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Review

Synthesis of fluorofurans and perfluoroalkylfurans

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ABSTRACT

In spite of a large number of publications describing the preparation of fluorinated furan derivatives, there is no systematized overview of the methods of their synthesis. In the present work we try to fill this gap and review the main schemes of syntheses of fluorofurans and perfluoroalkylfurans which contain a perfluoroalkyl group in the heterocycle and in the α-position of the carbon chain of substituents in the furan ring.

Contents

Abbreviations: Ac, acetyl; Acac, acetyl acetone; Bn, benzyl; Bz, benzoyl; *m*CPBA, *m*chloroperbenzoic acid; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCE, 1,2-dichloroethane; DCM, dichloromethane; DMAP, 4-(N,N-dimethylamino)pyridine; DME, 1,2-dimethoxyethane; DMS, dimethylsulfide; DMSO, dimethylsulfoxide; Fur, furyl; Hex, hexyl; HMPA, hexamethyl phosphoric acid triamide; LDA, lithium diisopropylamide; LHMDS, lithium hexamethyldisilazide; Ms, mesyl; Py, pyridine; R_f, perfluoroalkyl; TBAB, tetrabutylammonium bromide; TBAF, tetrabutylammonium fluoride; TBS, *tert*-butyldimethylsilyl; TDAE, tetrakis(dimethylamino)ethylene; Tf, trifluoromethane sulfonyl; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; TFDA, $FSO_2CF_2COOSiMe_3$; TMS, trimethylsilyl; Tol, tolyl; TTMPP, tris(2,4,6-trimethoxyphenyl)phosphine.

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1. Introduction

Organofluorine compounds, most of which are virtually absent in nature, have found a wide application in the modern pharmacology, medicinal chemistry, agriculture, etc. [1–6]. It is known that nearly 25% of all drugs contain at least one fluorine atom. What is the reason? Obviously, the introduction of the fluorine atom into organic molecule affects its polarity, polarization, and consequently solubility, lipophilicity and other physical characteristics of a compound, generally not changing its spatial structure [7,8]. Usually one can observe some increase in the biological activity of a compound due to the facilitation of its migration through cell membranes.

Among many drugs based on organofluorine compounds, fluorine-containing heterocycles have a special place. It is enough to mention anticancer drug 5-fluorouracil, antiviral *Efavirenz*, and antibacterial *Flurithromycine* (Fig. 1).

The introduction of a fluorine atom or perfluoroalkyl group into a heterocycle affects its chemical, physical, and biological properties. Recent reviews of Furin [9–11] and Burger et al. [12] are devoted to the synthesis of fluorinated, mostly nitrogen containing, heterocyclic compounds.

Organofluorine compounds with important pharmacological properties often contain fluorofuran or perfluoroalkylfuran fragments in their structures (Fig. 2). Thus compound **1**, analog of *trovirdine* LY 300046 HCl, reveals high anti-HIV activity [13]. The effect of the derivative **2** is similar to that of *Docetaxel* (Taxotere®), which is used in cancer chemotherapy for the treatment of advanced ovarian and breast cancer [14]. Trifluoromethylfuran **3** is an agonist of the EP prostanoids [15]. The derivative **4** is an antagonist of oxytocin, a well-known agent for stimulating contractility in human myometrium that is widely used for the induction of labour [16]. Some derivatives of trifluoromethylfuran reveal also antibacterial [17] and antiparasite activity [18] (for example, compounds **5** and **6**).

In spite of a large number of publications describing the preparation of fluorinated furan derivatives, there is no systematized overview of the methods of their synthesis. In the present work we try to fill this gap and review the main schemes of syntheses of fluorofurans and perfluoroalkylfurans which contain a perfluoroalkyl group (R_f) in the heterocycle and in the α-position of the carbon chain of substituents in the furan ring. The review is organized according to the type of fluorine-containing structures (Fig. 3). We consider methods of syntheses of furans with fluorine atom in α-position, β-position, and polyfluorofurans. This principle of classification was also applied for furans with a perfluoroalkyl group. Due to some specificity of the syntheses of furans containing a perfluoroalkyl group in the α-position of substituents, e.g. nucleophilic trifluoromethylation, an independent section is devoted to these methods.

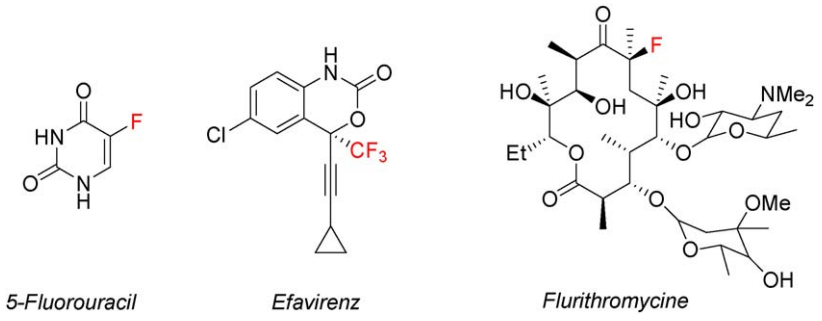


Fig. 1. Examples of fluorine-containing pharmaceuticals.

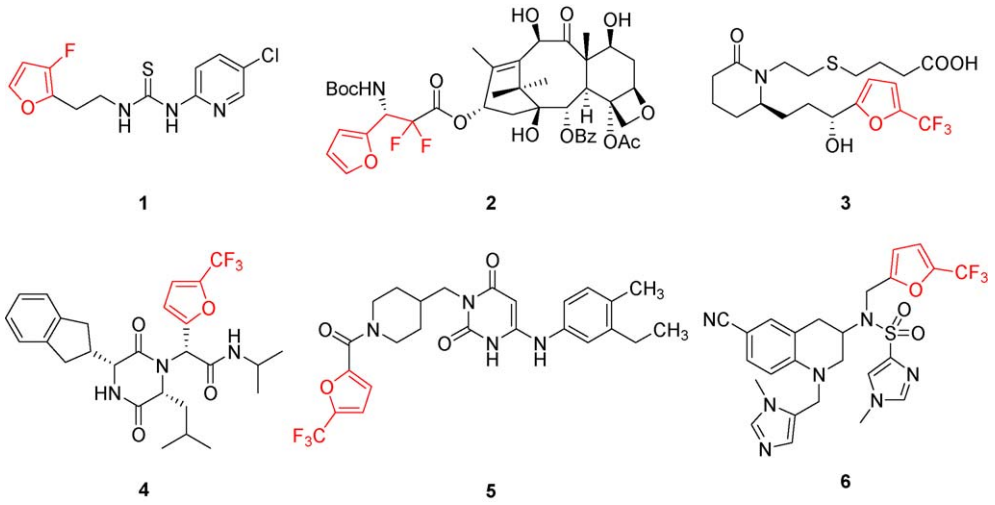


Fig. 2. Examples of fluorine-containing furans with pharmacological properties.

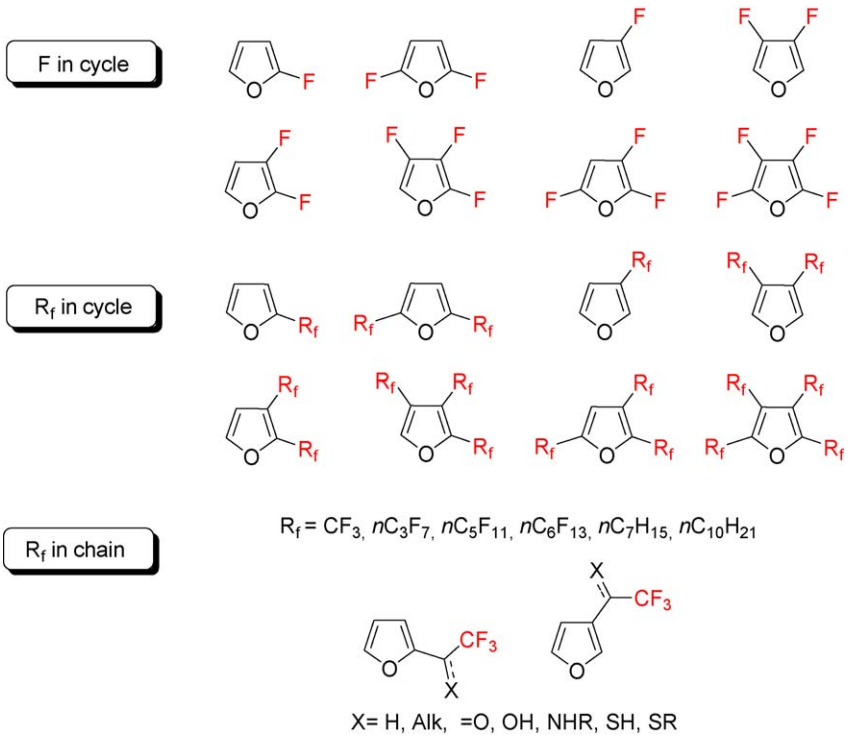


Fig. 3. Classification of fluorine-containing furans.

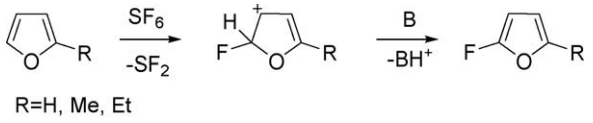
2. Synthesis of fluorofurans

All reported methods of fluorofuran synthesis can be classified into two main groups. The first one includes reactions of functionalization of the furan cycle; the second group includes heterocyclizations of different fluorinated precursors with the formation of the furan ring.

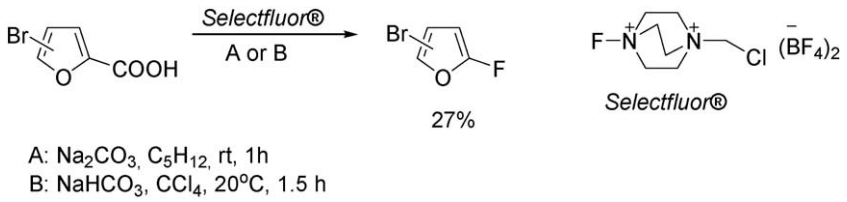
2.1. Synthesis of α-fluorofurans

2.1.1. Functionalizations of furan ring

The direct fluorination is a straightforward, but less selective and less effective method in the case of the furan cycle. Thus cesium fluoride CsF and gaseous fluorine F_2 allows to perform reactions with N-methylpyrrole and thiophene, but they are not suitable for the furan fluorination [19]. Selective introduction of the fluorine atom into the furan cycle is possible with the use of alternative electrophilic fluorinating agents and via combinations of fluorodecarboxylation or metallation–fluorination reactions. The suitable electrophilic agents for the furan fluorination are gaseous SF_3^+, produced by electron ionization of SF_6 and acting as a source of F^+, and *Selectfluor*®—1-(chlor-



Scheme 1.



Scheme 2.

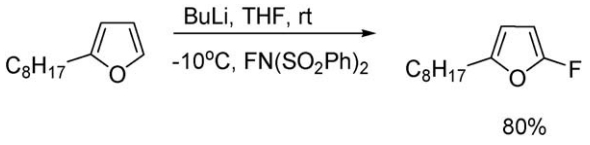
omethyl)-4-fluoro-1,4-diazobicyclo[2.2.2]octane tetrafluoroborate. In the first case, the obtained monofluorinated intermediates can be effectively deprotonated in a second reaction with a strong base such as N-methylpyrrolidine (Scheme 1) [20].

Authors [21,22] have used *Selectfluor* in fluorodecarboxylation of furan carboxylic acids. Thus the reaction of 2-bromo- and 3-bromofuran-5-carboxylic acids with *Selectfluor* in the presence of a base leads to corresponding fluorofurans at room temperature in a low yield (Scheme 2).

A more convenient method of α-fluorofurans synthesis is based on the metallation and reaction of 2-lithiofuran with a fluorinating agent such as N-fluoro-N-(phenylsulfonyl)benzenesulfonamide (Scheme 3) [23].

2.1.2. Heterocyclizations

An example of intermolecular heterocyclization with the formation of α-fluorofurans is the reaction of β,β-bis(trifluoromethyl) α,β-unsaturated ketones with tin (II) chloride and 1,5-electrocyclization [24,25]. The [4 + 1]-cycloaddition process of β,β-bis(trifluoromethyl) α,β-unsaturated ketones with tin (II) chloride results in the formation of a five-membered cycle, which undergoes heterolytic bond cleavage on heating to give dipolar species. The positive charge is localized at the metal center, and the negative charge is stabilized by a bis(trifluoromethyl)-substituted allylic anion, that weakens C–F bonds and fluoride elimination becomes possible. After splitting off the Sn fragment, an oxapentadienyl anion is formed. Its protonation in the presence of water gives 1-aryl-4,4-difluoro-3-(trifluoromethyl)but-3-en-1-ones (Scheme 4). The transformation of the latter into fluorinated furans has been achieved upon treatment with sodium hydride or LDA in DMSO or DMF at room temperature (Scheme 5) [26].



Scheme 3.

2.2. Synthesis of β-fluorofurans

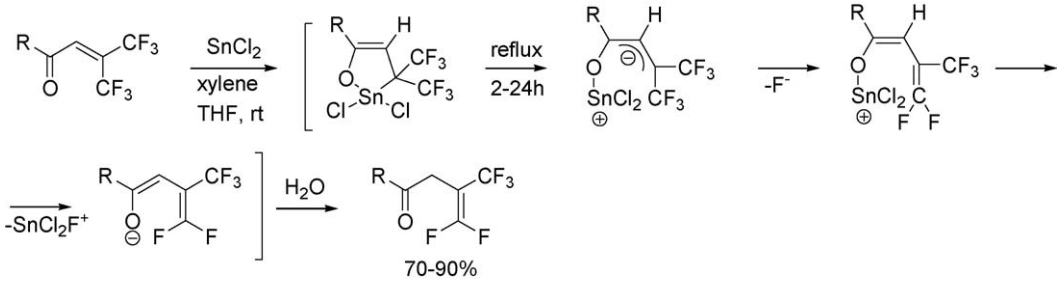
2.2.1. Functionalizations of furan ring

The metallation of the furan cycle can also be used in the synthesis of β-fluorofurans. Thus the lithiation of 3-bromo-2-*n*-octylfuran and reaction of the corresponding 3-lithiofuran with N-fluoro-N-(phenylsulfonyl)benzenesulfonamide gives 3-fluoro-2-*n*-octylfuran (Scheme 6) [23].

