Preparation of $\alpha,\beta$-unsaturated trifluoromethylketones and their application in the synthesis of heterocycles

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Abstract
The review is devoted to the preparation of $\alpha,\beta$-unsaturated trifluoromethyl ketones and the application of these building blocks in the synthesis of three- to seven-membered fluorinated heterocycles. The literature up to 2010 is highlighted.

Keywords: Fluorine, heterocycle, trifluoromethyl group, synthesis, $\alpha,\beta$-unsaturated CF$_3$-ketones

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1. Introduction

The trifluoromethyl group is a very important substituent in medicinal chemistry, due to its unique stereoelectronic properties. A trifluoromethyl group usually increases the lipophilicity of a molecule, improving its transport characteristics in vivo. Furthermore, the strength and durability of the C-F bond compared with the C-H bond (116 and 100 kcal/mol respectively) allows undesirable metabolic transformations to be avoided. So the introduction of trifluoromethyl groups into bioactive molecules has become very important in pharmaceutical studies, stimulating work directed towards the elaboration of synthetic methodology for compounds containing trifluoromethyl groups. Because of all these factors, organofluorine chemistry has been vigorously developing during the past two decades.

Most of the known approaches to the synthesis of CF₃-containing organic compounds suffer from serious drawbacks. First of all, the starting materials required for these methods are rather difficult to obtain, or they are fairly toxic and inconvenient to work with. Additionally, methods for direct fluorination and trifluoromethylation do not always allow the introduction of the CF₃-group at the required position of a molecule. As a result the more flexible “synthon” approach, based on the application of simple and readily available fluorine-containing compounds gains substantial interest. α,β-Unsaturated trifluoromethyl ketones are easily available compounds which can be prepared by various methods¹ and fairly convenient building blocks to prepare heterocyclic compounds containing a trifluoromethyl group.

2. Synthesis of α,β-Unsaturated Trifluoromethylketones

2.1. Synthesis of enones
2.1.1 Trifluoroacylation of alkenes, acetylenes and dienes. Activated alkenes 1 can be trifluoroacetylated with trifluoroacetic acid anhydride (TFAA). This is a widely applied method due to its simplicity and adaptability for a wide range of substrates such as vinyl ethers² vinyl sulfides,³
ketene dithioacetals, vinyl tellurides\textsuperscript{4}, vinyl amides, cyclic enamines\textsuperscript{5}, O-vinyloximes\textsuperscript{6}, and some activated dienes\textsuperscript{7}.

\[
\begin{align*}
\text{Scheme 1} \\
\text{Orthoacetates}\textsuperscript{8}, acetics and trithioorthoacetates 3 react with excess trifluoroacetic anhydride with elimination of alkyl or aryl trifluoroacetate (thioacetate) to give trifluoromethyl enones 4, i.e., they are transformed into the corresponding activated alkenes \textit{in situ}. \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 2} \\
\text{Under higher temperature the reactions of vinyl ethers 5 with a threefold excess of TFAA in the presence of pyridine result in the formation of diones 6 in high yields}\textsuperscript{9}. \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 3} \\
\text{Chloro(bromo) anhydrides of perfluoro carboxylic acids 7 can be also applied for acylation of alkenes 8}\textsuperscript{10}. Trifluoroacylation of 1,1-dichloroethene 10 is performed with trifluoroacetyl bromide and chloride 7 in the presence of aluminum halides because of low double bond activity.\textsuperscript{11} Noteworthy using AlBr\textsubscript{3} the only product formed is 2,2-dibromovinyltrifluoromethyl ketone 11b, whereas AlCl\textsubscript{3} gives the corresponding dichloroketone 11a. \\
\end{align*}
\]
Scheme 4

As a rule trifluoroacetylation of enamines leads to a complex mixture of products. However, less reactive 1-morpholinocyclohept-1-ene 12 gave doubly trifluoroacetylated product 13. Trifluoroacetylimidazole 14 and the complex 16 prepared from 4-dimethylaminopyridine 13 gave better results. 15

Scheme 5

It was demonstrated that N-oxides 19 of tertiary amines can be transformed into CF₃-enones 20 under treatment with TFAA via intermediate enamine formation. This reaction is called Potier-Polonovski rearrangement and has been applied for synthesis of alkaloids 21. 15

Scheme 6
The reaction of triethylamine with trifluoroacetyl chloride 24 at −30 °C leads to 4-diethylamino-1,1,1-trifluorobut-3-en-2-one 23.\textsuperscript{16}

\[
\begin{array}{c}
\text{O} \\
\text{NET}_3 \\
F_3C-Cl \\
\text{NET}_3 \\
\text{F}_3C-Cl \\
\text{H} \\
\text{F}_3C = CH \text{Et}_2N \\
\text{O} \\
\end{array}
\]

\[
\begin{array}{c}
\text{Me} \\
\text{N} \\
\text{TFAA} \\
\text{CN} \\
\text{NMe}_2 \\
\text{H} \\
\text{CN} \\
\text{NMe}_2 \\
\text{COCF}_3 \\
\end{array}
\]

\[
\text{Py} \\
\text{H} \\
\text{F}_3C \text{Cl} \text{O} \text{Et}_3 \\
\text{F}_3C \text{Cl} \text{O} \text{Et}_3 \\
\text{H} \\
\text{F}_3C \text{H} \text{O} \text{Et}_2\text{N} \text{Et}_2\text{N} \\
\text{COCF}_3 \\
\end{array}
\]

\[
\text{R}_2\text{NEt} \xrightarrow{\text{TFAA} \text{4 eq.}} \text{R}_2\text{N} = \text{Et, i-Pr} \\
\text{COOCF}_3 \\
\]

\[
\text{Me} \\
\text{N} \\
\text{TFAA} \\
\text{Me} \\
\text{COCF}_3 \\
\end{array}
\]

\[
\text{25 (96%)} \\
\text{26} \\
\text{27 (19 - 45%)} \\
\text{28 (~ 25 %)}
\]

\textbf{Scheme 7}

The proposed reaction mechanism includes oxidation of triethylamine by one equivalent of trifluoroacetyl chloride to give diethyl(vinyl)amine and the subsequent trifluoroacylation. Cyclic amines react in a similar way, for example, N-methylpiperidine is converted into enaminone 25 in 96% yield. Iso-tryptamine 26 can be trifluoroacetylated with TFAA to form enone 27.\textsuperscript{17} The reaction of triethylamine or diisopropylethylamine with TFAA leads to doubly trifluoroacetylated products 28.\textsuperscript{18}

Several examples for trifluoroacylation of enamides generated in situ from N-protected prolines 29 are known. The corresponding cyclic enaminoketones 30 were obtained in moderate to good yields. N-tosylpyrroline-2 31 reacts with TFAA and salen-manganese complex 32 as the catalyst to give cyclic enaminynone 33 in moderate yield.\textsuperscript{19} The derivative of 5-hydroxypyrrolidin-2-one 34 can be converted to enamide 35 under treatment with acetic anhydride. However, the formation of heterocyclic enaminoketone 36 is observed under treatment with more electrophilic TFAA.\textsuperscript{20}
Scheme 8

The unusual disubstituted CF₃-derivative of fulvene 37 was obtained by trifluoroacylation of cyclopentadiene with TFAA at room temperature using dimethylformamide as a solvent.²¹

Scheme 9

The electrophilicity of trifluoroacetic anhydride and other derivatives of trifluoroacetic acid is insufficient for trifluoroacylation of non-activated alkenes.²² The attempts of activation with Lewis acids were successful only for trifluoroacylation of aromatic compounds. However, TFAA can be activated by Me₂S-BF₃ complex. The trifluoroacylation in this case proceeds with alkenes able to form benzyl, allyl, cyclopropyl or tertiary cations. Arylsubstituted alkynes 38 can be trifluoroacylated as well to give sulfonium salts 39.²³ The demethylation of these salts results in the formation of enones 40. Subsequent oxidation of 40 by hydrogen peroxide makes it possible to synthesize sulfones 41. Alternatively sulfides 42 can be prepared by the Pt-catalyzed regioselective trifluoroacetylthiolation of alkynes using thioesters 43.²⁴
2.1.2 Trifluoroacylation of organometallics. CF₃-enones can be prepared by acylation of vinylic organometallic compounds. The first trifluoromethyl containing enone, 1,1,1-trifluoro-4-phenylbut-3-en-2-one 45, was synthesized in low yield by the reaction of styrylmagnesium bromide with trifluoroacetic acid in 1959.²⁵

Azaenolates 46 can be acylated by N-substituted trifluoroacetimidoyl chlorides 47 to lead after hydrolysis β-enaminoketones 48.²⁶ Alternatively the trifluoroacylation of 49 with ethyl trifluoroacetates allows obtaining enaminoketones 50 directly in one stage.²⁷
Reaction of trifluoroacetimidoyl iodides 51 with various alkenes and alkynes in the presence of a palladium catalyst can be used for preparation of imino-derivatives of alkenyl 52 and alkynyl ketones 53.28 Similarly, phosphonates 56 were prepared via reaction of diethyl allylphosphonate 55 with 54. Subsequently compound 56 easily undergoes the migration of double bonds and after deprotonation, Wittig reaction and hydrolysis gave dienones 57.29

![Scheme 13](image)

**Scheme 13**

Pd-catalyzed cross-coupling reaction of thioesters 58 with the corresponding alkenyl boronic acids 59 was used for the preparation of β-aryl-CF3-enones 60.30

![Scheme 14](image)

**Scheme 14**

2.1.3 Condensations and similar reactions. The condensation of 1,1,1-trifluoroacetone 61 with aromatic or α,β-unsaturated aldehydes is catalyzed by the piperidine - acetic acid system in THF and makes it possible to prepare trifluoromethyl containing conjugated enones, dienones and polyenones (retinoids) 62. A drawback of this method is self-condensation of 1,1,1-trifluoroacetone. Therefore this reagent should be taken in more than 10-fold excess.31
\[
\text{Scheme 15}
\]

\(\alpha,\beta\)-Unsaturated ketones are often prepared by condensation of \(\beta\)-dicarbonyl compounds with aldehydes and ketones. However, \(\beta\)-dicarbonyl compounds (for example 63) containing a perfluoroalkyl substituent yields a mixture of products in a relatively low yield.\(^{32}\)

\[
\begin{align*}
\text{Me} & \quad \text{CF}_3 \\
\text{O} & \\
pip & \\
der & \\
\text{AcOH}, 20 \degree C & \\
\rightarrow & \\
\text{R} & \quad \frac{R'=\text{Ar}}{\text{vinyl}}
\end{align*}
\]

\[
\text{Scheme 16}
\]

Conjugated \(\text{CF}_3\)-diene-dione 64 has been synthesized in high yield by reaction (catalyzed by [Ru]/\(\text{CF}_3\text{CO}_2\text{H}\)) of terminal propargylic alcohol 65 with hexafluoroacetylacetone 66 via Meyer–Schuster rearrangement and subsequent aldol-type condensation.\(^{33}\)

\[
\begin{align*}
\text{PhOH} & \quad \text{H} & \quad \text{Ph} & \quad \text{H} \\
\text{65} & \quad + & \quad \text{F}_3\text{C} & \quad \text{O} & \quad \text{C} & \quad \text{F}_3 \\
\text{66} & \quad \rightarrow & \quad \text{R} & \quad \frac{R'=\text{Alk}, \text{Ar}}{\text{H}_2\text{N} \quad \text{O}} \\
\text{64} & \quad 90\% &
\end{align*}
\]

\[
\text{Scheme 17}
\]

The condensation of trifluoroacetoacetic acid esters 67 with aldehydes in the presence of traditional catalysts leads to \(\text{CF}_3\)-enones 68 in moderate yields, better yields gave silica gel treated with (3-aminopropyl)triethoxysilane.\(^{34}\) Derivative 69 is formed by the reaction of 67 and triethylorthoformiate. Subsequent reaction with urea gives \(\beta\)-enamidoketone 69a.\(^{35}\)

\[
\begin{align*}
\text{R}^1\text{CHO} & \quad + & \quad \text{F}_3\text{CCO}_2\text{Et} & \quad \rightarrow & \quad \text{R}^1 & \quad \frac{\text{CO}_2\text{Et}}{\text{H}_2\text{NOCCHN}} \\
\text{67} & \quad (43-70\%) & \quad \text{68} & \quad \text{69a} &
\end{align*}
\]
The reaction of β-iminophosphonate anions with aldehydes (the Horner - Emmons reaction) yields perfluoroalkylated enones 72 as the final products.

