Preparation of α,β-unsaturated trifluoromethylketones and their application in the synthesis of heterocycles

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Abstract

The review is devoted to the preparation of α,β-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, α,β-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 CF_3-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 CF_3-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 methods[1] 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 ethers[2] vinyl sulfides,[3]

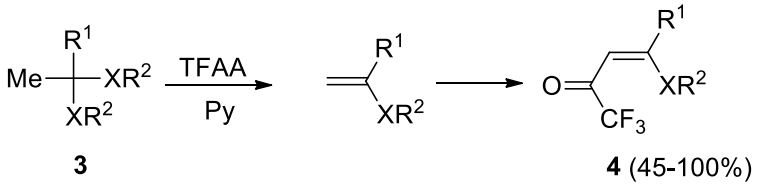
ketene dithioacetals, vinyl tellurides,[4] vinyl amides, cyclic enamines,[5] O-vinyloximes,[6] and some activated dienes.[7]

1 **2**

Y = H, Alk, Ar, SAr; X = O, S, Te, NSO_2R^2, $NCOR^3$; R^1, R^2, R^3 = Alk, Ar

Scheme 1

Orthoacetates,[8] acetals 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 *in situ*.

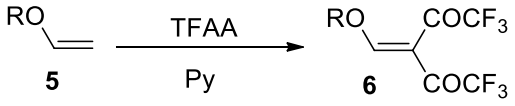


3 **4** (45-100%)

R^1 = Alk, Ar, XR^2; R^2 = Me, Et, Ar; X=O,S

Scheme 2

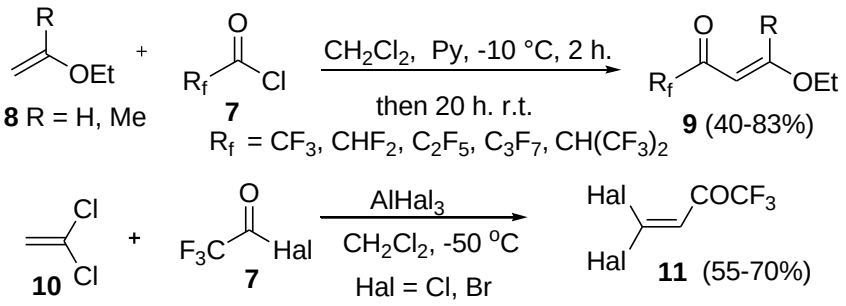
Under higher temperature the reactions of vinyl ethers **5** with a threefold excess of TFAA in the presence of pyridine result in the formation of diones **6** in high yields.[9]



5 **6**

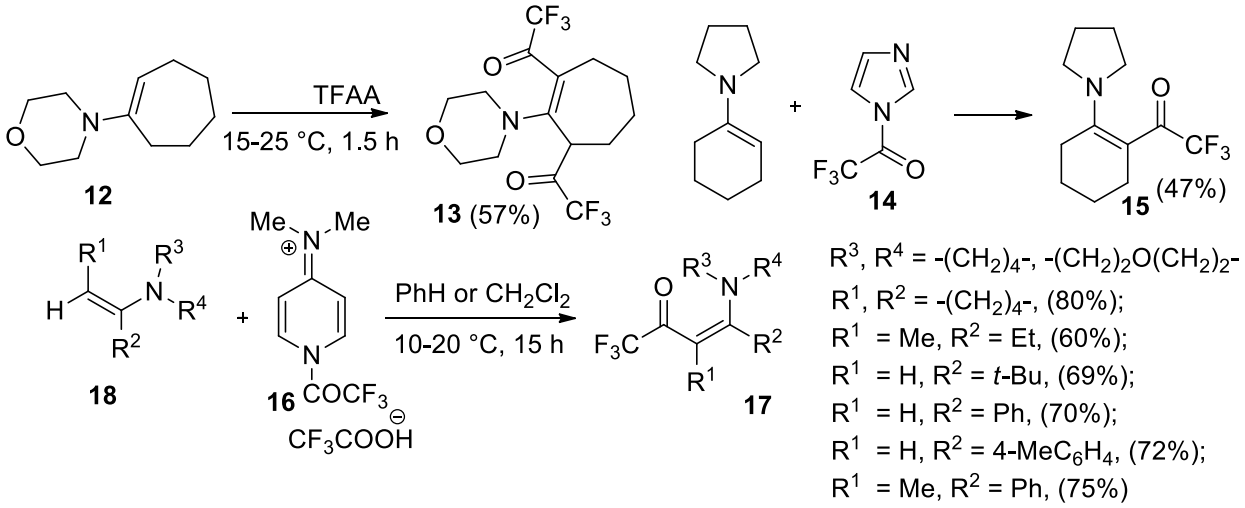
Scheme 3

Chloro(bromo) anhydrides of perfluoro carboxylic acids **7** can be also applied for acylation of alkenes **8**.[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.[11] Noteworthy using $AlBr_3$ the only product formed is 2,2-dibromovinyltrifluoromethyl ketone **11b**, whereas $AlCl_3$ gives the corresponding dichloroketone **11a**.



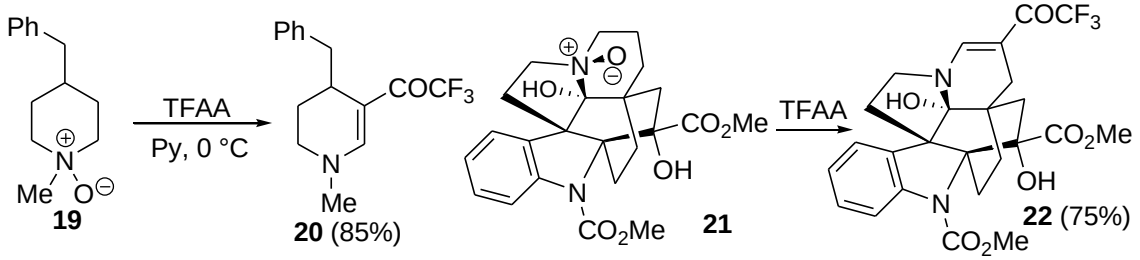
Scheme 4

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[12] **14** and the complex **16** prepared from 4-dimethylaminopyridine[13] gave better results.[14]



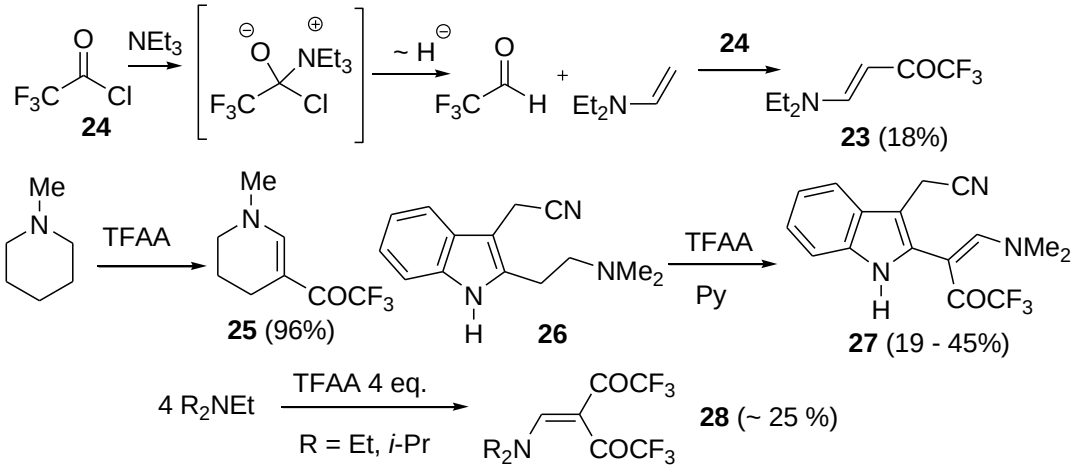
Scheme 5

It was demonstrated that N-oxides **19** of tertiary amines can be transformed into CF_3-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 **22**.[15]



Scheme 6

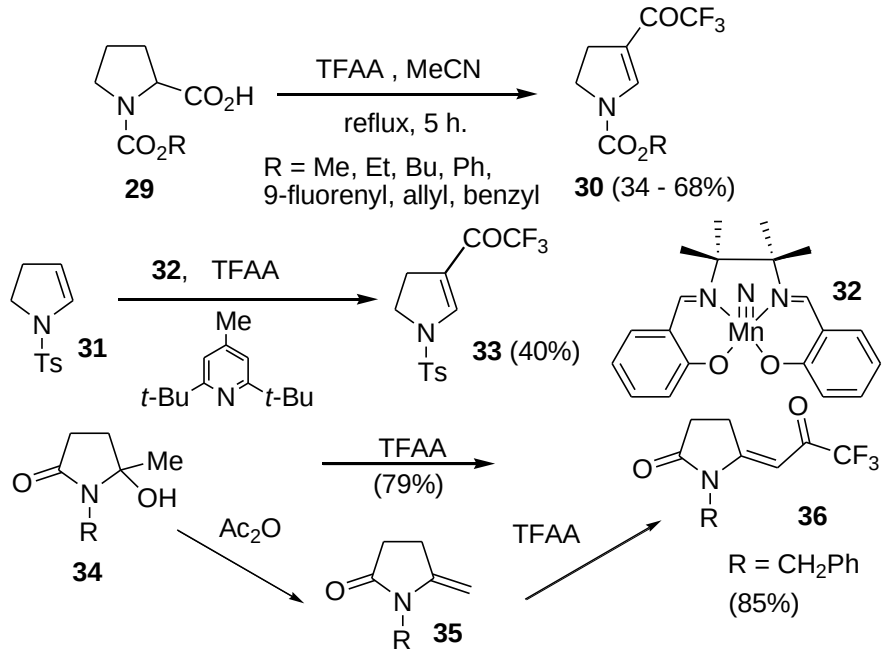
The reaction of triethylamine with trifluoroacetyl chloride **24** at –30 °C leads to 4-diethylamino-1,1,1-trifluorobut-3-en-2-one **23**.[16]



Scheme 7

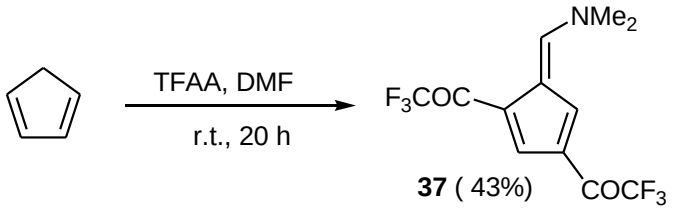
The proposed reaction mechanism includes oxidation of triethylamine by one equivalent of trifluoroacetyl chloride to give diethyl(vinyl)amine and the subsequent trifluoroacylation. Cyclic amines react in a similar way, for example, N-methylpiperidine is converted into enaminone **25** in 96% yield. Iso-tryptamine **26** can be trifluoroacetylated with TFAA to form enone **27**.[17] The reaction of triethylamine or diisopropylethylamine with TFAA leads to doubly trifluoroacetylated products **28**.[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 enaminonone **33** in moderate yield.[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.[20]



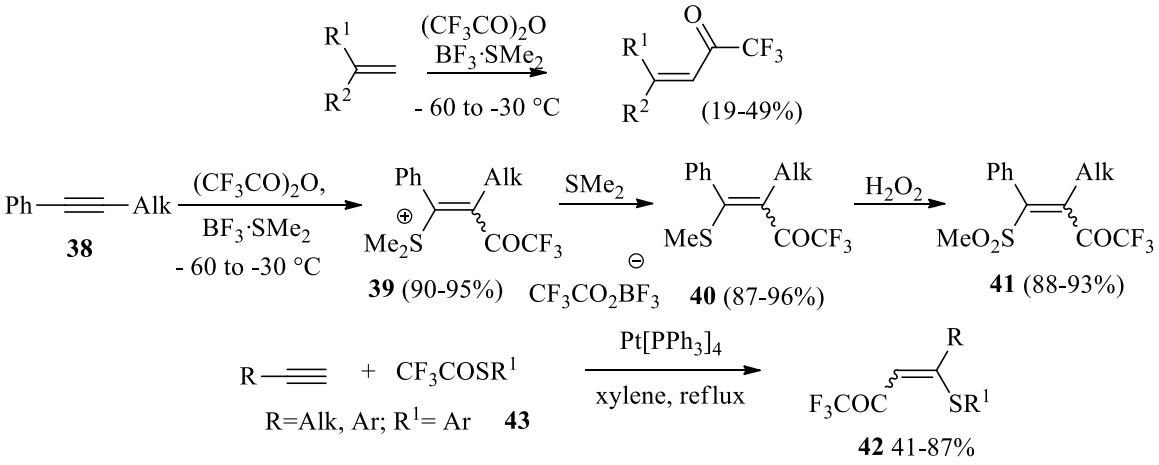
Scheme 8

The unusual disubstituted CF_3-derivative of fulvene **37** was obtained by trifluoroacylation of cyclopentadiene with TFAA at room temperature using dimethylformamide as a solvent.[21]



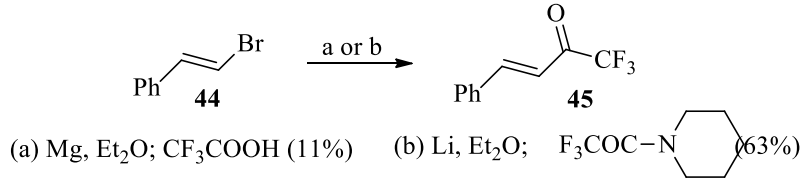
Scheme 9

The electrophilicity of trifluoroacetic anhydride and other derivatives of trifluoroacetic acid is insufficient for trifluoroacetylation 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 Me_2S-BF_3 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]



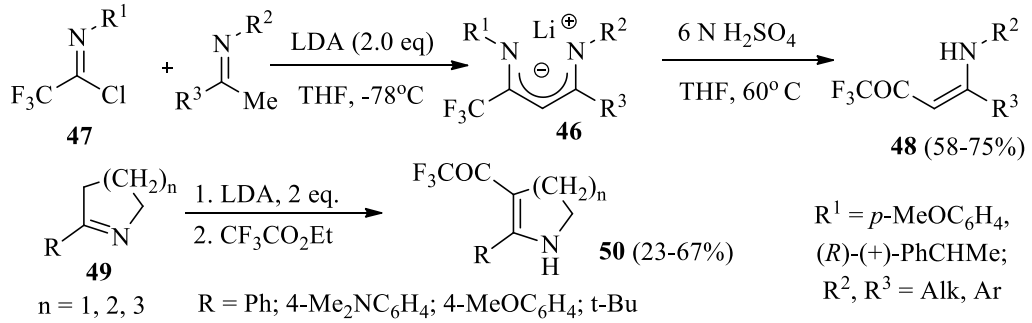
Scheme 10

2.1.2 Trifluoroacylation of organometallics. CF_3-enones can be prepared by acylation of vinylic organometallic compounds. The first trifluoromethyl containing enone, 1,1,1-trifluoro-4-phenyl-but-3-en-2-one **45**, was synthesized in low yield by the reaction of styrylmagnesium bromide with trifluoroacetic acid in 1959.[25]



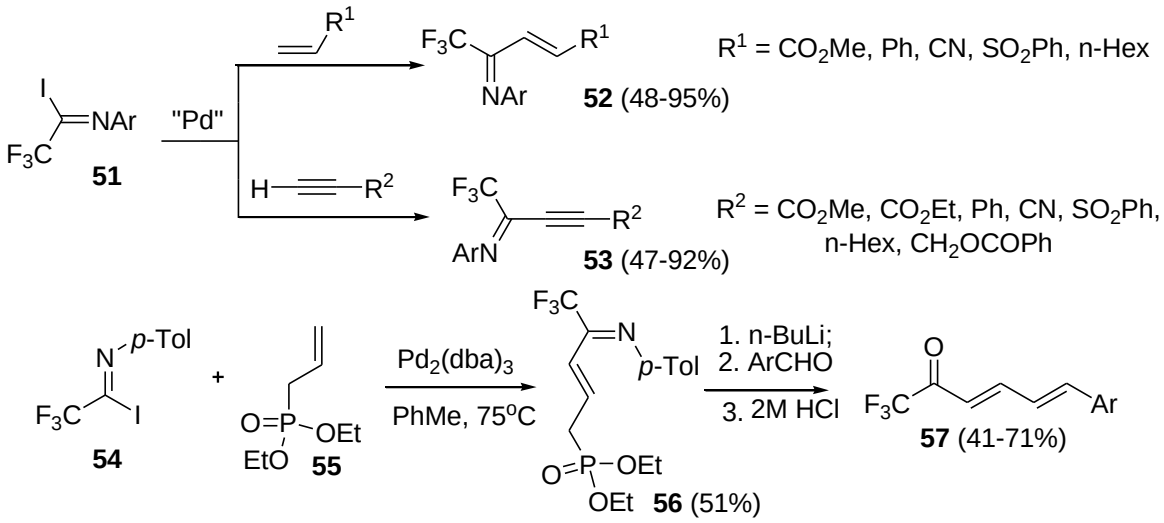
Scheme 11

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]