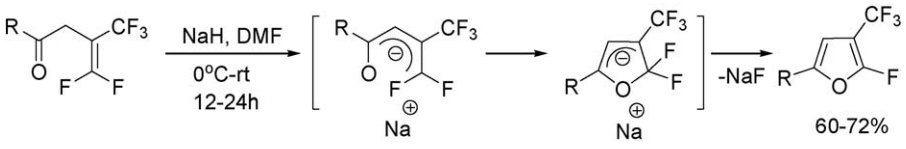
2.2.2. Heterocyclizations

β-Fluorofuran derivatives are obtained via metallation-silylation of 3-fluorofuran-2(5H)-ones formed as a result of acid-catalyzed cyclization of 2-fluoroalk-2-enoates (Schemes 7 and 8) [27,28]. The starting compound in the synthesis of 4-chloro-3-fluorofuran-2(5H)-one can be sodium salt of 2,3,4-trichloro-2-fluorobutanoic acid (Scheme 8) [29].

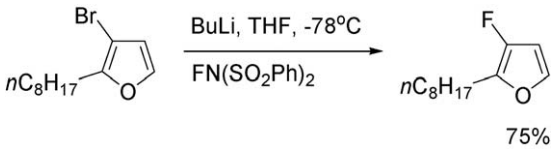
Another described method of the synthesis of β-fluorofurans is based on the cyclization with the participation of activated



Scheme 4.



Scheme 5.

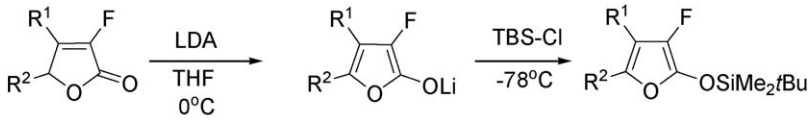


Scheme 6.

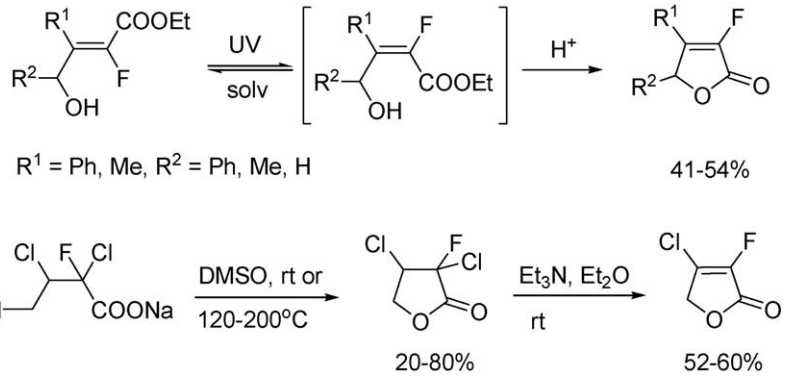
electron deficient triple bond. *gem*-Difluorohomopropargyl alcohols give 3,3-difluoro-4,5-dihydrofurans in the presence of catalytic amounts of $AgNO_3$. Treatment of these dihydrofurans with SiO_2 yields the corresponding 3-fluorinated furans. The aromatization takes place even during silica gel chromatography or distillation. Attempts to induce aromatization using basic (NaOH, *t*BuOK, NaH) or acidic ($BF_3{\cdot}Et_2O$, BCl_3) conditions have failed completely (Scheme 9) [30]. The cyclization can be induced by ICl in refluxing THF in the presence of the base Na_2CO_3. The microwave irradiation of the reaction mixture for 5 min gives 3-fluorinated furans in 62–76% yields when R = *n*Hex, R^1 = Ph, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, and nonaromatic 3,3-difluoro-4,5-dihydrofurans when R = *n*Hex, $R^1 = BnOCH_2$; $R = BnOCH_2$, R^1 = Ph; $R = R^1$ = Ph [31].

Treatment of difluoroalcohol with potassium *tert*-butoxide in *tert*-butylalcohol provides 3-fluorofurans in one step (Scheme 10) [32]. The possible mechanism of the furan ring-closure includes the formation of acetylenic epoxide intermediate.

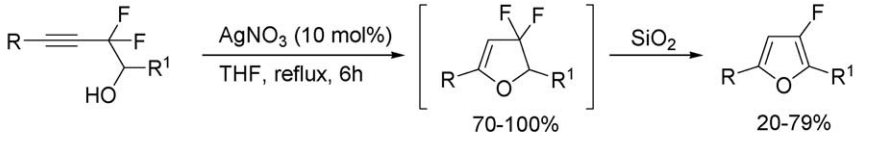
Another method of the synthesis of β-fluorofurans involves acidic hydrolysis of *gem*-difluorocyclopropyl acetals and ketals formed in difluorocarbene [1 + 2]-cycloaddition to 1,3-dioxolanes of α,β-unsaturated aldehydes and ketones (Scheme 11). The mechanism of transformation includes the formation of a cation with subsequent simultaneous furan ring closure (Scheme 12). In the case of *gem*-difluorocyclopropyl acetals and ketals with the donating methoxy group in *p*-position of the phenyl ring, furans are the sole isolated products. Acetals with electron-withdrawing groups in *p*-position of aromatic ring give the mixture of fluorofurans and *gem*-difluorocyclopropyl ketones with a predom-



Scheme 7.

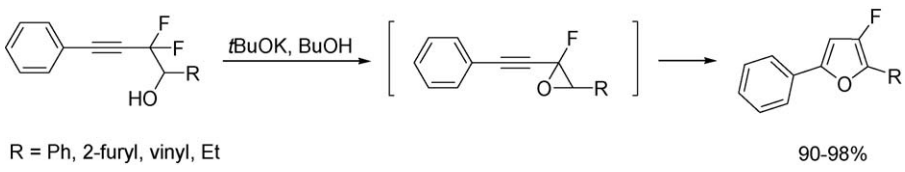


Scheme 8.

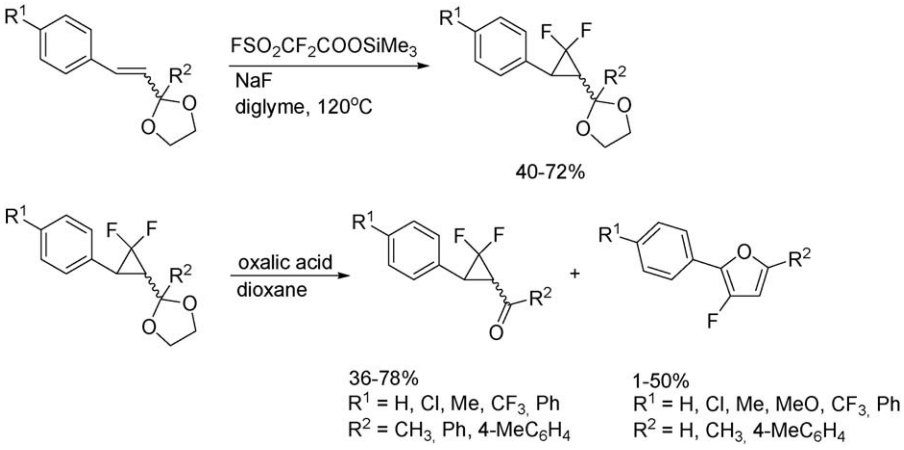


R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2,4-$Me_2C_6H_3$, 4-ClC_6H_4, 4-$CF_3C_6H_4$, 2-FC_6H_4
R = H, Ph, TIPS, *n*Hex, $BnOCH_2$

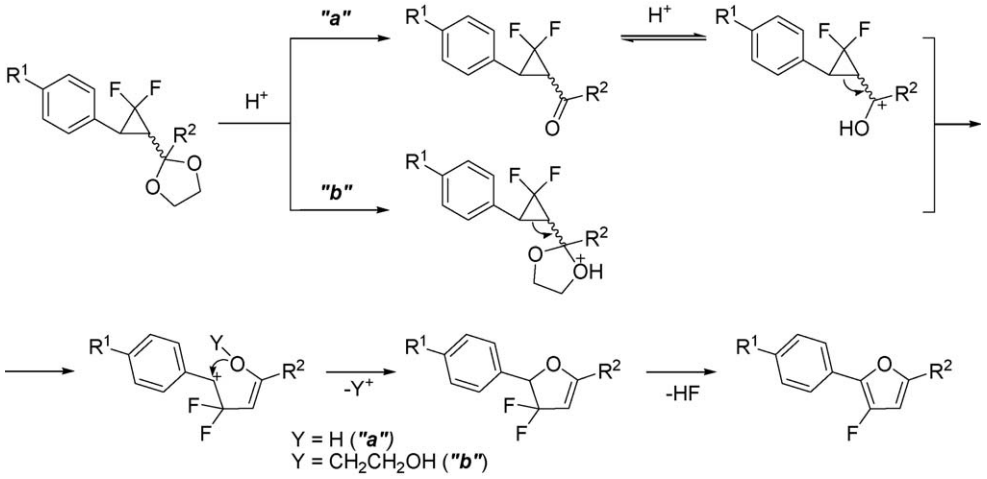
Scheme 9.



Scheme 10.



Scheme 11.



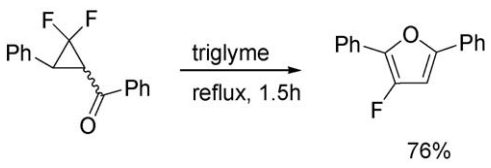
Scheme 12.

inance of the latter. The hydrolysis of ketals containing electron-withdrawing groups yields ketones as the sole or major products [33].

The fact that 1-benzoyl-2,2-difluoro-3-phenylcyclopropane gives 3-fluoro-2,5-diphenylfuran upon heating for 1.5 h at 216 °C in high yield, can be an evidence to the proceeding of the reaction via path "a" (Schemes 12 and 13) [34].

2.3. Synthesis of polyfluorofurans

The scheme of the synthesis of tetrafluorofuran, which was the first prepared tetrafluorinated five-membered aromatic heterocycle, consists in the reaction of tetrahydrofuran with cobalt trifluoride at 100–120 °C and the treatment of mixed isomers with aqueous alkali [35]. The reaction results in the mixture of fluorinated derivatives, but the yields of trifluoro- and difluorofurans are lower in comparison to tetrafluorofuran (Scheme 14) [36].

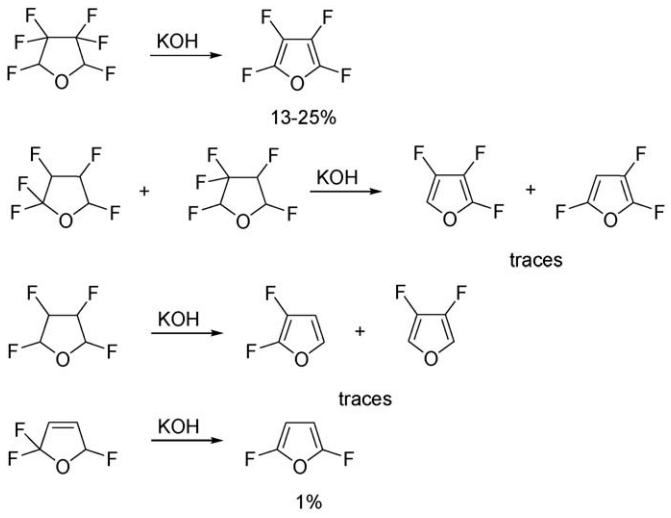


Scheme 13.

3. Synthesis of perfluoroalkyl- and fluoroalkylfurans

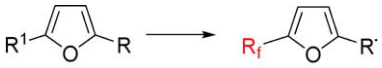
3.1. Synthesis of α-perfluoroalkylfurans

All methods of perfluoroalkylfurans synthesis can also be classified into two main groups: functionalizations of the furan



Scheme 14.

Table 1
Synthesis of α-fluoroalkyl and α-perfluoroalkylfurans via transformation of α-substituent.



$R^1 \rightarrow R_f$	R	Reactant	Conditions	Yield (%)	References
$COOH \rightarrow CF_3$	$COOH \rightarrow CF_3$	SF_4	185 °C, 45 h	50	[37,38]
$CHO \rightarrow CHF_2$	NO_2	SF_4	65 °C, 8 h	28	[39]
$COCH_3 \rightarrow CF_2CH_3$	NO_2	SF_4	75 °C, 10 h	25	[39]
$COOH \rightarrow CF_3$	NO_2	SF_4	120 °C, 7 h	37	[39]
$CH_2OH \rightarrow CH_2F$	H	SF_4	−50 °C, 24 h, Et_3N, cyclohexane or CH_2Cl_2	20	[40]
$COOH \rightarrow CF_3$	NO_2, COOH	SF_4, HF	40–50 °C, 24 h	65–81	[41]

ring and heterocyclizations of different precursors. Among well-known methods of α-perfluoroalkylfurans synthesis based on furan derivatives one can distinguish the direct introduction of fluoroalkyl group into α-position of the furan ring and transformations of existent α-substituents.

3.1.1. Functionalizations of furan ring

In α-fluoroalkyl and α-perfluoroalkylfurans syntheses based on the fluorination of existent α-substituents in the furan ring, furan-2-carboxylic acids, aldehydes, ketones, and alcohols are common substrates (Table 1) [37–41].

Thus the reaction of the furan-2,5-dicarboxylic acid with sulfur tetrafluoride at 180 °C leads to 2,5-bis(trifluoromethyl)furan. 5-(Trifluoromethyl)furan-2-carboxylic acid is also formed in 4% yield as a minor product of this transformation [37,38].

5-Nitrofuran-2-carboxylic acid and 2-acetyl-5-nitrofuran give 2-difluoromethyl-5-nitrofuran and 2-(α,α-difluoroethyl)-5-nitrofuran correspondingly under similar conditions at 120 °C [39].

The reaction of 2-furylmethanol with sulfur tetrafluoride in the presence Et_3N at −50 °C results in formation of 2-fluoromethylfuran in 20% yield [40].

The fluorination of furan-2-carboxylic acids in anhydrous HF proceeds under milder conditions (40–50 °C) and gives 2-trifluoromethylfurans in 65–81% yields [41].

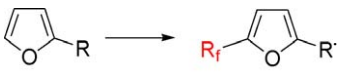
For the direct introduction of perfluoroalkyl groups into aromatic substrates several approaches can be employed, namely nucleophilic, electrophilic, and radical perfluoroalkylation [42]. Radical perfluoroalkylation can be performed under thermal, photolytic, oxidative, and reductive conditions.

