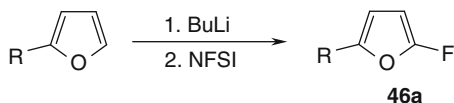
Another method for the synthesis of substituted 3-fluoropyrroles **45b** requires the use of  $\text{AuCl}_3$  as a catalyst (Scheme 27) [39].



**Scheme 27** Synthesis of 3-fluoropyrroles **45b** via  $\text{AuCl}_3$  – catalyzed heterocyclization

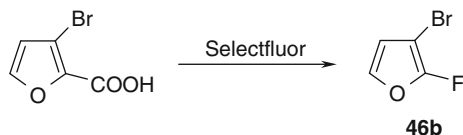
Preparative synthesis of *N*-fluoropyrrole was not found in the available literature. The inversion process of *N*-fluoropyrrole was recently investigated in detail using ab initio and density functional techniques [40].

Convenient preparative methods for the synthesis of parent 2- and 3-fluorofurans (**46** and **47**) have not been documented. Some thermochemical parameters of 2-fluorofuran (**46**) were calculated using ab initio G3 method [41]. Derivatives of both 2- and 3-fluorofurans (**46** and **47**) are known. 2-Fluorofurans **46a** can be prepared by the direct fluorination of furan derivatives with NFSI (Scheme 28) [42].



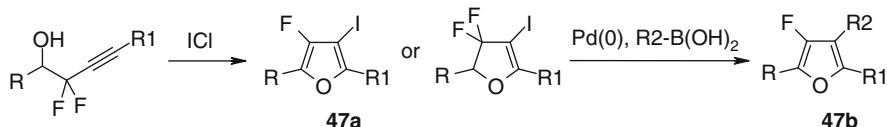
**Scheme 28** Synthesis of 2-fluorofurans **46a**

Fluorodecarboxylation of 2-furancarboxylic acids with Selectfluor® (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-tetrafluoroborate) can also be used for the preparation of 2-fluorofurans (e.g., **46b**, Scheme 29) [43].



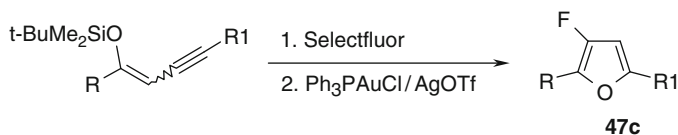
**Scheme 29** Synthesis of 3-bromo-2-fluorofuran **46b**

Heterocyclization of appropriate fluorinated acyclic compounds was successfully used for the synthesis of 3-fluorofurans (**47a** and **47b**). One of the recently developed methods employs iodocyclization of *gem*-difluorohomopropargyl alcohols (Scheme 30) [44].



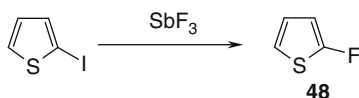
**Scheme 30** Iodocyclization of *gem*-difluorohomopropargyl alcohols

Nonfluorinated acyclic compounds can be converted to 3-fluorofurans **47c** via a sequence of fluorination and heterocyclization in the presence of a gold(I)/silver catalyst (Scheme 31) [45].



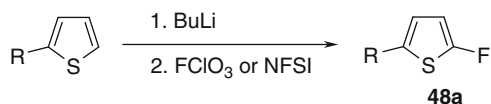
**Scheme 31** Fluorination and heterocyclization with gold(I)/silver catalyst

Parent 2- and 3-fluorothiophenes (**48** and **49**) and their derivatives are known. 2-Fluorothiophene (**48**) was first prepared from 2-iodothiophene more than 60 years ago (Scheme 32) [46].



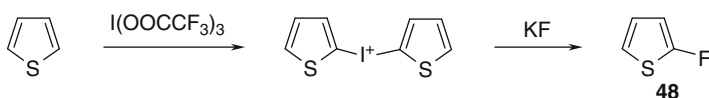
**Scheme 32** Synthesis of 2-fluorothiophene (**48**)

Modern methods for the synthesis of 2-fluorothiophene (**48**) and its derivatives (**48a**) entail the use of electrophilic fluorinating agents, such as  $\text{FCIO}_3$  [47] or NFSI (Scheme 33) [42]. Regioselective fluorination of 2-thienyllithium can also be achieved with *N*-fluoroquinuclidinium fluoride [48].



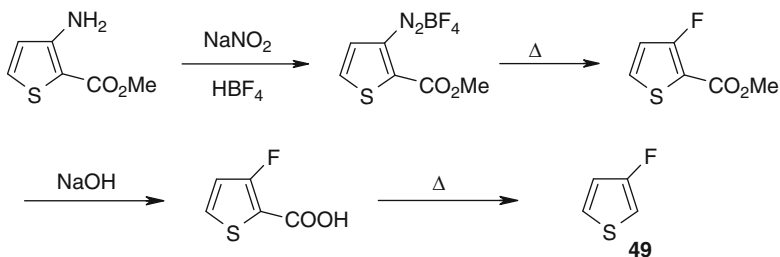
**Scheme 33** Regioselective fluorination of 2-thienyllithium

Nucleophilic fluorination of iodonium salts can be used for the synthesis of 2-fluorothiophene (**48**, Scheme 34). This reaction is sensitive to the nature of the counter-anion. The best results were achieved with di-2-thienyliodonium hexafluorophosphate [49].