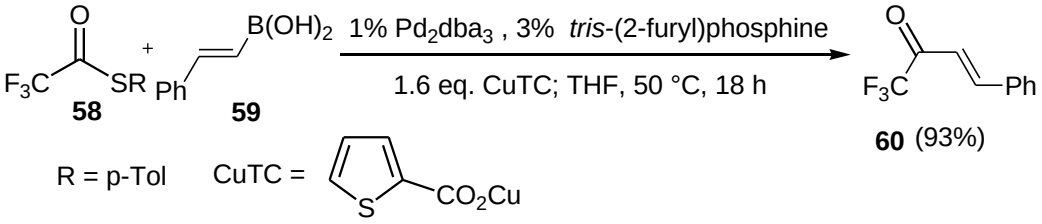
Scheme 12

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]



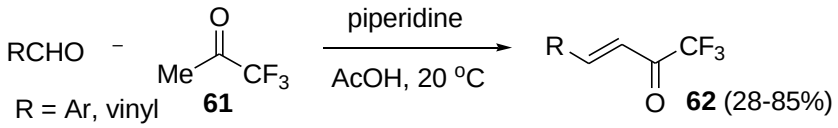
Scheme 13

Pd-catalyzed cross-coupling reaction of thioesters **58** with the corresponding alkenyl boronic acids **59** was used for the preparation of β-aryl-CF_3-enones **60**.[30]



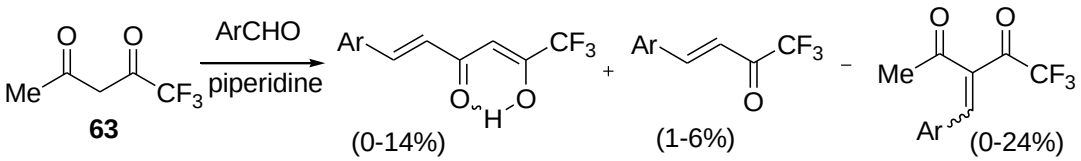
Scheme 14

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]



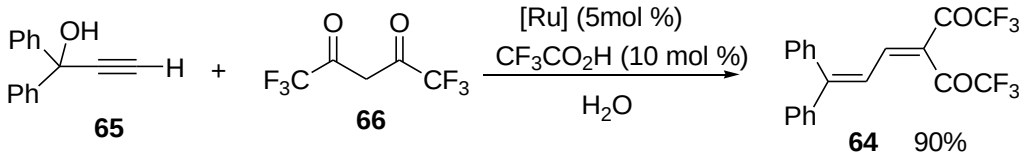
Scheme 15

α,β-Unsaturated ketones are often prepared by condensation of β-dicarbonyl compounds with aldehydes and ketones. However, β-dicarbonyl compounds (for example **63**) containing a perfluoroalkyl substituent yields a mixture of products in a relatively low yield.[32]



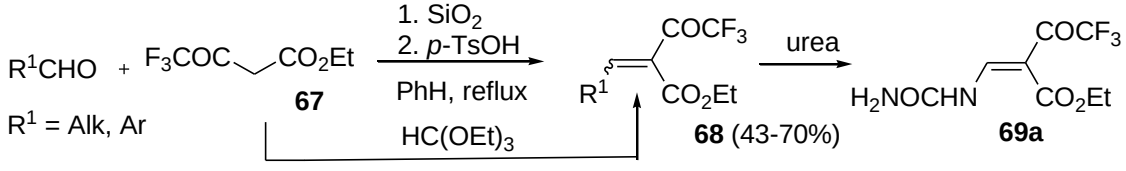
Scheme 16

Conjugated CF_3-diene-dione **64** has been synthesized in high yield by reaction (catalyzed by [Ru]/ CF_3CO_2H) of terminal propargylic alcohol **65** with hexafluoroacetylacetone **66** via Meyer–Schuster rearrangement and subsequent aldol-type condensation.[33]



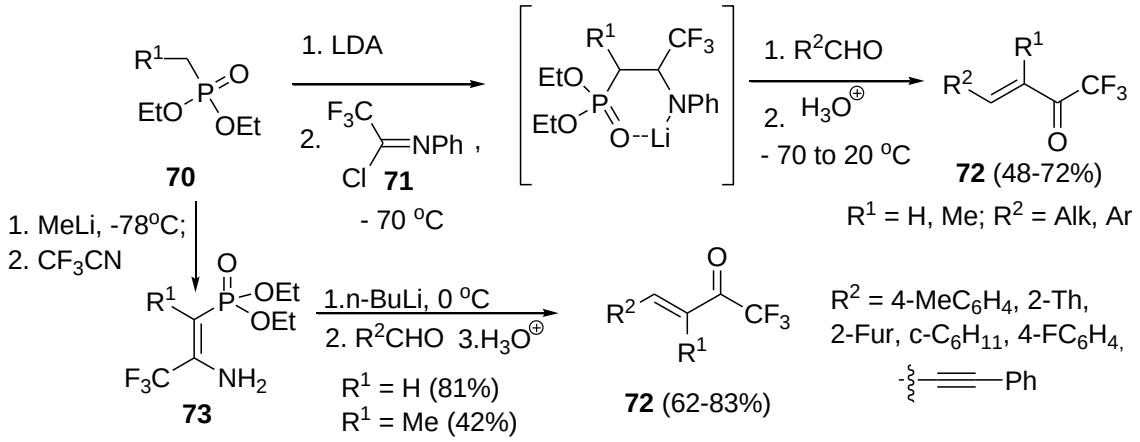
Scheme 17

The condensation of trifluoroacetoacetic acid esters **67** with aldehydes in the presence of traditional catalysts leads to 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 β-enamidoketone **69a**.[35]



Scheme 18

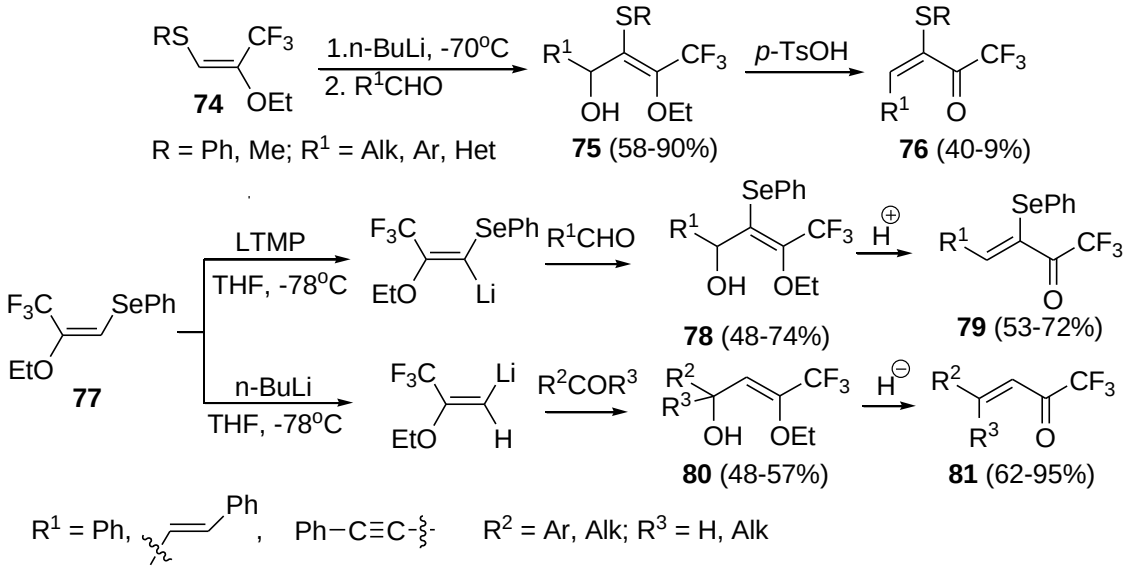
The reaction of β-iminophosphonate anions with aldehydes (the Horner - Emmons reaction) yields perfluoroalkylated enones **72** as the final products.



Scheme 19

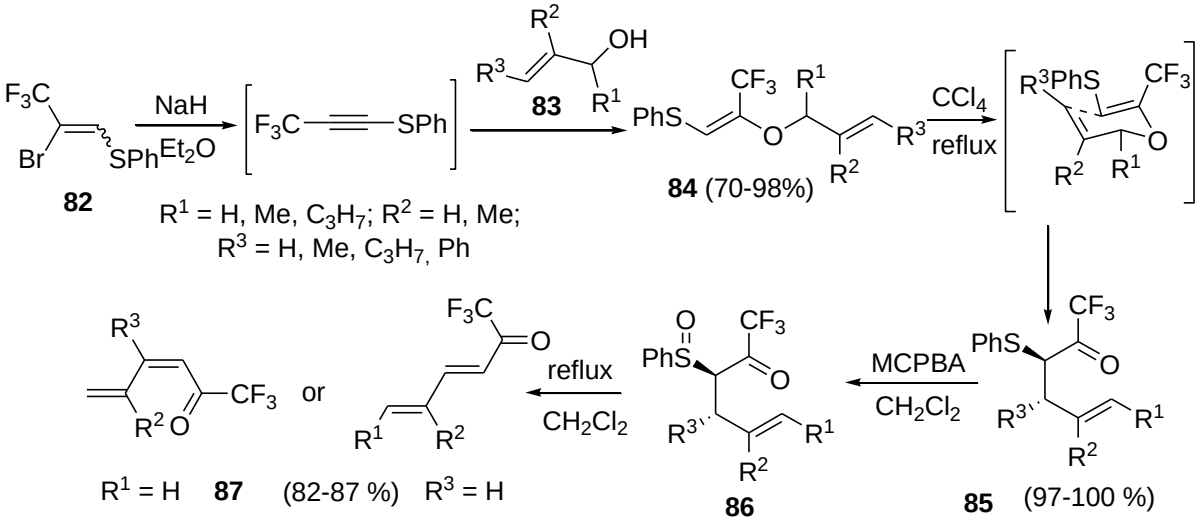
β-Iminophosphonate anions can be obtained from diethyl alkylphosphonates **70** and trifluoroacetimidoyl chlorides **71** as a one-pot procedure. Subsequent reaction with aldehydes leads to **72** in good yields. Enaminophosphonates **73** can be prepared by condensation of phosphonates **70** with trifluoroacetonitrile.[36]

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

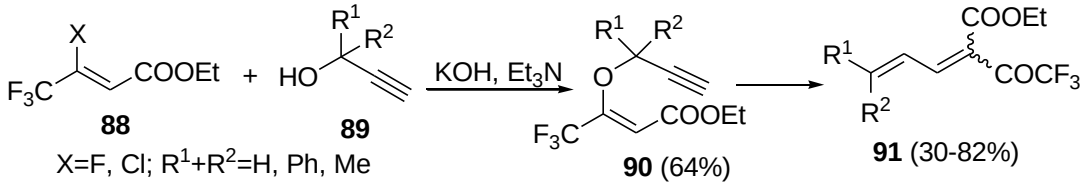
Claisen rearrangement has been also used for synthesis of CF_3-dienones. 1-Phenylsulfanyl-2-bromo-3,3,3-trifluoropropene **82** served as starting material.



Scheme 21

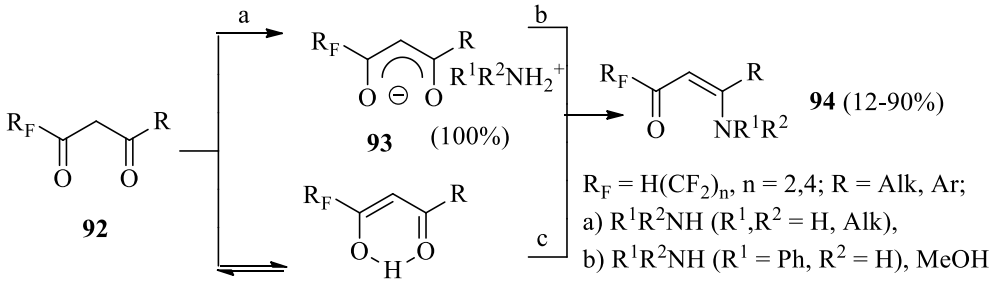
The reaction of **82** with sodium hydride leads to CF_3-acetylene which reacted with various allylic alcohols **83** to form vinyl ethers **84**. Subsequent heating generate γ,δ-unsaturated ketones **85**. Target dienone **87** was formed by oxidation of phenylsulfanyl group in **85** with *m*-chloroperbenzoic 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]



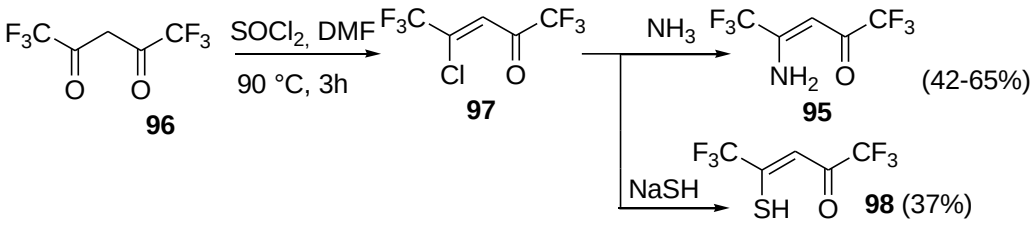
Scheme 22

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 enaminones **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 – BF_3 complex and $Zn(ClO_4)_2$) accelerate the reaction.[41]



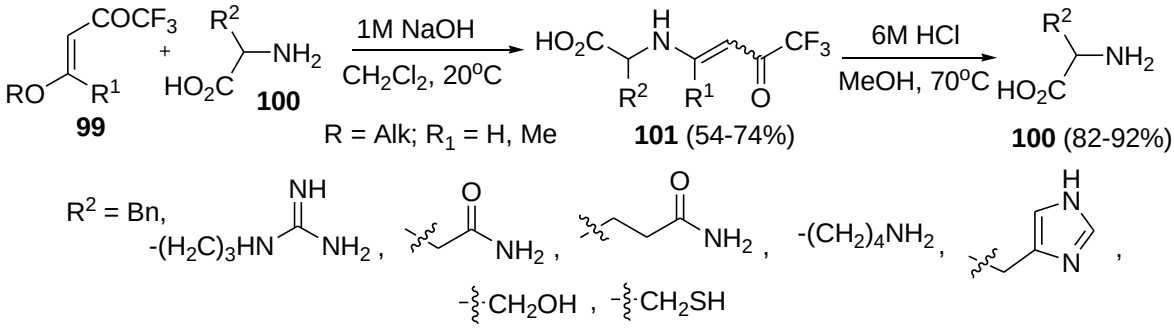
Scheme 23

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 $SOCl_2$ in the presence of DMF as a catalyst or with the Vilsmeier reagents (DMF/$POCl_3$ or DMF/$(COCl)_2$). This approach has also been used to synthesize hexafluoromono-thioacetylacetone **98** existing in enol form.[42]



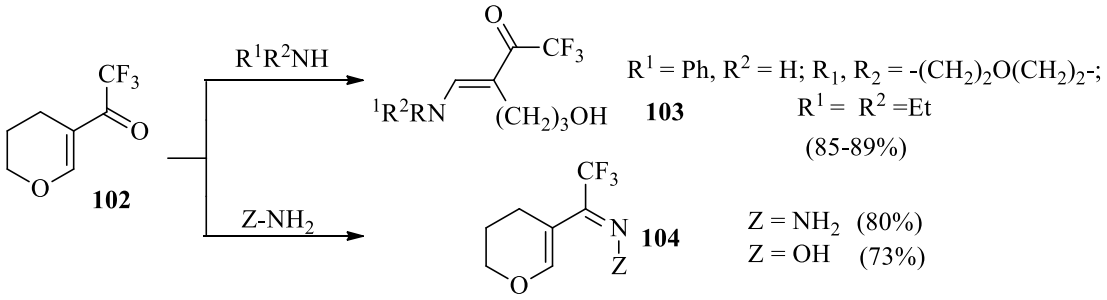
Scheme 24

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.[43]



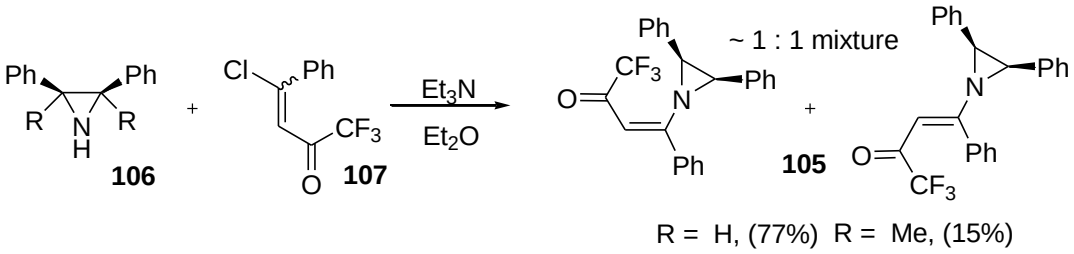
Scheme 25

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**.[44]



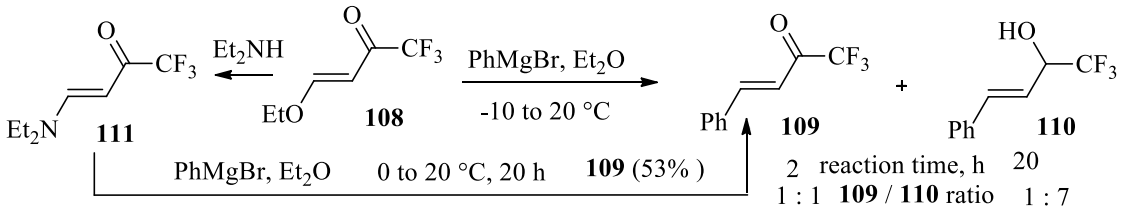
Scheme 26

Ketones **105** containing aziridine fragment in β-position were prepared by reaction of *cis*-1,2-diphenylaziridine **106** with CF_3-enone **107** containing chlorine atom in the β-position. Reaction proceeds with the formation of mixture of *E*-*Z*-isomers of ketone **105**.[45]