The thermal trifluoromethylation of furan with CF_3I results in formation of α-trifluoromethylfuran in low yields: 10% at 120 °C and 19% at 160 °C (Table 2) [43–54]. Upon using $Te(CF_3)_2$ as a trifluoromethylation agent the yield of α-trifluoromethylfuran increases. However, small amounts of dihydrofuran derivatives are also formed along with the product of the substitution (Scheme 15) [43].

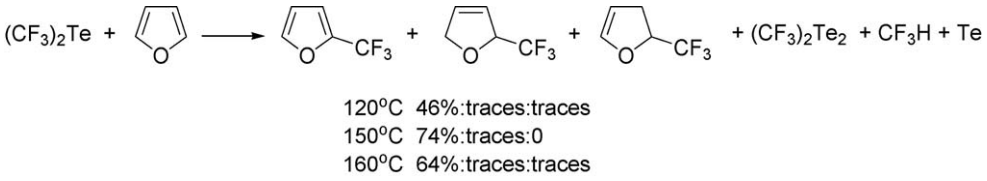
The reaction of furan with $nC_{10}F_{21}I$ proceeds at 190 °C in 58% yield [44]. The photolytic trifluoromethylation of furan derivatives is usually performed with CF_3I, which can easily generate trifluoromethyl radical. Thus unsubstituted furan gives the 2-trifluoromethyl derivative in 40% yield (168 h) [43]; 2-nonylfuran does in 51% yield (40 h) [44]. The mixture of the aromatic and nonaromatic products is formed upon using of $Te(CF_3)_2$ or $Sb(CF_3)_3$. In this case, the yields of α-trifluoromethylfuran amount to 24 and 12%, respectively. Trifluoromethylation of furan with $Hg(CF_3)_2$ almost does not proceed.

The convenient method of introduction of perfluoroalkyl groups is based on the use of perfluorocarboxylic acids and XeF_2. For example, the reaction of CF_3COOH with XeF_2 gives xenon (II) trifluoroacetate, decomposing at room temperature with the formation of trifluoromethyl radical. Such transformations allow us to introduce various perfluoroalkyl groups into aromatic substrates under mild conditions (Table 2) [46–48].

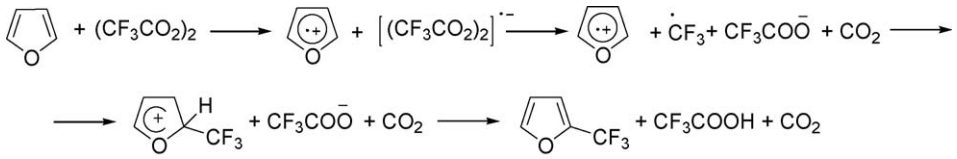
Table 2
Synthesis of α-perfluoroalkylfurans via radical and electrophilic substitution of hydrogen.



R_f	R	Reactant	Conditions	Yield (%)	References
CF_3	H	CF_3I	160 °C, 240 h	19	[43]
CF_3	H	$Te(CF_3)_2$	150 °C, 30 h	74	[43]
$nC_{10}F_{21}$	H	$nC_{10}F_{21}I$	190 °C, 24 h 180 °C, 4 h	58 48	[44]
CF_3	H	CF_3I	rt, hν, 148 h	40	[43]
CF_3	nC_9H_{19}	CF_3I	rt, hν, 40 h	51	[45]
CF_3	H	$Te(CF_3)_2$	rt, hν, 264 h	24	[43]
nC_3F_7	COOMe	nC_3F_7COOH, XeF_2	CH_2Cl_2, 35 °C, 2 h	33	[46]
CF_3	CHO	CF_3COOH, XeF_2	CH_2Cl_2, 0–20 °C, 2 h	30	[48]
nC_3F_7	H, CH_3, CH_3OCO	$(nC_3F_7CO_2)_2$	Freon-113, 40 °C, 3 h	17–98	[49]
CF_3	H	$(CF_3CO_2)_2$	Freon-113, 60 °C, 5 h	53	[50]
CF_2Cl	CH_3O	$(CF_2ClCO_2)_2$	Freon-113, 60 °C, 4 h	34	[51]
$CFCF_3(OCF_2CFCF_3)_nOnC_3H_7$	H	$(nC_3F_7O(CFCF_3CF_2O)_n\ CFCF_3COO)_2$	40 °C, 5 h	62($n=0$) 71($n=1$) 96($n=2$)	[52]
CF_3	H	$CF_3I(Ph)OSO_2CF_3$	CH_2Cl_2, rt, 30 min	87	[53]
nC_3F_7	H	$[nC_3F_7Fe(CO)_4]^+BF_4^-$	AgF, rt, 15 h	40	[54]



Scheme 15.



Scheme 16.

Bis(perfluoroacyl)peroxides obtained from perfluorocarboxylic acids anhydrides and hydrogen peroxide in Freon $CF_2ClCFCl_2$ can also be used as perfluoroalkylation agents (Scheme 16) [49].

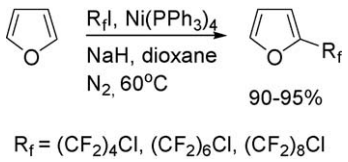
The reaction of furan with bis(perfluoroacetyl)peroxide results in the formation of trifluoromethylation product at 60 °C in 53% yield [50]. The trifluoromethylation proceeds via electron transfer from the substrate to peroxide and further decomposition of anion-radical with generation of trifluoromethyl radical. The reaction of the latter with furyl cation-radical leads to the final product. The proposed mechanism is shown in Scheme 16. 2-Methoxyfuran reacts with $(CF_2ClCO_2)_2$ under the same conditions to give 5-difluorochloromethyl-2-methoxyfuran [51].

Electrophilic perfluoroalkylation of furan derivatives is usually performed with the use of iodonium salts $R_fI(Ar)X$, where perfluoroalkyl radical is bonded with a heteroatom bearing a positive charge. Thus the trifluoromethylation of furan with $CF_3I(Ph)OSO_2CF_3$ proceeds in DCM at room temperature for 30 min in 87% yield (Table 2). 2,6-Di-*tert*-butyl-4-methylpyridine is used as a base in this reaction [53].

Cationic complex $[C_3F_7Fe(CO)_4]^+BF_4^-$ can also act as perfluoroalkylation agent. The reaction proceeds via electrophilic substitution and leads to the product in low to moderate yields [54] (Table 2).

The reaction with R_fI in the presence of tetrakis(triphenylphosphine)nickel and sodium hydride represents an example of catalytic perfluoroalkylation. The transformation takes 3–8 h; the yields of α-fluoroalkylfurans amount to 90–95% (Scheme 17) [55].

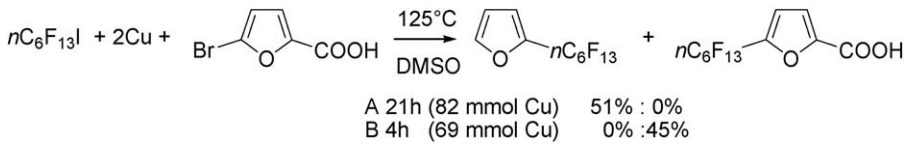
Along with the substitution of the hydrogen atom in the furan cycle, to introduce perfluoroalkyl group one can use the substitution of halogen. For example, 5-bromo-furan-2-carboxylic acid reacts with $nC_6F_{13}I$ in the presence of copper with the formation of products of perfluoroalkylation and reductive dehalogenation (Scheme 18; the yields of isolated products are cited) [56]. The reaction proceeds in DMSO at 125 °C. When preformed organocopper compound $C_6F_{13}Cu$ is used (method B), the time of transformation sharply decreases. The major product in this case is 5-perfluoroalkylfuran-2-carboxylic acid.



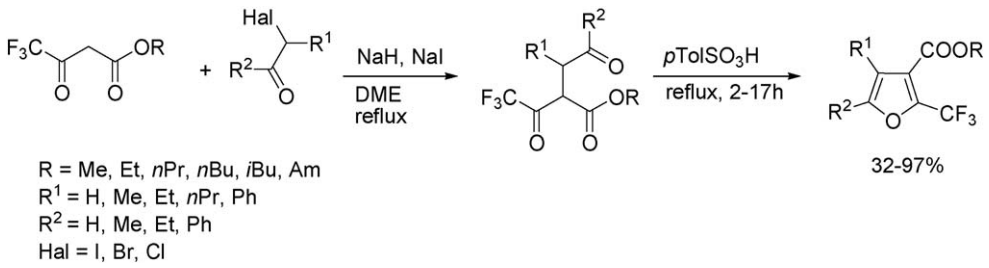
Scheme 17.

3.1.2. Heterocyclizations

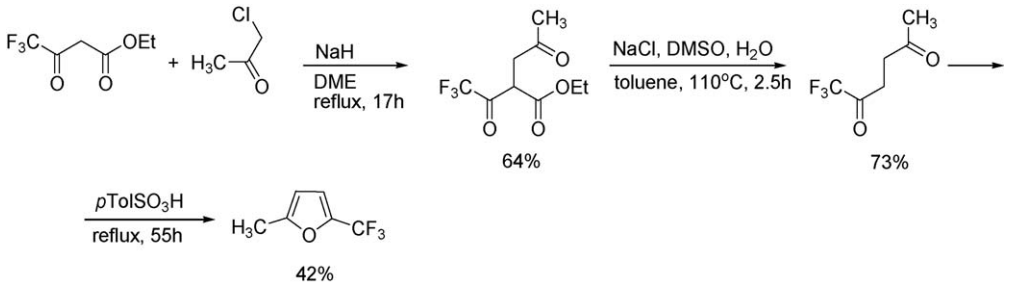
The main part of the methods of α-trifluoromethylfurans synthesis via heterocyclizations is based on transformations of trifluoromethyl ketones or tautomeric trifluoromethyl allylic alcohols derivatives. The cyclization of trifluoromethyl 1,4-diketones has found wide applications in everyday practice. The mentioned diketones are readily available via alkylation of trifluoroacetoacetates [57–63]. Obtained esters of 2-trifluoromethylfuran-2-carboxylic acids serve as starting compounds in the synthesis of corresponding acids, alcohols, and furans (Scheme 19) [64].



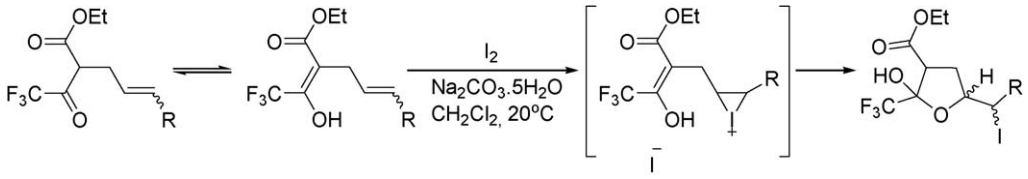
Scheme 18.



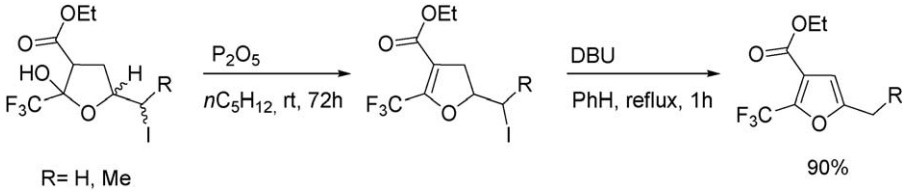
Scheme 19.



Scheme 20.



Scheme 21.



Scheme 22.

Decarboxylation can precede the heterocyclization step. Thus improved synthesis of 2-methyl-5-trifluoromethylfuran consists in alkylation of ethyl 4,4,4-trifluoroacetoacetate with chloroacetone, hydrolysis, decarboxylation, and final cyclization of 1,1,1-trifluoro-2,5-hexanedione in the presence of *p*TolSO$_3$H (Scheme 20) [63].

2-Trifluoromethylated tetrahydrofurans obtained via iodocyclization of γ-unsaturated ethyl trifluoroacetoacetates also can serve as precursors of fluorinated furans [65]. The reaction is usually performed in an aprotonic solvent such as MeCN or DCM in the presence of sodium carbonate or hydrogen carbonate and iodine. The proposed mechanism involves attack on the iodonium ion by the oxygen atom of the enolate leading to tetrahydrofuran (Scheme 21). The final aromatization is achieved by successive treatment with P_2O_5 in *n*-pentane and DBU in refluxing benzene (Scheme 22).

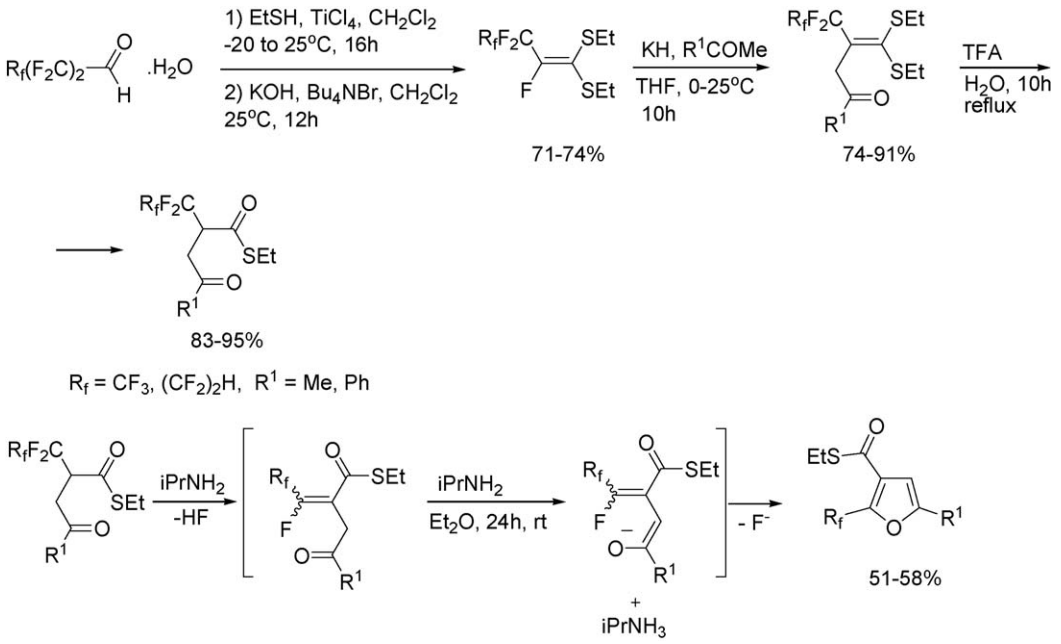
γ-Ketothioesters are easily transformed into furans in one step by simple treatment with diisopropylamine in diethyl ether. The mechanism of transformation includes HF elimination, deprotonation, and intramolecular Michael addition/fluoride elimination sequence (Scheme 23). Starting γ-ketothioesters are available from perfluoroketene dithioacetals [66–68].