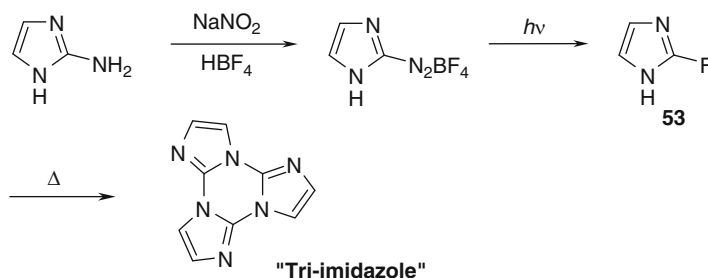
**Scheme 34** Nucleophilic fluorination of iodonium salts

Radiolabeled [18F] 3-fluorothiophene (**49**) together with 2-fluorothiophene (**48**) were detected in the reaction mixture produced by direct fluorination of thiophene with [18F] elemental fluorine [50]. Pure samples of 3-fluorothiophene (**49**) can be prepared using a four-step synthetic procedure starting from methyl 3-aminothiophene-2-carboxylate (Scheme 35) [51].



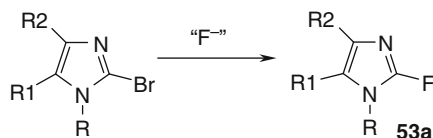
**Scheme 35** Synthesis of 3-fluorothiophene (**49**)

Both C- and N-monofluorinated imidazoles are known. 2-Fluoroimidazole (**53**) was prepared via the Schiemann-type photochemical decomposition of the corresponding diazonium tetrafluoroborate in water [52]. The synthesis can be performed in solvent-free conditions using ionic liquids [53]. The compound **53** is not stable and trimerizes spontaneously to produce so-called “tri-imidazole” (aka the imidazole cyclic trimer, Scheme 36) [54]. This compound can be prepared more conveniently by the thermal decomposition of copper imidazolate [55].



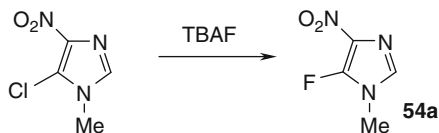
**Scheme 36** Synthesis of 2-fluoroimidazole (**53**) and "tri-imidazole"

Nucleophilic fluorination of certain 2-bromoimidazole derivatives leads to 2-fluoroimidazoles (**53a**, Scheme 37). The success of this reaction depends on the proper protection of the NH group and the presence of additional electron withdrawing groups, which facilitate the reactions. Spray-dried KF with 18-crown-6 was successfully used in the synthesis of 1-methyl-2-fluoro-4,5-dicyanoimidazole [56]. Tetraalkylammonium fluorides, such as anhydrous tetramethylammonium fluoride (TMAF) and tetrabutylammonium fluoride (TBAF), are also effective sources of fluoride ion. The best yields were achieved in dry DMF [57].



**Scheme 37** Nucleophilic fluorination of 2-bromoimidazoles

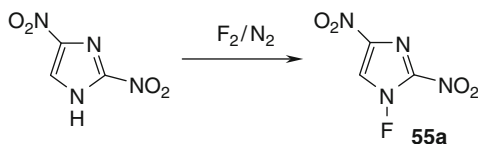
4(5)-Fluoroimidazole (**54**) was prepared similarly to 2-fluoroimidazole (**53**) via the photochemical decomposition of diazonium tetrafluoroborate [52]. Modern methods for the synthesis of 4(5)-fluoroimidazole derivatives (such as **54a**) include nucleophilic fluorination with anhydrous TBAF [58] (Scheme 38).



**Scheme 38** Synthesis of 5-fluoro-1-methyl-4-nitroimidazole (**54a**)

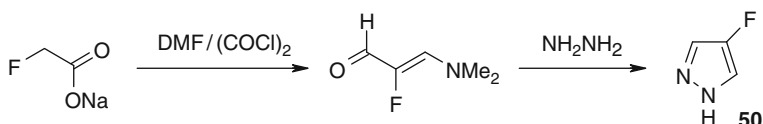
2,4- and 4,5-Dinitro derivatives of *N*-fluoroimidazole (**55**) were prepared by direct fluorination of corresponding dinitroimidazoles with elemental fluorine (Scheme 39). As expected, 1-fluoro-2,4-dinitroimidazole (**55a**) is a potent electrophilic fluorinating agent [59].