Scheme 19

β-Iminophosphonate anions can be obtained from diethyl alkylphosphonates 70 and trifluoroacetimidoyl chlorides 71 as a one-pot procedure. Subsequent reaction with aldehydes leads to 72 in good yields. Enaminophosphonates 73 can be prepared by condensation of phosphonates 70 with trifluoroacetonitrile.36

Sulfanyl substituted ethyl (1,1,1-trifluoromethyl)vinyl ethers 74 can be easily lithiated with n-BuLi. Structurally similar selenium compounds 77 can be converted to lithium derivatives by lithiation to vinyl position or by Se-Li exchange. In both cases the reactions with various aldehydes form allylic alcohols 78 or 80 correspondingly. Subsequent acidic treatment leads to trifluoromethylketones 79 or 81.37

Scheme 20
Claisen rearrangement has been also used for synthesis of CF₃-dienones. 1-Phenylsulfanyl-2-bromo-3,3,3-trifluoropropene 82 served as starting material.

Scheme 21

The reaction of 82 with sodium hydride leads to CF₃-acetylene which reacted with various allylic alcohols 83 to form vinyl ethers 84. Subsequent heating generate γ,δ-unsaturated ketones 85. Target dienone 87 was formed by oxidation of phenylsulfanyl group in 85 with m-chloroperbenzoic acid and syn-elimination of sulfenic acid from sulfoxide 86.³⁸

Claisen reaction was also studied for vinyl propargyl ethers. 88 reacted with propargylic alcohols 89 to form vinyl ether 90. Claisen rearrangement with further double-bond migration takes place under heating in toluene at 80ºC leading to 91 as a mixture of Z/E isomers.³⁹

Scheme 22

2.1.4 Nucleophilic substitution at the β-position. α,β- Unsaturated trifluoromethylketones having heteroatom in β-position (e.g. alkoxy-, dialkylamino-substituted) can be involved into the reactions with nucleophiles by “addition-elimination” mechanism with further formation of new α,β-unsaturated trifluoromethyl ketones. Trifluoromethyl enaminoles 94 can be synthesized by the reaction of 1,3 dicarbonyl compounds 92 containing trifluoroacetyl fragment with primary and secondary amines and diamines.⁴⁰ Lewis acids (ether – BF₃ complex and Zn(ClO₄)₂) accelerate the reaction.⁴¹
Scheme 23

Enaminones 95 can be obtained by the reaction of ammonia or amines with β-chlorovinyl ketones 97 prepared by reaction of polyfluorinated β-diketones with SOCl₂ in the presence of DMF as a catalyst or with the Vilsmeier reagents (DMF/POCl₃ or DMF/(COCl)₂). This approach has also been used to synthesize hexafluoromono-thioacetylacetone 98 existing in enol form.

Scheme 24

The alkoxy enones 99 react easily with various amines. They can be used as selective protecting groups for α-amino group of α-aminoacids 100 to form 101. The cleavage of this protective group is performed by treatment with hydrogen chloride in methanol.

Scheme 25

5-Trifluoroacetyl-3,4-dihydro-2H-pyran 102 reacts with many nucleophiles such as amines and Grignard reagents to give the ring opening products 103. Hydrazine and hydroxylamine attack the carbonyl carbon of the title compound to form hydrazone or oxime 104.
Ketones 105 containing aziridine fragment in β-position were prepared by reaction of cis-1,2-diphenylaziridine 106 with CF₃-enone 107 containing chlorine atom in the β-position. Reaction proceeds with the formation of mixture of E-Z-isomers of ketone 105.⁴⁵

The enone 108 reacts with the phenylmagnesium bromide to give a mixture of β-trifluoroacetylstyrene 109 and allylic alcohol 110 in overall yield of 40-60%. The reaction of phenylmagnesium bromide with 4-diethylamino-1,1,1-trifluorobut-3-en-2-one 111 occurs more unambiguously. It gives only β-trifluoroacetylstyrene 109 in moderate yield.⁴⁶

The reactions of various Grignard and organolithium reagents with enones 112a,b proceed stereoselectively leading to the formation of CF₃-enones 113a. Using the reaction of lithiated ferrocene allows preparing the corresponding CF₃-enones 114-116.⁴⁷ Additionally enones 112a were used for the preparation of conjugated trifluoromethylenones 113b containing acetylenic fragment by the reaction with lithiated acetylenes.⁴⁸
Scheme 29

The similar reaction of organolithium derivatives with cyclic enaminoketones 117 was applied to the synthesis of cyclobutene ketones 118. The formation of corresponding hydroxyketones 119 as byproducts was observed.\(^\text{49}\)

Scheme 30

The cross-coupling reaction for the synthesis of bicyclic cyclobutene ketones 120 containing substituents in β-position was applied. The reaction of arylzinc-derivatives with the corresponding bromide 121 in the presence of \((\text{Ph}_3\text{P})_4\text{Pd}\) catalyst was used.\(^\text{50}\)

Scheme 31

Trifluoromethyl enones 122 can also be synthesized using the reaction of various zinc dialkyl- and diaryl-cuprates with 123. In the case of zinc dialkylcuprates, the reaction is accompanied by side formation of the double addition products 124.\(^\text{51}\)
The reactions of trifluoroacetylated vinyl ethers 125 with organoboron compounds 126 allows to prepare highly stereoselectively the corresponding dienones 127 and enynes 128.52

\[
\text{Scheme 32}
\]

\[
\begin{align*}
\text{R}^1 & = \text{n-Bu; i-Bu, Ph; R = Ar, Alk; X = (CN)ZnCl}_2, \text{ZnCl} \\
\end{align*}
\]

\[
\begin{align*}
\begin{array}{ccc}
R^1Te & \rightarrow & R_2CuX \\
-78 & \rightarrow & -30 ^\circ C \\
\end{array}
\end{align*}
\]

The reactions of trifluoroacetylated vinyl ethers 125 with organoboron compounds 126 allows to prepare highly stereoselectively the corresponding dienones 127 and enynes 128.52

\[
\text{Scheme 33}
\]

\[
\begin{align*}
\begin{array}{ccc}
\text{Bu} & \rightarrow & \text{COCF}_3 \\
\text{EtO} & \rightarrow & \text{CH}_2\text{Cl}_2 \\
20 ^\circ C & \rightarrow & \text{~140 h} \\
\end{array}
\end{align*}
\]

\[
\begin{align*}
\begin{array}{ccc}
\text{R}^1 & = \text{H, Me, Ph} \\
\text{R}^2 & = \text{H, Br; R}^3 & = \text{H, Me, Ph} \\
\end{array}
\end{align*}
\]

\[
\text{β-Alkoxyl substituted trifluoromethyl enone 129 are used as the starting compounds in a large number of syntheses, such as the reactions with diverse nucleophiles – electron rich aromatic compounds. This reaction in the presence of zinc chloride can be carried out only for reactive aromatic compounds such as indoles, pyrroles and N,N-dimethylaniline. Other heterocyclic compounds such as furan, 2-methylfuran and thiophene do not reacted. Also this reaction was used for preparation of β-uracil substituted CF}_3\text{-enone 131.46,53}
\]

\[
\text{Scheme 34}
\]

\[
\begin{align*}
\begin{array}{ccc}
\text{R}^3 & = \text{Me, i-Pr} \\
\text{R}^1 & = \text{H, Me, Ph} \\
\text{R}^2 & = \text{H, Me} \\
\end{array}
\end{align*}
\]
A number of works is devoted to application of 4-sulfonyl-1,1,1-trifluorobut-3-en-2,2-diols 132 for synthesis of various β-amino and β-thio-α,β-unsaturated trifluoromethylketones. Compounds 132 can be prepared by oxidation of β-thiosubstituted enones 133 using 50% H$_2$O$_2$ in the presence of trifluoroacetic acid or utilizing 98% H$_2$O$_2$ solution in the presence of trifluoroacetic acid anhydride. Similarly sulfoxide 134 can be prepared.$^{54}$

![Scheme 35](image)

The reaction of 132 with various amines leads to the corresponding enaminoketones 135 in high yields. The reaction of 132 with various thiols shows the new pathway to β-sulfanylenones 136.$^{55}$ Compounds 132 are very reactive electrophiles and were used for the preparation of CF$_3$-enones 137 containing heterocyclic substituent in β-position by the reaction with furans, indoles, pyrroles, triazole, imidazole, pyrazole and their benzo-derivatives.$^{56}$

![Scheme 36](image)

New highly electrophilic reagent 138 obtained by oxidation of 139 was applied for the synthesis of α-phenylsulfonyl enones 140, 141 by reaction with aromatics and heteroaromatics.$^{57}$
Scheme 37

Enones 142 containing OTs group in α-position to carbonyl group are formed under treatment of allylic alcohols 143 with sulfuric acid. Compounds 143 were prepared from lithium derivative 144 and carbonyl compounds. Intermediate lithium derivative 144 can be synthesized from fluoroalkene 145 and also by direct metallation of 146 with 2 equivalents of n-BuLi.58

Scheme 38

Polyfluorinated aldehydes 147 were used for synthesis of β-enaminoketones 148. Target N-substituted β-enaminoketones 148 are formed in good yields by reflux of acetonitrile solution of polyfluorinated aldehydes with various amines in the presence of water.59

Scheme 39
β-(Thio)alkoxy-substituted trifluoromethyl enones 149 and 150 react with ammonia and primary and secondary amines (including aromatic ones) to give β-amino-substituted enones (enaminones) 151 in high yields.60

![Scheme 40](image)

The substitution of one alkoxy-group in enone 152 was used for synthesis of O,N-acetals-aminals of trifluoroacetyketene 153 in aqueous medium.61

![Scheme 41](image)

The example of synthesis of β-selenoenones 154 using the reaction of methoxyenones 155 with methyl- and phenylselenol in the presence of BF₃-diethyl etherate was described.62

![Scheme 42](image)

The introduction of cyano-group in the β-position of α,β-unsaturated trifluoromethyl ketones can essentially broaden their synthetic potential as building blocks. Depending on the solvent and catalyst applied individual products 156 and 157 or their mixture can be obtained. β-Cyanoenone 158 was also prepared by treatment of 156 with concentrated sulfuric acid.63
2.1.5 Modification of the α-position. The addition of halogen to the double bond of enones followed by dehydrohalogenation of intermediate dihaloketone 159 allows preparation of α-chloro(bromo)-α,β-unsaturated trifluoromethyl ketones 160. The iodoenone was prepared using ICl in 75% yield.\(^64\)

![Scheme 43](image)

Scheme 44

The reaction of CF₃-enaminoketones 161 with tosylisocyanate leads to mixture of the adducts 162 and 163 depending on the substituent in the enaminoketone.\(^65\)