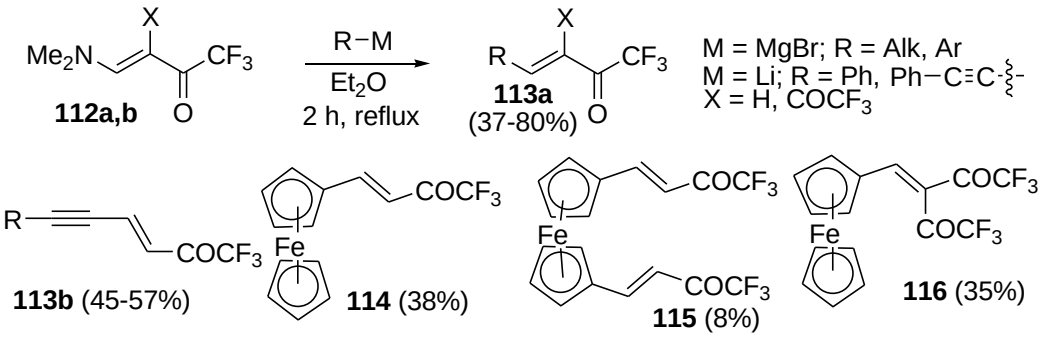
Scheme 27

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]



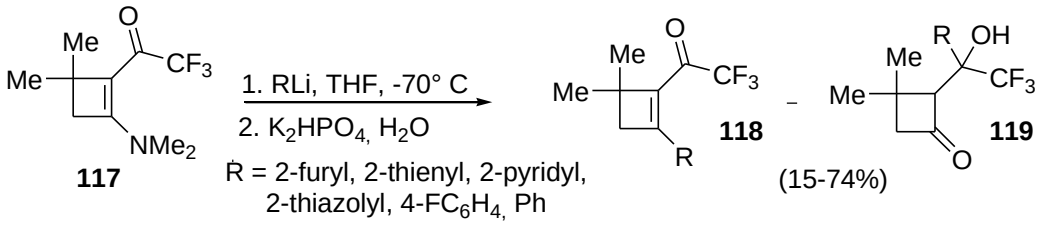
Scheme 28

The reactions of various Grignard and organolithium reagents with enones **112a,b** proceed stereoselectively leading to the formation of CF_3-enones **113a**. Using the reaction of lithiated ferrocene allows preparing the corresponding CF_3-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]



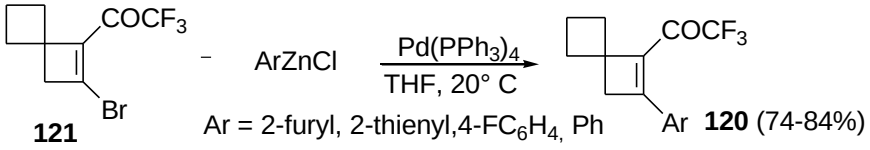
Scheme 29

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.[49]



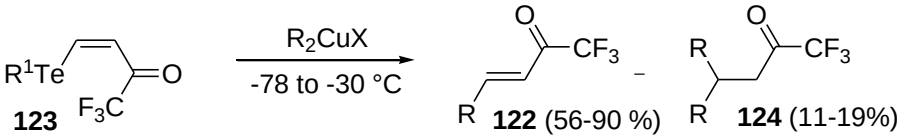
Scheme 30

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 $(Ph_3P)_4Pd$ catalyst was used.[50]



Scheme 31

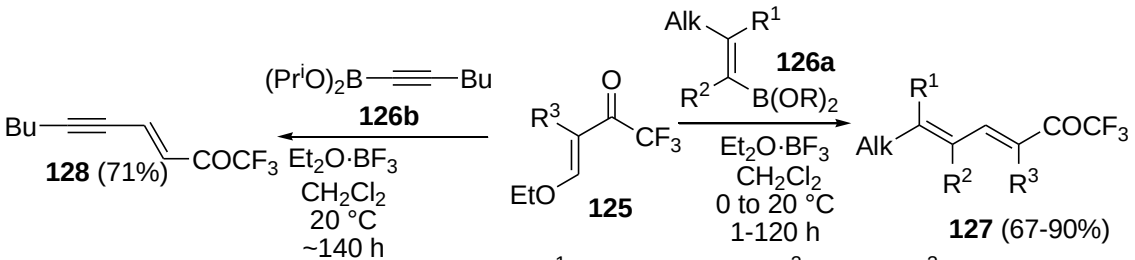
Trifluoromethyl enones **122** can also be synthesized using the reaction of various zinc dialkyl- and diaryl-cuprates with **123**. In the case of zinc dialkylcuprates, the reaction is accompanied by side formation of the double addition products **124**.[51]



R^1 = n-Bu, *i*-Bu, Ph; R = Ar, Alk; X = $(CN)ZnCl_2$, ZnCl

Scheme 32

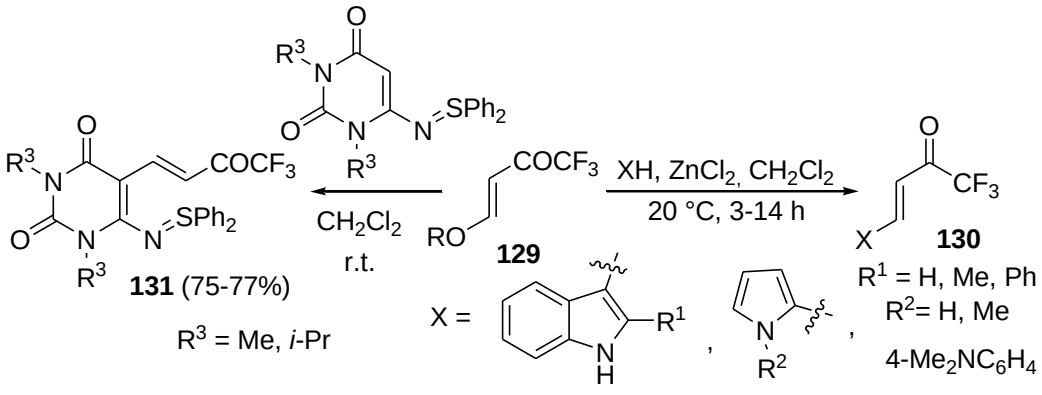
The reactions of trifluoroacetylated vinyl ethers **125** with organoboron compounds **126** allows to prepare highly stereoselectively the corresponding dienones **127** and enynones **128**.[52]



R = Et, *i*-Pr; R^1 = H, Me, Ph, Br; R^2 = H, Br; R^3 = H, Me, Ph

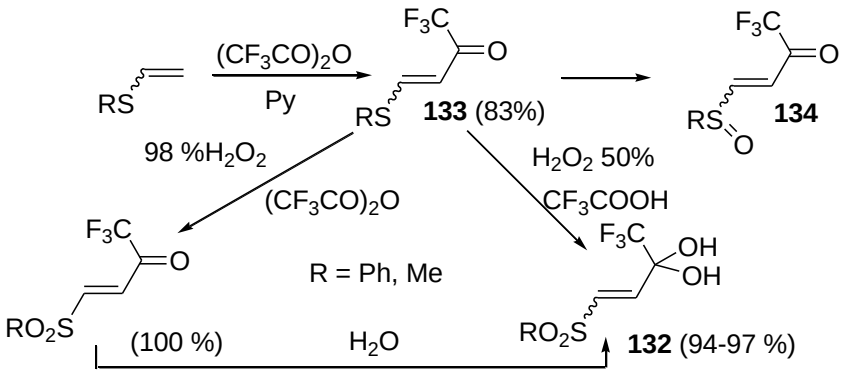
Scheme 33

β-Alkoxy substituted trifluoromethyl enones **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-enone **131**.[46, 53]



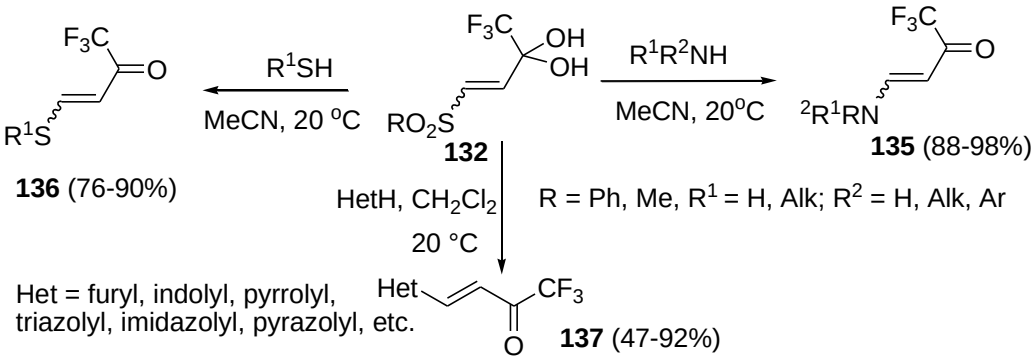
Scheme 34

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_2O_2 in the presence of trifluoroacetic acid or utilizing 98% H_2O_2 solution in the presence of trifluoroacetic acid anhydride. Similarly sulfoxide **134** can be prepared.[54]



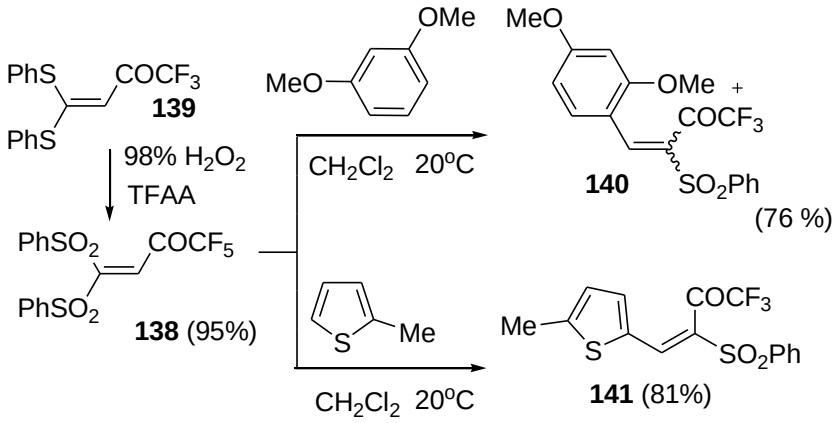
Scheme 35

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]



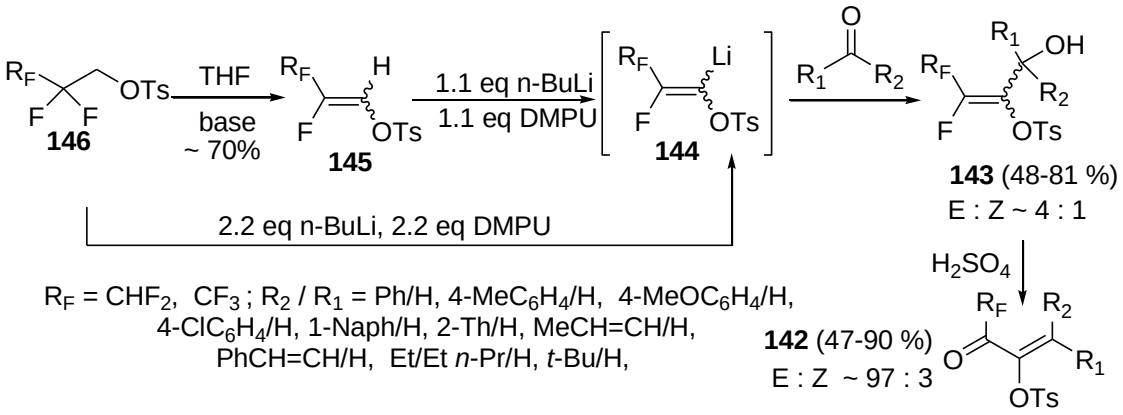
Scheme 36

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]



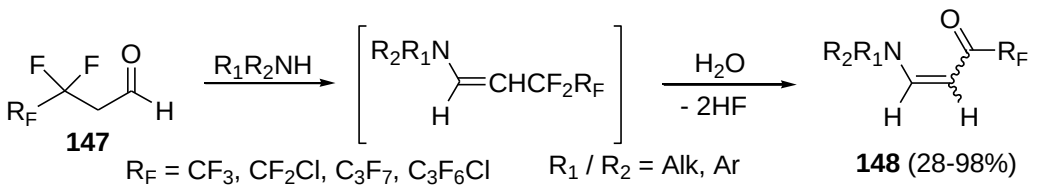
Scheme 37

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]



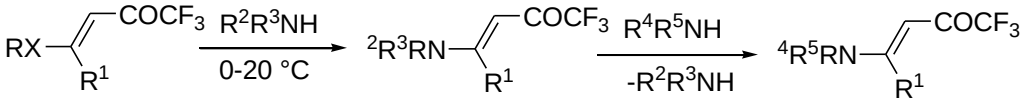
Scheme 38

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

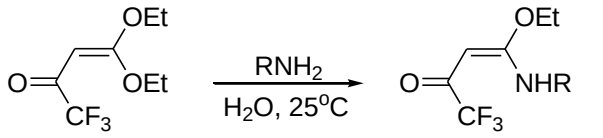
β-(Thio)alkoxy-substituted trifluoromethyl enones **149** and **150** react with ammonia and primary and secondary amines (including aromatic ones) to give β-amino-substituted enones (enaminones) **151** in high yields.[60]



149 (X = O) R = Alk; R_1 = H, Me, Ph; **151** (56-100%) **151a** (75-100%)
150 (X = S) R^2,R^4 = H, Alk; R^3, R^5 = H, Alk, Ar

Scheme 40

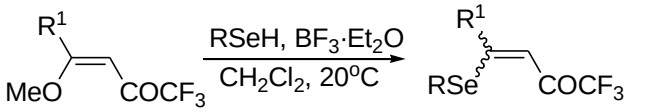
The substitution of one alkoxy-group in enone **152** was used for synthesis of O,N-acetals-aminals of trifluoroacetylketene **153** in aqueous medium.[61]



152 **153** (60-89%)

Scheme 41

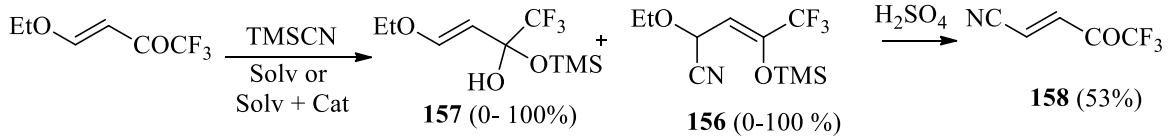
The example of synthesis of β-selenoenones **154** using the reaction of methoxyenones **155** with methyl- and phenylselenol in the presence of BF_3-diethyl etherate was described.[62]



155 R = Me, Ph; R_1 = H, Alk, Ar **154** (79-88%)

Scheme 42

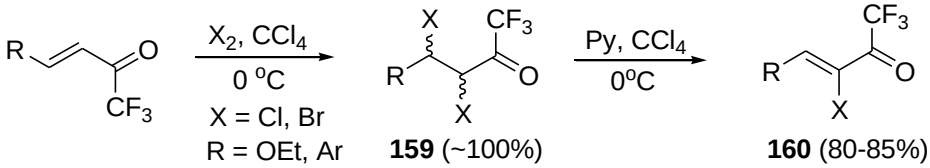
The introduction of cyano-group in the β-position of α,β-unsaturated trifluoromethyl ketones can essentially broaden their synthetic potential as building blocks. Depending on the solvent and catalyst applied individual products **156** and **157** or their mixture can be obtained. β-Cyanoenone **158** was also prepared by treatment of **156** with concentrated sulfuric acid.[63]



Cat = Et_3N, i-Pr_2NEt, DMAP, N-methylephedrine, LiBr,
$TiCl_4$, $Et_2O{\cdot}BF_3$, $(i\text{-}PrO)_4Ti$, CF_3SO_3TMS, I_2, ZnI_2, $LiClO_4$, $Hg(CF_3COO)_2$

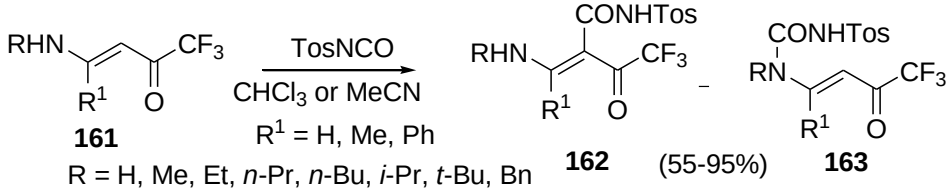
Scheme 43

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 44

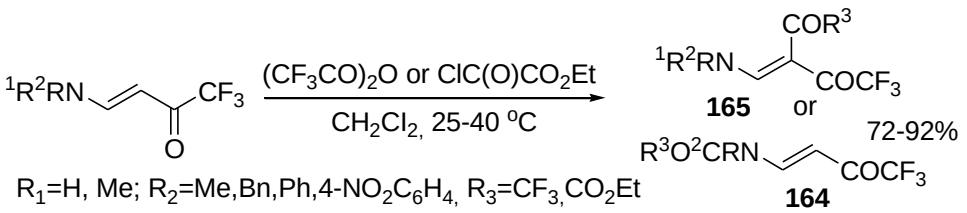
The reaction of CF_3-enaminoketones **161** with tosylisocyanate leads to mixture of the adducts **162** and **163** depending on the substituent in the enaminoketone.[65]