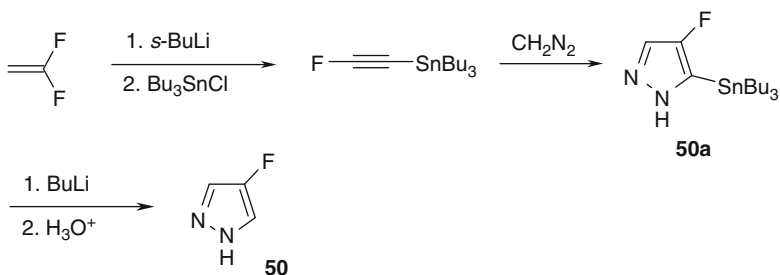
**Scheme 39** Synthesis of 1-fluoro-2,4-dinitroimidazole (**55a**)

Parent 4-fluoropyrazole (**50**) was initially prepared in several steps from fluoroacetic acid [60, 61]. An improved two-step synthesis of 4-fluoropyrazole (**50**) was recently reported (Scheme 40) [62]. The synthetic utility of this approach is somewhat limited due to the toxicity of fluoroacetic acid and its derivatives.



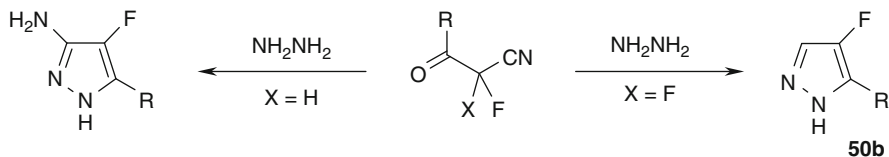
**Scheme 40** Synthesis of 4-fluoropyrazole (**50**)

Derivatives of 4-fluoropyrazole (**50**) can be prepared by a variety of methods. Recent reports include the synthesis of versatile 5-tributylstannyl-4-fluoropyrazole (**50a**) and parent 4-fluoropyrazole (**50**) from 1,1-difluoroethylene (Scheme 41) [63].



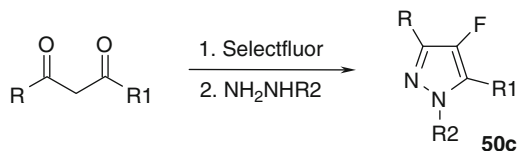
**Scheme 41** Synthesis of 5-tributylstannyl-4-fluoropyrazole (**50a**) and 4-fluoropyrazole (**50**)

A new synthesis of 4-fluoropyrazoles (**50b**) from the reaction of fluoro- and difluoroacetonitrile derivatives with hydrazine was recently described (Scheme 42). In the latter case, the formation of the heterocyclic ring was accompanied by the elimination of one fluorine atom [64].



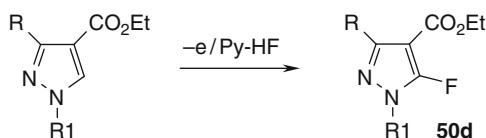
**Scheme 42** Heterocyclization of fluoro- and difluoroacetonitrile derivatives

Direct fluorination of 3,5-disubstituted pyrazoles having open 4 positions with diluted elemental fluorine is usually regioselective and yields mainly 4-fluoropyrazoles [65]. Microwave-induced fluorination was successfully employed for the preparation of substituted 4-fluoropyrazoles (**50c**) with Selectfluor® (Scheme 43). Defluorinated Selectfluor® catalyzes the heterocyclization of 1,3-dicarbonyl compounds with hydrazines, thus allowing one-pot synthesis of the desired 4-fluoropyrazoles directly from 1,3-diketones and substituted hydrazines [66].



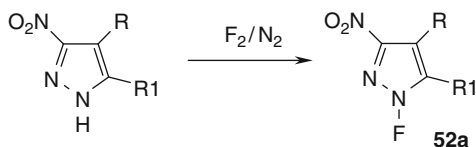
**Scheme 43** One-pot synthesis of 4-fluoropyrazoles **50c**

3(5)-Fluoropyrazoles can be prepared by a variety of methods described above. In addition, substituted ethyl pyrazole-4-carboxylates **50d** can be regioselectively fluorinated in the 5-position using electrochemical fluorination methods (Scheme 44) [67].



**Scheme 44** Electrochemical fluorination of ethyl pyrazole-4-carboxylates

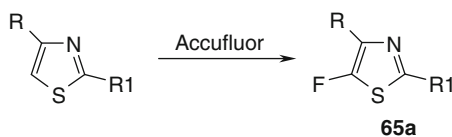
Synthesis of *N*-fluoropyrazole (**52**) derivatives was recently reported. The compounds were prepared by direct N-fluorination of nitropyrazoles with elemental fluorine (Scheme 45). N-fluorination of nitropyrazoles is a regioselective process and produces only one isomer with the fluorine atom in the most remote position from the nitro group. *N*-fluoronitropyrazoles **52a** are of interest as energetic materials [68].



**Scheme 45** Synthesis of *N*-fluoronitropyrazoles **52a**

Ring-fluorinated oxazoles are known. They easily react with nucleophiles and therefore could serve as valuable intermediates for the synthesis of polymers [69]. The more chemically stable 5-fluorothiazoles (**65a**) can be prepared by direct

fluorination of substituted thiazoles with Accufluor® (1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), Scheme 46) [70].