![Scheme 44](image)

Scheme 45

The acylation reaction of secondary CF₃-β-enamino ketones with TFAA or ethoxyoxalyl chloride led regioselectively to N-acylated enamiones 164 in good yields. On the other hand, when tertiary enaminones were used, the acylation reaction led to C-acylated enamiones 165.\(^66\)

![Scheme 45](image)

Scheme 46
2.1.6 Other methods. The standard way for preparation of α,β-unsaturated ketones from aliphatic ketones is the treatment with phenylselenyl chloride followed by oxidation and elimination of PhSeOH. This method was used for preparation of cyclic CF₃-enone 166 from 1,3-diketone 167.⁶⁷

![Scheme 47]

Trifluoromethyl-containing allylic alcohols 168 can be oxidized into the corresponding enones 169 on treatment with the Dess-Martin reagent or Swern reagent (DMSO - oxalylchloride/triethylamine). Manganese dioxide in CH₂Cl₂ was also used for this purpose. Nowadays this method has become customary because of development of synthetic approach to allylic alcohols using Ruppert reagent (TMS-CF₃).⁶⁸

![Scheme 48]

The corresponding acrylic esters can be converted into α,β-unsaturated trifluoromethyl ketones 171 by addition of Ruppert reagent (TMS-CF₃) using cesium fluoride as the catalyst. The intermediate acetals 170 can be hydrolyzed by acid.⁶⁹ The reactions of the acyl chlorides with trifluoromethylsilver generated in situ proceed selectively in EtCN giving the corresponding trifluoromethylketones 171 in moderate yields.⁷⁰

![Scheme 49]

2.2 Synthesis of acetylenic CF₃-ketones
The set of methods for preparation of acetylenic CF₃-ketones is much narrow than the set for preparation of CF₃-enones. There are only several universal methods for preparation of acetylenic
CF₃-ketones. The classical method is the trifluoroacylation of anions 172 generated from terminal alkynes with TFAA, ethyl or trifluoroethyl trifluoroacetate to form 173.⁷¹

\[
\begin{align*}
\text{R} & \quad \equiv \quad \equiv \quad \text{Li} \\
172 & \quad \quad \quad 1) \quad \text{n-BuLi} / \text{THF} \\
& \quad \quad \quad 2) \quad \text{CF}_3\text{COX} \\
\text{R} & \quad \equiv \quad \text{COCF}_3 \\
173 & \quad \quad \quad \text{X} = \text{Cl, OCOCF}_3, \text{OEt, OCH}_2\text{CF}_3 \\
& \quad \quad \quad \text{(69-90%)}
\end{align*}
\]

**Scheme 50**

Another convenient method is the sequence for the preparation of secondary propargylic alcohols 174 starting with acetylenes and fluoral with further oxidation into ketones 175.⁷² The CF₃-containing alkynone 176 was synthesized by reaction of aldehyde 177 with TMSCF₃ followed by oxidation of alcohol 178 with Dess-Martin periodinane.⁷³

\[
\begin{align*}
\text{Li} & \quad \equiv \quad \text{CH(OEt)}_2 \\
177 & \quad \quad \quad \text{CF}_3\text{CHO} \\
& \quad \quad \quad \text{THF, 0 °C} \\
\text{F}_3\text{C} & \quad \equiv \quad \text{CH(OEt)}_2 \\
174 & \quad \quad \quad \text{MnO}_2 \\
& \quad \quad \quad \text{CH}_2\text{Cl}_2 \\
\text{F}_3\text{C} & \equiv \quad \text{CH(OEt)}_2 \\
175 & \quad \quad \quad \text{Dess-Martin reagent} \\
& \quad \quad \quad \text{CH}_2\text{Cl}_2, \text{r.t.} \\
& \quad \quad \quad \text{0.5 h} \\
\text{TsN} & \quad \equiv \quad \quad \equiv \quad \text{CHO} \\
176 & \quad \quad \quad \text{CF}_3 \\
& \quad \quad \quad \text{OH} \\
& \quad \quad \quad \text{(90%)}
\end{align*}
\]

**Scheme 51**

Electrophilic substitution of trimethylstannyl-group under the treatment with molecular halogens of trimethylstannyl trifluoroacetylacetylene 180 was used for the preparation of halogen-derivatives of trifluoroacetylacetylenes 181. The acetylene 180 can be prepared using the reaction of bis-trimethylstannylacetylene 179 and TFAA. Analogous synthesis of parent trifluoroacetylacetylene was proposed by the reaction with trifluoroacetic acid.⁷⁴

\[
\begin{align*}
\text{Me}_3\text{Sn} & \quad \equiv \quad \equiv \quad \text{SnMe}_3 \\
179 & \quad \quad \quad \text{TFAA} \\
& \quad \quad \quad \text{Me}_3\text{Sn} \quad \equiv \quad \text{CO} \quad \equiv \quad \text{SnMe}_3 \\
180 & \quad \quad \quad \text{X}_2 \\
& \quad \quad \quad \text{X} = \text{Cl (85%), Br (87%), I (50%)} \\
& \quad \quad \quad \text{CF}_3\text{COOH} \\
181 & \quad \quad \quad \text{X} = \text{H (85%)}
\end{align*}
\]

**Scheme 52**

1,4-Addition of dialkylcuprates to acetylenic ketones 182 is highly regioselective but it is not stereoselective and gives products 183 in moderate yields. The application of cyanocuprates results in higher yields and in a nearly 100% regioselectivity of the reaction. However, in some cases cyanohydrins are the products of the reaction.⁷⁵ The reactions of alkynyl trifluoromethyl ketones with aromatic amines afford β-amino-substituted CF₃-enones 185 in good yields.⁷⁶
3. Application of $\alpha,\beta$-Unsaturated CF$_3$-Ketones to the Synthesis of Heterocycles

3.1 Synthesis of three- and four-membered heterocycles

The perfluorinated CF$_3$-enone 186 was produced by pyrolysis of perfluorodihydrofuran 187 which in turn is prepared by high temperature hydrolysis of tetrafluoroethene tetramer 188. The fluorinated oxirane 189 and azetidine 190 were prepared using the reaction of 186 with NaOCl and primary amines correspondingly.

3.1.1 Synthesis of pyrrole derivatives. The reaction of diethoxyenone 191 with NaCN was described for the synthesis of the corresponding pyrrolidone 192. It was shown that various enones 193 react with NaCN to give the corresponding pyrrolidones 194 as the mixture of diastereomers. Subsequent dehydration proceeds with migration of double bond and leads to formation of pyrrole-3-one-2 195.
Other derivatives of trifluoromethyl pyrrole 196 were prepared using reaction of dithiazole 197 (prepared from Appel salt) with primary amines.80

\[
\begin{align*}
\text{R}^1 \text{C}l &\quad \text{CH}_2\text{Cl}_2 \text{ or THF} &\quad \text{R}^3\text{NH}_2 \\
\text{S} \quad \text{N} &\quad \text{F}_3\text{C} &\quad \text{NH}_2 &\quad \text{F}_3\text{C} \\
\text{R}^2 \text{Cl} & &\quad \text{X} & &\quad \text{R}^3
\end{align*}
\]

\(196 \text{(22-55%)}\)

**Scheme 56**

Photolytic rearrangement of aziridine-substituted enaminoketones 198 was used for the preparation of the CF₃-pyrrole derivatives.81 Depending on the substituents of starting ketone 198 the pyrrole 199 or the mixture of diphenylpyrrole 200 and dibenzoindole 201 were formed.

\[
\begin{align*}
\text{hv} &\quad \text{R} = \text{Me} &\quad \text{R}^1 = \text{Me}, \text{t-Bu}; \text{R}^2 = \text{H}, \text{Ph} \\
\text{hv} &\quad \text{R} = \text{H} &\quad \text{R}^1 = \text{Me}, \text{t-Bu}; \text{R}^2 = \text{H}, \text{Ph}
\end{align*}
\]

**Scheme 57**

The acylation of enaminoketones 202 with oxalyl chloride was applied for the preparation of 1H-pyrrole-2,3-diones 203.82

\[
\begin{align*}
\text{F}_3\text{C} &\quad \text{R}^1 &\quad \text{O} &\quad \text{NHR}^2 \\
\text{O} &\quad \text{O} &\quad \text{Cl} &\quad \text{Cl} \\
\text{R}^2 & &\quad \text{F}_3\text{C} &\quad \text{R}^1 &\quad \text{O} &\quad \text{NHR}^2 \\
\text{R}^2 & &\quad \text{F}_3\text{C} &\quad \text{R}^1 &\quad \text{O} &\quad \text{NHR}^2
\end{align*}
\]

**Scheme 58**

Novel approach for the synthesis of alkoxy and amino pyrrole derivatives 204a,b has been elaborated using the reaction of azidomethylenones 205a,b with trimethylphosphine.83
Scheme 59

The viability of a reaction sequence based on the reaction of α-amino acids with the alkoxy enone 206 followed by a cyclization promoted by TFAA was established. All steps of the synthesis can be done in one-pot to give various CF₃-pyrroles 207 including condensed pyrroles.

Scheme 60

Dimethoxyethylamine substituted enaminones 208 can be cyclized easily in the presence of TFA to the corresponding 3-trifluoroacetylpyrroles 209 in good yield.

Scheme 61

Imino-derivative of unsaturated trifluoromethyl-containing ketones 210 was cyclized in the presence of palladium on carbon to 5-trifluoromethylpyrrolidone 211.
Scheme 62

α,β - Unsaturated ketones are efficient dipolarophiles in catalytic asymmetric 1,3-dipolar cycloaddition with azomethine ylides 212. The efficiency of this protocol strongly relies on the use of CuI-Fesulphos catalysts, leading to highly functionalized CF₃-substituted pyrrolidine 213 in good yields, moderate to high endo/exo-selectivities and high enantiocontrol (81-96% ee).  

Scheme 63

A new one-pot strategy for the synthesis of 3-trifluoroacetyl pyrroles 214 was elaborated. The reaction of 215 with primary amines followed by oxidation with PCC leads to 1,1,1-trifluoro-3-(2-ethanal)-4-alkylaminobut-3-en-2-ones cyclizing to pyrroles 214.