The addition of thiophenol to γ-hydroxy α,β-unsaturated trifluoromethyl ketones in the presence of a base also results in heterocyclization (Scheme 24). The tetrahydrofuran intermediate is easily converted to furan upon the treatment with concentrated sulfuric acid in refluxing benzene or toluene [69].

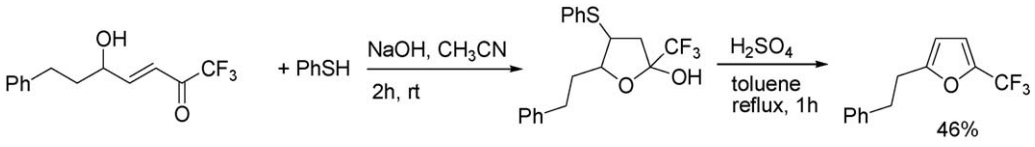
Other method of α-trifluoromethylfurans synthesis is based on Ag-catalyzed intramolecular cyclization of 3-aryl-2-(2-phenylethynyl)-1-(trifluoromethyl)allyl alcohols, which are available from α,β-unsaturated trifluoromethyl ketones. The latter are transformed into the corresponding 1-iodinated intermediates by I_2 in pyridine. The reduction of keto-group according to Luche method and consequent coupling with phenylacetylene lead to the key intermediates, 3-alkynylallylic alcohols. The final cyclization is performed upon heating in the presence of AgOTf in DCE (Scheme 25) [70] The similar cyclizations of 3-alkynylallylic alcohols under basic conditions [71] or catalyzed by Ru [72] and Pd [73] were used for the synthesis of polysubstituted furans, but all attempts to obtain trifluoromethylfurans by these strategies have failed [74].

The oxidation of 4-aryl-1,1,1-trifluorobut-3-yn-2-ones in the system TFA-CH_2Cl_2-PbO_2 gives 2-aryl-4-arylcarbonyl-5-trifluoromethyl-3-trifluoroacetylfurans in 22–66% yield (Scheme 26) [75,76]. The formation of furans takes place in the case of ketones with electron-donating groups, such as methyl or methoxy groups. The unreactivity of ketones containing *tert*-butyl group in the phenyl ring can be explained by the difficulty of their oxidation. Further increase in the number of methoxy substituents or introduction of a methylenedioxy group favors strong oxidation to produce tarry products. The mechanism of the reaction (Scheme 26) includes the generation of radical-cation, which is able to react with the starting molecule. The oxidation of this radical-cation intermediate gives dication. Alternatively the latter can be formed as a result of dimerization of initially generated radical-cations. The cationic centers in the dication intermediate derived from trifluoromethyl ketones are highly electrophilic due to the presence of electron-withdrawing trifluoroacetyl groups; therefore, one of these centers is capable of reacting with such a relatively weakly nucleophilic center as the carbonyl oxygen atom of the $COCF_3$-group in the same molecule. The aromatization of intermediate and further hydrolysis lead to the 2-substituted 5-trifluoromethyl-3-trifluoroacetylfurans.

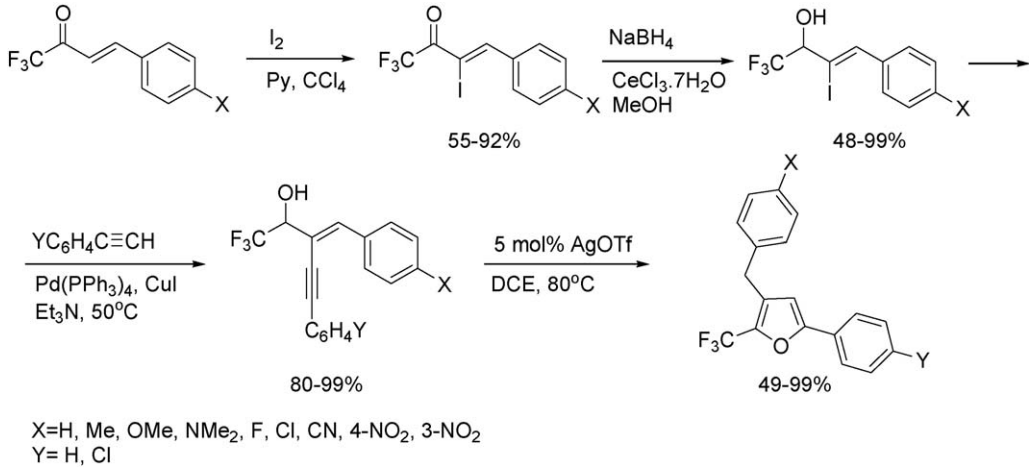
The simple route to the furans containing CF_3-group in the α-position of the cycle is based on thermolysis of β-keto trimethylsilyl enol ethers (Scheme 27). The transformation proceeds via the formation of α-allenic ketones. The starting ethers are available from the corresponding β-diketones and trimethylsilyl chloride [77].



Scheme 23.



Scheme 24.



Scheme 25.

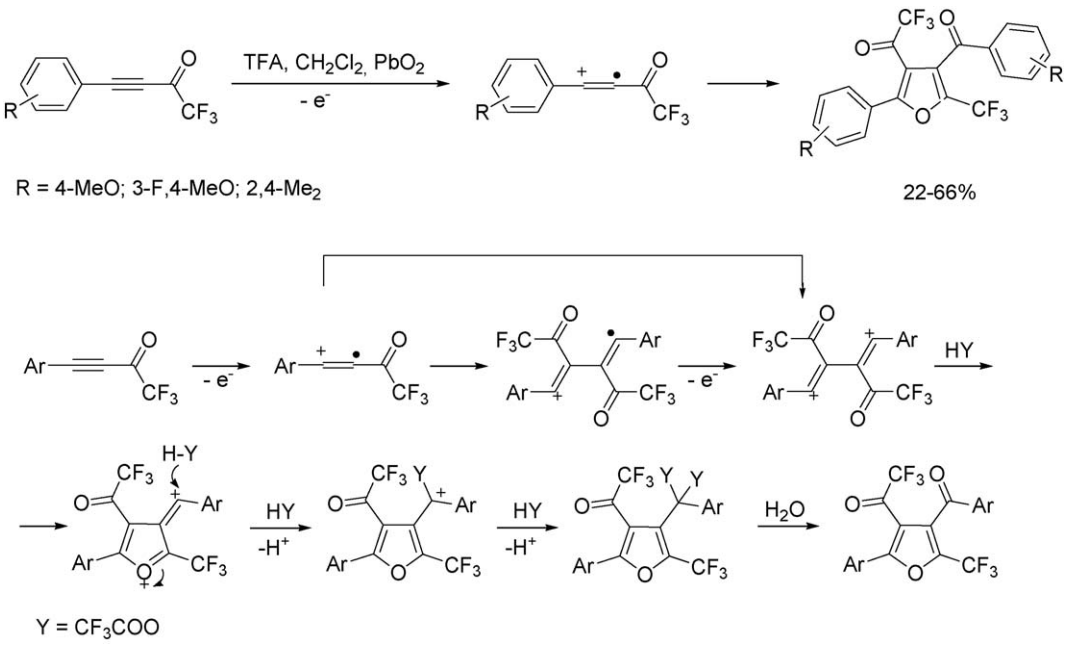
2,4-Disubstituted furans with fluoromethyl group in the position 2 are obtained from the allene oxides. The precursors of the latter are diepoxysilanes, which could be synthesized from the reaction of easily accessible α-substituted acroleins with vinylsilane followed by epoxidation of double bonds and elimination of the hydroxyl group (Scheme 28) [78].

5-Trifluoromethylfuran-3-one existing predominantly in the tautomeric 3-hydroxyfuran form is prepared from the condensation of the substituted oxirane with ethyl trifuoroacetate in the presence of sodium isopropoxide (Scheme 29) [79].

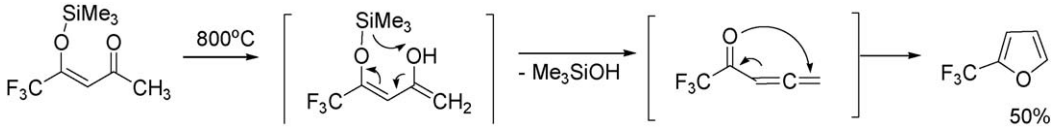
The cyclization of aminoketenimines formed as a result of the reaction of *t*-butyl isocyanide with 1,1,1-trifluoro-4-arylbutane-2,4-diones leads to trifluoromethyl-substituted 2,3-diaminofurans (Scheme 30). Probably, the initial α,α-addition of the CH-acid to the isocyanide and subsequent nucleophilic addition of another molecule of the isocyanide yields intermediate, which is converted into aminoketenimine system by proton transfer. The refluxing of aminoketenimines in chloroform for 2–5 h gives furans in 95–100% yields [80].

3.1.3. Cycloaddition

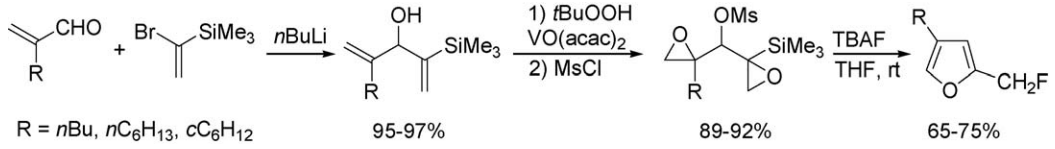
The convenient method of α-trifluoromethylfuran synthesis is based on the [4 + 2]-cycloaddition reaction of acetylenes to α-trifluoromethyloxadiazole derivatives and subsequent nitrogen



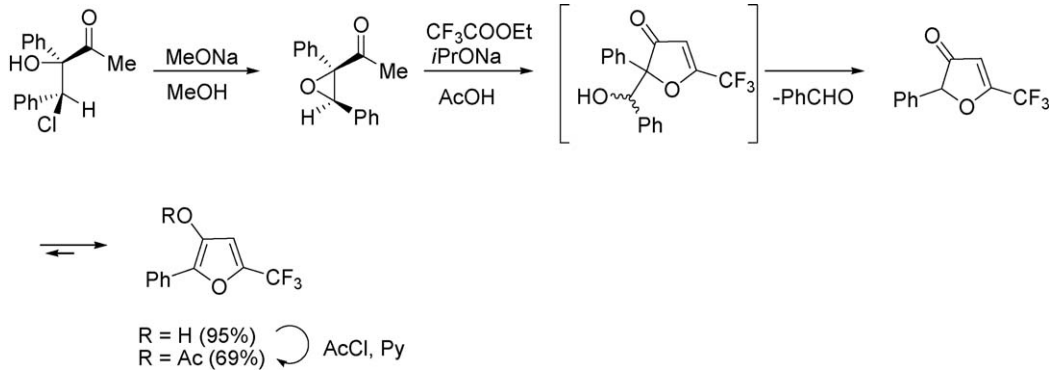
Scheme 26.



Scheme 27.



Scheme 28.



Scheme 29.

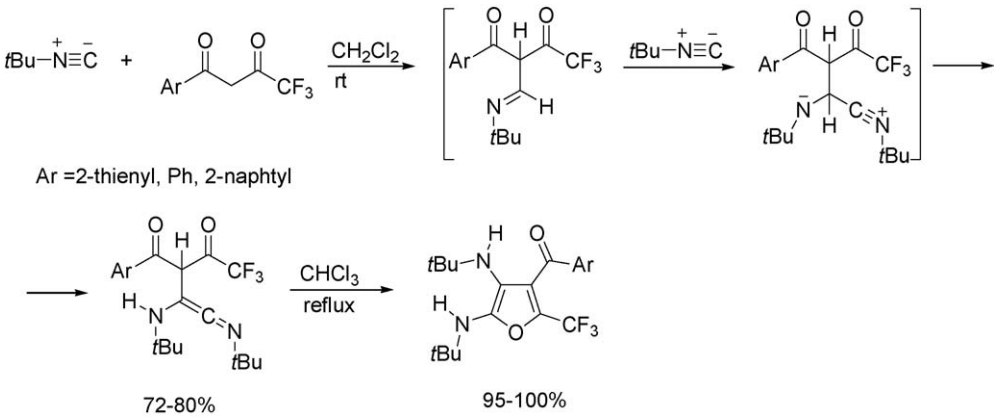
elimination (Scheme 31). The reaction proceeds under sufficiently mild conditions leading to α-trifluoromethylfurans in moderate yields [81].

Ethyl 2-diazo-fluoroalkylacetoacetates reacting with vinyl ethers in the presence of rhodium (II) can also be used as starting compounds in the heterocyclizations. Dihydrofurans obtained from the 1,3-dipolar cycloaddition to enol ether aromatize via alcohol elimination in the presence of acid [82]. The proposed mechanism is presented in Scheme 32.

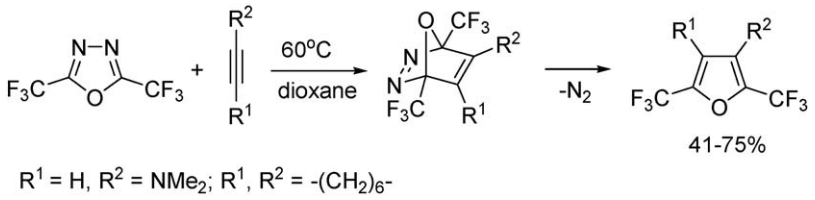
3.2. Synthesis of β-perfluoroalkylfurans

3.2.1. Functionalizations of furan ring

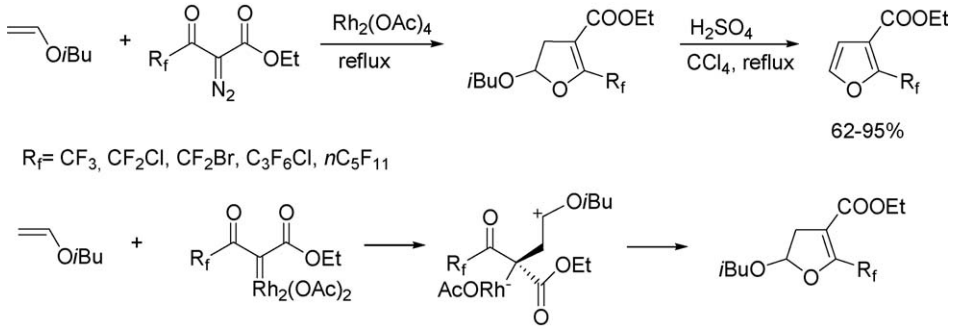
The direct introduction of trifluoromethyl group into the β-position of unsubstituted furan ring can be performed via gas-phase trifluoromethylation. The reaction is not selective and also leads to α-trifluoromethylfuran as a minor product (Scheme 33). The predominance of the β-substitution product in gas-phase can be explained by the formation of more stable intermediate III [83].