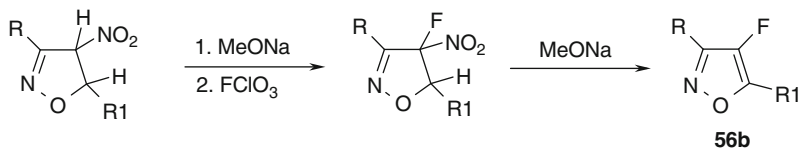
**Scheme 46** Fluorination of thiazoles with Accufluor®

The synthesis of parent 4-fluoroisoxazole (**56**) from fluoroacetic acid is similar to the synthesis of 4-fluoropyrazole (**50**) [60, 61]. Substituted 4-fluoroisoxazoles were prepared from 2-fluoro-1,3-dicarbonyl compounds and hydroxylamine [71]. Direct fluorination of 3,5-disubstituted isoxazoles with Selectfluor® leads to corresponding 3,5-disubstituted 4-fluoroisoxazoles **56a** (Scheme 47) [72].



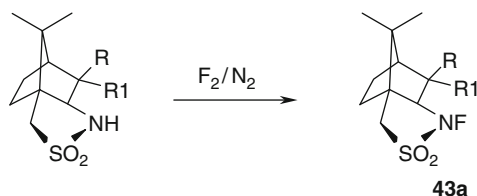
**Scheme 47** Fluorination of 3,5-disubstituted isoxazoles with Selectfluor®

Fluorination of 4-nitroisoxazoline salts with  $\text{FCIO}_3$ , followed by the elimination of  $\text{HNO}_2$ , represents another approach to the synthesis of substituted 4-fluoroisoxazoles **56b** (Scheme 48) [73].



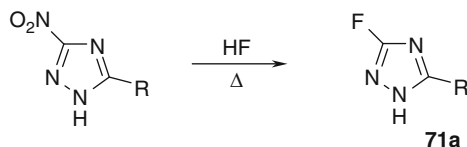
**Scheme 48** Synthesis of substituted 4-fluoroisoxazoles **56b**

*N*-fluoroisothiazolidines (**43**, predominantly known in the form of 1,1-oxide derivatives, or *N*-fluorosultams, including chiral *N*-fluorosultams **43a**, Scheme 49) are important electrophilic fluorinating agents [74]. Their applications in the enantioselective synthesis of chiral fluoroorganic compounds were recently reviewed [75].



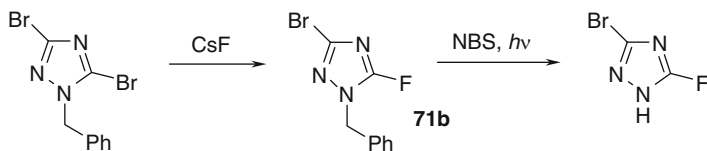
**Scheme 49** Synthesis of chiral *N*-fluorosultams **43a**

Parent 3(5)-fluoro-1,2,4-triazole (**71**) was prepared almost 40 years ago by fluorodenitration of 3(5)-nitro-1,2,4-triazole with HF at elevated temperatures [76]. This procedure provides a route to other 3(5)-fluoro-1,2,4-triazole derivatives **71a** (Scheme 50).



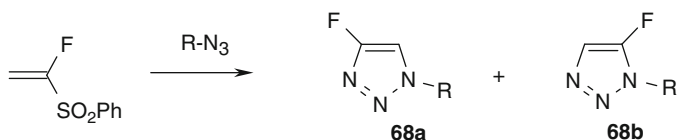
**Scheme 50** Synthesis of 3(5)-fluoro-1,2,4-triazoles **71a**

Halogen exchange reactions were successfully employed in the synthesis of 5-fluoro-1,2,4-triazoles (e.g., **71b**, Scheme 51) [77]. The substitution reaction is assisted by the enhanced reactivity of the 5-position in the 1,2,4-triazole ring.



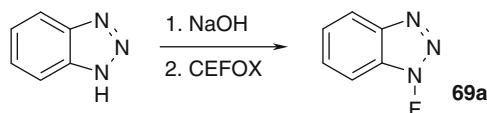
**Scheme 51** Nucleophilic fluorination of 5-bromo-1,2,4-triazoles

Unlike 3(5)-fluoro-1,2,4-triazole (**71**), the preparative synthesis of parent 4(5)-fluoro-1,2,3-triazole (**68**) was not reported in the available literature. Substituted 4(5)-fluoro-1,2,3-triazoles are known. One of the recently reported procedures utilizes fluorovinyl sulfones as fluoroacetylene equivalents for cycloaddition with azides leading to substituted 4- and 5-fluoro-1,2,3-triazole derivatives **68a** and **68b**. As expected, the cycloaddition reaction is not regioselective (Scheme 52) [78].