R = H, Me, Et, *n*-Pr, *n*-Bu, *i*-Pr, *t*-Bu, Bn

Scheme 45

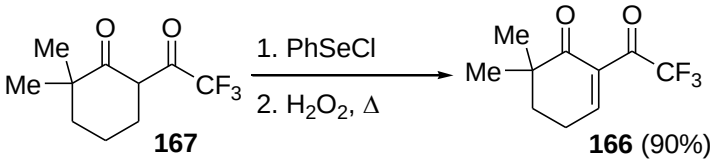
The acylation reaction of secondary CF_3-β-enamino ketones with TFAA or ethoxyoxalyl chloride led regioselectively to N-acylated enaminones **164** in good yields. On the other hand, when tertiary enaminones were used, the acylation reaction led to C-acylated enaminones **165**.[66]



R_1=H, Me; R_2=Me,Bn,Ph,4-$NO_2C_6H_4$, R_3=CF_3,CO_2Et

Scheme 46

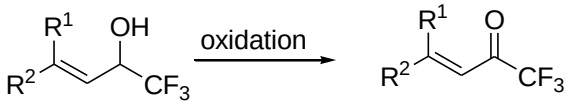
2.1.6 Other methods. The standard way for preparation of α,β-unsaturated ketones from aliphatic ketones is the treatment with phenylselenyl chloride followed by oxidation and elimination of PhSeOH. This method was used for preparation of cyclic CF_3-enone **166** from 1,3-diketone **167**.[67]



167 **166** (90%)

Scheme 47

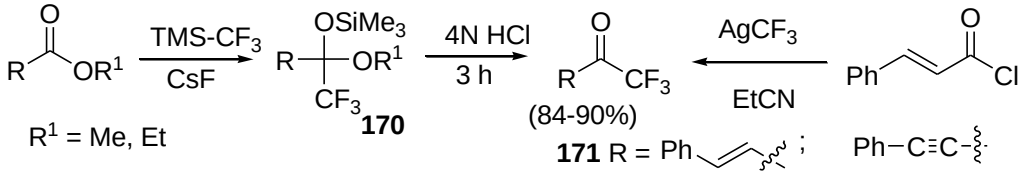
Trifluoromethyl-containing allylic alcohols **168** can be oxidized into the corresponding enones **169** on treatment with the Dess-Martin reagent or Swern reagent (DMSO - oxalylchloride/triethylamine). Manganese dioxide in CH_2Cl_2 was also used for this purpose. Nowadays this method has become customary because of development of synthetic approach to allylic alcohols using Ruppert reagent (TMS-CF_3).[68]



168 R^1, R^2 =H, Alk, Ar **169**

Scheme 48

The corresponding acrylic esters can be converted into α,β-unsaturated trifluoromethyl ketones **171** by addition of Ruppert reagent (TMS-CF_3) 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]



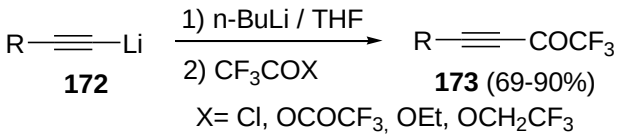
170

Scheme 49

2.2 Synthesis of acetylenic CF_3-ketones

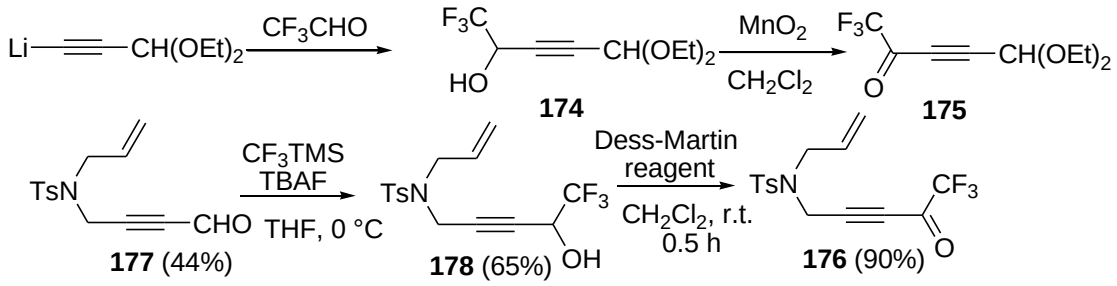
The set of methods for preparation of acetylenic CF_3-ketones is much narrow than the set for preparation of CF_3-enones. There are only several universal methods for preparation of acetylenic

CF_3-ketones. The classical method is the trifluoroacylation of anions **172** generated from terminal alkynes with TFAA, ethyl or trifluoroethyl trifluoroacetate to form **173**.[71]



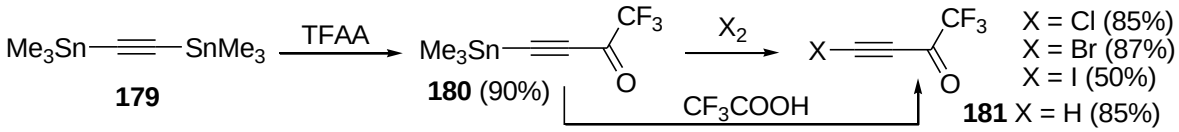
Scheme 50

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 CF_3-containing alkynone **176** was synthesized by reaction of aldehyde **177** with $TMSCF_3$ followed by oxidation of alcohol **178** with Dess-Martin periodinane.[73]



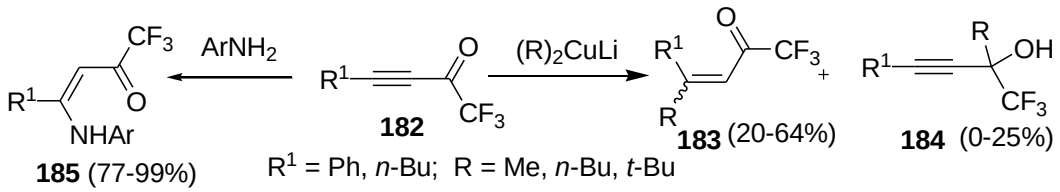
Scheme 51

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]



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 CF_3-enones **185** in good yields.[76]

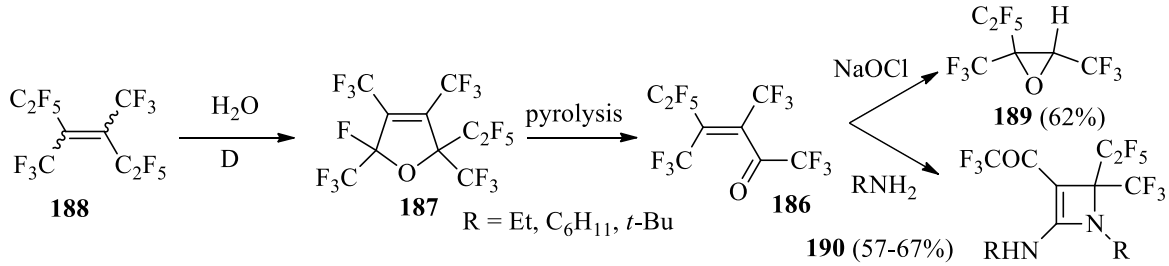


Scheme 53

3. Application of α,β-Unsaturated CF3-Ketones to the Synthesis of Heterocycles

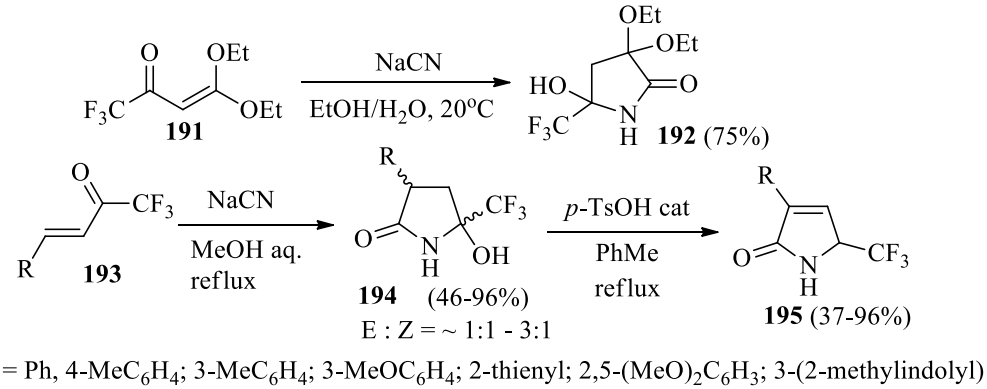
3.1 Synthesis of three- and four-membered heterocycles

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**.[77] The fluorinated oxirane **189** and azetidine **190** were prepared using the reaction of **186** with NaOCl and primary amines correspondingly.



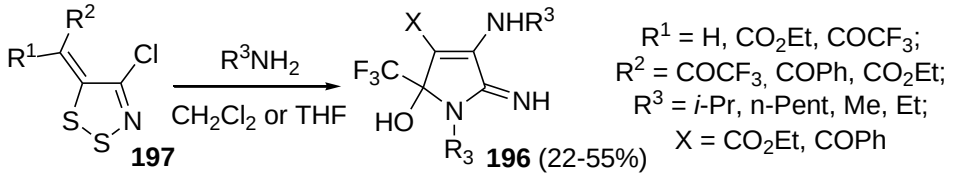
Scheme 54

3.1.1 Synthesis of pyrrole derivatives. The reaction of diethoxyenone **191** with NaCN was described for the synthesis of the corresponding pyrrolidone **192**.[78] It was shown that various enones **193** react with NaCN to give the corresponding pyrrolidones **194** as the mixture of diastereomers.[79] Subsequent dehydration proceeds with migration of double bond and leads to formation of pyrroline-3-one-2 **195**.



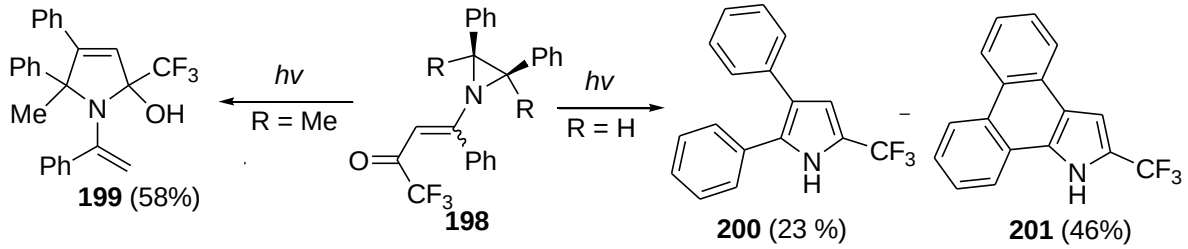
Scheme 55

Other derivatives of trifluoromethyl pyrrole **196** were prepared using reaction of dithiazole **197** (prepared from Appel salt) with primary amines.[80]



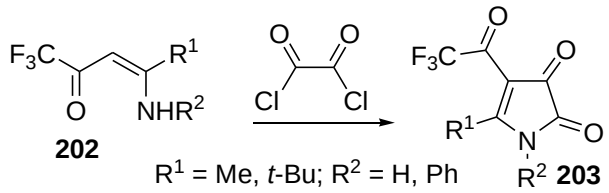
Scheme 56

Photolytic rearrangement of aziridine-substituted enaminoketones **198** was used for the preparation of the CF_3-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.



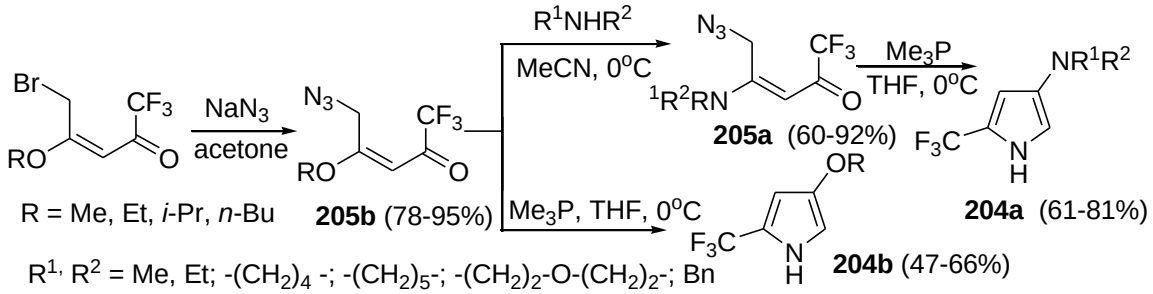
Scheme 57

The acylation of enaminoketones **202** with oxalyl chloride was applied for the preparation of 1*H*-pyrrole-2,3-diones **203**.[82]



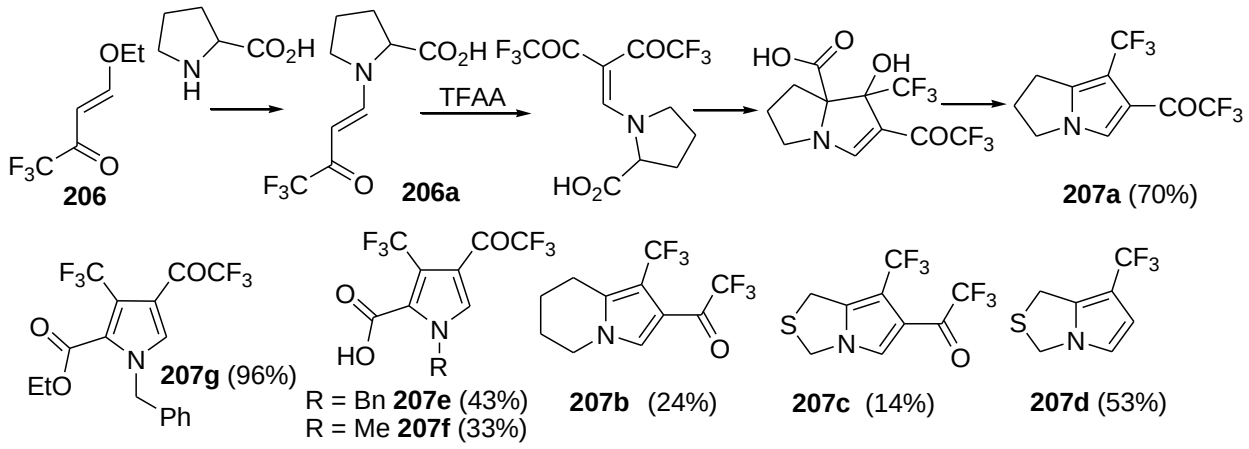
Scheme 58

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]



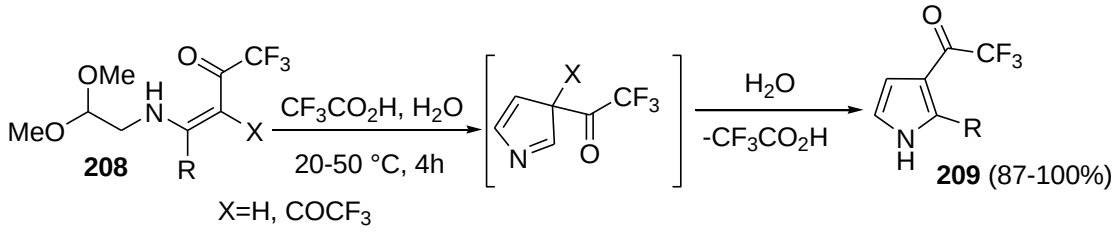
Scheme 59

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.[84] All steps of the synthesis can be done in one-pot to give various CF_3-pyrroles **207** including condensed pyrroles.