Scheme 30.



Scheme 31.

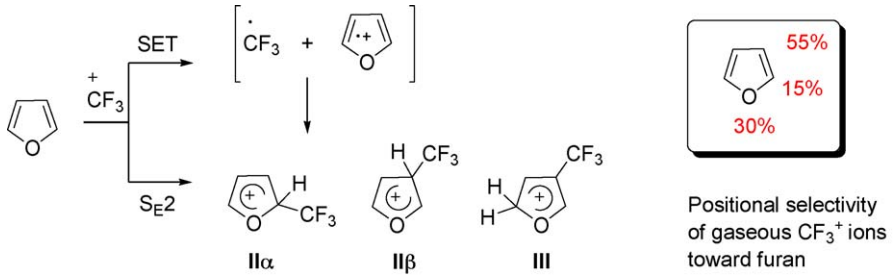


Scheme 32.

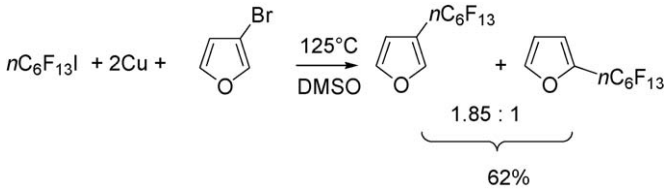
Preliminary electrostatic interactions also take place between n-electrons of furan and the cationic centers of the electrophile resulting in the formation of the covalently bonded oxonium intermediate, which may slowly rearrange to its more stable isomer IIα. The preference of CF_3^+-attack for β-carbons of furan (ca. 78%) confirms a substitution route proceeding via the classical S_E2 mechanism (Scheme 33).

The reaction of 3-bromofuran with $nC_6F_{13}I$ in the presence of copper in DMSO leads to the product of β-perfluoroalkylation (Scheme 34) [56]. 2-Perfluorohexylfuran is also formed as a minor product of this reaction.

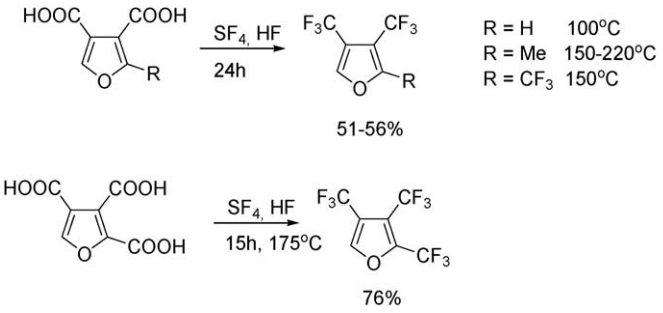
Among methods of β-trifluoromethylfurans synthesis via functionalization of the furan ring the fluorination of furan carboxylic acids should be noted. The reaction of furan-3,4-dicarbocylic acid with sulfur tetrafluoride in the HF medium at 100–120 °C gives 3,4-bis(trifluoromethyl)furan. The reaction of 2-methyl-, 2-trifluoromethyl furan-3,4-dicarbocylic acids and furan-2,3,4-tricarboxylic acid proceeds similarly at 150–220 °C (Scheme 35) [62,84]. Depending on the reaction temperature and amounts of sulfur tetrafluoride the products of complete and partial fluorination can be obtained (Scheme 36) [37]. The carboxylic groups at the position 3 are fluorinated easier than those in the position 2.



Scheme 33.



Scheme 34.



Scheme 35.

The fluorination of 2,5-dimethylfuran-3,4-dicarbocylic acid with sulfur tetrafluoride in the absence of HF also gives the mixture of trifluoromethyl derivatives with the predominance of 2,5-dimethyl-4-trifluoromethylfuran-3-carbocylic acid fluoride anhydride and 2-methyl-3,4,5-tris(trifluoromethyl)furan (Scheme 37) [85].

3.2.2. Heterocyclizations

One of the most well-known methods of β-trifluoromethylfurans synthesis is based on reaction of 3-bromo-1,1,1-trifluoropropanone with ethyl acetoacetate derivatives in the presence of a strong base. Obtained 4,5-dihydro-4-trifluoromethyl furans aromatize in the presence of pTolSO$_3$H (Scheme 38) [86].

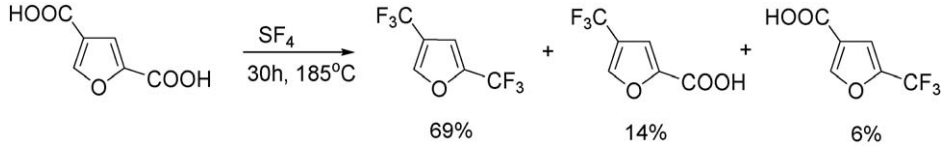
Alkylation of 4,4,4-trifluoroacetoacetate results in the formation of di(trifluoromethyl)dihydrofuran derivative. The final aromatization can be performed by heating of dihydrofuran in acetic anhydride in the presence of $ZnCl_2$ [63].

2,5-Diethyl-3,4-bis(trifluoromethyl)furan is formed upon treatment of 4,5-bis(trifluoromethyl)octa-3,6-dione with sulfuric acid at room temperature (Scheme 39) [87]. The starting diketone is obtained via the addition reaction of propionaldehyde to hexafluorobut-2-yne under γ-ray irradiation.

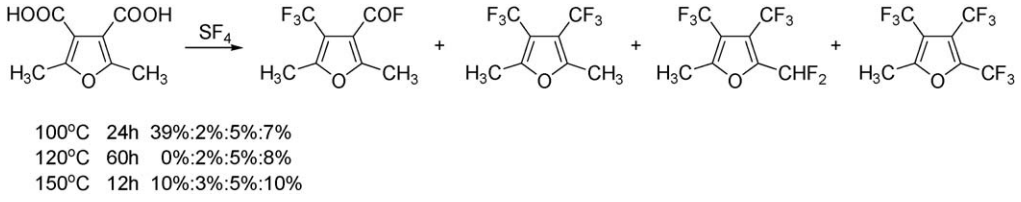
The simple method of 3,4-diperfluoroalkylfurans synthesis via the unique type of reaction of 1-alkyl-F-1-alkenyl phosphates catalyzed by fluoride-ion, leads to furan derivatives in 31–69% yields (Scheme 40) [88]. Among examined catalysts, TBAF appeared to be the most efficient. THF as a solvent gives more satisfactory results. The aromatization of intermediate dihydrofurans proceeds in the presence of triethylamine at room temperature. The proposed mechanism includes dephosphorylation followed by cyclocondensation reaction (Scheme 40).

The heterocyclization of 2-trifluoromethyl-4-hydroxy-dienes also affords 3-trifluoromethylfurans in high yields. 2-Bromo-2-trifluoromethylethenyl phenyl sulfide obtained *in situ* can serve as a precursor of trifluoromethyl phenylsulfanyl acetylene. The latter easily undergoes nucleophilic Michael addition reaction. Thus the reaction of methylene active compound with sodium hydride gives carbanion, which attacks acetylene in the β-position to afford diene with (1E,3E)-geometry. Due to the presence of the strong electron-withdrawing groups in the molecule the enol form is produced exclusively. The final cyclization is performed in refluxing decalin or acetic acid in the presence of sodium acetate and 1,4-benzoquinone (Scheme 41) [89].

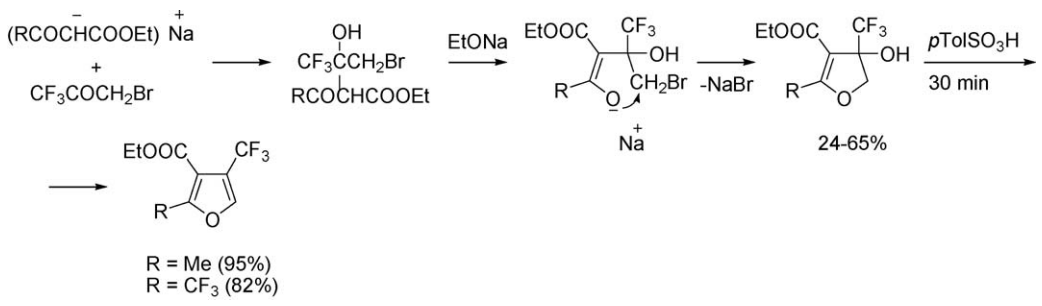
Substituted β-trifluoromethylfurans can be obtained from trifluoromethyl derivatives of (E)-2-en-4-ynoic alcohols formed as a result of palladium-catalyzed coupling of (E)-O-protected



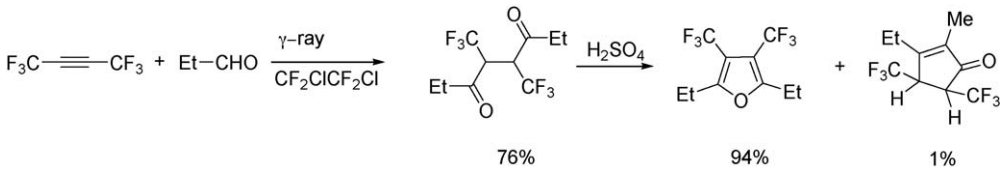
Scheme 36.



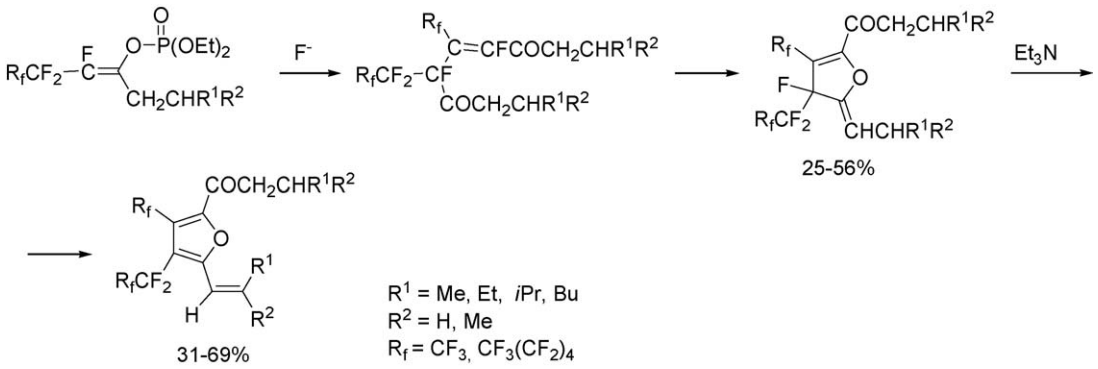
Scheme 37.



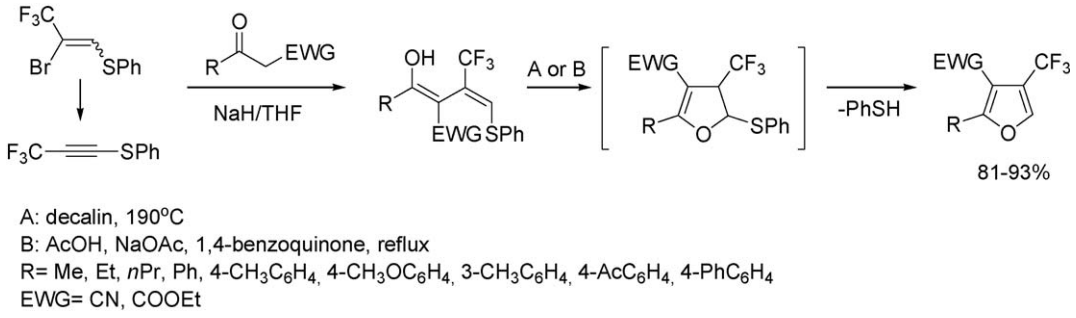
Scheme 38.



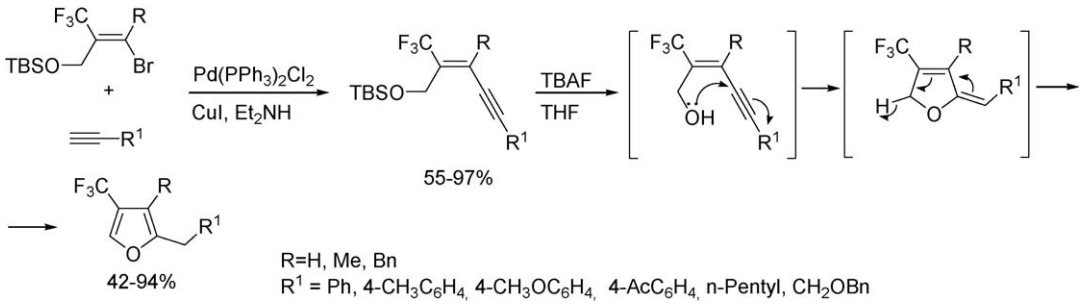
Scheme 39.



Scheme 40.



Scheme 41.



Scheme 42.

2-trifluoromethyl-1-bromo-1-substituted allylic alcohols with terminal alkynes [90]. The mechanism of the transformation includes the deprotection of TBS group followed by a ring-forming through intramolecular nucleophilic attack to alkyne in *5-Exo-Dig* mode and the final *in situ* aromatization of intermediates (Scheme 42).