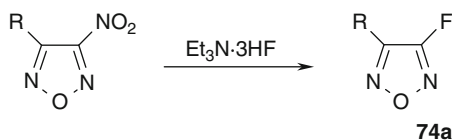
**Scheme 52** Synthesis of 4- and 5-fluoro-1,2,3-triazoles **68a** and **68b**

N-fluorinated 1,2,3-triazoles (**69** and **70**) appear to be stable enough to be isolated, although the reported examples so far were limited to 1-fluoro-benzo-1,2,3-triazole (**69a**). The compound was first prepared using an anionic electrophilic fluorinating agent, cesium fluoroxysulphate (CEFOX, Scheme 53), but the use of other conventional fluorinating agents, such as diluted elemental fluorine, is also feasible [79].



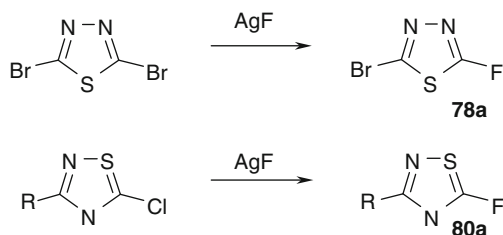
**Scheme 53** Synthesis of 1-fluoro-benzo-1,2,3-triazole (**69a**)

Reports concerning monofluorinated oxadiazoles and thiadiazoles appear to be very limited. Recently, substituted 3(4)-fluoro-1,2,5-oxadiazoles (fluorofurazanes, **74a**) were successfully prepared by fluorodenitration of the corresponding nitrofurazanes (Scheme 54) [80].



**Scheme 54** Synthesis of fluorofurazanes **74a** via fluorodenitration

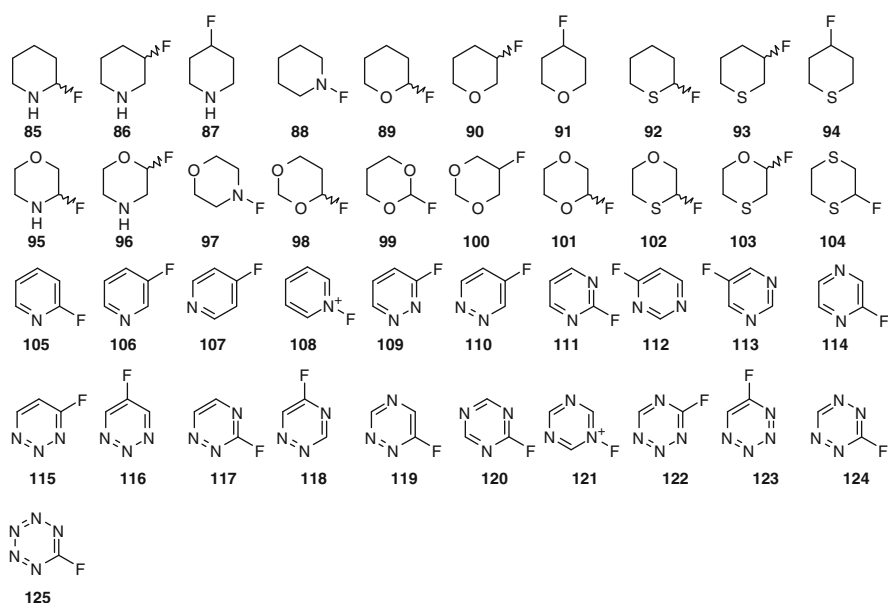
Derivatives of 2-fluoro-1,3,4-thiadiazole (**78**) as well as isomeric 5-fluoro-1,2,4-thiadiazole (**80**) were prepared almost 50 years ago by the action of AgF on the corresponding halothiadiazoles (Scheme 55) [81]. The synthesis of the parent fluorothiadiazoles **78**, **79** and **80** has so far received little attention.



**Scheme 55** Nucleophilic fluorination of halo-thiadiazoles

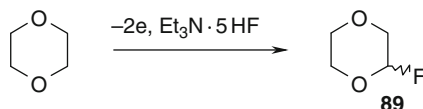
## 5 Six-Membered Monofluoroheterocycles

The family of six-membered monofluoroheterocycles includes several prominent compounds, such as parent 2-fluoropyridine (**105**) and 5-fluorouracil, a derivative of 5-fluoropyrimidine (**113**, Fig. 5).



**Fig. 5** Six-membered monofluoroheterocycles

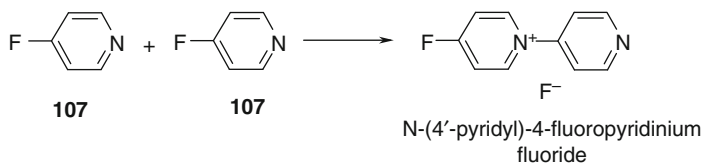
Saturated six-membered monofluorinated heterocycles are well represented in the recent literature. For example, 2-fluorodioxane (**89**) was prepared in satisfactory yield by electrochemical fluorination of dioxane in  $\text{Et}_3\text{N} \cdot 5\text{HF}$  (Scheme 56) [28].