Scheme 64

Reaction of CF₃CO -substituted primary ketene N,O-acetals 216 with 1,2,4,5-tetrazine-3,6-dicarboxylate 217 yields by [4+2] cycloaddition tetrafunctionalized pyridazines 218 converted into aminopyrrole derivatives 219 under reductive conditions.
Scheme 65

3.1.2 Synthesis of furan derivatives. The oxidative dimerization of acetylenic ketone 220 under the treatment with PbO₂ results in formation of substituted furan 221 bearing CF₃- and COCF₃ groups in moderate yields.⁸⁹

Scheme 66

Trifluoromethyl furan derivatives 222 were prepared by reaction of dithiazole 223 with secondary amines.⁸⁰

Scheme 67

The reaction of γ-hydroxy enone 224 with thiophen leads to tetrahydrofuran derivative 225. The compound 225 eliminates water and thiophenol to give the corresponding furan 226.⁶⁸ᵃ

Scheme 68
The reaction of 227 with isocyanides occurs at room temperature without catalysts to give stable 1,4-cycloaddition products - substituted dihydrofurans 228.\(^{90}\)

\[
\begin{align*}
\text{227} & \xrightarrow{R-N=O^\ominus} \text{228} \\
\text{F}_3\text{C} & \text{Me} & \text{F}_3\text{C} & \text{Me} & \text{R} & \text{Me} & \text{Me} & \text{N} & \text{R} \\
\text{20\textdegree C, 14 days} & & & & & & & & \\
\text{R} & = \text{t-Bu, c-Hex} & & & & & & & & \\
\text{228 (90-92\%)} & & & & & & & & \\
\end{align*}
\]

**Scheme 69**

The ketones 229 were iodinated and subsequently reduced to give the corresponding alcohols 231 which are then subjected to coupling with phenylacetylene to furnish alcohols 232. Final cyclization by means of AgOTf leads to 2-(trifluoromethyl)furan 233 in fair yield.\(^{91}\)

\[
\begin{align*}
\text{229} & \xrightarrow{I_2} \text{230 (55-92\%)} \\
\text{F}_3\text{C} & \text{Me} & \text{F}_3\text{C} & \text{Me} \\
\text{NaBH}_4 & \xrightarrow{\text{Ar}} & \text{231 (48-99\%)} \\
\text{CeCl}_3 & \xrightarrow{\text{Pd(PPh}_3)_4} & \text{232 (80-99\%)} \\
\text{AgOTf} & \xrightarrow{\text{F}_3\text{C} & \text{O} & \text{Ar}} & \text{233 (49-99\%)} \\
\text{X} & = \text{H, CH}_3, \text{OCH}_3, \text{NO}_2, \text{N(CH}_3)_2, \text{F, Cl, CN, p-NO}_2, \text{m-NO}_2 \\
\end{align*}
\]

**Scheme 70**

### 3.1.3 Synthesis of thiophene derivatives.

Acetylenic ketone 234 was successfully applied as starting compound for preparation of 3-CF\(_3\)-thiophene-2-carboxylates 235 by reaction with methyl thioglycolate.\(^{72}\) The cyclization of sulfide derivatives 236 in the presence of a base demonstrated the formation of 237.\(^{92}\)

\[
\begin{align*}
\text{234} & \xrightarrow{1. \text{HSCH}_2\text{CO}_2\text{Me, THF, 0 \textdegree C}} \text{235 (79\%)} \\
\text{F}_3\text{C} & \text{O} & \text{OEt} & \text{EtO} & \text{EtO} \\
\end{align*}
\]

\[
\begin{align*}
\text{236} & \xrightarrow{2. \text{Cs}_2\text{CO}_3 / \text{MgSO}_4 (1 : 2), \text{MeOH, 0 \textdegree C - r.t.}} \text{237} \\
\text{S} & \text{CO}_2\text{Et} & \text{CO}_2\text{Et} & \text{CO}_2\text{Et} & \text{CO}_2\text{Et} \\
\text{Ph} & \text{CF}_3 & \text{Ph} & \text{Ph} & \text{Ph} \\
\end{align*}
\]

**Scheme 71**
3.1.4 Synthesis of pyrazoles and their derivatives. The first example of using a trifluoromethyl enone (β-trifluorooacetylstyrene) for the synthesis of pyrazole derivatives dates back to 1959. However, vigorous studies of the reactions of CF₃-enones have been investigated only in recent years. The reactions of ketone 238 with N-substituted hydrazines depending on structure of starting hydrazine lead to individual pyrazole or to the mixture of regioisomers 239 and 240.

![Scheme 72]

The reactions of hydrazines with β-alkoxy-substituted enones have been investigated. The reaction of 241 with N-methylhydrazine gives two isomeric dihydropyrazoles 242 and 243 in various ratios. These pyrazolines undergo dehydration to form pyrazoles 244 and 245.

![Scheme 73]

Depending on condition applied the reactions of β-methoxy-CF₃-enones 246 with phenylhydrazine give pyrazoles 247, 248 or pyrazoline 249.

![Scheme 74]

The reaction of 4-hydrazo-7-chloroquinoline 250a with 251 was investigated for antimalarial screening of 252 and 253. The corresponding pyrimidine derivatives 255 containing dihydropyrazole substituent are potential analgesics and antipyretics. Similarly prepared
trifluoromethyl substituted pyrazolines 256a,b exhibit antimicrobial activity against yeast, fungi, bacteria, and alga. The compounds bearing indole moiety 256c were found dual inhibitors of cyclooxygenases (COXs) and lipoxygenases (LOXs).96

Scheme 75

The reactions of various aryl- and hetaryl substituted hydrazines with 257 containing acetyl group in α-position lead the heterocyclization is directed to acetyl-group for arylhydrazines and to trifluoroacetyl-group for methylhydrazine to form pyrazoles 258, 259.97

Scheme 76

The pathway of the reaction for ketone 260 with perfluorophenylhydrazine due to its reduced basicity differs from that of reaction with phenylhydrazine. The reaction of 260 with phenylhydrazine leads to pyrazole 261 while the same reaction with pentafluorophenylhydrazine leads to the formation of pyrazoline 262 dehydrated into 263 using P2O5.98
Scheme 77

Ethoxy-, hydroxy- and aminopyrazole derivatives 265 were obtained in good yields by the reaction of diethoxyenone 264 (O,N-acetals-aminals of 266) with hydrazines.78,99

Scheme 78

The reaction of α-bromo-β-ethoxy-CF₃-enone 267 with aryl hydrazines proceeds 100% regioselectively to open new effective way to the synthesis of 4-bromo-5-CF₃-pyrazoles 268.100

Scheme 79

Isomeric 5-chloro (bromo) substituted pyrazoles 272 were prepared by the reaction of β,β-dihalogen-substituted trifluoromethylketones 269 with N,N-dimethylhydrazine.101 The mechanism of the reaction consists of initial dimethylhydrazone 270 formation with subsequent intramolecular attack of nucleophilic fragment on β-carbon atom of vinyl group and demethylation of 271 with dimethylhydrazine. Isomeric salts 273 with potential high herbicide activity were prepared in the reaction of enones 274 with N,N'-dimethylhydrazine.102
Scheme 80

An interesting example of application of trifluoroacetyl pyrrole 275 for preparation of pyrazoles 276 was described.\(^{103}\) In view of the pharmacological interest in heterocycles bearing both CF\(_3\)-appendage and \(\beta\)-aminoethyl side chain the method is very attractive. The reaction of cyclic enaminoketones 277 with hydrazine leads to pyrazoles 278 containing aminoalkyl side chain.\(^{27b}\) The reaction of hydrazine with \(\beta\)-trifluoroacetyldihydropyran and \(\beta\)-trifluoroacetyldihydropyran 279 leads to the corresponding pyrazole 280.\(^ {71b}\)

Scheme 81

Similarly the pyrazoles 282 containing 1,3-dithiopropyl substituent were prepared from CF\(_3\)-enones containing a dialkyldithio-fragment in the \(\beta\)-position 281.\(^ {104}\)

Scheme 82
An efficient synthesis of 1-cyanoacetyl-5-trifluoromethyl-4,5-dihydro-1H-pyrazoles 283 in the ionic liquid ([bmim][BF₄]) has been reported.¹⁰⁵

\[ \text{CN} \quad \text{NHNH}_2 + \begin{array}{c} \text{O} \\ \text{R}^2 \end{array} \quad \begin{array}{c} \text{O} \\ \text{R}^1 \end{array} \quad \text{[bmim]}\text{BF}_4 \quad \text{HCl} \quad \longrightarrow \quad \begin{array}{c} \text{F}_3\text{C} \\ \text{N} \\ \text{O} \\ \text{R}^2 \end{array} \quad \begin{array}{c} \text{R}^1 \end{array} \quad 283 \quad \text{62-90%} \]

Scheme 83

Using double excess of ketones 284 in the reaction with aminoguanidine carbonate the formation of pyrazolinepyrimidines 285 is observed. These compounds can be easily dehydrated into the corresponding pyrazolylpyrimidines 286.¹⁰⁶

\[ \text{NH}_2\text{NHCO(NH)}\text{NH}_2\text{H}_2\text{CO}_3 \quad \text{EtOH, 4 h, reflux} \quad \longrightarrow \quad \begin{array}{c} \text{F}_3\text{C} \\ \text{N} \\ \text{O} \\ \text{H} \\ \text{R} \end{array} \quad \begin{array}{c} \text{F}_3\text{C} \\ \text{N} \\ \text{O} \\ \text{CF}_3 \end{array} \quad \begin{array}{c} \text{CF}_3 \end{array} \quad \text{285 (39-85%)} \]

\[ \text{H}_2\text{SO}_4\text{con}, \text{CH}_2\text{Cl}_2 \quad \text{4 h, reflux} \quad \longrightarrow \quad \begin{array}{c} \text{F}_3\text{C} \\ \text{N} \\ \text{O} \\ \text{CF}_3 \end{array} \quad \begin{array}{c} \text{R} \end{array} \quad \begin{array}{c} \text{F}_3\text{C} \\ \text{N} \\ \text{O} \\ \text{CF}_3 \end{array} \quad \text{286 (70-76%)} \]

Scheme 84

The reaction of 284 with thiosemicarbazide leads to the corresponding hydroxy dihydropyrazoles 287 in high yields.¹⁰⁷ They can be transformed into N-unsubstituted pyrazoles 288 in high yields using acidic hydrolysis. The ketone 289 has the hidden bromoketone fragment; it was applied for forming thiazole connected with pyrazoline 291.¹⁰⁸

\[ \text{CN} \quad \text{OH} \quad \text{H}_2\text{N} \quad \text{N} \quad \text{H}_2\text{N} \quad \text{H}_2\text{CO}_3 \quad \text{MeOH} \quad \text{F}_3\text{C} \quad \text{N} \quad \text{O} \quad \text{R}^2 \quad \text{R}^1 \quad \text{287 (73-96%)} \]

\[ \text{96%} \text{H}_2\text{SO}_4 \quad \text{reflux 4 h} \quad \text{57-75%} \quad \text{288} \]

\[ \text{F}_3\text{C} \quad \text{O} \quad \text{MeO} \quad \text{R} \quad \text{289} \quad \text{Br} \quad \text{290} \quad \text{CH}_2\text{Cl}_2, 35^\circ\text{C} \quad \text{MeO} \quad \text{CF}_3 \quad \text{291 (90%)} \]

Scheme 85
The reaction of 284 with 2-pyridylcarboxamidrazone 292 leads to pyrazoline 293. Reaction is accompanied with imine fragment of amidrazone hydrolysis. The compounds 294 react with copper (II) chloride to give 1:1 adducts in which the donor fragment of the molecules is isomerized into their cyclic pyrazolic forms.109

Scheme 86

Enones 296 containing no replaceable β-substituents form pyrazolidines 297 which can be dehydrated to the corresponding pyrazolines 298. In case of the reaction of ketone 299 with phenylhydrazine tetrahydropyrazole 300 was obtained 100% stereoselectively.110

Scheme 87

β-Trifluoroacetylstyrene 301 reacts with hydrazines to afford pyrazolines 302. Oxidation of 302 with lead tetraacetate affords the corresponding pyrazole 303 in a moderate yield.111 When β-trifluoroacetylstyrene reacts with methylhydrazine, a mixture of isomeric pyrazolines 305a,b (in ~1 : 3 ratio) is formed. The reaction with 1,2-dimethylhydrazine gives pyrazolidine.110a
Scheme 88

Enone 301 reacted with semicarbazide or thiosemicarbazide in an acidic medium to afford semicarbazone 306a or thiosemicarbazone 306b cyclized in the presence of EtONa to 307.112

Scheme 89

The perfluorinated derivative of pyrazolidine 310 was obtained by the reaction of 311 with hydrazine. This product 310 is a stable solid subliming in vacuum without decomposition.77