3.2.3. Cycloaddition

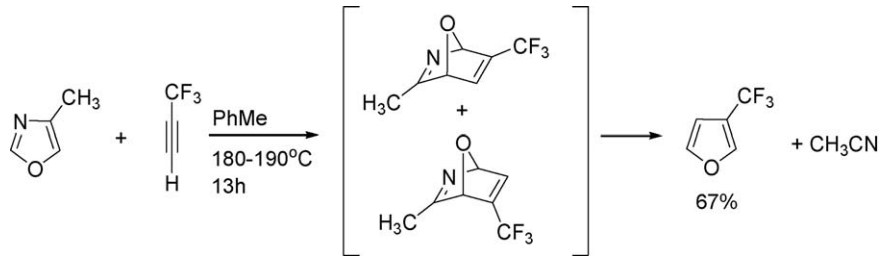
The convenient method of β-trifluoromethylfurans synthesis is based on Diels–Alder reaction followed by [4 + 2]-cleavage. For example, the reaction of 3,3,3-trifluoropropyne with 4-methyloxazole in toluene at 180–190 °C gives β-trifluoromethylfuran in 67% yield (Scheme 43) [91].

Furan can easily react with fluoroalkyl derivatives of acetylenes as heterodiene [92–96]. Intermediate 7-oxa-[2.2.1]-bicyclo-2,5-dienes afford β-trifluoromethylfurans upon hydrogenation and consequent pyrolysis (Scheme 44) [92,95–100] or via reaction with 2,3,4,5-tetraphenylcyclopentadienone (Scheme 45) [93,94]. This method allows to obtain furans with various perfluoroalkyl groups in one or two positions of the furan ring.

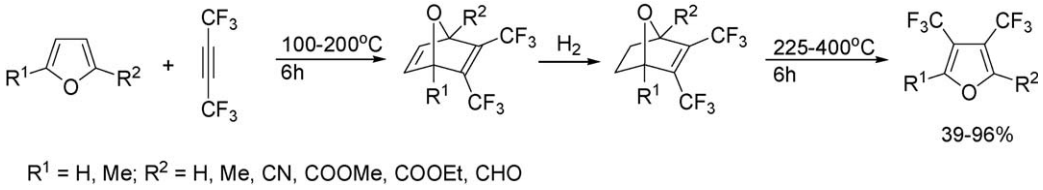
3.3. Synthesis of polyperfluoroalkylfurans

3.3.1. Functionalizations of furan ring

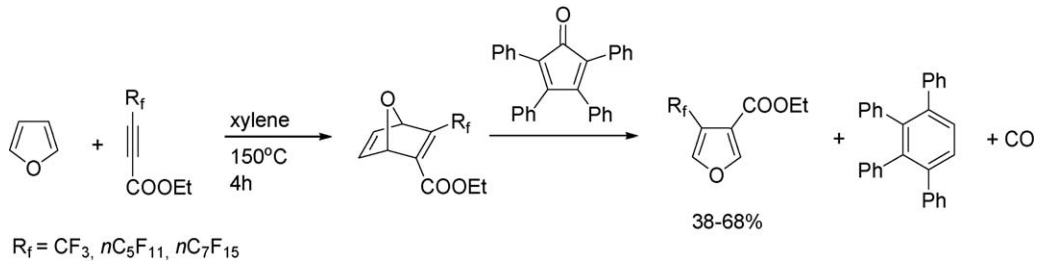
The reaction of furan tetracarboxylic acid with sulfur tetrafluoride in the anhydrous HF medium leads to the formation of 4,6-



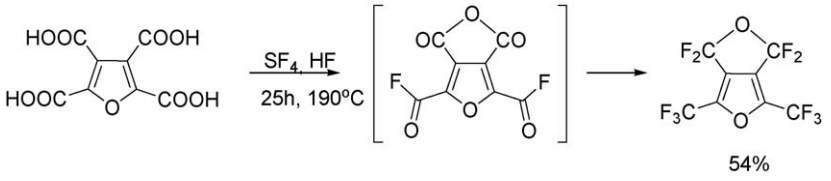
Scheme 43.



Scheme 44.



Scheme 45.



Scheme 46.

bis(trifluoromethyl)-1,1,3,3-tetrafluoro-1,3-dyhydrofuro[3,4-*c*]furan. It proceeds via the formation of intermediate 4,6-dioxo-4,6-dihydrofuro[3,4-*c*]furan-1,3-dicarbonyl difluoride (Scheme 46) [84]. Some reactions of this type are already mentioned above (Scheme 37 [85]).

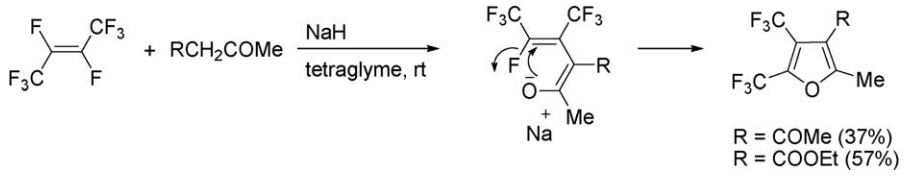
3.3.2. Heterocyclizations

The reaction of perfluorobutene-2 with acetyl acetone or ethyl acetate in the presence of sodium hydride in tetraglyme affords furans containing trifluoromethyl groups in α- and β-positions [101]. The mechanism of the transformation involves O-anion formation and consequent ring-closure process (Scheme 47).

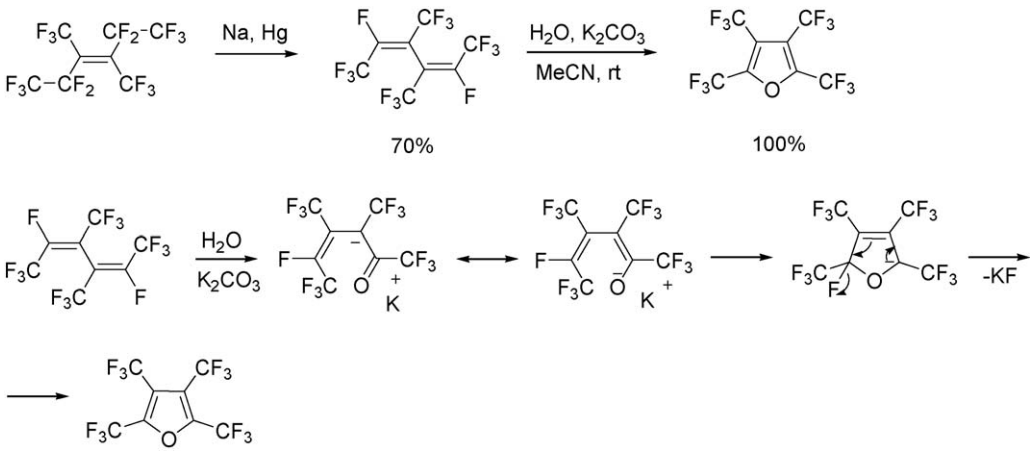
Perfluorotetramethylfuran is formed as a result of the hydrolysis of perfluorobutadiene. The latter can be obtained upon treatment of perfluoro-3,4-dimethylhex-3-ene with sodium amalgam [102]. The proposed mechanism includes the addition of water to perfluorobutadiene and the formation of ketone intermediate [103,104]. The further electrocyclic reaction and fluoride-ion elimination lead to perfluorotetramethylfuran (Scheme 48).

The reaction of perfluoro-3,4-dimethylhexene-3 with different alcohols or aldehydes and bases proceeds similarly (Scheme 49) [105–107]. The intermediate perfluoro-2,5-dihydrotetramethylfuran gives perfluorotetramethylfuran upon heating in the presence of the iron powder under nitrogen or by refluxing in tetraglyme in the presence of a base [108].

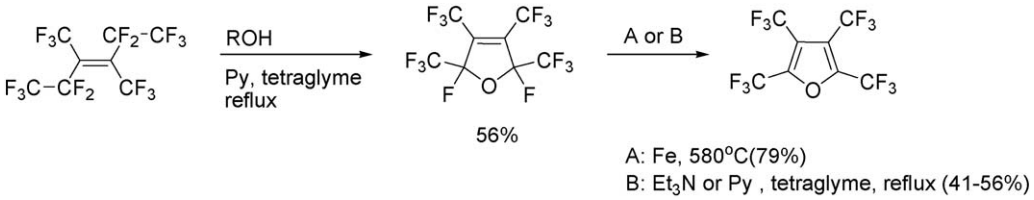
Another method of the perfluorotetramethylfuran synthesis is based on the transformation of trifluorosubstituted cyclopropenyl ketone. The recyclization of the latter can proceed under



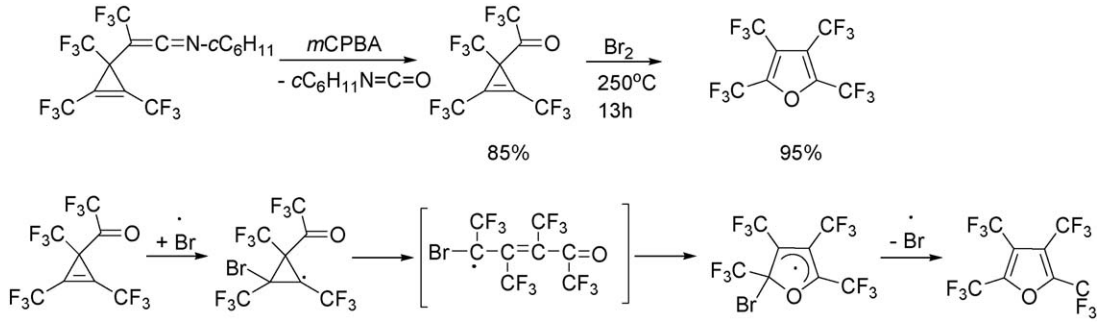
Scheme 47.



Scheme 48.



Scheme 49.



Scheme 50.

irradiation with sunlamp [109] or as bromine-catalyzed isomerization [110] (Scheme 50). The ketone is available from the reaction of perfluorobut-2-ene with cyclohexyl isocyanide and subsequent treatment of the obtained ketenimine with *m*CPBA in trichlorobenzene [110].

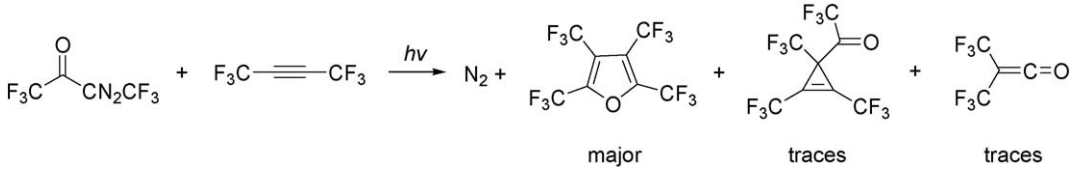
3.3.3. Cycloaddition

The gas-phase photolysis of perfluorodiazo ketones in the presence of perflurobut-2-yne gives the mixture of products with the predominance of perfluorotetramethylfuran [111,112]. The reaction path involves the formation of ketocarbene and its 1,3-addition to acetylene. In the case of 1,2-addition cyclopropenyl ketone is formed; the Wolf rearrangement gives the corresponding ketene (Scheme 51).

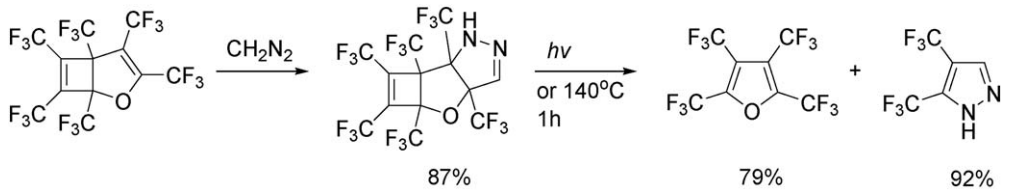
The dipolar cycloaddition of diazomethane to hexakis(trifluoromethyl)-2-oxabicyclo[3.2.0]heptadiene leads to cycloadduct, which was transformed into perfluorotetramethylfuran and 3,4-bis(trifluoromethyl) pyrazole upon heating (Scheme 52) [113]. Hexakis(trifluoromethyl)-2-oxabicyclo[3.2.0]heptadiene is valence isomer of hexakis(trifluoromethyl)oxepin forming by the reaction of hexakis(trifluoromethyl)benzvalene ozonide with triphenylphosphine [114].

3.4. Synthesis of some fluoroalkylfurans and their derivatives

The introduction of functionalized difluoromethyl group into the furan ring is possible via reaction with PhS-CF_2R under irradiation (Scheme 53) [115–117]. Photo-initiated S-CF_2 bond

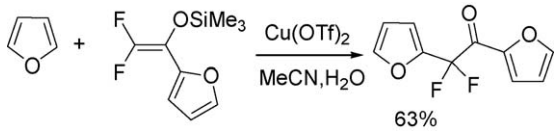


Scheme 51.

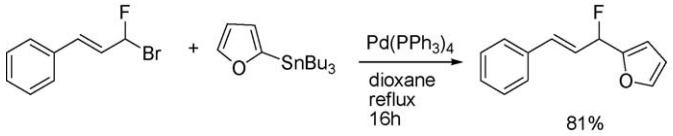


Scheme 52.

Scheme 53.



Scheme 54.



Scheme 55.

cleavage in the presence of furan substrate provides radical substitution products in moderate yields.

Oxidative cross-coupling of α-furyl-β,β-difluoroenolsilyl ether with furan in the presence of $Cu(OTf)_2$ affords fluorosubstituted furyl ketone in 63% yield (Scheme 54) [118]. 2-Furancarboxylate is less reactive and gives the product in 61% yield. This reaction proceeds in wet acetonitrile smoothly.

Palladium-catalyzed Stille coupling allows to obtain 1-furyl-1-fluorostyrene. Thus the reaction of β-bromo-β-fluorostyrene with organostannane leads to 1-fluoro-1-furyl derivative in 81% yield (Scheme 55) [119].

The fluorination of substituted hydroxyl group in furyl-2,2,2-trichloroethanole gives trichlorofluoroethyl furan (Scheme 56). Tetrafluorophosphorane $PhPF_4$ is used as a fluorination agent in this case [120].

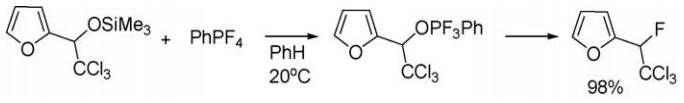
4. Synthesis of furans with perfluoroalkyl group in the α-position of substituents

Taking into consideration some specificity of the syntheses of furans containing a perfluoroalkyl group in the α-position of substituents, e.g. nucleophilic trifluoromethylation, an independent section is devoted to these methods.

4.1. Synthesis of trifluoroethylfurans and their related derivatives

4.1.1. Functionalizations of furan ring

The simple method of the synthesis of the mentioned compounds with substituents in the position 2 of the furan ring is based on the "alkylation reaction" of the furan substrates.