**Scheme 56** Electrochemical fluorination of dioxane

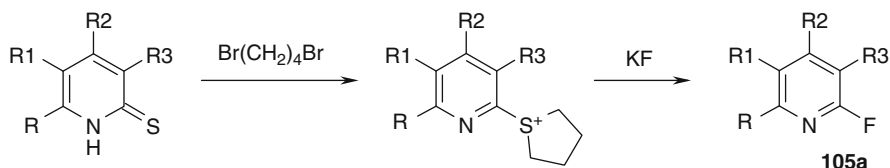
Availability and literature precedence for monofluorinated azines with one, two, three, four, and five nitrogen atoms decline progressively. NMR spin–spin coupling constants of higher monofluorinated azines, including elusive 6-fluoropentazine (**125**), were calculated only recently [82, 83].

Fluoropyridines with one fluorine atom are probably the most explored subgroup of monofluorinated heterocycles. All monofluoropyridines (2-,3-,4-, and *N*-fluoropyridines, **105**, **106**, **107**, and **108**, respectively) are now commercially available. Halogen exchange using KF as the fluorine source and decomposition of diazonium salts in HF are equally effective in the preparation of C-fluoropyridines. Although initial attempts to prepare 4-fluoropyridine (**107**) via the diazotation-fluorination route were not successful, the compound was eventually produced under optimized reaction conditions [84]. Unlike 3-fluoropyridine (**106**), 4-fluoropyridine (**107**) is not chemically stable and easily produces the self-condensation product, *N*-(4'-pyridyl)-4-fluoropyridinium fluoride (Scheme 57), similar to 2-fluoroimidazole (**53**) [54]. Salts of 4-fluoropyridine (**107**) are more chemically stable [84].



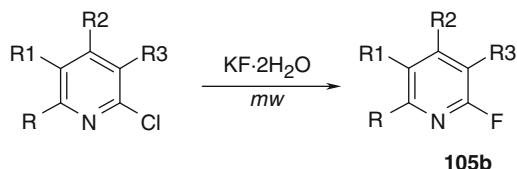
**Scheme 57** Self-condensation of 4-fluoropyridine (**107**)

2-Fluoropyridines were successfully prepared by fluorodenitration of 2-nitropyridines with TBAF [85] and from 2-chloropyridines using the “proton sponge”/ $\text{Et}_3\text{N}\cdot 3\text{HF}$  system [86]. Fluorodenitration is also effective in the synthesis of 3-fluoropyridines [85]. Recent advances in the synthesis of poly-substituted 2-fluoropyridines (**105a**) include the use of a positively charged sulfonium fragment as a leaving group (Scheme 58) [87]. The required cationic intermediates, 2-pyridylsulfonium salts, can be prepared from available pyridine-2(1H)-thiones.



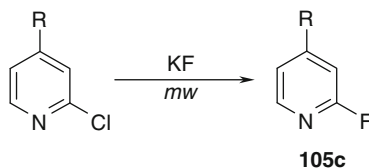
**Scheme 58** Nucleophilic fluorination of 2-pyridylsulfonium salts

Nucleophilic fluorination of 2-halopyridines usually requires anhydrous conditions due to the inferior reactivity of the hydrated fluoride anion. Microwave heating presents an opportunity to overcome this limitation. Affordable KF hydrate ( $\text{KF} \cdot 2\text{H}_2\text{O}$ ) proved to be as effective as spray-dried KF under microwave condition (Scheme 59) [88]. It is speculated that preferential heating and subsequent dehydration of  $\text{KF} \cdot 2\text{H}_2\text{O}$  crystals under microwave conditions is responsible for this activity enhancement in the synthesis of 2-fluoropyridines **105b**.



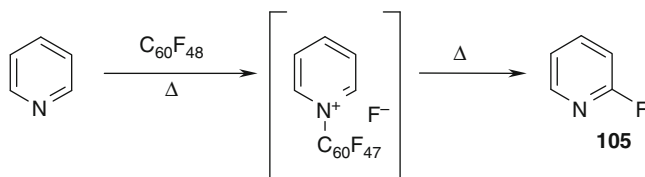
**Scheme 59** Microwave-assisted synthesis of 2-fluoropyridines **105b**

Microwave heating also provides notable rate enhancements in the synthesis of 2-fluoropyridyl derivatives of [3,2-c]pyrazolo-corticosteroids **105c** via nucleophilic fluorination (Scheme 60). A relative rate ratio of 3:1 for microwave versus conventional heating was obtained by kinetic experiments [89].



**Scheme 60** Microwave-assisted nucleophilic fluorination of 2-chloropyridines

The reaction of pyridine with  $\text{C}_{60}\text{F}_{48}$  and other highly fluorinated fullerenes leads to 2-fluoropyridine (**105**). In this case,  $\text{C}_{60}\text{F}_{48}$  acts as both an activator and a source of fluoride ions. The reaction is likely to proceed via the initial formation of a complex between pyridine and  $\text{C}_{60}\text{F}_{48}$  (Scheme 61) [90].