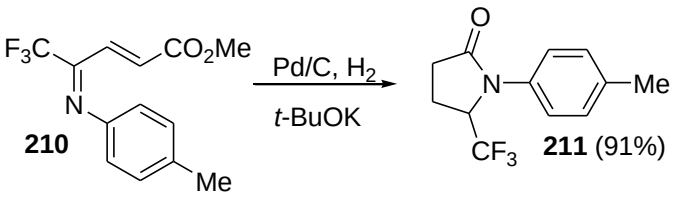
Scheme 60

Dimethoxyethylamine substituted enaminones **208** can be cyclized easily in the presence of TFA to the corresponding 3-trifluoroacetylpyrroles **209** in good yield.[85]



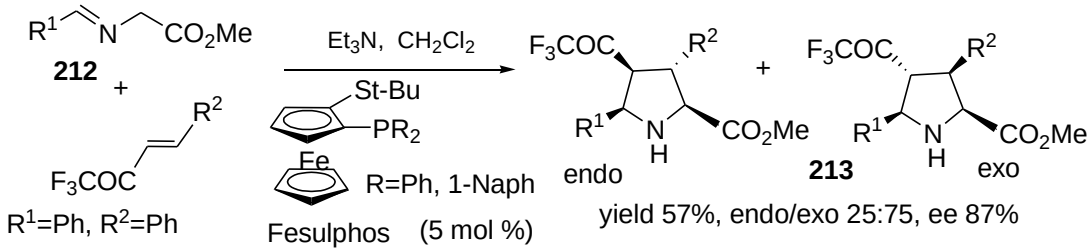
Scheme 61

Imino-derivative of unsaturated trifluoromethyl-containing ketones **210** was cyclized in the presence of palladium on carbon to 5-trifluoromethylpyrrolidone **211**.[28]



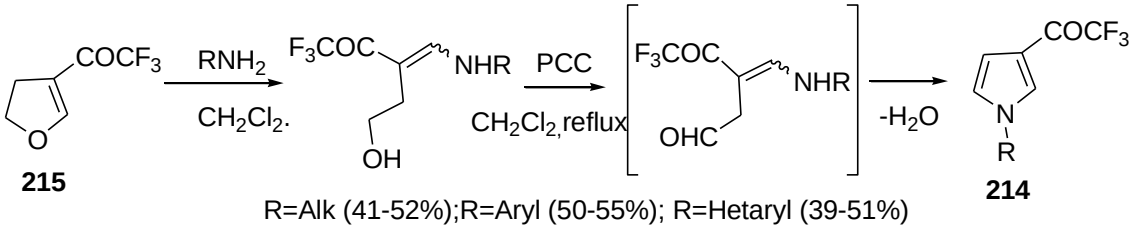
Scheme 62

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 CF_3-substituted pyrrolidine **213** in good yields, moderate to high *endo*/ *exo*-selectivities and high enantiocontrol (81-96% ee).[86]



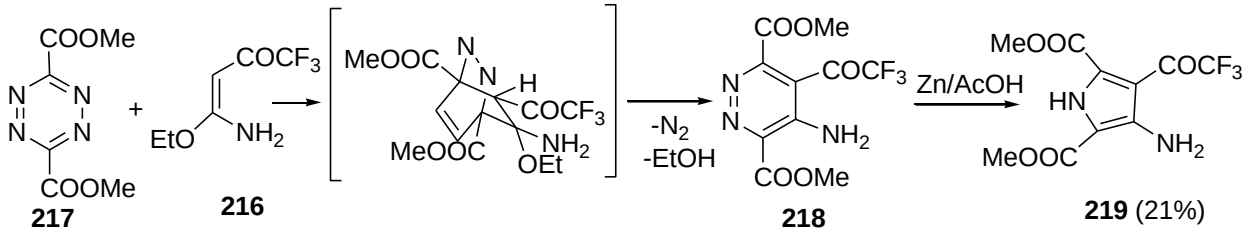
Scheme 63

A new one-pot strategy for the synthesis of 3-trifluoroacetyl pyrroles **214** was elaborated.[87] 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**.



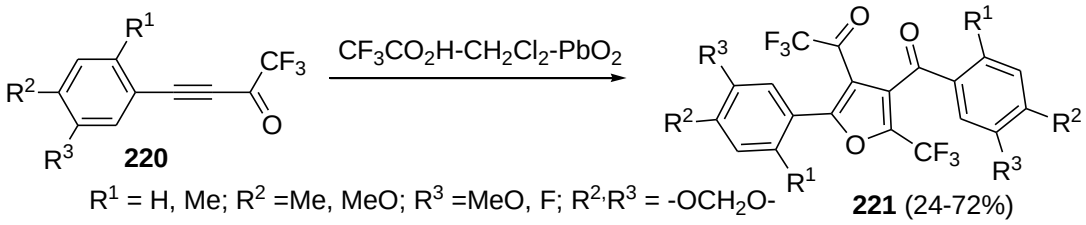
Scheme 64

Reaction of CF_3CO -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.[88]



Scheme 65

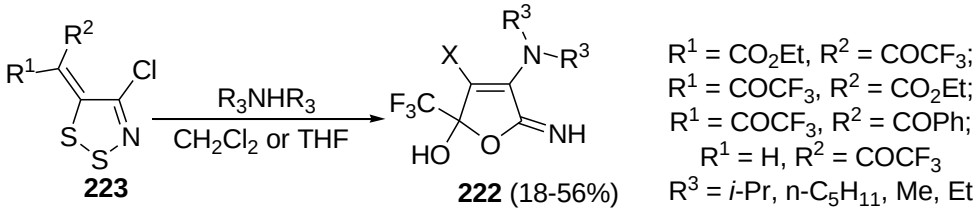
3.1.2 Synthesis of furan derivatives. The oxidative dimerization of acetylenic ketone **220** under the treatment with PbO_2 results in formation of substituted furan **221** bearing CF_3- and $COCF_3$ groups in moderate yields.[89]



R^1 = H, Me; R^2 =Me, MeO; R^3 =MeO, F; R^2,R^3 = -OCH_2O-

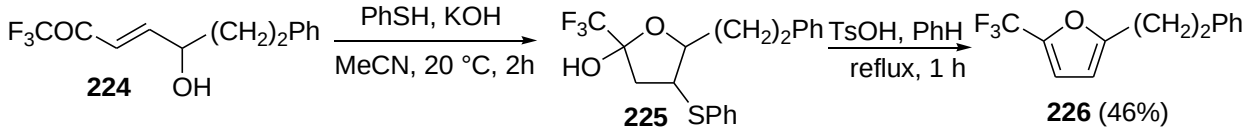
Scheme 66

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



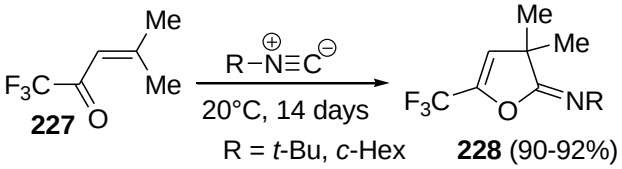
Scheme 67

The reaction of γ-hydroxy enone **224** with thiophenol leads to tetrahydrofuran derivative **225**. The compound **225** eliminates water and thiophenol to give the corresponding furan **226**.[68a]



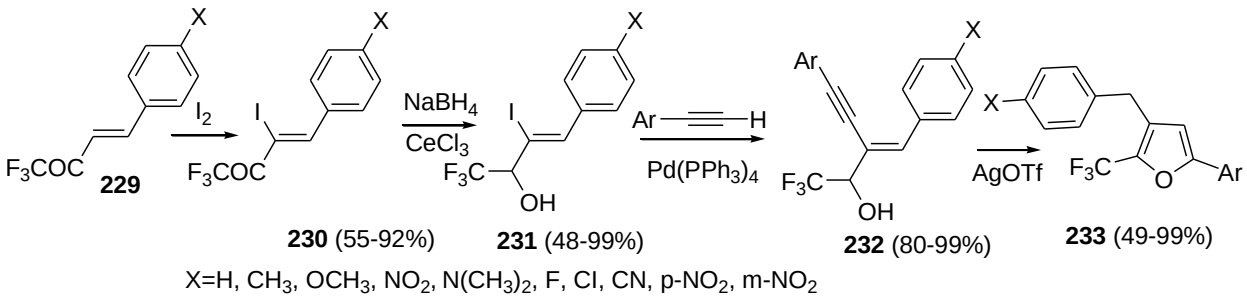
Scheme 68

The reaction of **227** with isocyanides occur at room temperature without catalysts to give stable 1,4-cycloaddition products - substituted dihydrofurans **228**.[90]



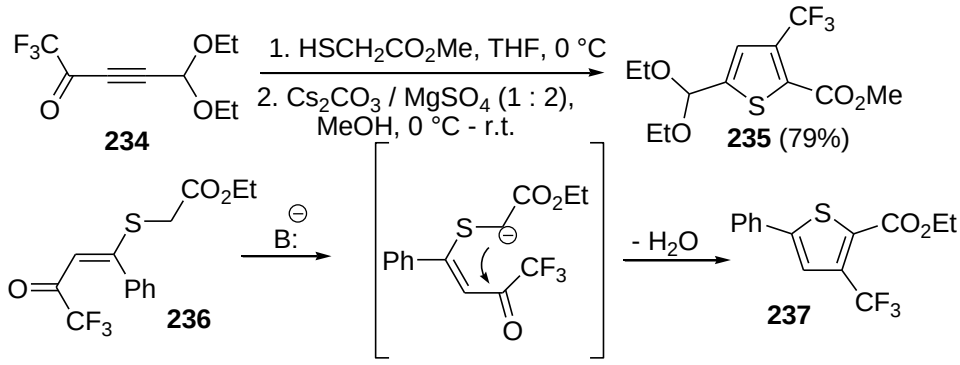
Scheme 69

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)furans **233** in fair yield.[91]



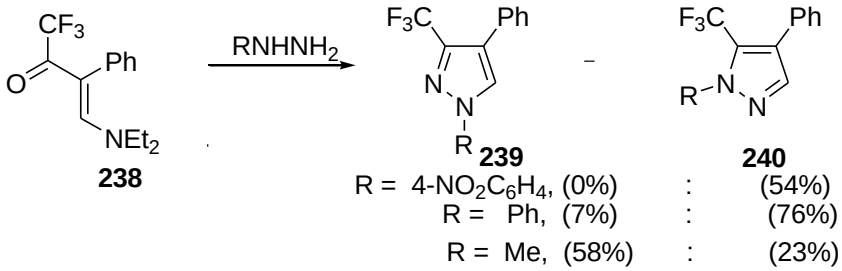
Scheme 70

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]



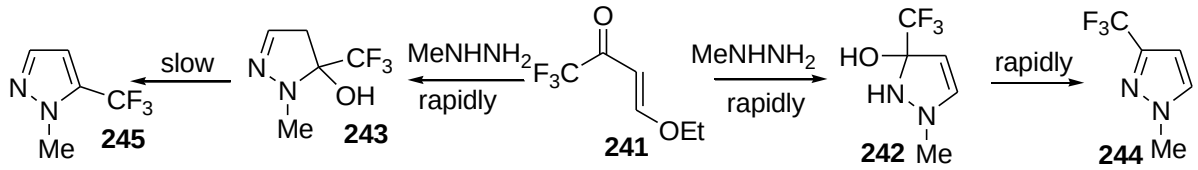
Scheme 71

3.1.4 Synthesis of pyrazoles and their derivatives. The first example of using a trifluoromethyl enone (β-trifluoroacetylstyrene) for the synthesis of pyrazole derivatives dates back to 1959.[25] However, vigorous studies of the reactions of CF_3-enones have been investigated only in recent years.[93] 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**.



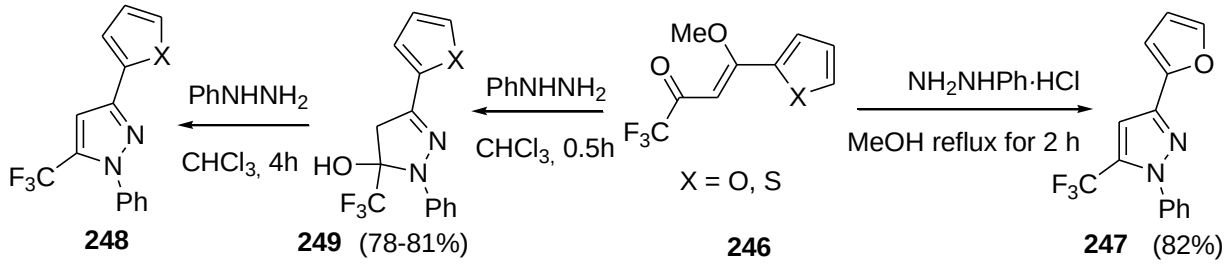
Scheme 72

The reactions of hydrazines with β-alkoxy-substituted enones have been investigated.[94] 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

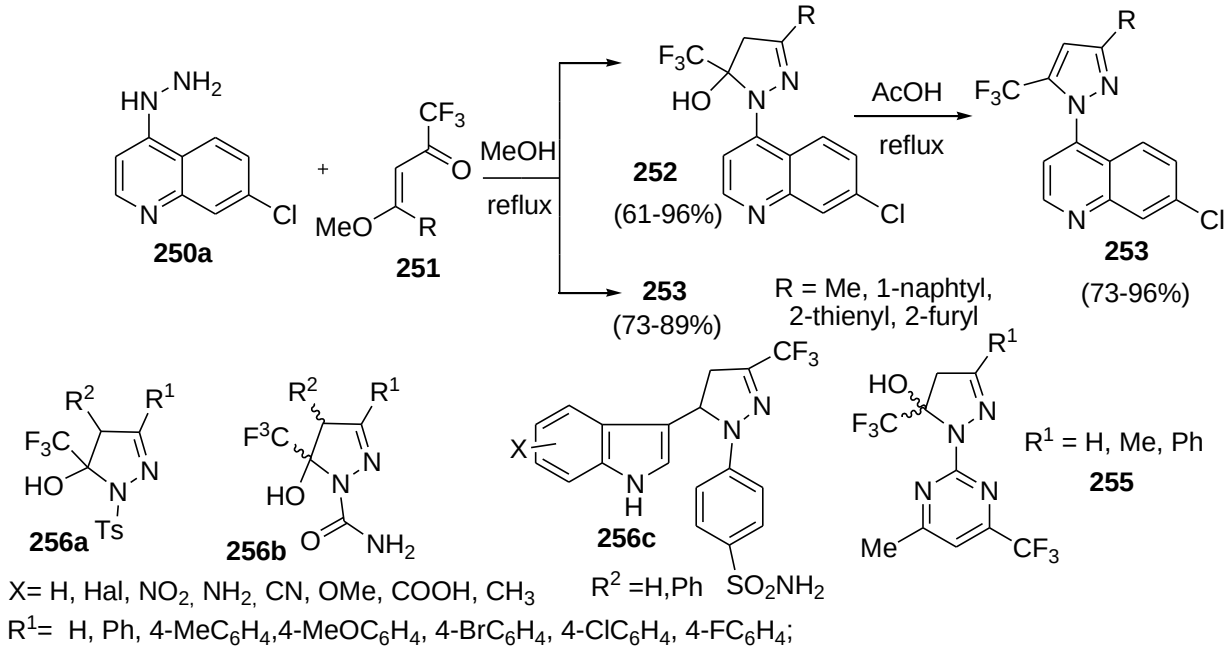
Depending on condition applied the reactions of β-methoxy-CF_3-enones **246** with phenylhydrazine give pyrazoles **247, 248** or pyrazoline **249**.[95]



Scheme 74

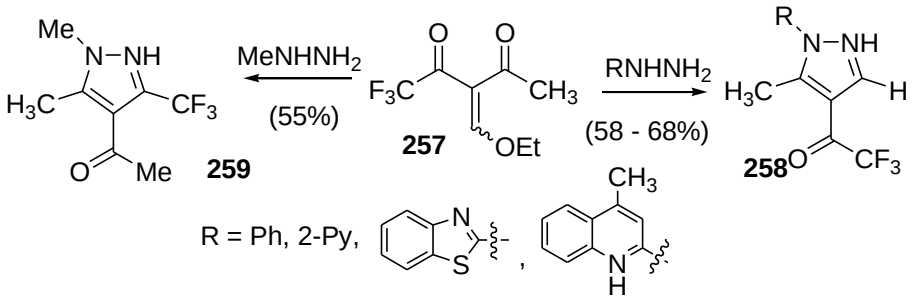
The reaction of 4-hydrazo-7-chloroquinoline **250a** with **251** was investigated for antimalarial screening of **252** and **253**. The corresponding pyrimidine derivatives **255** containing dihydropyrazole substituent are potential analgesics and antipyretics. Similarly prepared

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]



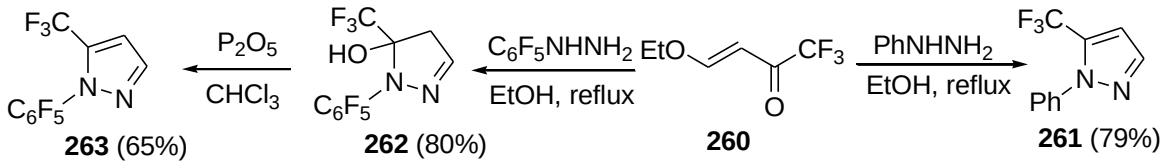
Scheme 75

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]



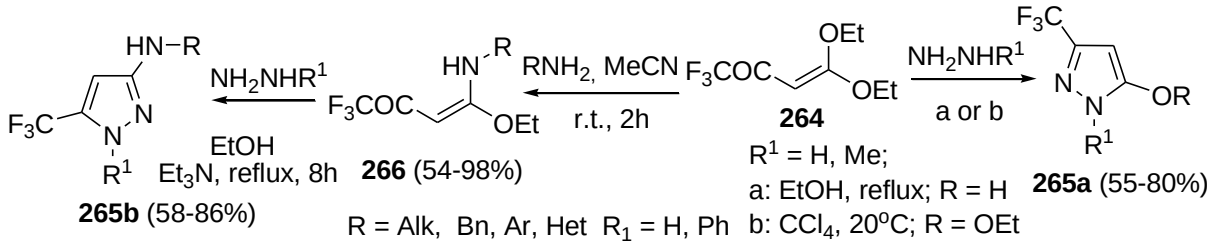
Scheme 76

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 P_2O_5.[98]



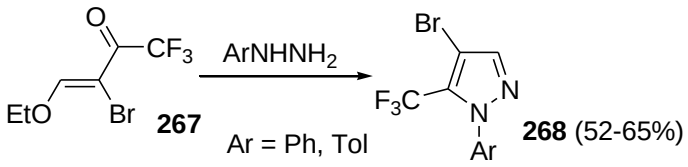
Scheme 77

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]