Scheme 56.

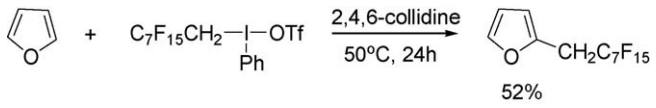
For this purpose the compounds of $R_fI(Ph)X$ type are widely used. Thus furan reacts with $C_7F_{15}CH_2I(Ph)OTf$ in the presence of 2,4,6-collidine in a sealed tube (50 °C, 24 h) to produce α-1,1-dihydroperfluorooctylfuran in 52% yield (Scheme 57) [121].

The alkylation reaction of the furan derivatives with 2-(perfluoropropan-2-ylidene)malononitrile gives products of 2-substitution exclusively. The reaction with furan proceeds at room temperature in 3 months (63%) [122]. 2-Methoxyfuran reacts with 2-(perfluoropropan-2-ylidene)malononitrile at 0 °C in 93% yield (Scheme 58) [123,124].

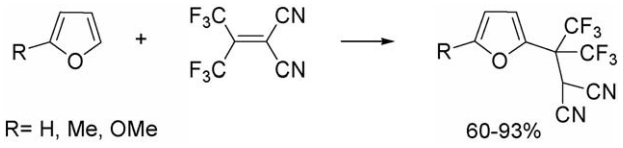
The introduction of fluoroalkyl or perfluoroalkyl group into the furan ring is also possible via its organometallic derivatives [125–129]. For example, 2-lithiofuran reacts with fluorinated β-oxophosphonium salt to produce perfluoroalkyl vinylfurans (Scheme 59) [127]. The reaction of 2-lithiofuran with perfluorocyclopentene proceeds in 74–79% yields; 3-lithiofuran reacts in 57–100% yields under the same conditions (Scheme 60) [129].

4.1.2. Heterocyclizations

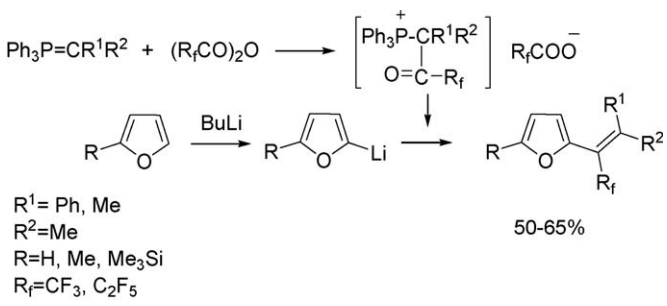
Another method of synthesis of the substituted 3-trifluoroethylidenefurans is based on the palladium-catalyzed hetero-



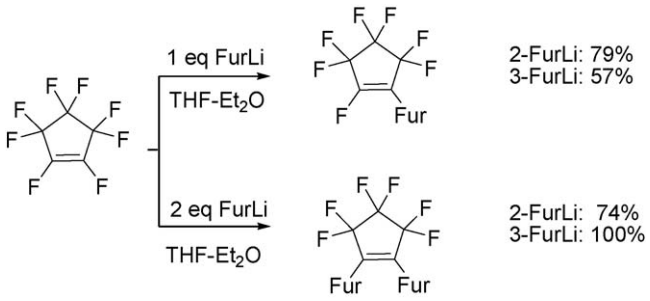
Scheme 57.



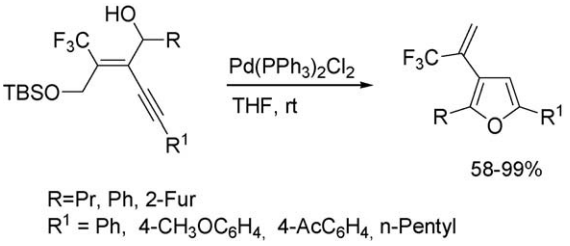
Scheme 58.



Scheme 59.



Scheme 60.



Scheme 61.

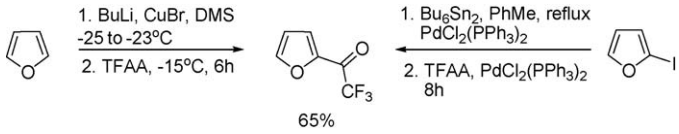
cyclization of 2-alkynyl-3-trifluoromethyl allylic alcohols (Scheme 61). The reaction proceeds at room temperature in high yields [130,131].

4.2. Synthesis of trifluoroacetylfurans

4.2.1. Functionalizations of furan ring

Several typical systems are usually used to introduce trifluoroacetyl group into aromatic substrates: trifluoroacetyl chloride - $AlCl_3$ or Py, trifluoroacetic anhydride (TFAA) in the presence of acid, trifluoroacetyl triflate. More detailed information about trifluoromethyl ketones synthesis is described in the review [132]; some advances in the field of organofluorine chemistry are covered in the article [133].

Trifluoroacetyl chloride is nonconvenient in handling due to its low boiling point (−19 °C). Triflate and anhydride allow to perform reactions with activated aromatic substrates in moderate yields. For example, the reaction of furan and 2-methylfuran with trifluoroacetic anhydride at 20 °C results in formation of 2-trifluoroacetyl derivatives in 75% and 58% yield respectively [134–136]. Trifluoroacetylation of furan phosphonate derivative in the presence of $SnCl_4$ proceeds in 43% yield (Table 3) [136–138]. Iodine can be used as a catalyst of this transformation [138].



Scheme 62.

Other approach to trifluoroacetyl derivatives synthesis is based on the metallation reaction and reaction of obtained organometallic compound with trifluoroacetic acid derivatives. Furan affords organocopper compound upon treatment with BuLi and $CuBr{\cdot}Me_2S$. The following reaction with TFAA gives 2-trifluoroacetylfuran in 65% yield (Scheme 62) [139]. The treatment of furan with BuLi and ethyl trifluoroacetate also yields 2-trifluoroacetyl derivative [140–143]. Trifluoroacetyl amides can be used in this reaction along with ethyl trifluoroacetate [144]. 2-Halogenofuran can also serve as a starting material. For example, 2-iodofuran reacts with hexaalkyldistannane in the presence of palladium catalyst followed by coupling of acetyl chloride or TFAA with organotin compound to produce 2-trifluoroacetylfuran in 65% yield (Scheme 62) [145].

The convenient and selective method for the preparation of 2-trifluoroacetylfuran involves treatment of furan-2-carboxylic acid chloride with trifluoromethyl silver generated *in situ* from the reaction of Me_3SiCF_3 with silver (I) fluoride. The transformation proceeds in DCM in 61% yield (Scheme 63) [146].

The reaction of fluorovinylzinc reagent with furan-2-carboxylic acid chloride in the presence of palladium affords 2-fluorovinyl-2-furyl ketone in 50% yield (Scheme 63) [147].

Difluoromethyl-2-furyl ketone can be prepared in three steps including the reaction of furfural with $LiCF_2P(O)(OEt)_2$, oxidation of the obtained alcohol, and dephosphonylation (Scheme 64) [148].

4.2.2. Cycloaddition

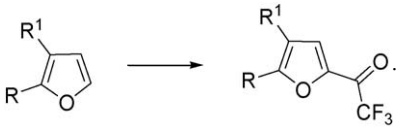
[3 + 2]-Cycloaddition of 2-alkylthio-5-trifluoroacetyl-1,3-oxathiolylium-4-olates into acetylenes also produces substituted 2-trifluoroacetylfurans (Scheme 65) [149].

4.2.3. Heterocyclizations

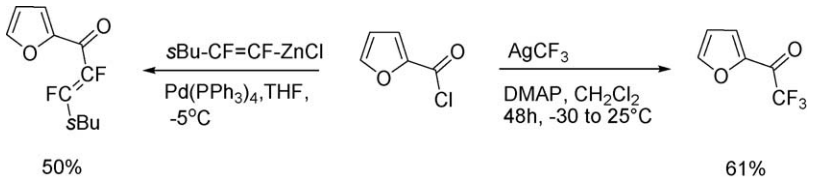
2-Fluoroacetylfuran derivative is formed as a result of condensation of triketone obtained from ethyl fluoroacetate and methyl-*t*-butyl ketone in the presence of a base (Scheme 66) [150].

Several methods of 3-trifluoroacetylfurans synthesis are already described above (Scheme 26) [75,76].

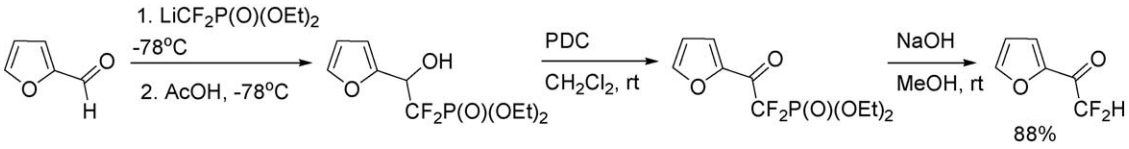
Table 3
Direct trifluoroacetylation of furans.



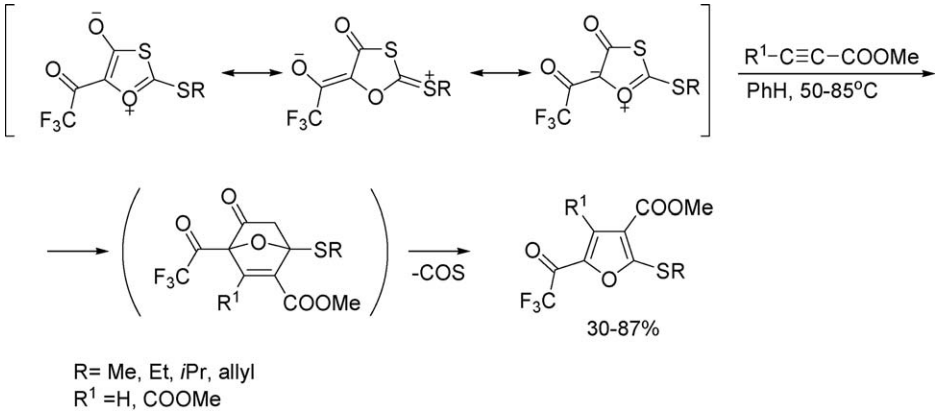
R	R^1	Conditions	Yield (%)	References
H	H	TFAA, PhH, 20 °C, 5 h	75	[136]
CH_3	H	TFAA, PhH, 20 °C, 5 h	58	[136]
$CH_2PO(OC_2H_5)_2$	H	TFAA, $SnCl_4$, 40–60 °C, 5 h	43	[137]
CH_3	$CH_2PO(OC_2H_5)_2$	TFAA, 40–60 °C, 5 h	65	[137]
Me_3C	H	TFAA, 0.03 mmol I_2, 20 °C, 24 h	72	[138]
Me_3Si	H	TFAA, 0.03 mmol I_2, 70 °C, 32 h	48	[138]
Et_3Si	H	TFAA, 0.03 mmol I_2, 70 °C, 26 h	51	[138]
Me_3Ge	H	TFAA, 0.03 mmol I_2, 70 °C, 2 h	26	[138]
Et_3Ge	H	TFAA, 0.03 mmol I_2, 55 °C, 1 h	64	[138]



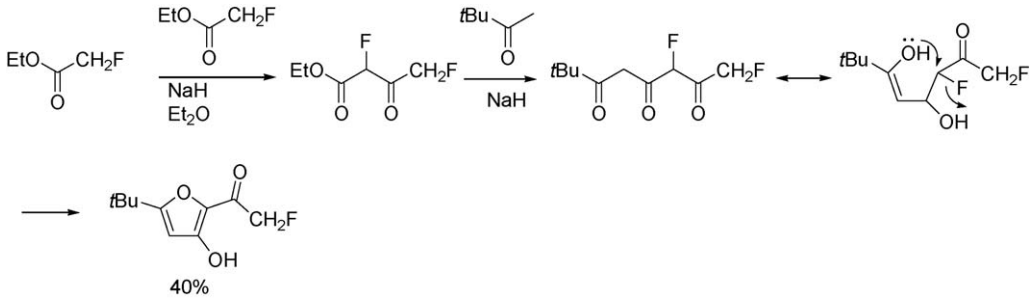
Scheme 63.



Scheme 64.



Scheme 65.



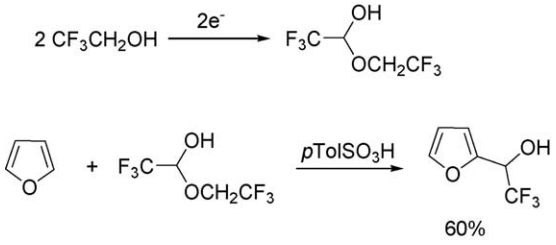
Scheme 66.

4.3. Synthesis of 1-furyltrifluoroethanols and their related derivatives

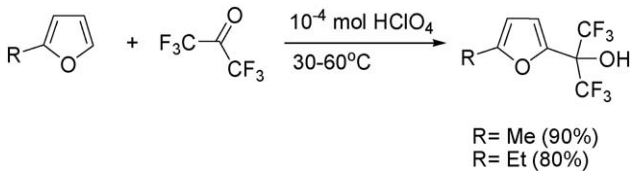
4.3.1. Functionalizations of furan ring: alkylation

To obtain 1-aryl-2,2,2-trifluoroethanols usually two main approaches are used: the direct introduction of the α-hydroxytrifluoroethyl group into the furan ring and nucleophilic trifluoromethylation of aldehydes.

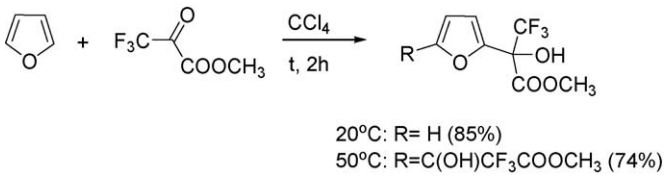
The introduction of the α-hydroxytrifluoroethyl group into the furan ring is performed by treatment of furan with trifluoroacetaldehyde hemiacetals in the presence of an acid [151]. The reaction with commercially available trifluoroacetaldehyde ethyl hemiacetal in the presence of *p*TolSO$_3$H leads to 1-furyl-2,2,2-trifluoroethanol in trace amounts (5%). More active trifluoroacetaldehyde 2,2,2-trifluoroethyl hemiacetal obtained from electrochemical oxidation of 2,2,2-trifluoroethanol gives the product in 60% yield (Scheme 67). The use of $ZnCl_2$ as a catalyst of the transformation allows to obtain 1-furyl-2,2,2-trifluoroethanol from furfural and trifluoroacetaldehyde hemiacetal in 61–68% yields. The reaction is usually performed at 110–120 °C for 10–24 h [152]. The reaction of 2-alkylfurans with gaseous hexafluoroacetone in the presence of traces of $HClO_4$ gives hydroxyhexafluoro-*i*-propyl furans in good yields (Scheme 68) [153]. Sulphuric acid is



Scheme 67.