Scheme 90

The reaction of acetylenic CF3-ketones 312 with hydrazines was also used for the preparation of CF3-substituted pyrazoles 313 in excellent yield.113
tert-Butylhydrazones 314 react with enone 315 giving rise to 4-trifluoroacetylpyrazoles 318. A possible mechanism includes replacement of the ethoxy group by the hydrazone, subsequent cyclization to pyrazolines 317 and oxidation to pyrazoles 318 by atmospheric oxygen.\textsuperscript{114}

The ketones 320 react with diazoalkanes 319 forming pyrazolines 321 100\% regioselectively and highly stereoselectively. Using the trifluoroacetylated acetylene 322 in the reaction with ethyl diazoacetate allows preparing the pyrazole 323.\textsuperscript{115}

\textbf{3.1.4 Synthesis of isoxazole (isoselenoazole) derivatives.} The reactions of $\beta$-alkoxy-substituted enones 324 with hydroxylamine follow different pathways depending on the structure of the enone. Thus acyclic enones and enones containing no oxygen atom in the ring are converted into isoxazolines 325,\textsuperscript{60a,78} which can be dehydrated on treatment with $\text{P}_2\text{O}_5$ or concentrated $\text{H}_2\text{SO}_4$ to give the corresponding isoxazoles 326 or 327.
Scheme 94

O-Vinyl oximes 328 react readily with trifluoroacetic anhydride to give CF₃-enones 329. 4,5-Dihydro-1,2-oxazole 330 was isolated as the single product when the reaction mixture was treated after trifluoroacylation with aqueous NaHCO₃.¹¹⁶

Scheme 95

The reaction of β-methoxy CF₃-enones 335 with hydroxylamine hydrochloride was investigated. 4,5-Dihydroisoxazoles 336 were obtained in high yields and they can be transformed into the corresponding isoxazoles 337 using concentrated sulfuric acid, or directly using the excess of HCl.¹¹⁷

Scheme 96

The use of cyclic β-alkoxy-CF₃-enone 338 allows preparing isoxazoles 341 and 342 and their dihydro-derivatives 339 and 340 containing functional groups in high yields.¹¹⁸
Scheme 97

Analogously enones 343 were converted into isoxazolines 346, which result from opening of the furan or pyran ring. However, when the reaction is carried out at higher temperatures, it gives rise to tetrahydrofuran and tetrahydropyran derivatives 345, formed apparently upon dehydration of aldehyde oximes 344, resulting from cyclization of the starting enones. The reactions of cyclic enaminoketones 347 with hydroxylamine lead to dihydroisoxazoles 348 containing aminoalkyl side chain as the single diastereomers. Compounds 348 can be dehydrated with sulfuric acid into isoxazoles 349 in high yields.\(^{27b}\)

Scheme 98

The reaction of 350 with N-methylhydroxylamine hydrochloride proceeds as Michael addition forming 351 or the isoxazoles 352 depending on the substituent in 350.\(^{119}\)

Scheme 99
The reaction of 353 or 354 with hydroxylamine hydrochloride gave the corresponding ethoxy-derivative of isoxazoline 355 or amino-substituted isoxazoles 356 in good yield.99

Scheme 100

In case of 1,3-dipolar cycloaddition of ketone 357 with nitrile oxides both C=C and C=O participating in the formation of isoxazole rings to afford 1,4,2-dioxazole 359.120

Scheme 101

[2+3]-Cycloaddition of β-ethoxy-CF3-enone 357 with N-methyl-C-arylnitrones 360 results in the isoxazolidines 361. These compounds can not be isolated due to transformation to diol 362 and ethanol elimination product 363 under column chromatography purification.121

Scheme 102

Ketones containing no alkoxy-groups in β-position 364 can also be used for the preparation of isoxazoles 365. Diaryl-substituted isoxazole with unusual regiochemistry 365 was synthesized using the reaction with hydroxylamine with further aromatization by treatment with iodine.121

Scheme 103
The reaction of 366 with hydroxylamine in an acidic medium gives rise to oxime 367, which does not tend to cyclize. The reaction with hydroxylamine in the presence of an equimolar amount of sodium ethoxide gives isoxazolidines 368 in good yields.\(^{122}\)

![Scheme 104](image)

Isoxazolines 372 and isoxazoles 373 were also obtained in good yields in the reaction of alkynyl ketones 369 with hydroxylamine. This reaction performed in an acid medium gives oxime 370, which cyclizes to isomeric isoxazole 371.\(^{113}\)

![Scheme 105](image)

Isoselenoazoles 374, otherwise available only with difficulty, can easily be prepared by consecutive treatment of enones 375 with bromine and ammonia.\(^{62}\)

![Scheme 106](image)

### 3.1.5 Synthesis of oxazoles.

The reaction of acetylenic CF\(_3\)–ketones 376 with methyl isocyanoacetate catalyzed with AgClO\(_4\) leads to the formation of the dihydrooxazole 377 in high yields.\(^{123}\)

![Scheme 107](image)
4-Oxazolines 378 were obtained by the amination of 379 with nosyloxycarbamates through a domino reaction involving a fast rearrangement of unstable 2-trifluoroacetyl aziridines 380.124

\[
\begin{align*}
\text{F}_3\text{COC} & \quad \text{O} \quad \text{NsONHC}O_2\text{R} \\
\text{379} & \quad \text{NaH} \\
Y = \text{Ar}, \text{Het}, \text{OEt} \quad \text{R} = \text{Et}, \text{t-Bu} \\
\end{align*}
\]

Scheme 108

3.1.6 Synthesis of triazoles. The reaction of ketone 381 with various azides leads to the formation of the corresponding trifluoroacetyl triazoles 382 hydrated to diols 383.125

\[
\begin{align*}
& \quad \text{COCF}_3 \quad \text{EtO} \quad \text{RN}_3 \\
& \quad \text{381} \quad \text{R = Ar, Bn} \\
& \quad 80^\circ \text{C} \quad \text{24-144 h} \\
& \quad \text{R-N-} \quad \text{N-} \\
& \quad \text{N} \quad \text{N} \\
& \quad \text{382 (51-88%)} \\
& \quad \text{H}_2\text{O} \\
& \quad \text{R-N-} \quad \text{N-} \\
& \quad \text{N} \quad \text{N} \\
& \quad \text{383} \\
\end{align*}
\]

Scheme 109

3.2 Synthesis of six-membered heterocycles

3.2.1 Synthesis of pyridines and their derivatives. Though there are few methods for preparation of CF₃-containing pyridines. The synthesis of the 6-CF₃-nicotinonitrile 384 based on the reaction with β-dimethylaminoacrylonitrile 385 followed by the treatment of intermediate product 386 with ammonium acetate was proposed.126

\[
\begin{align*}
& \quad \text{F}_3\text{COC} \quad \text{+} \quad \text{NC} \quad \text{PhMe} \\
& \quad \text{381} \quad \text{385} \quad \text{Me}_2\text{N} \quad \text{Me}_2\text{N} \\
& \quad \text{NC} \quad \text{386 (73%)} \\
& \quad \text{NH}_4\text{OAc} \quad \text{DMF} \\
& \quad \text{384 (82%)} \\
\end{align*}
\]

Scheme 110

The synthesis of 2-arylamino 6-CF₃-derivatives of the nicotinonitrile 387 was elaborated using enone 388. The key step of the method is the cyclization of ketone 388 with β,β-diaminosubstituted acrylonitrile 389 generated in situ by the reaction of 390 with anilines.127

\[
\begin{align*}
& \quad \text{H}_2\text{N} \quad \text{MeCN} \quad \text{ArNH}_2 \\
& \quad \text{O} \quad \text{388} \quad \text{OBu-i} \\
& \quad \text{390} \quad \text{389} \quad \text{MeCN, reflux, 6 h} \\
& \quad \text{387 (24-83%)} \\
\end{align*}
\]

Scheme 111
The reaction of the enone 391 with β-aminocrotononitrile results in the formation of 6-trifluoromethylidihydropyridine 392 in a low yield; oxidation of this product leads to the corresponding aromatic derivative 393.128

Scheme 112

The reaction of enone 381 with N-acylacacetamidrazones 394 allows to prepare 2-hydrazone-derivatives of ethyl 6-trifluoromethylnicotinate 395 in good yields.129

Scheme 113

Enaminophosphonates containing fluoroalkyl substituents 396 were used for the regioselective preparation of polysubstituted pyridine derivatives 398 by the reaction with fluorinated α,β-unsaturated ketones 397 at high temperature in the absence of solvent.130

Scheme 114

New approach for the synthesis of 2-CF3 pyridines 399 containing various arylamino-substituents in the 4-position exploits the reaction of CF3-enone 400 with various aromatic amines including heterocyclic ones. The subsequent reaction of formed enaminketone 401 with the DMF dimethylacetal leads to dienones 402 which undergo cyclization in high yields to the targeted 2-CF3-4-arylaminopyridines 399 with ammonium acetate. Analogous approach is based on the use of 2-aminopyridine derivatives for the synthesis of the 2-CF3-4-pyridylaminopyridines 403. The same
method was used for the preparation of 2-CF₃-pyridine derivatives 404 possessing anticancer activity.¹³¹

![Diagram of chemical reactions](image)

Scheme 115

CF₃-enones 405 react with enamin esters 406 to afford fairly stable hydroxypyridines 407. The hydroxypyridines 407 were dehydrated to form dihydropyridines 408.¹³²

Scheme 116

The Gantsch type synthesis of the 1,4-dihydropyridines 409 used the reaction of dihydrothiophene-3(2H)-one-1,1-dioxide 410 with CF₃-enone 411. The intermediate compound 412 was isolated as the mixture of diastereomers and without further purification utilized in the next step. The target 1,4-dihydropyridine derivative 409 was prepared in good yield.¹³³

Scheme 117
4-Amino-2-CF₃-pyridine 413 was prepared in moderate yield using the reaction of ketone 414 with ammonia under heating at high pressure.⁷¹b

![Scheme 118]

Several works are devoted to the methods for the synthesis of the pyridine derivatives using iminates. For instance, ketone 415 was involved in the reaction with iminate 416 prepared from lithiated alkyltrimethylsilanes 417 and aromatic nitriles. The ketone 419 was used for the synthesis of the trifluoromethylpyridine 420 by the reaction with lithiated imine 421.¹³⁴

![Scheme 119]

Ketone 421a reacts easily with 1,3-diketones and 1,3-ketoesters 423 in the presence of trifluoroacetic acid to give α-trifluoromethylpyridines 422a. Similar methods for preparation of pyridines 422b,c involving the reaction of alkoxyenones 424 with CH-acids were described.¹³⁵
Scheme 120

2-CF₃-pyridine 425 was prepared in very low yield by the reaction of the enamine 426 with ammonium acetate and the ketone 427 by reflux in triglyme.¹³⁶

Scheme 121

The reaction of trifluoromethyl ketones 428 with cyanoacetamide in isopropanol in the presence of calcinated KF leads to stereoselective formation of piperidones 429a,b in high yields. Dehydration gives dihydropyridines 430a,b.¹³⁷

Scheme 122
The reaction of CF$_3$-enone 431 with cyanothioacetamide depending on conditions permits preparation of the isomeric pyridinemethiones 432 and 433 in good yields. The similar method for preparation of pyridine-2-thiols as N-methylmorpholine salts 435 is based on the reaction of enones 434 and cyanothioacetamide in the presence of double excess of N-methylmorpholine.\textsuperscript{138}