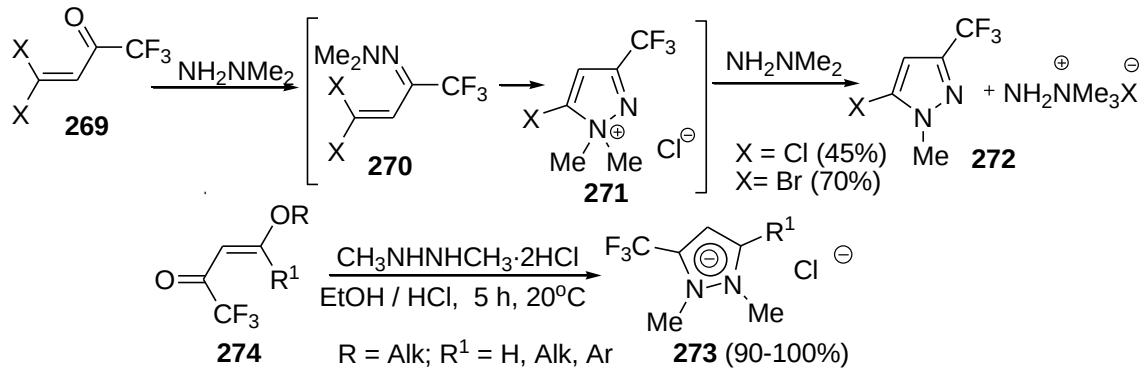
Scheme 78

The reaction of α-bromo-β-ethoxy-CF_3-enone **267** with aryl hydrazines proceeds 100% regioselectively to open new effective way to the synthesis of 4-bromo-5-CF_3-pyrazoles **268**.[100]



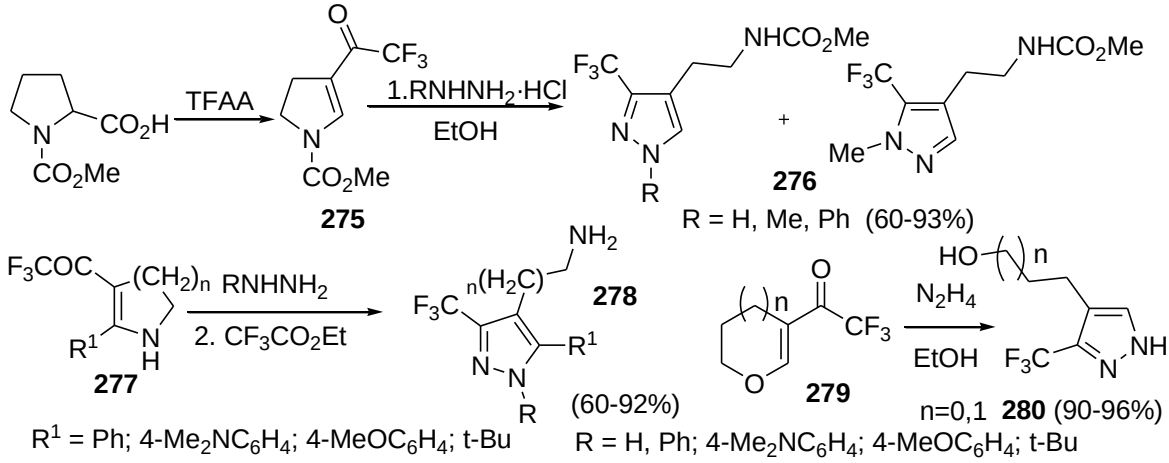
Scheme 79

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]



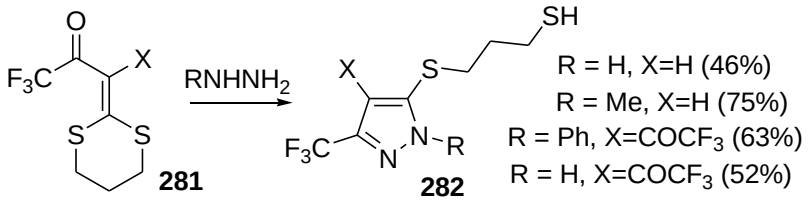
Scheme 80

An interesting example of application of trifluoroacetyl pyrroline **275** for preparation of pyrazoles **276** was described.[103] In view of the pharmacological interest in heterocycles bearing both CF_3-appendage and β-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 β-trifluoroacetyldihydropyran and β-trifluoroacetyldihydrofuran **279** leads to the corresponding pyrazole **280**.[71b]



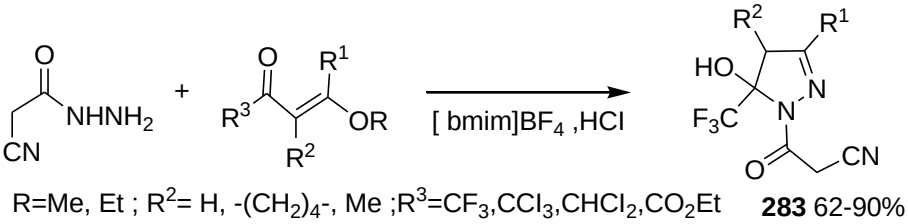
Scheme 81

Similarly the pyrazoles **282** containing 1,3-dithiopropyl substituent were prepared from CF_3-enones containing a dialkyldithio-fragment in the β-position **281**.[104]



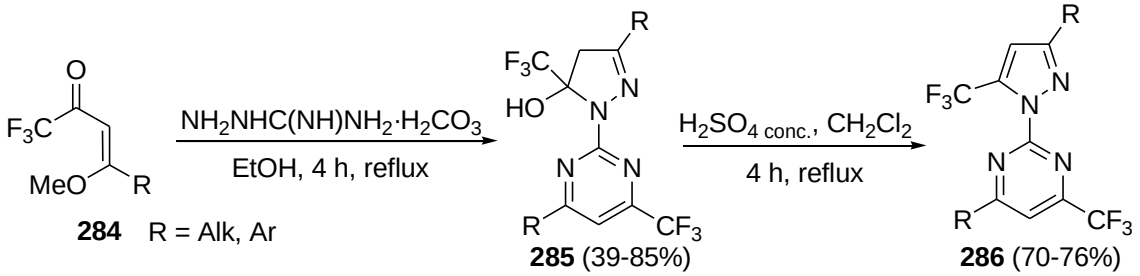
Scheme 82

An efficient synthesis of 1-cyanoacetyl-5-trifluoromethyl-4,5-dihydro-1H-pyrazoles **283** in the ionic liquid ([bmim][BF_4]) has been reported.[105]



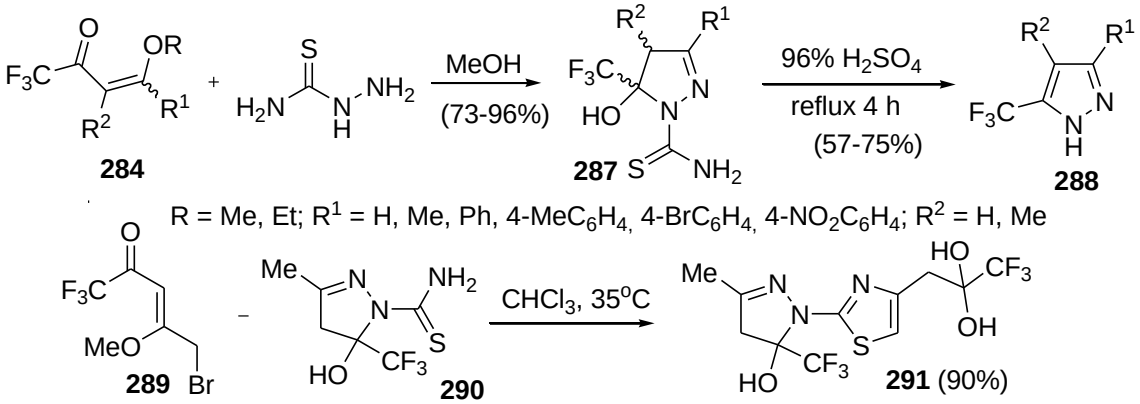
Scheme 83

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]



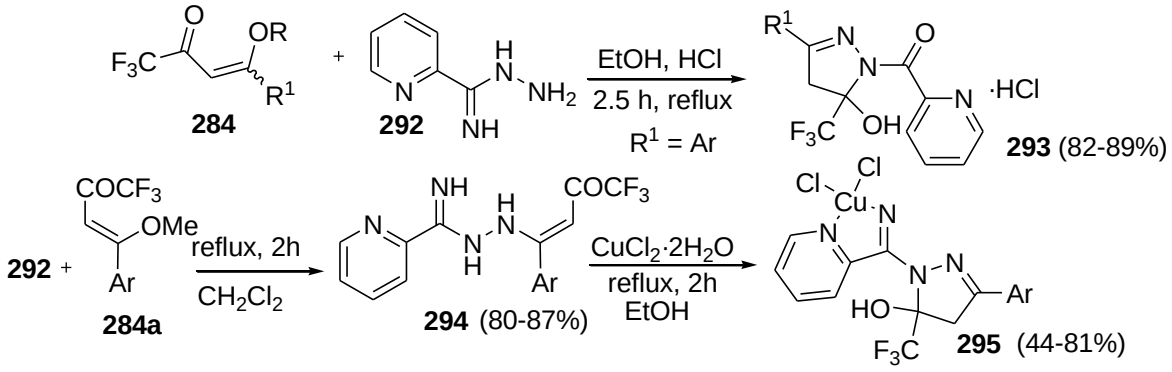
Scheme 84

The reaction of **284** with thiosemicarbazide leds 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]



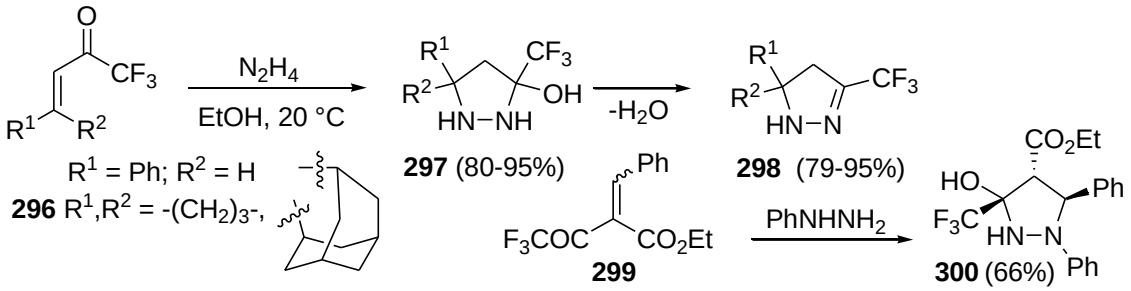
Scheme 85

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]



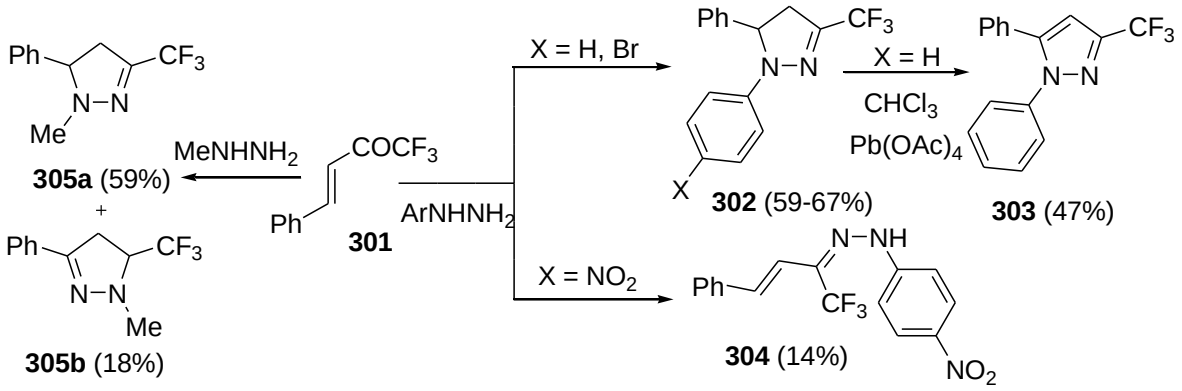
Scheme 86

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]



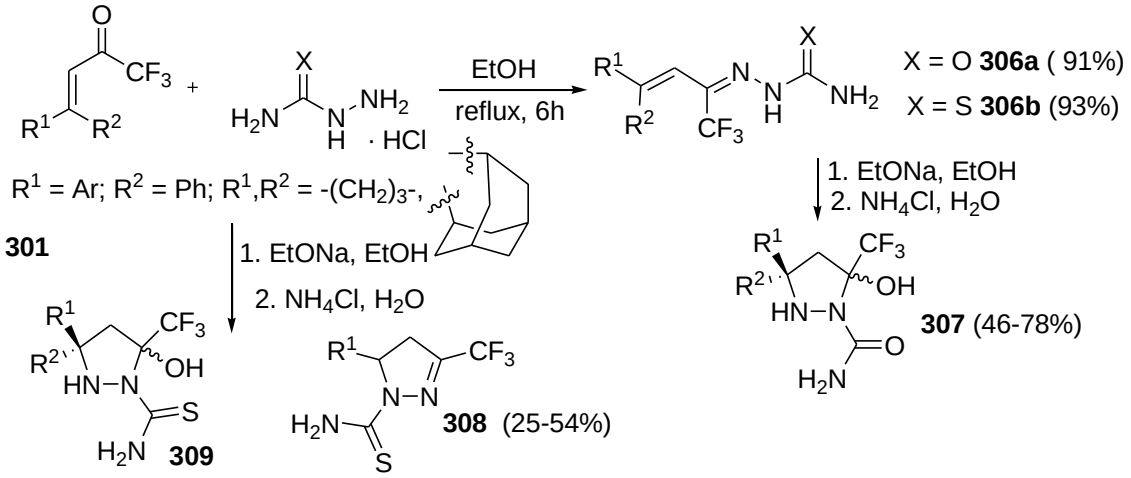
Scheme 87

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]



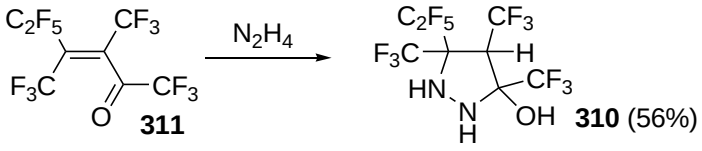
Scheme 88

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]



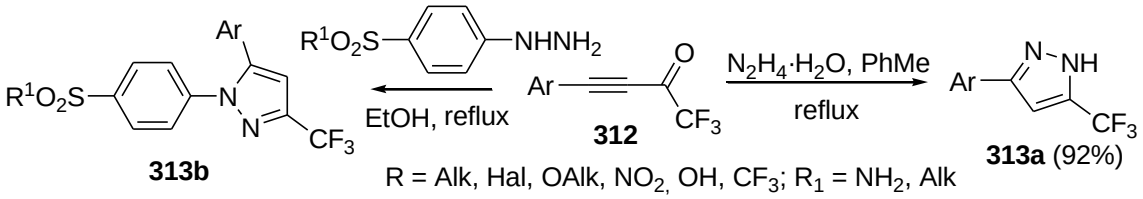
Scheme 89

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]



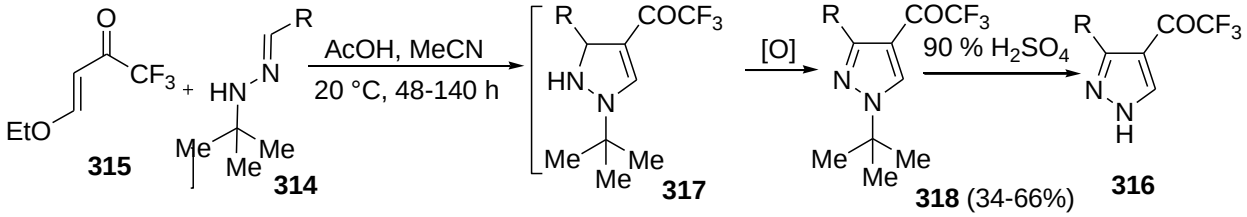
Scheme 90

The reaction of acetylenic CF_3-ketones **312** with hydrazines was also used for the preparation of CF_3-substituted pyrazoles **313** in excellent yield.[113]



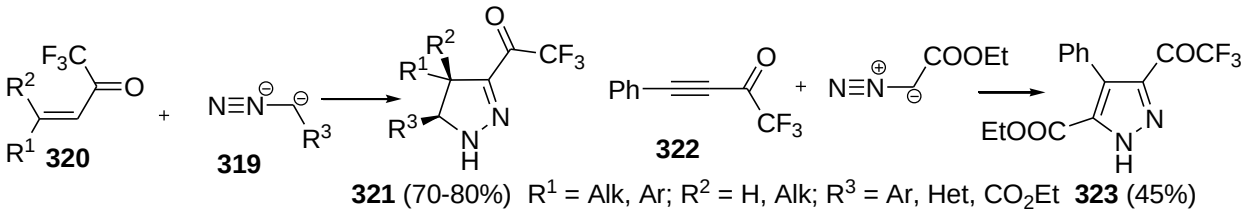
Scheme 91

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.[114]



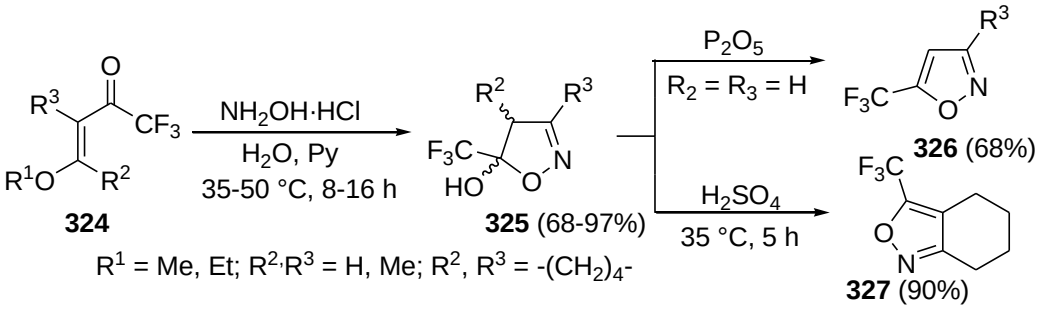
Scheme 92

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**.[115]



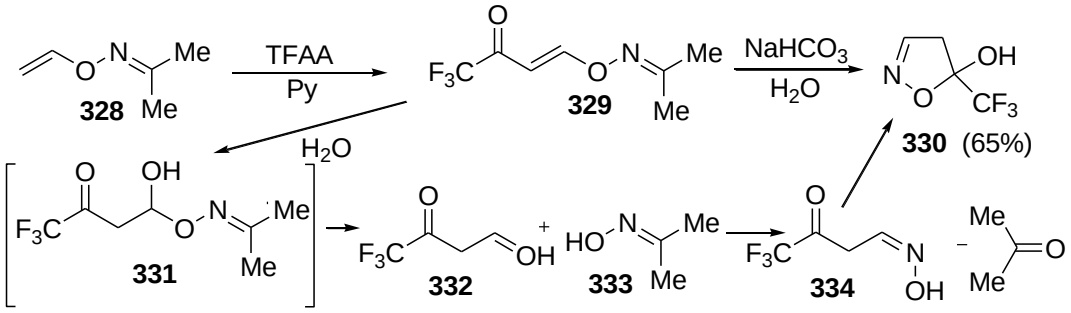
Scheme 93

3.1.4 Synthesis of isoxazole (isoselenoazole) derivatives. The reactions of β-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**,[60a,78] which can be dehydrated on treatment with P_2O_5 or concentrated H_2SO_4 to give the corresponding isoxazoles **326** or **327**.