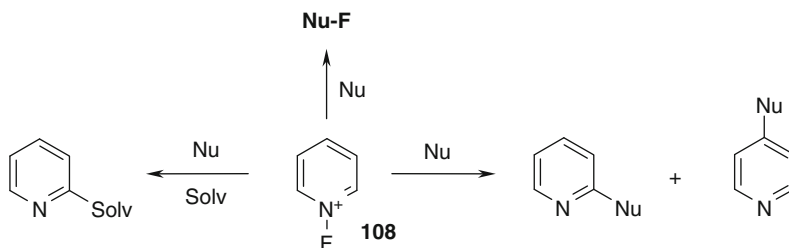


**Scheme 61** Fluorination of pyridine with  $\text{C}_{60}\text{F}_{48}$

*N*-fluoropyridinium salts (**108**) were originally prepared from pyridine and elemental fluorine, still a method of choice for the commercial production of

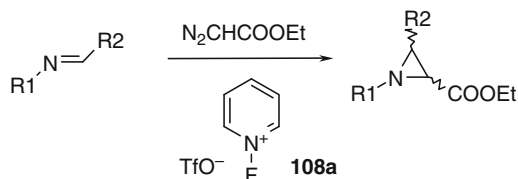


these salts. Other electrophilic fluorinating agents, including CEFOX and fluorine nitrate (FONO<sub>2</sub>), are also effective [79, 91]. *N*-fluoropyridinium salts (**108**) have a rich chemistry, and can act as both electrophilic fluorinating agents and precursors of reactive intermediates, such as 2-pyridyl cations/carbenes [92]. Addition of certain nucleophiles at the 2- and 4-positions via cine/tele nucleophilic substitution of hydrogen was also reported (Scheme 62) [93].



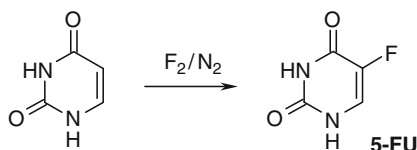
**Scheme 62** Chemical transformations of *N*-fluoropyridinium salts (**108**)

*N*-fluoropyridinium triflate (**108a**) was successfully used as a catalyst in the reaction between *N*-substituted imines and ethyl diazoacetate (Scheme 63). The authors reported excellent yields of *N*-substituted aziridines [94].



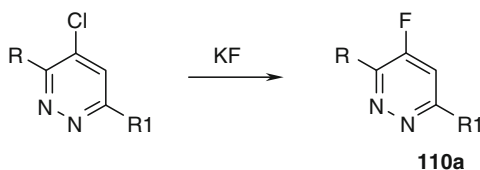
**Scheme 63** Catalytic properties of *N*-fluoropyridinium triflate (**108a**)

Monofluorinated pyrimidines are of special importance among other fluorinated azoles due to the anticancer properties of 5-fluorouracyl, commonly known as **5-FU** [95]. Several methods for the synthesis of **5-FU** are known, including the industrially important direct fluorination of uracyl (Scheme 64), and the more laboratory-convenient fluorination with Selectfluor® [96]. Other monofluorinated pyrimidines can be prepared by nucleophilic fluorination of corresponding chloropyrimidines. A pyrimidine ring is substantially more activated compared to a pyridine ring so these substitution reactions usually proceed in relatively mild conditions [97].



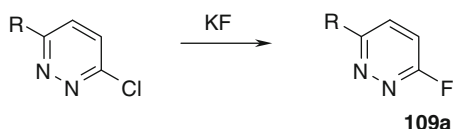
**Scheme 64** Preparation of 5-fluorouracyl (**5-FU**)

Ionic liquids were successfully used in the preparation of substituted 4(5)-fluoropyridazines (**110a**, Scheme 65). The yields were moderately better under the microwave-heating conditions. The results were indicative of an assumption that the 4(5)-positions in these monochlorinated pyridazines are more active toward nucleophilic fluorination compared to the 3(6)-positions [98]. A different activity pattern was observed for polychlorinated pyridazines: the 4(5)-positions were found to be less active than the 3(6)-positions [99].



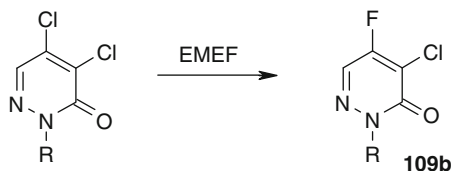
**Scheme 65** Nucleophilic fluorination of 4(5)-chloropyridazines

Substituted 3(6)-fluoropyridazines (**109a**) were prepared from corresponding 3(6)-chloropyridazines and KF in the presence of a phase transfer agent (Scheme 66). The use of a phase transfer agent for chlorine–fluorine exchanges improves the yields of fluoropyridazines [100]. The “proton sponge”/Et<sub>3</sub>N•3HF system is also an efficient fluorinating reagent for the synthesis of substituted 3(6)-fluoropyridazines (**109a**) via halogen exchange [86, 101].