Scheme 123

A novel method for the preparation of CF$_3$- pyridines 436 was elaborated recently. First step is the synthesis of $\alpha$-hydroxydihydropyrans 437 by reaction of 438 and $\alpha$-cyanoacetophenones 439. Second step is transformation of 437 with ammonium acetate to form tetrahydropyridines 440. Third is the dehydration of 440 to give dihydropyridines 441. The final stage is oxidation into the target pyridines 436 with DDQ. All compounds were prepared in good yields.\textsuperscript{139}

Scheme 124

It has been found that chloroacetonitrile reacts with 442 in the presence of zinc and trimethylchlorosilane to produce the $\beta$-trimethylsilyloxynitrile 443 and the elimination product 444. 4-Trifluoromethyl-2-pyridone 445 was prepared in good yield after reflux of 443 and 444 mixture in concentrated HCl. Chlorination of 445 with POCl$_3$ gave 446.\textsuperscript{140}

Scheme 125
Treatment of enones 447 with eight equivalents of magnesium and chlorotrimethylsilane in DMF leads to difluoro-derivative of Danishefsky-diene 448. Hardly available 5,5-difluoro-derivatives of dihydropyridone-4 450 were obtained using aldimines 449 as dienophiles.¹⁴¹

\[
\text{Mg (8 eq), TMSCl (8 eq.), DMF, 50°C, 3 min}
\]

**Scheme 126**

A chemoselective synthesis of alkoxy or alkylamino substituted tetrahydropyridines bearing trifluoroacetyl group 451a,b was elaborated by reaction of primary amines with ketone 452.¹⁴²

\[
\text{COCF}_3 \text{R}_1 \text{NH}_2 \text{R}_1 = \text{Alk, Ar, Pyridinyl}
\]

**Scheme 127**

### 3.2.2 Synthesis of quinolines and benzoquinolines.

β-Arylamino-substituted enones 453 were cyclized to 2-trifluoromethyl- 454 and 4-CF₃-quinolines 455 under treatment with acids.¹¹³ POCl₃, ZnCl₂ and PPA were used as catalysts.¹⁴³

\[
\text{POCl}_3, 100°C, 6h \text{ or PPA, 165°C, 3h}
\]

**Scheme 128**

Quinolines 455 are the products of “normal” cyclization, while the mechanism of formation of 2-trifluoromethylquinolines 454 is the question of further investigations. The ratio of the products depends on the nature of acidic catalyst applied and the structure of the enone. Cyclization of enones with R² = H gives only 2-trifluoromethylquinolines 454. When R² = Alk or Ph, 4-trifluoromethylquinolines 455 are formed predominantly.¹⁴⁴
Various enaminoketones 456a were used for preparation of benzo[h]quinolines 457a. The target heterocycles 457 were obtained in good yields using TFA as cyclizing agent. The alkoxyketones 456b can be used for the synthesis of isomeric 4-CF₃-benzo[h]quinolines 457b. The enaminoketones 456c prepared from 1-naphthylamine were cyclized with PPA.¹⁴⁵

![Scheme 129](image)

Scheme 129

The enaminodione 458 reacts with aromatic amines in the presence of catalytic amounts of FeCl₃ to give N-aryl-substituted enaminodiones 459, which cyclize on treatment with PPA or TiCl₄, the yields of the reaction products 460 being substantially higher in the case of TiCl₄.

![Scheme 130](image)

Scheme 130

The synthesis of CF₃-derivatives of dihydrobenzo[c]acridine 461 is based on the application of CF₃-enone 462 obtained from tetralone-1.¹⁴⁶ In the reaction of 462 with various substituted anilines the formation of enaminoketones 463 is observed. Compounds 463 are cyclized to the target dihydrobenzo[c]acridines 461 in high yields by treatment with polyphosphoric acid.

![Scheme 131](image)

Scheme 131
A simple and general one-pot synthesis of 2-trifluoromethylquinolines \textit{464} from anilines and enaminoketone \textit{465} was elaborated. Treatment of \textit{465} with triflic anhydride caused the formation of 3-trifloxy-3-trifluoromethylpropeniminium triflate \textit{466} which was found to react with electron-rich aromatics to give corresponding CF$_3$-quinolines \textit{464} in excellent yields.\textsuperscript{147}

![Scheme 132](image)

The effective method for preparation of 2-substituted 4-quinolinecarbaldehydes \textit{467} is based on the reaction of acetylenic ketones \textit{468} with 2-aminothiophenol. The reaction proceeds through formation of diacetal \textit{469} which is hydrolyzed with formic acid.\textsuperscript{148}

![Scheme 133](image)

Imino-derivatives of \textit{470} can be also applied for the synthesis of quinolines derivative \textit{471} in good yield under dehydrogenation (Pd/C).\textsuperscript{28}

![Scheme 134](image)

**3.2.3 Synthesis of pyrans, thiopyrans and their derivatives.** Diels-Alder reaction of difluorinated Danishefsky-diene \textit{472} with various aldehydes was studied. The corresponding pyran-4-ones \textit{473} were obtained in moderate yields. The asymmetric synthesis of dihydropyrone \textit{474} using Ti(IV)-\textit{(R)-BINOL} catalyst was demonstrated.\textsuperscript{141}
Scheme 135

An attempt to prepare unsubstituted CF₃-enone 475 from ethyl trifluoroacetoacetate have been unsuccessful due to spontaneous dimerization of 475 to give dihydropyran 476.¹⁴⁹

Scheme 136

The reactions of trifluoromethyl enones 477 with malonodinitrile in the presence of pyrrolidine as a catalyst gave the corresponding pyrans 478.¹³⁷

Scheme 137

The ketone and diol form of compounds 479 can be used as heterodiene in the Diels-Alder reaction to reveal the stereoselective approach for dihydropyrans 480.¹⁴⁹

Scheme 138
The cycloaddition of $\alpha,\beta$-unsaturated aldehydes 481 with 482 leads to unexpected cycloadducts 483 having alkoxy-group migrated as a mixture of cis-trans-isomers.\(^{121}\)

\[
\begin{align*}
\text{COF}_3^+ \quad & \quad \text{CHO}^+ \\
R^1\text{O}^+ \quad & \quad \text{R}^2\text{R}^3\text{CHO}^+ \\
482 \quad & \quad 481 \\
\text{R}^1 = \text{Et, } \text{i-Bu} & \quad \text{R}^2 = \text{H, Me; } \text{R}^3 = \text{H, Me} \\
140 \degree \text{C, } 8 \text{ h} & \quad \text{35-46\%} \\
\end{align*}
\]

Scheme 139

The inverse-electron-demand hetero-Diels–Alder reaction of 484 occurred under mild conditions using a chiral diphenylprolinol silyl ether as the catalyst. The corresponding trifluoromethyl-dihydropyran-2-ones 485 were obtained with high ee and transformed to 486.\(^{150}\)

\[
\begin{align*}
\text{EtCHO} \quad & \quad \text{catalyst (20 mol %)} \\
\text{Ph} \quad & \quad \text{CF}_3 \text{Cl}_2 \text{r.t.} \\
484 & \quad 485 \\
\text{O} & \quad \text{OH} \\
\text{OH} & \quad \text{H} \\
\text{OH} & \quad \text{Me} \\
\text{Me} & \quad \text{Et}_3\text{N} \\
63\%, \text{ ee } 97\%, \text{ anti/syn } >95:5 \\
\end{align*}
\]

Scheme 140

The influence of various Lewis acids on the cycloaddition reaction of $\beta$-alkoxy CF$_3$-enones 487 with vinyl ethers 488 was investigated. The highest ratio of diastereoisomers was obtained using TiCl$_4$. The preparation of chiral CF$_3$-dihydropyran-2-ones 491 was also investigated. In this case the reaction of CF$_3$-ene 490 containing chiral substituent in $\beta$-position was used. The application of TiCl$_4$ gave the target pyrans 491 in high yields but de is very low.\(^{151}\)

\[
\begin{align*}
\text{F}_3\text{C} \quad & \quad \text{CO} \quad \text{OR}^1+ \quad \text{OR}^2 \quad 10 \text{ min-3 days} \\
487 \quad & \quad 488 \\
\text{R}^1 = \text{Et, Bn} & \quad \text{R}^2 = \text{Et, Bn} \\
\text{-78 \degree C, cat} & \quad \text{-78 \degree C, cat} \\
\text{cat} = \text{TiCl}_4, \text{TiCl}_2(\text{O-i-Pr})_2, \text{AlCl}_3, \text{EtAlCl}_2, \text{Et}_2\text{AlCl, ZnCl}_2 & \quad \text{cat} = \text{TiCl}_4, \text{EtAlCl}_2, \text{Et}_2\text{AlCl, ZnCl}_2 \\
\text{A} & \quad \text{B} \\
\text{A} / \text{B} = \text{from 20/13 up to 86/0 \%} & \quad \text{A} / \text{B} = \text{from 20/13 up to 86/0 \%} \\
\end{align*}
\]

Scheme 141
Cycloaddition proceeds especially easily for 492 due to the presence of the second strong EWG increasing the reactivity of trifluoromethylenones 492 as heterodienes.

Scheme 142

The reaction is carried out at room temperature to give 493 in high yields. Thioethers reacted similarly to give single diastereomers of pyrans 494. Aryl vinyl ethers react with trifluoroacetic anhydride to give the corresponding bis(trifluoroacetyl) derivatives 492a. It was found that these compounds are unstable. However, they can be introduced without isolation in the reaction with a second equivalent of aryl vinyl ether to form 495 in good yields.152

The solid-phase methodology can be successfully applied to the cycloaddition of β-benzyloxy-CF₃-enone 496 and vinyl ether 497. The reaction is catalyzed with europium(III) complex and proceeds in moderate yield though with high stereoselectivity. The target pyran 498 was obtained after the treatment 499 with LiBHEt₃. The reaction of 496a with vinyl ethers affords 3,4-dihydro-2H-pyrans 500 and 501 in good yields.153

Scheme 143
A new multistep synthesis of tri- and difluoromevalonates 502 starting from 503 has been developed. Enantiomers of fluoromevalonates can be obtained by chromatography separation.\(^{154}\)

![Scheme 144](image)

Cyano substituted dihydropyrans 504 were obtained in the reaction of 505 with \(\alpha\)-cyanoketones. The reaction proceeds in the presence of calcinated KF 100% stereoselectively.\(^{155}\)

![Scheme 145](image)

Pyran derivatives 507 were obtained as the single diastereomer in the reaction of trifluoroacetylstyrene with 4-methylthiophenol. The second reaction product was Michael adduct 506. Depending on the reaction conditions each of the two products can be obtained selectively.\(^{156}\)

![Scheme 146](image)

The reaction of trifluoromethyl enones with ammonium hydrosulfide depends on the structure of the initial enone. For instance, trifluoroacetylstyrene reacts stereospecifically yielding tetrahydrothiapyran 508 as one diastereoisomer. The reaction with cyclobutylsubstituted enone 509 affords a mixture of \(cis\)- and \(trans\)-diastereomers 510a,b in 1:1 ratio.\(^{157}\)
Scheme 147

The reaction of 511 with 2-mercaptobenzaldehyde leads to thiochromanes 512 which can be easily transformed into 2H-thiochromenes 513 by heating. The intermediate thiochromane 512 were isolated only in case of CF$_3$-ene having the phenyl substituent.$^{156}$

\[
\begin{align*}
R^1 = \text{Ph}, R^2 = \text{H}; R^1 = 2-\text{Th}, R^2 = \text{H}; R^1 = \text{N-methylpyrrolyl}, R^2 = \text{H}; R^1, R^2 = -(\text{CH}_2)_3-
\end{align*}
\]