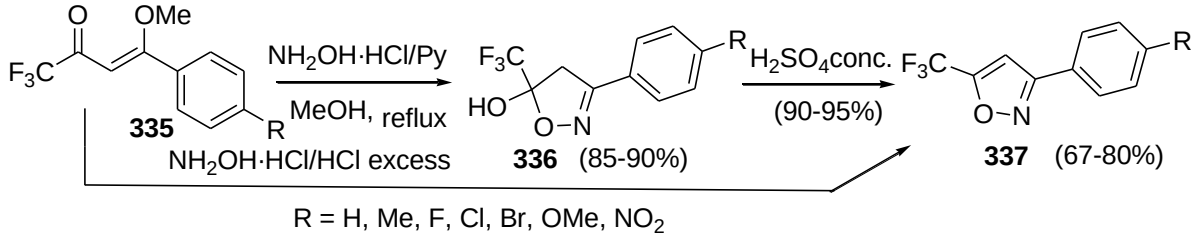
Scheme 94

O-Vinyl oximes **328** react readily with trifluoroacetic anhydride to give CF_3-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 $NaHCO_3$.[116]



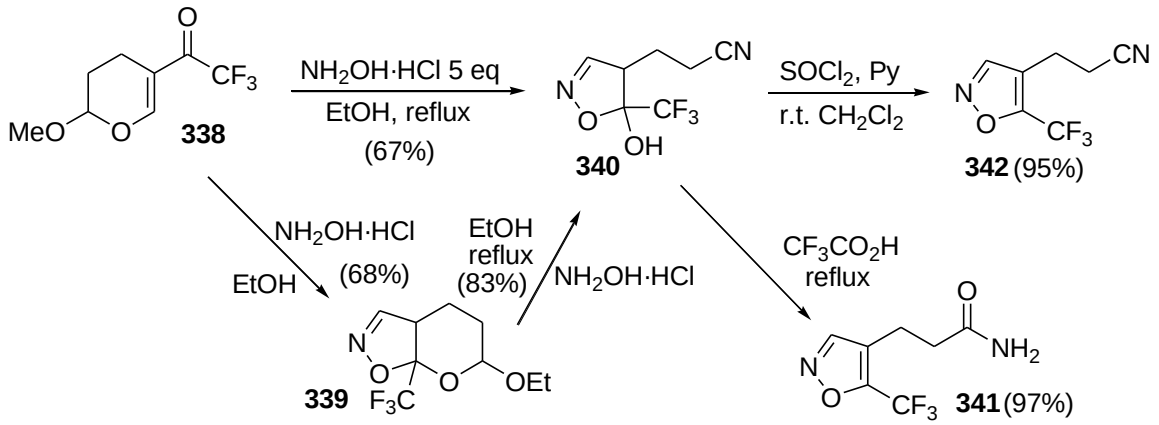
Scheme 95

The reaction of β-methoxy CF_3-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]



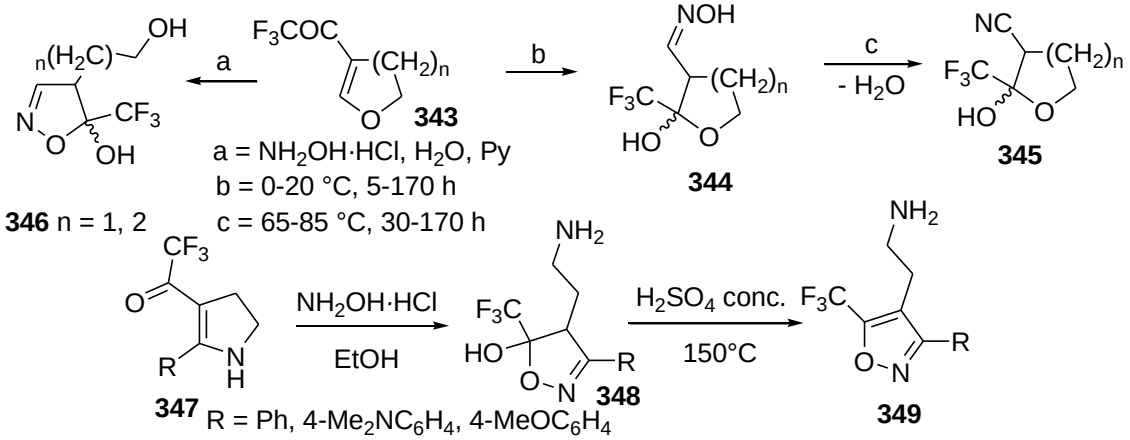
Scheme 96

The use of cyclic β-alkoxy-CF_3-enone **338** allows preparing isoxazoles **341** and **342** and their dihydro-derivatives **339** and **340** containing functional groups in high yields.[118]



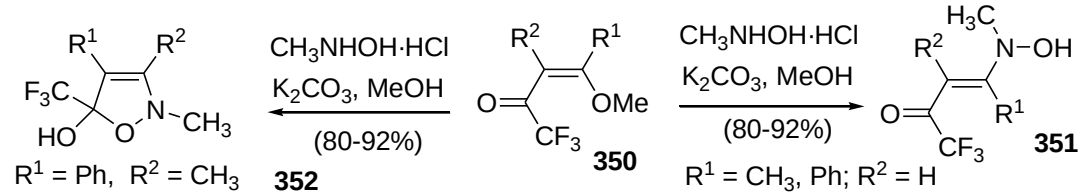
Scheme 97

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 recyclization 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]



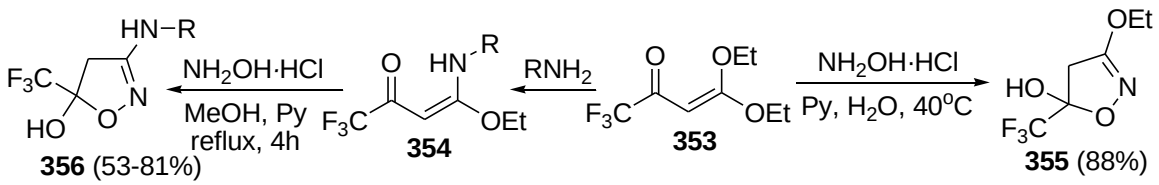
Scheme 98

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]



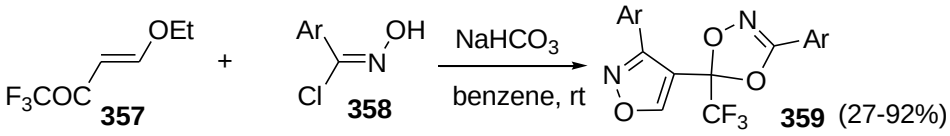
Scheme 99

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]



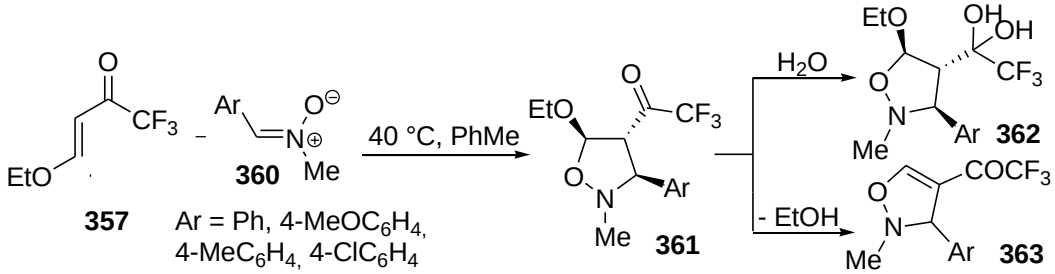
Scheme 100

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]



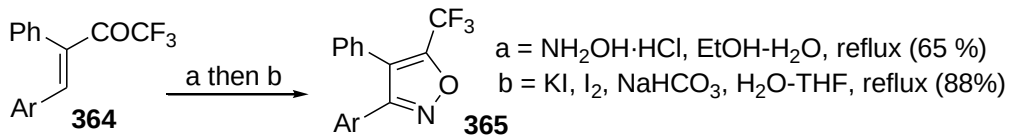
Scheme 101

[2+3]-Cycloaddition of β-ethoxy-CF_3-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]



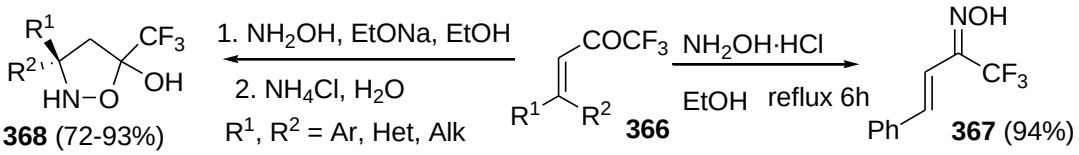
Scheme 102

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]



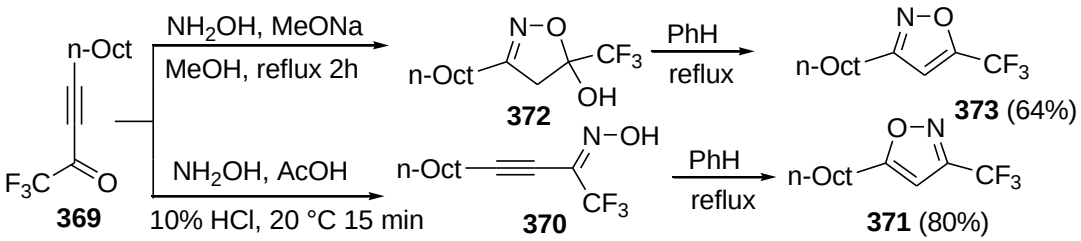
Scheme 103

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]



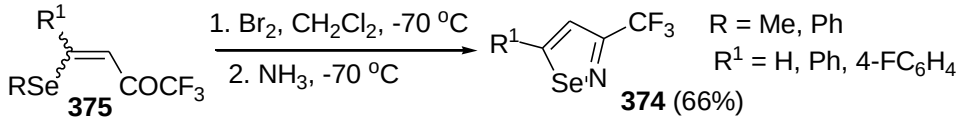
Scheme 104

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]



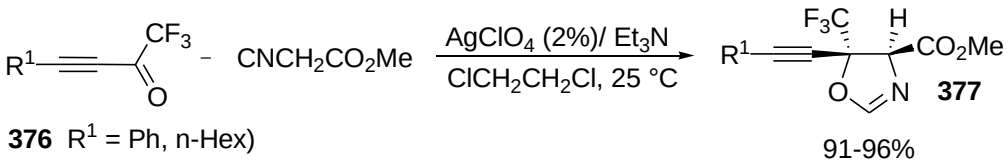
Scheme 105

Isoselenoazoles **374**, otherwise available only with difficulty, can easily be prepared by consecutive treatment of enones **375** with bromine and ammonia.[62]



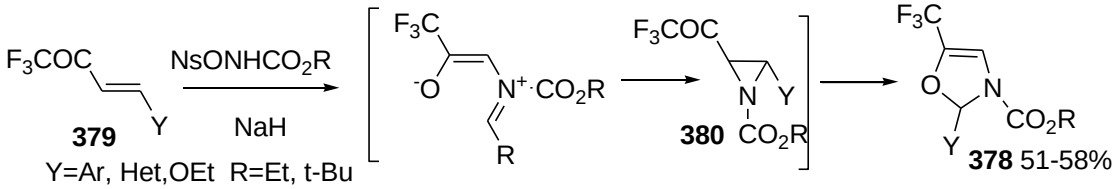
Scheme 106

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]



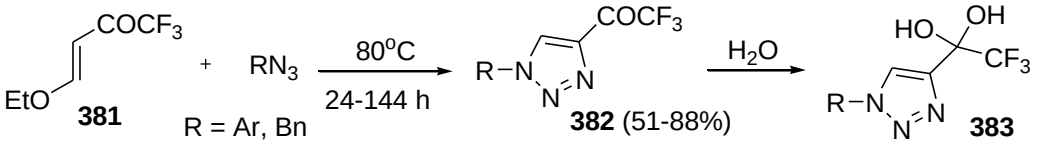
Scheme 107

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]



Scheme 108

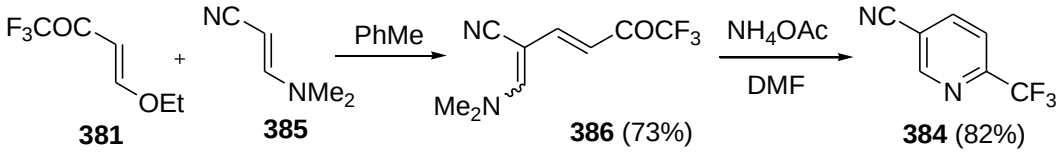
3.1.6 Synthesis of triazoles. The reaction of ketone **381** with various azides leads to the formation of the corresponding trifluoroacetyl triazoles **382** hydrated to diols **383.**[125]



Scheme 109

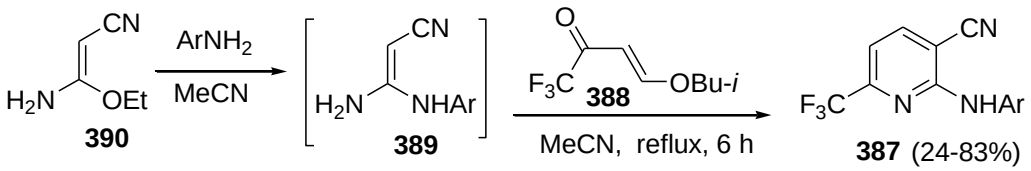
3.2 Synthesis of six-membered heterocycles

3.2.1 Synthesis of pyridines and their derivatives. Though there are few methods for preparation of CF_3-containing pyridines. The synthesis of the 6-CF_3-nicotinonitrile **384** based on the reaction with β-dimethylaminoacrylonitrile **385** followed by the treatment of intermediate product **386** with ammonium acetate was proposed.[126]



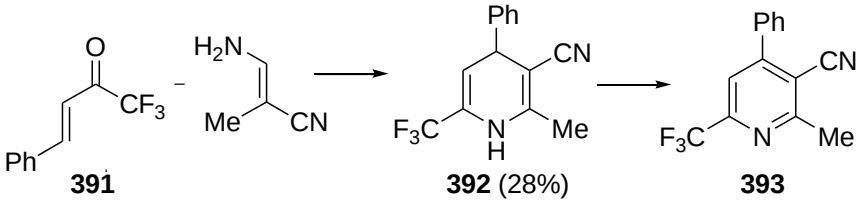
Scheme 110

The synthesis of 2-arylamino 6-CF_3-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]



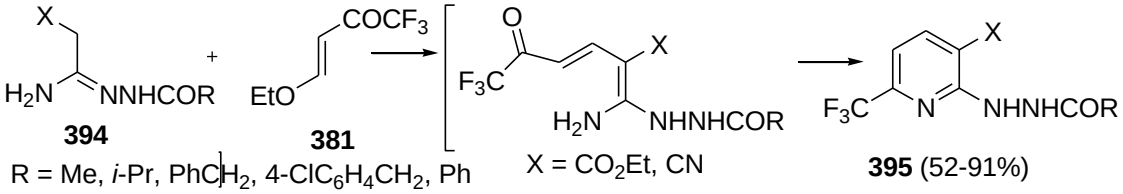
Scheme 111

The reaction of the enone **391** with β-aminocrotononitrile results in the formation of 6-trifluoromethyldihydropyridine **392** in a low yield; oxidation of this product leads to the corresponding aromatic derivative **393**.[128]