Scheme 68.



Scheme 69.

less effective as a catalyst of this transformation [154]. It can be performed with hexafluoroacetone hydrate in liquid phase. The yields of products amount to 90% [155].

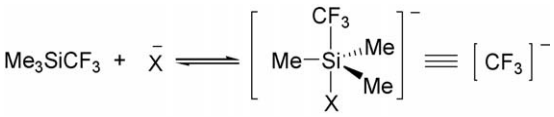
The reaction of furan with methyl 3,3,3-trifluoro-2-oxopropanoate at room temperature leads to methyl 3,3,3-trifluoro-2-(furan-2-yl)-2-hydroxypropanoate in 85% yield. The use of 2 moles of the alkylation agent gives the same results due to the deactivation of the furan ring by electron-withdrawing group. The formation of disubstituted product is observed only at 50 °C (Scheme 69) [156,157]. The reaction can also be performed in the presence of copper triflate [158]. In the case of 2-methylfuran the yield amounts to 95% [159]. 3,3,3-Trifluoro-2-oxopropanoate amide can also serve as alkylation agent [160].

When positions 2 and 5 of the furan ring are occupied, the alkylation proceeds predominantly at alkyl substituents. Thus the reaction of hexafluoroacetone with 2,5-dimethylfuran gives the mixture of products in the ratio of 1:3 (Scheme 70) [161].

4.3.2. Nucleophilic trifluoromethylation

Nucleophilic trifluoromethylation has greatly expanded over the last 20 years and is extensively used for furan derivatives functionalization. The traditional nucleophilic trifluoromethylation reagents, differing in the trifluoromethyl anion generation ways, are summarized in the review [39]. Among them, one can distinguish Ruppert–Prakash reagent ($TMSCF_3$) (Scheme 71) with nucleophilic and electrophilic initiators, the system fluoroform-base, trifluoroacetamide and trifluoromethanesulfinamide derivatives, trifluoromethylacetophenone-N,N-dimethyltrimethylsilylamine adduct, trifluoromethyl iodide/tetrakis(dimethylamino)ethylene (TDAE), phenyl trifluoromethyl sulfide, sulfoxide, and sulfone (Table 4) [162–174].

Thus trifluoromethylation of furfural with Ruppert–Prakash reagent proceeds in 94% yield. The transformation is catalyzed by tetrabutyl ammonium bromide TBAB [162], tris(2,4,6-trimethoxyphenyl)phosphine TTMPP [163], and Lewis acids [164,165].



Scheme 71.

The reaction of furfural with fluoroform gives the product of trifluoromethylation with lower yield (43%) [166]. This reaction proceeds in the presence of dimsyl-K formed upon treatment of DMSO with KH. Dimsyl-K is able to deprotonate fluoroform affording active trifluoromethyl anion.

The reaction of furfural with $PhSO_2CF_2H$ in the presence of the base LHMDS proceeds analogously [167].

Electrochemical reduction of CF_3Br in DMF using zinc anode also allows preparation trifluoromethylated alcohols from correspondent aldehydes [168].

One more approach to trifluoromethylation of aldehydes is based on the reduction of trifluoromethyl iodide with tetrakis(dimethylamino)ethylene (TDAE) [169]. The reaction involves an initial formation of the charge–transfer complex between CF_3I and TDAE. The following single-electron transfer of two electrons from TDAE to CF_3I generate a complex between $TDAE^{2+}$ and CF_3^-, which is able to attack the starting compound.

Unsubstituted trifluoromethanesulfinamide is also an effective trifluoromethylation agent [170]. It allows to perform reactions with a wide range of aldehydes and ketones under mild conditions. The yield of trifluoromethylfuryl alcohol amounts to 90% in this case.

Other trifluoromethylation agent is obtained via the reaction of trifluoromethylacetophenone and N,N-dimethyltrimethylsilylamine. This adduct reacts with carbonyl compounds in the presence of CsF to afford trifluoromethyl carbinols in high yields [171,172].

The active trifluoromethyl anion is also generated from phenyl trifluoromethyl sulfide upon treatment with a solution of Et_3GeNa in HMPA. The yields of corresponding alcohols are in the range of 86–96% (Table 4) [173,174].

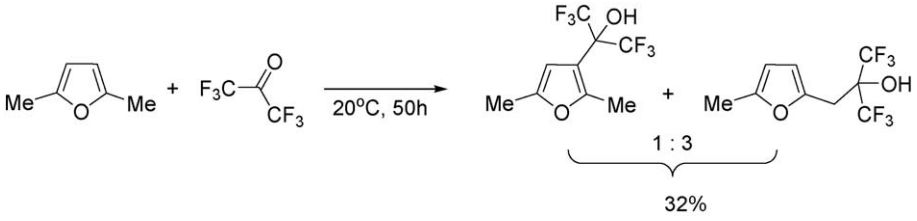
The reaction of furfural with $ClCF_2COOMe$ in the presence of zinc (Reformatsky reaction) gives methyl 2,2-difluoro-3-(furan-2-yl)-3-hydroxypropanoate (Scheme 72) [175–177].

Reactions of furfural with β-aminovinyl chlorodifluoromethyl ketones can be catalyzed by indium powder. The transformation proceeds in THF in 95% yield [178]. One of the methods of furyldifluoroethanol synthesis is based on the reaction of furfural with difluoroenamines in the presence of Lewis acids (Scheme 73) [179].

4.4. Synthesis 1-furyltrifluoroethylamines and their related derivatives

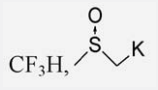
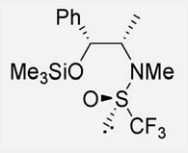
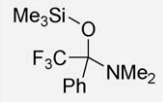
4.4.1. Functionalizations of furan ring: alkylation

Methods of 1-aryl-2,2,2-trifluoroethylamines synthesis are generally similar to methods of preparation of 1-aryl-2,2,2-trifluoroethanols. The most widespread of them are based on the alkylation reaction of aromatic substrates with the introduc-



Scheme 70.

Table 4
Nucleophilic trifluoromethylation of furfural.

Reactant	Conditions	Yield (%)	References
Me_3SiCF_3	TBAB, THF, rt, 24 h	94	[162]
Me_3SiCF_3	TTMPP, THF, rt, 30 min	82	[163]
CF_3H,	DMF, −40 °C to rt, 2 h	43	[166]
			
CF_3Br	DMF, TBAB	50	[168]
CF_3I	TDAE, DMF, −20 °C to rt, $h\upsilon$, 12 h	82	[169]
	CsF, DME, TBAB, rt, 24 h	90	[170]
	CsF, THF, reflux, 20 h	73	[171,172]
$PhSCF_3$	Et_3GeNa, THF, HMPA, −60 °C	96	[173,174]

tion of the trifluoroethylamino group and nucleophilic trifluoromethylation of imines.

For the preparation of 1-aryl-2,2,2-trifluoroethylamines, imines of hexafluoroacetone and trifluoroacetaldehyde are used as alkylation reagents [180,181].

For example, alkylation of furan with N-benzoyl trifluoroacetylimine in the presence of $BF_3{\cdot}OEt_2$ affords 1-furyl-2,2,2-trifluoroethylamine in 63% yield (Scheme 74) [182,183].

Trifluoromethylsulfonyl imine obtained from hexafluoroacetone and sulfinyl amine also reacts with furan in the presence of CsF at −50 °C (Scheme 75) [184].

4.4.2. Nucleophilic trifluoromethylation

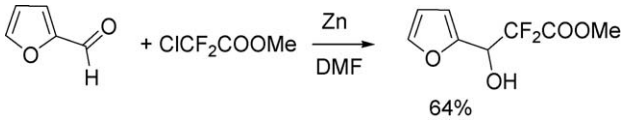
Typical trifluoromethylation reagents, e.g. Ruppert–Prakash reagent, are used for the nucleophilic trifluoromethylation reaction of imines (Table 5) [185–189].

The similar approach to the synthesis of 1-furyltrifluoroethylhydroxylamine consists in trifluoromethylation of furyl nitrone (Scheme 76) [190]. α,α-Bis(trifluoromethyl)amine derivative is formed as a by-product of this transformation. Modified reaction conditions, using 3.0 equiv of $TMSCF_3$, provided the highest yield of α,α-bis(trifluoromethyl)amine.

4.4.3. Other methods

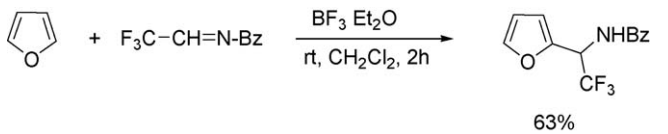
The preparation of 1-aryl-2,2,2-trifluoroethylamines is also possible via oximes of corresponding trifluoroacetyl derivatives [191].

The unusual reaction of 5-fluoro-2-phenyl-4-trifluoromethyloxazole with 2-hydroxymethylfuran in the presence of KOH leads to the amino derivative of 3-trifluoroethylfuran (Scheme 77) [192]. The key step is 1,3-benzyl shift from the oxygen to carbon atom.

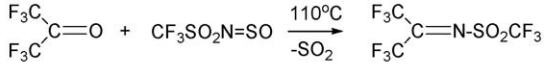


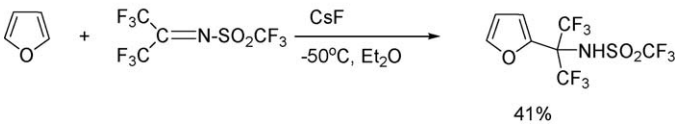
Scheme 72.

Scheme 73.



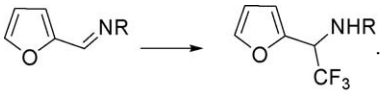
Scheme 74.



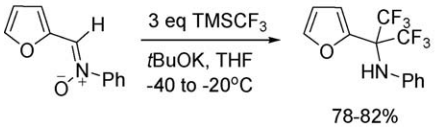


Scheme 75.

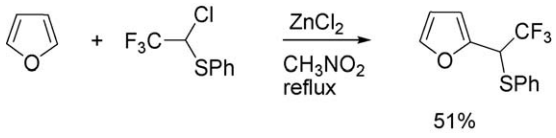
Table 5
Nucleophilic trifluoromethylation of furfurylimines.



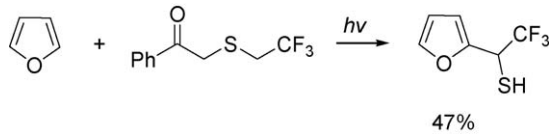
Reactant	R	Conditions	Yield (%)	References
Me_3SiCF_3	*c*Hex	TFA, KHF_2, MeCN/DMF, rt, 3 h	75	[185]
	$CHPh_2$		63	
Me_3SiCF_3	$CHPh_2$	TFA, KHF_2, MeCN, rt, 15 h	65	[185]
Me_3SiCF_3	$CHPh_2$	TfOH, KHF_2, MeCN/DMF, rt, 18 h	70	[185]
Me_3SiCF_3	Ph	CsF, THF, SiO_2, HCl	54	[186]
Me_3SiCF_3	NHBz	$BF_3{\cdot}Et_2O$, AcONa, DMF, rt, 2 h	70	[187]
$TMSCF_2SPh$	SO*t*Bu	TBAB, DMF	72	[188]
$PhSCF_3$	Ph	Et_3GeNa, THF, HMPA, −60 °C	98	[189]



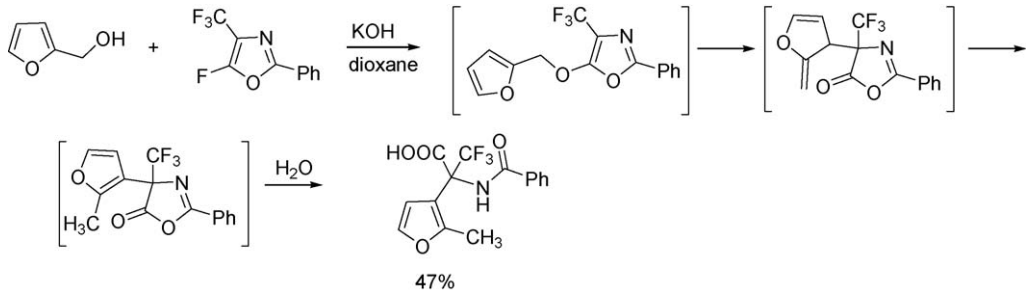
Scheme 76.



Scheme 78.



Scheme 79.



Scheme 77.

4.5. Synthesis 1-furyltrifluoroethanethiols and their related derivatives

Introduction of 2,2,2-trifluoro-1-(phenylthio)ethyl group into the furan substrate is possible via alkylation with 1-chloro-2,2,2-trifluoroethyl phenyl sulfide in the presence of Lewis acids. The substitution proceeds only in the position 2 of the furan ring (Scheme 78) [193,194].

Another approach to the introduction of trifluoroethanethiol group into the furan substrate is based on photolysis of phenacyl sulfides (Scheme 79) [195]. 2,5-Dimethylfuran does not react under this conditions.

5. Conclusions

As it can be seen from the cited data, the main part of the known methods of fluorine-containing furans syntheses has been developed over the last 20 years. The development of modern fluorination agents, organometallic chemistry, and homogeneous catalysis has opened new possibilities in the synthesis of fluoro- and perfluoroalkylfurans; some of them may find their application in pharmacology, agriculture, and industry in future. From the other side, there is not enough information about reactivity of fluorinated furans. Taking in mind diverse reactivity of the furan derivatives [196,197], e.g. cycloaddition and ring opening reactions with the formation of 1,4-diketones, one can expect that transformation of its fluorinated derivatives can also become a valuable method of fluorinated aromatic and heterocyclic compounds syntheses. In conclusion, the present review offering the systematization of methods of fluorine-containing furan syntheses, can be of interest for the specialists in the field of fluoroorganic chemistry as well as heterocyclic synthesis.

Acknowledgements

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