Scheme 148

The reaction of 2-aminothiophenol with cyclic $\beta$-alkoxyenones 514 leads to formation of benzothiazolines 515 binding with tetrahydrofuran and tetrahydropyran ring.$^{158}$

\[
\begin{align*}
\text{Scheme 149}
\end{align*}
\]

Spiro-pyrene derivative 518 were obtained in good yields in the reaction of trimethylsilyl ethers 516 with $\beta$-ethoxy ketone 517 catalyzed by boron trifluoride-diethyl ether complex.$^{159}$

\[
\begin{align*}
\text{Scheme 150}
\end{align*}
\]
The Knoevenagel condensation of ethyl trifluoroacetoacetate with salicylaldehydes provides a simple and convenient approach to substituted (trifluoromethyl)-2H-chromene 519 via intermediate formation of enones 520. The subsequent recyclization of 519 affording previously unknown 3-(trifluoroacetyl)coumarins 521 in moderate to good yields.\(^{160}\)

![Scheme 151]

The Me_3SiOTf-mediated reactions of dimethoxy-substituted CF_3-enones 522 with 1,3-bis(silyloxy)-1,3-butadienes 523 afford pyran-4-ones 524.\(^{161}\)

![Scheme 152]

![Scheme 153]
The reaction of \(525\) with N-arylated glycines \(526\) in the presence of \(\text{Ac}_2\text{O}\) leads to \(2H\)-pyran-2-ones derivatives \(527\). The reaction between enones and thiourea \(528\) bearing a methylene group activated by an electron-withdrawing substituent leads to formations pyrones \(529\).162

### 3.2.4 Synthesis of pyrimidines and their derivatives

Trifluoromethylpyrimidines \(530\) are formed when \(\beta\)-ethoxycarbonyl \(531\) is allowed to react with formamide in the presence of ammonia chloride or with the compounds of the urea series.163 2-Bromo-4-(trifluoromethyl)pyrimidine \(533\) was prepared by reaction of \(532\) with phosphorus tribromide.164 Enamidoketone \(534\) was used for preparation of pyrimidine derivative \(535\).35 The heterocyclization was carried out under basic conditions.

**Scheme 154**

The reactions of CF\(_3\) enone \(538\) containing the ethoxycarbonyl group in the \(\alpha\)-position with thiourea and guanidine sulfate gave the corresponding dihydro- \(539\) and tetrahydro-derivative \(540\) in moderate yields.110 The reaction of a sterically hindered trifluoromethyl enone \(541\) having an adamantane fragment with thiourea affords dihydropyrimidine \(542\).165

**Scheme 155**
Cyclic CF₃-enones 543 were applied for the preparation of 2-pyrimidones 544 and their thio-analogous using the reaction with urea and thiourea.¹⁶⁶

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{CF}_3 & \quad \text{n(H}_2\text{C)} \\
\text{CF}_3 & \quad \text{n(H}_2\text{C)} \quad \text{BF}_3\text{Et}_2\text{O} \quad \text{H}_2\text{N} \quad \text{NH}_2 \\
\text{CF}_3 & \quad \text{O} \\
\text{Z} & \quad \text{O} (31-65\%) \\
\text{Z} & \quad \text{S} (18-35\%) \\
\end{align*}
\]

Scheme 156

The reaction of series of CF₃-enones 545a,b with acet- and benzamidine was carried out.¹⁶⁷ The formation of pyrimidine 546 or the mixture of 546 and its tetrahydro-derivative 547 is observed. In the case of enones 545b subsequent dehyration and oxidation of intermediate adducts 548 without isolation permits preparation of 549 in high yields. The possibility of application of 551 for the synthesis of pyrimidine 552 derivatives was shown.¹⁶⁸

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{O} \\
\text{R}^2 & \quad \text{R}^1 \\
\text{H} & \quad \text{Cl} \\
\text{NH}_2 & \quad \text{NH} \\
\text{HR}^2 & \quad \text{H} \\
\text{method A or B} & \quad \text{method A: 1M NaOH solution method B: EtOH} / \text{EtOK or MeOH} / \text{MeOna} \\
\text{R}^1 & \quad \text{R}^2 \\
\text{Ph} & \quad \text{Ph} \\
\text{R}^2 & \quad \text{Ph} \\
\text{CF}_3 & \quad \text{O} \\
\text{R}^1 & \quad \text{R}^2 \\
\text{method A: 1M NaOH solution method B: EtOH} / \text{EtOK or MeOH} / \text{MeOna} \\
\text{MeCN, reflux} & \quad \text{MeCN, reflux} \\
\text{R}^1 & \quad \text{R}^2 \\
\text{Ph} & \quad \text{Ph} \\
\text{CF}_3 & \quad \text{O} \\
\text{R}^1 & \quad \text{R}^2 \\
\text{1. POCl}_3, \text{Py, SiO}_2 & \quad \text{2. MnO}_2 \\
\text{R}^1 & \quad \text{R}^2 \\
\text{Ph} & \quad \text{Ph} \\
\text{CF}_3 & \quad \text{O} \\
\text{R}^1 & \quad \text{R}^2 \\
\text{1. POCl}_3, \text{Py, SiO}_2 & \quad \text{2. MnO}_2 \\
\text{R}^1 & \quad \text{R}^2 \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

Scheme 157

The one-pot synthesis of substituted 2-acetylaminoypyrimidines 554 using the reaction of 553 with 1-acetylguanidine was elaborated. The acetylamino group of 2-acetylaminoypyrimidines can be hydrolyzed to afford the corresponding 2-aminopyrimidines 555.¹⁶⁹ The N’-benzylidenehydrazino pyrimidines 556 were obtained through one-step cyclocondensation of N-guanidinobenzylimines and 4-alkoxyenones in good yields. Most heterocycles were isolated as a single diastereoisomer (E-
N-substituted pyrimidinones 557 were synthesized by condensation of enones 553 with excess N-methyl- and N-allylureas.\(^{171}\)

The reaction of β- alkoxyvinyl CF\(_3\) - ketones 553 with 2-methyl-2-thiopseudourea sulfate carried out in the presence of sodium hydroxide solution furnishing substituted 4-CF\(_3\)-2-methylsulfanyl-tetrahydropyrimidines 558 in good yields, but the product was unstable and rapidly lost an alcohol and water molecule to give the parent aromatic pyrimidine 559.\(^{172}\) The compound 560 reacts with methylisothiouronium sulfate forming directly the corresponding pyrimidine 561 in moderate yield.\(^{64a}\)

Scheme 158

The cyclocondensation of 553 toward the nonsymmetric dinucleophile - N-methylthiourea was chosen to study its regiochemistry. Depending on the temperature and the reaction time the open-chain products 562 or pyridinethiones 563 were obtained.\(^{173}\)
Analogous reaction was used for synthesis of 2-dimethylamino-derivative 566 showed cardiotonic activity.\textsuperscript{174} The target product 566 was obtained in high yield.

Scheme 160

The enaminodione 567 has been introduced in reactions with urea derivatives. The reaction with guanidine affords pyrimidine 568 in good yield. The reaction with \textit{O}-methylisourea affords 1-methoxypyrimidine 569 and 1-diethylaminopyrimidine 570 because diethylamine formed in the reaction reacts with methoxypyrimidine 569\textsuperscript{84b}

Scheme 161

The work was undertaken to apply the methodology of the synthesis of fluorinated aminopyrimidines analogous to trimethoprim (TMP)\textsuperscript{175} - the reference drug for prophylaxis and treatment of opportunistic infections due to \textit{Pneumocystis carinii} and \textit{Toxoplasma gondii}. Enaminoketones 571 were reacted with guanidine to give 572.

Scheme 162

Four novel pyrimidines were prepared to investigate the effects of on NTPDase activity in a synaptosomal fraction obtained from rat cerebral cortex.\textsuperscript{176} The pyrimidine 573 was prepared by the cyclocondensation reaction of 574 with 1,2-dimethyl-isothiourea. The synthesis of 575 was
achieved from the cyclization of hydrazine 576 with the ketone 574. The pyrimidine 577 was prepared by the oxidation of 2-methylsulfanyl-pyrimidine 578 with MCPBA which underwent nucleophilic displacement of the 2-methylsulfonyl group by hydrazine hydrate to furnish the 2-hydrazino-pyrimidine 576 in excellent yield.

Scheme 163

The reaction of 2-guanidinopyrimidine 579 with 580 and cyclic enones 580a leads to dipyrimidylamines 581 or their condensed dihydrofuran and dihydropyran derivatives 582.177

Scheme 164

Enaminoketone 583 reacts with various aldehydes in the presence of ammonia to give dihydropyrimidines 584 in good yields. Oxidation of 584 with DDQ at room temperature for 24h in acetonitrile caused smooth dehydrogenation to give the desired pyrimidines 585 having both trifluoromethyl and trifluoroacetyl groups which are not easily obtained by other methods.178
The reactions of CF₃-enone 586 with several N,N-binucleophiles gave various 2-substituted pyrimidines 587 containing 1,3-dithiopropyl substituent.¹⁰⁴

![Scheme 166](attachment:image)

**Scheme 166**

The example of application of trifluoroacetyl pyrroline 588 for preparation of pyrimidines 589 was also described. In this case the reaction is less selective. Nevertheless, the products 589 are very attractive objects for medicinal chemistry.¹⁰³

![Scheme 167](attachment:image)

**Scheme 167**

The multicomponent reaction of CF₃-enone 590, primary amine and formaldehyde was used for the synthesis of tetrahydropyrimidines 591 in moderate to high yields.¹⁷⁹

![Scheme 168](attachment:image)

**Scheme 168**

β-Alkoxy-CF₃-enones 592 were also used for preparation of various CF₃-pyrimidines 593 containing 3-oxo-2,3-dihydropyrazole substituent.¹⁸⁰ These compounds are of particular interest as the potential anti-inflammatory nonsteroid agents. Similarly pyrimidines 594 were synthesized by reaction of 595 with 592.¹⁸¹ β-Trifluoroacetylstyrene reacts with aminoguanidine to give compound 597 containing tetrahydropyrimidine and pyrazoline moieties. In this case, water is eliminated only from the five-membered ring.¹¹⁰
Scheme 169

3.2.5 Synthesis of 1,2-, 1,3- and 1,4-thiazines. The reaction of β-alkoxy-CF3-enones 592 with S,S-dimethylsulfoximine 598 gave 599 cyclized into the derivatives of 1,2-thiazine-1-oxide 600 in high yields.182

Scheme 170

The reactions of trifluoromethyl enones 601 with thiourea and thioacetamide in an acidic medium afford dihydrothiazines 602. Both reactions are regiospecific ones and give one isomer formed upon the addition of sulfur at the double bond and nitrogen of the carbonyl group.183

Scheme 171
The reaction of \( \beta, \beta \)-dibromo-CF\(_3\)-ketone 603 with thioacetamide and thiourea lead regioselectively to the corresponding 1,3-thiazine derivatives 604 in good yields.\(^{15e}\)

![Scheme 172](image)

**Scheme 172**

Dihydrothiazine 605 can be prepared using the reaction of ketone 606 with 2-aminoethanethiol with the subsequent oxidative cyclization of the adduct 607. The reaction with 2-aminothiophenol results in the formation of benzothiazine derivative 609 by heating.\(^{158}\)

![Scheme 173](image)

**Scheme 173**

3.2.6 Synthesis of 1,3-oxazines and 1,2,3-oxathiazines. The reaction of \( \beta \)-alkoxy-CF\(_3\)-enones 610 with ethyl carbamate 611 leads to formation of enamidoketones 612. Subsequent reduction into 613 and cyclization to oxazines 614. One of the evaluated compounds 614 exhibited significant activity against tested microorganism strains.\(^{184}\)

![Scheme 174](image)

**Scheme 174**

3.2. Synthesis of seven-membered heterocycles
3.2.1 Synthesis of 1,4-diazepines (benzoanalogues) and 1,5-benzoxazepines. 5-Trifluoromethyl-2,3-dihydro-1,4-diazepines 615 were prepared by the reaction of CF\(_3\)-enone 616 with 1,2-propylenediamine.\(^{43b}\) The reaction gave two isomeric products 615a,b in a nearly 1:1 ratio. Similarly 1,4-diazepines 617 were prepared in good yields with ethylenediamine using microwave
irradiation (MW), whereas carrying out the reaction in refluxing xylene resulted in a complicated mixture of products. Benzodiazepines have been considered the most extensively consumed psychoactive drugs worldwide due to their anxiolytic and anticonvulsant activity.