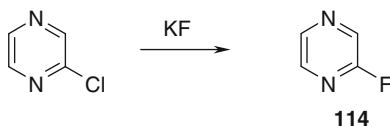
**Scheme 66** Nucleophilic fluorination of 3(6)-chloropyridazines

Various 4-fluoropyridazinones **109b** were prepared by nucleophilic fluorination with a novel fluorinating reagent, *N*-ethyl(hexamethylenetetraammonium) fluoride (EMEF, Scheme 67). Good regioselectivity was observed in the presence of the two chlorine atoms [102].



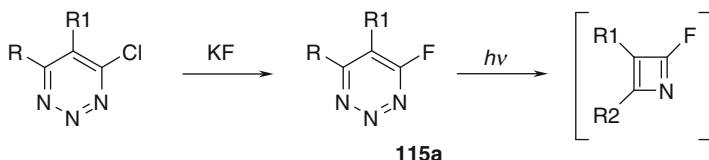
**Scheme 67** Synthesis of 4-fluoropyridazinones **109b**

The simplest method for the synthesis of the parent 2-fluoropyrazine (**114**) entails nucleophilic fluorination of 2-chloropyrazine with KF in *N*-methylpyrrolidone (Scheme 68) [103]. This method, with some variations, is applicable for the preparation of a variety of substituted 2-fluoropyrazines [104].



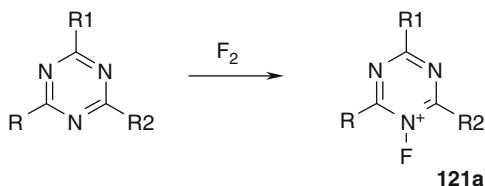
**Scheme 68** Synthesis of 2-fluoropyrazine (**114**)

Derivatives of C-fluorinated triazines (**115**, **116**, **117**, **118**, **119**, and **120**) can be prepared by nucleophilic fluorination of corresponding chlorinated triazines [105, 106]. The fluorine atom in C-fluorinated triazines is activated by the presence of three nitrogen atoms and allows facile synthesis of other functionalized triazines [105, 106]. Photolysis of C-fluorinated 1,2,3-triazines **115a** leads to transient formation of unstable fluoroazetes via the loss of N<sub>2</sub> (Scheme 69) [107].



**Scheme 69** Synthesis and photolysis of 4(6)-fluoro-1,2,3-triazines **115a**

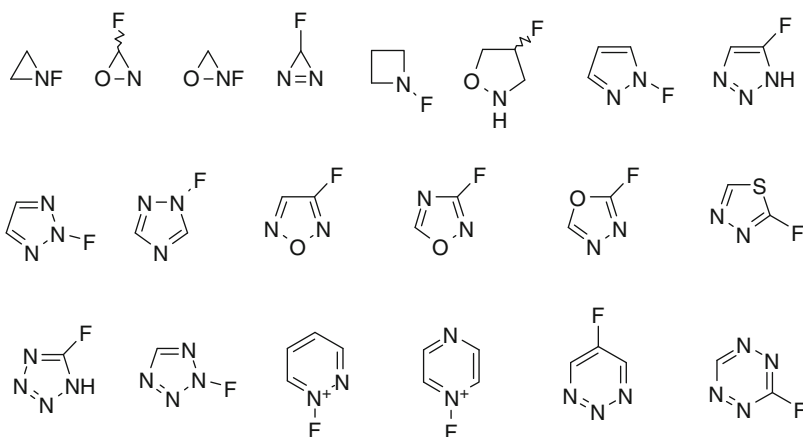
Derivatives of the N-fluorinated 1,3,5-triazinium cation (**121**) are also known. They were prepared by the action of elemental fluorine on the corresponding 1,3,5-triazines (Scheme 70) [108]. Substituted 1-fluoro-1,3,5-triazinium salts **121a** are potent electrophilic fluorinating agents capable of fluorinating nonactivated aromatic compounds [109]. The crystal structure of 1-fluoro-2,4,6-trimethoxy-1,3,5-triazinium cation revealed very short N<sup>+</sup>-F bond typical of these types of compounds [110].



**Scheme 70** Synthesis of 1-fluoro-1,3,5-triazinium salts **121a**

## 6 Conclusions: The “Wish List”

Several years ago, we noted several “white spots” on the map of fluorinated heterocycles – compounds whose convenient synthesis, elucidation of physical–chemical properties, and subsequent utilization might be of academic and practical interest [1]. Many of these compounds were monofluorinated heterocycles, including 3-fluorothiazole (49), the facile synthesis of which was reported in 2008 [51]. Parent monofluorinated heterocycles with several heteroatoms, and N-fluorinated heterocycles deserve particular attention since only a few of them are currently available. Some heterocycles from our current “wish list” are presented below (Fig. 6).



**Fig. 6** Monofluoroheterocycles – the “wish list”

**Acknowledgments** This chapter – a contribution from the Discovery Chemistry Project – is dedicated to the memory of Kirill Gennadievich Nikishin (1967–2010).

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