Scheme 175

The high yield preparation of benzodiazepines 618 by one-step reaction of 619 with o-phenylenediamines was shown. The reactions with o-aminophenol or o-aminothiophenol yield 1,5-oxazepines or 1,5-thiazepines 620 respectively. The reaction of trifluoromethyl enones 621 having no eliminating group in β-position with o-phenylenediamine affords 622.

Scheme 176

The trifluoromethyl-4,5-dihydro-3H-pyrido[2,3-b][1,4]diazepin-4-ols 623 were obtained by cyclocondensation of 4-methoxy-CF₃-enones 624 with 2,3-diaminopyridine. The reactions proceed regiospecifically in a moderate to good yields. The compounds 623 were also obtained from intramolecular cyclization reaction of the respective trifluoroacetyl enamines 625.
Scheme 177

Useful approach to the preparation of new CF$_3$-containing 1,5-benzoxazepines 626 was presented. The reaction of enaminoketones 627 with DMF-DMA results in the corresponding dienamines 628. Its cyclization with H$_2$SO$_4$ give the fluorinated 1,5-benzoxazepines 626.$^{188}$

Scheme 178

3.3 Synthesis of other condensed heterocycles

Treatment of enaminoketone 629 with methylamine or acetic acid leads to the formation of 2-CF$_3$-benzimidazole 630. The destruction of skeleton of the starting ketone 629 takes place.$^{43b}$

Scheme 179

The benzimidazolyl- and benoxazolyl CF$_3$-ketones 631 were obtained in high yields in the reaction of $\alpha$-phenyldiamine and $\alpha$-aminophenol with $\beta,\beta$-dibromoketone 632a and diethoxyketone 632b.$^{101}$

Scheme 180
Ketone 632b was applied for the synthesis of triazadibenzocrysenes 633. These polycondensed heterocycles containing various substituents were prepared in good yields from 2-perimydinylamines 634.189

Scheme 181

The pyrimidine derivatives 635 have been prepared by the reaction of 636 with aminotriazoles and aminotetrazoles. The intermediate tetrahydro derivatives 637 were obtained as single diastereomer.190 The analogous reaction was investigated for β-enaminoketone 638. The reaction leads directly to condensed heterocyclic compounds 639, bypassing the intermediate tetrahydro derivatives. The reaction proceeds in 100% regioselective manner.191

Scheme 182

The reaction of CF3-enone 640 with aminoazoles was used for the preparation of dihydro- 641 and tetrahydroazolopyrimidines 642. In case of aminotriazole and aminotetrazole the reaction proceeds 100% stereoselectively to form 642 having cis-orientation of CF3- and Ph- groups.192 An effective and regioselective method for the synthesis of 7-CF3 substituted azolopyrimidines 643 from CF3-ketones 644 with 5(3)-aminoazoles was proposed.193
Scheme 183

The condensation of 6-aminouracil derivatives 647 and CF₃-enones 648 provides preparation of CF₃-derivatives of pyrido[2,3-d]pyrimidine 645a,b and dihydro-derivative 646.¹⁹⁴

Scheme 184

Photoinduced cyclization of uracil-substituted ketones 649 having sulfimino-substituent was used for the preparation of pyrrolo[2,3-d]pyrimidine-2,4-diones 650 containing CF₃-group.⁵³

Scheme 185

In a similar manner, the reaction of 5-aminopyrazole 651 or aminopyrazolo[3,4-b]pyridine derivatives 652 gives rise to formation of condensed pyridine systems 653-655. On exposure to microwave radiation trifluoromethyl-substituted derivatives of pyrido[2',3':3,4]pyrazolo[1,5-a]pyrimidine 655 are formed in good yields from ketones 656.¹⁹⁵
Scheme 186

The corresponding pyrido[1,2-a]pyrimidine derivatives 657 are formed in good yields by heating the dienone 658 in toluene or acetic acid solution.\textsuperscript{131b}

Scheme 187

The reaction of ketones 662 (X = Cl, Br, I) with 2-aminopyridine leads to imidazopyridine 663. In case of X = Cl the formation of mixture of two products is observed. It was shown that the reaction of ketone 659 with pyridinium (isoquinolinium) salts 660 in the presence of the base leads to indolizines 661 due to the oxidation of intermediate dihydroderivatives with air.\textsuperscript{196}
The synthesis of imidazopyridines 665 using the reaction of 666 with several 2-aminopyridines was described. The reaction proceeds regio- and stereoselectively (the intermediate dihydroderivatives 667 were isolated as the single diastereomer). This reaction is the exception of the commonly observed direction for the reaction of 666 with amines because usually it leads to the products of sulfonyl-group substitution. Noteworthy that the electrophilic attack is directed on C^3 carbon atom of 666 due to the EWG properties of sulfonyl group.\(^{197}\)

\[
\begin{align*}
&\text{F}_3\text{C} \text{OH} \quad \text{H}_2\text{O} \\
&\text{RO}_2\text{S} \quad \text{MeCN} \\
&\text{666} \quad \text{R} = \text{Ph, Me}; \text{R}^1 = \text{H, Alk, Ar, Hal} \\
&\text{667} \quad \text{(80-96\%)} \\
&1. \text{H}_2\text{SO}_4, 20^\circ\text{C}, 10\text{ min} \\
&2. \text{KOH/H}_2\text{O}, 20^\circ\text{C}, \text{pH 7} \\
&\text{665} \quad \text{(84-95\%)}
\end{align*}
\]

**Scheme 189**

The synthesis of various heterocyclic systems using the reaction of enones 666 with several diazoles was investigated. Reflux of 666 with 3-aminopyrazoles leads to formation of pyrazolopyrimidines 667a. In several cases, the isomeric pyrazolopyrimidines 667b were formed as the second product. Using aryl-substituted aminopyrazoles the reaction proceeded stereoselectively forming 667a as the only isomer. In the reaction of ketones 666 with 2-amino-1\(H\)-benzimidazole the formation of imidazopyridines 668 was observed. The analogous regioselectivity is observed in the reaction of enones 666 with various 3-amino-1,2,4-triazoles and 5-aminotetrazoles. 7-Trifluoromethyl-substituted cycloadduct 669a dominates in most cases. However, the reaction in acetonitrile gave triazolopyrimidines 669b.\(^{198}\)

\[
\begin{align*}
&\text{F}_3\text{C} \text{OH} \quad \text{AcOH reflux} \\
&\text{RO}_2\text{S} \quad \text{MeCN, reflux} \\
&\text{666} \quad \text{R} = \text{Ph, Me}; \text{X} = \text{HC, AlkC, ArC, N} \\
&\text{669a} \quad \text{CF}_3 \quad \text{(70-90\%)} \\
&\text{669b}
\end{align*}
\]

**Scheme 190**
The reaction of 2-amino-1,3,4-thiadiazoles with 666 proceeds in high yields and with high stereoselectivity although the products 670 and 671 contain two asymmetric centers. This is probably due to hydrogen bond between hydroxy- and the phenylsulfonyl group.\(^{199}\)

![Scheme 192](image)

Scheme 192

As the scaffold for the construction of condensed heterocyclic systems several 2-aminothiazoles were used. The isomer 672a dominates among the products of this reaction. The effort to use 2-amino-4-aryl-1,3-thiazoles failed because the reaction leads to predominate formation of enaminoketones 673 – the products of sulfonyl-group nucleophilic substitution. In the reaction of benzothiazoles the heterocycles 674 are formed as single reaction product only in the case of compounds having no substituent in the position 4. Furthermore, the cyclization with 2-aminobenzothiazoles proceeds regio- and stereoselectively.\(^{200}\)

![Scheme 193](image)

Scheme 193

The alkylation of pyridinethiones 676 with methyl iodide and \(\alpha\)-bromoacetophenone was studied. The corresponding methylthio- and phenacylthio-derivatives of nicotinonitrile 677 were obtained in good yields. These compounds 677 were also used for heterocyclization into the corresponding benzoylthieno[2,3-b]pyridines 678 treating 677 with potassium hydroxide.\(^{201}\)
Scheme 194

The enone 679 can be applied for the preparation of the vinylogous of Vilsmeier-type reagent 680. The complex 680 can be used for the different purposes. For example, the reaction of 2,2'-bis-indolyl 681 with 680 leads to formation of pentacyclic compound 682. The reaction of N,N’-dipyrrylmethane 683 with 680 leads to aldehyde 684 formation.

Scheme 195

4. Conclusion

Summarizing the facts given in the review, one might say that α,β-unsaturated trifluoromethylketones exhibit a very high synthetic potential as molecular building blocks containing trifluoromethyl group. α,β-unsaturated trifluoromethylketones are widely used in modern organic synthesis, especially for the preparation of fluorinated heterocyclic compounds. However, the application of these very useful molecular building blocks is not restricted by this area.

The peculiarities of α,β-unsaturated trifluoromethyl ketones are their high reactivity towards nucleophiles, as well as high chemo, regio- and stereoselectivity in these reactions. The distinctive trait is the stability of gem-hydroxy-trifluoromethyl fragments, sometimes very resistant to the action of dehydrating agents.
5. References


Authors' Biographies

Valentine G. Nenajdenko was born in 1967 in Ivanovo, Russia. He graduated from Moscow State University (Lomonosov) in 1991. He received his Ph.D. degree under the supervision of Professor E.S. Balenkova in 1994 researching the synthesis and application of unsaturated CF₃ ketones. In 2000 he received Dr. of Chemistry degree involving the chemistry of sulfonium and iminium salts. In 2003 he became full Professor of Organic Chemistry at the Department of Chemistry of Moscow State University. His scientific interests include organic synthesis, asymmetric catalysis, the chemistry of sulfur and fluorine containing compounds, heterocyclic chemistry, multicomponent reactions. He have been a supervisor of 13 postgraduate studies. Prof. Nenajdenko is head of the Scientific Committee and Jury of International Mendeleev Chemistry Olympiad. He was the winner of the Academiae Europeae Award in 1997, the Russian President Award in 1996, the Prize for the best scientific work at the Department of Chemistry of Moscow State University in 2001 and 2007, the Shuvalov Award in 2001, the Russian President Award in 2004, Russian Science Support Foundation in 2005, Moscow State University Awards in 2006, 2007 and 2008.

Elizabeth S. Balenkova was born in Moscow in 1926. She graduated from Moscow State University in 1950 and then she was a postgraduate student of the Department of Chemistry of Moscow State University. She received her Ph.D. degree under the supervision of academician B.A. Kazansky in 1953 for the research concerning medium ring hydrocarbons. Since that, she has been working at Moscow State University as a senior researcher (1959) and full professor (1986). She was a supervisor of 27 postgraduate and 63 diploma works. Her research interests are in the area of organic synthesis, electrophilic addition reaction, chemistry of heterocyclic and sulfur compounds.