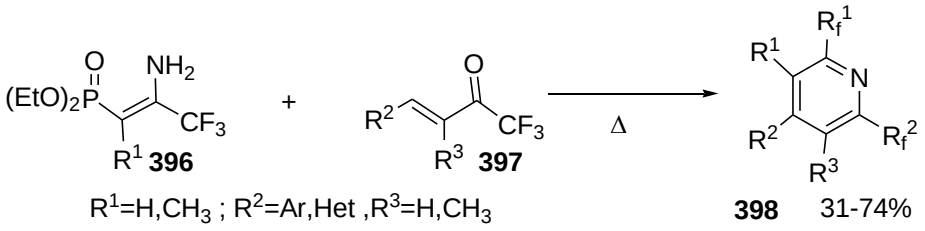
Scheme 112

The reaction of enone **381** with N-acylacetamidrazones **394** allows to prepare 2-hydrazo-derivatives of ethyl 6-trifluoromethylnicotinate **395** in good yields.[129]



Scheme 113

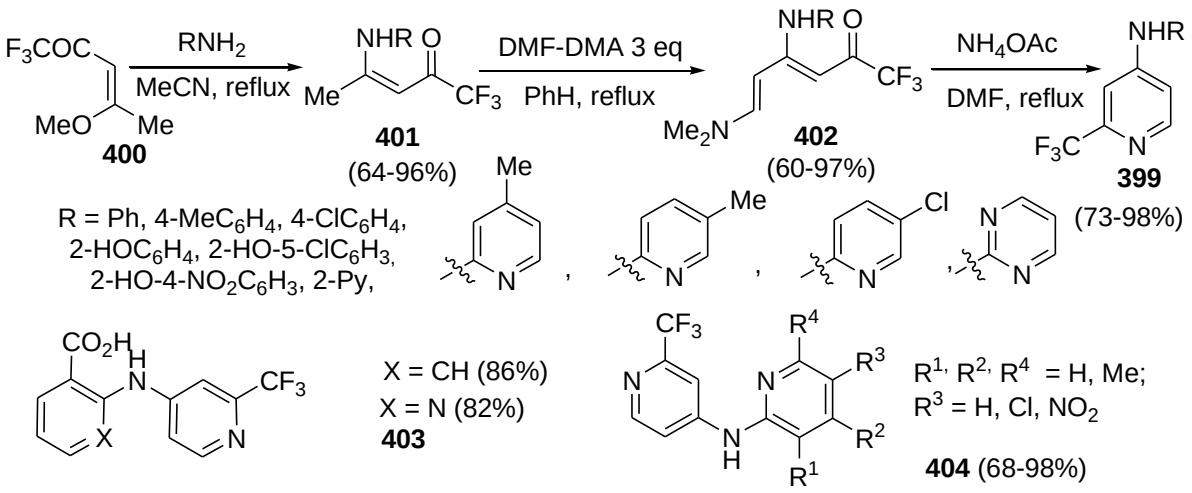
Enaminophosphonates containing fluoroalkyl substituents **396** were used for the regioselective preparation of polysubstituted pyridine derivatives **398** by the reaction with fluorinated α,β -unsaturated ketones **397** at high temperature in the absence of solvent.[130]



Scheme 114

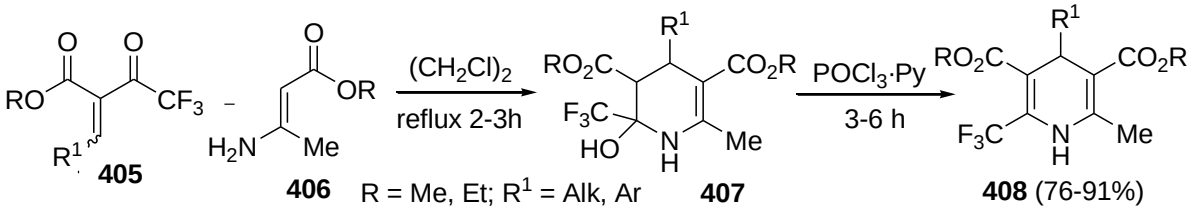
New approach for the synthesis of 2-CF_3 pyridines **399** containing various arylamino-substituents in the 4-position exploits the reaction of CF_3-enone **400** with various aromatic amines including heterocyclic ones. The subsequent reaction of formed enaminoketone **401** with the DMF dimethylacetal leads to dienones **402** which undergo cyclization in high yields to the targeted 2-CF_3-4-arylaminopyridines **399** with ammonium acetate. Analogous approach is based on the use of 2-aminopyridine derivatives for the synthesis of the 2-CF_3-4-pyridylaminopyridines **403**.The same

method was used for the preparation of 2-CF_3-pyridine derivatives **404** possessing anticancer activity.[131]



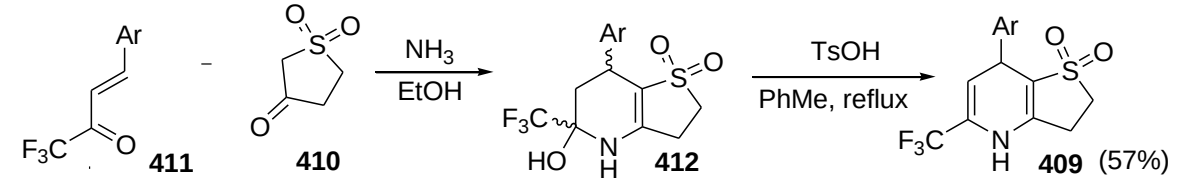
Scheme 115

CF_3-enones **405** react with enamino esters **406** to afford fairly stable hydroxypyridines **407**. The hydroxypyridines **407** were dehydrated to form dihydropyridines **408**.[132]



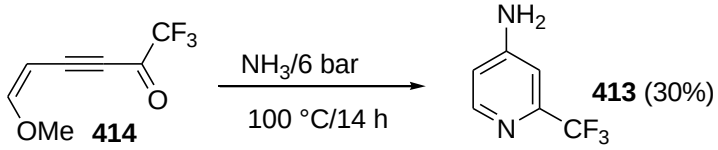
Scheme 116

The Gantsch type synthesis of the 1,4-dihydropyridines **409** used the reaction of dihydrothiophene-3(2*H*)-one-1,1-dioxide **410** with CF_3-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]



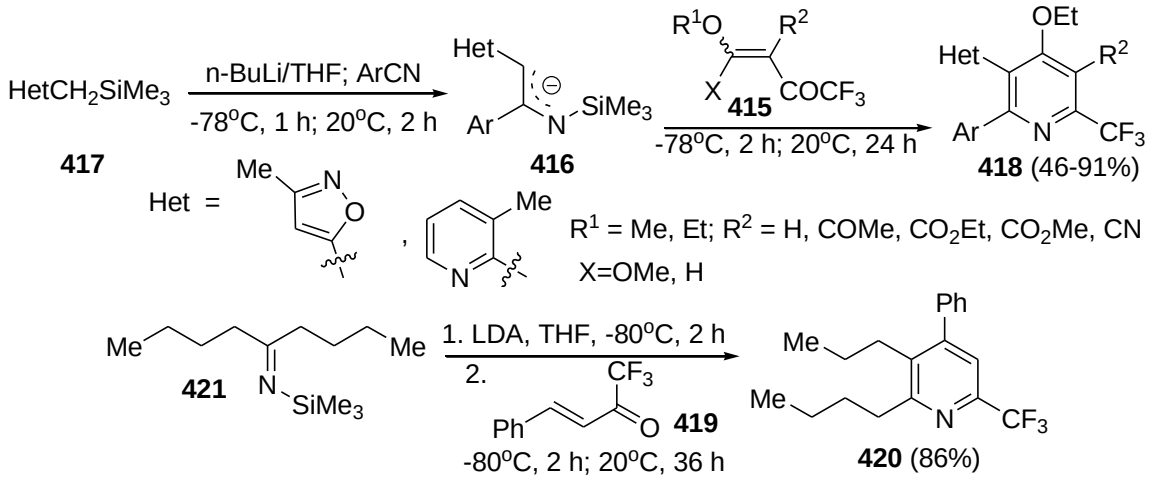
Scheme 117

4-Amino-2-CF_3-pyridine **413** was prepared in moderate yield using the reaction of ketone **414** with ammonia under heating at high pressure.[71b]



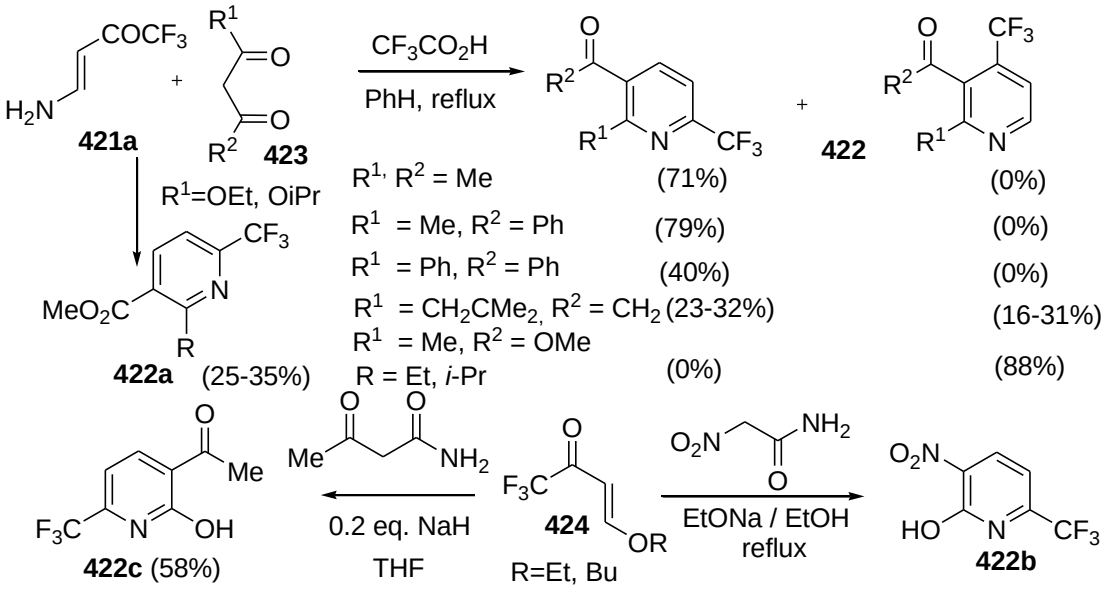
Scheme 118

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]



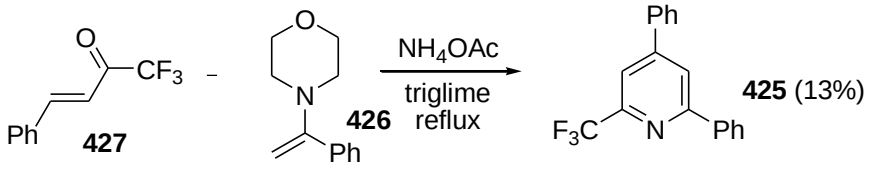
Scheme 119

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]



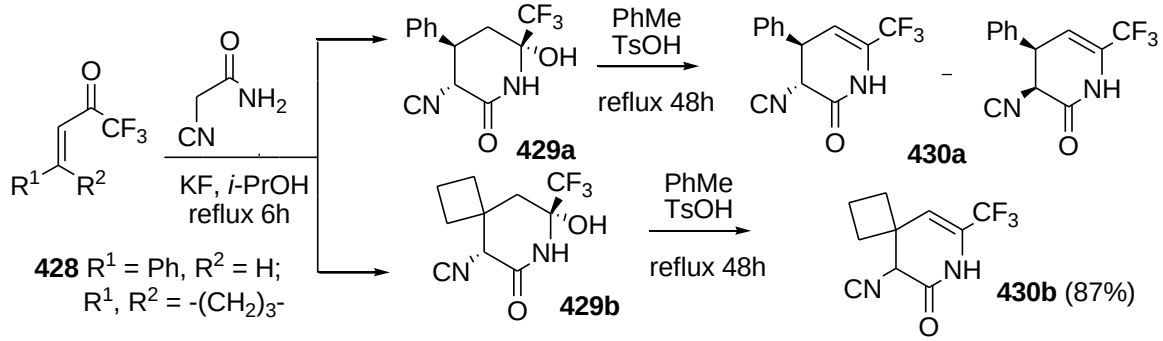
Scheme 120

2-CF_3-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]



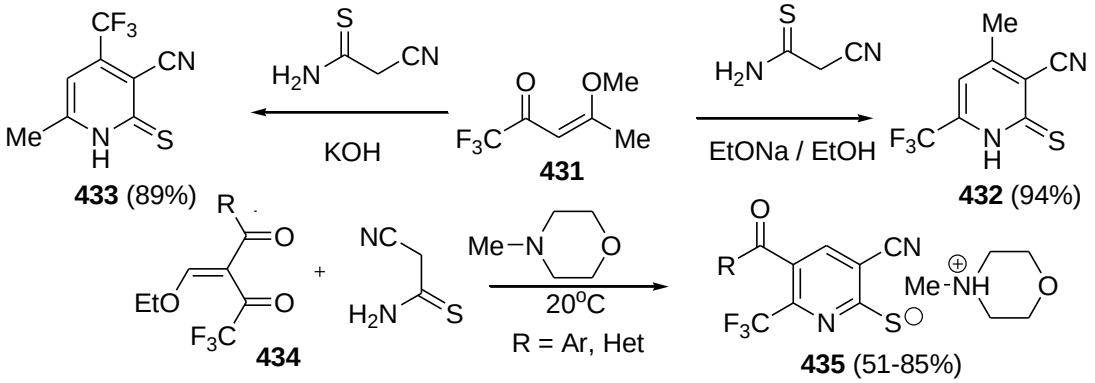
Scheme 121

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]



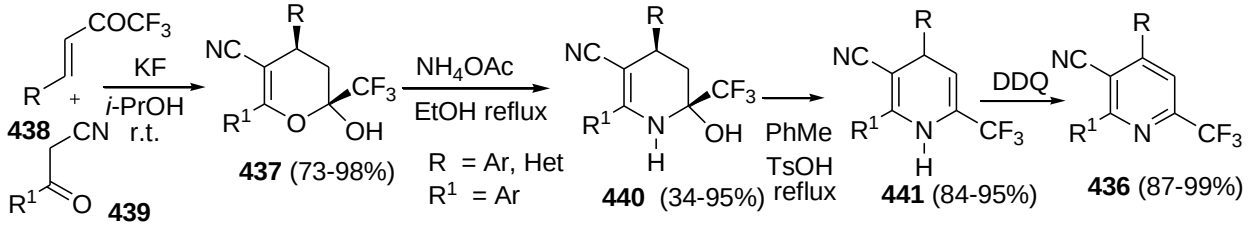
Scheme 122

The reaction of CF_3-enone **431** with cyanothioacetamide depending on conditions permits preparation of the isomeric pyridinethiones **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.[138]



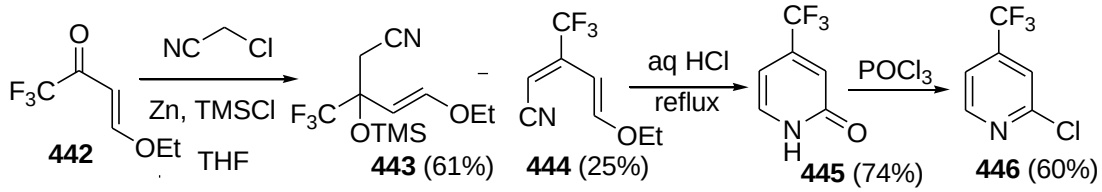
Scheme 123

A novel method for the preparation of CF_3- pyridines **436** was elaborated recently. First step is the synthesis of α-hydroxydihydropyrans **437** by reaction of **438** and α-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.[139]



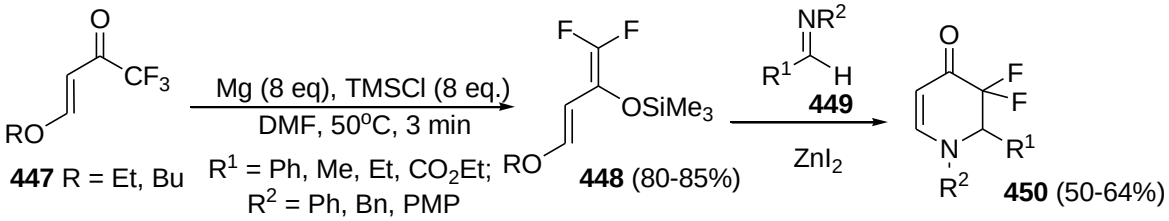
Scheme 124

It has been found that chloroacetonitrile reacts with **442** in the presence of zinc and trimethylchlorosilane to produce the β-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**.[140]



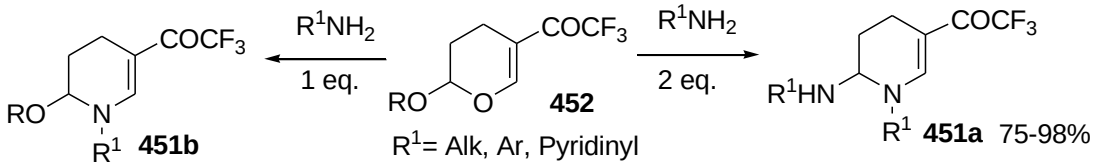
Scheme 125

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]



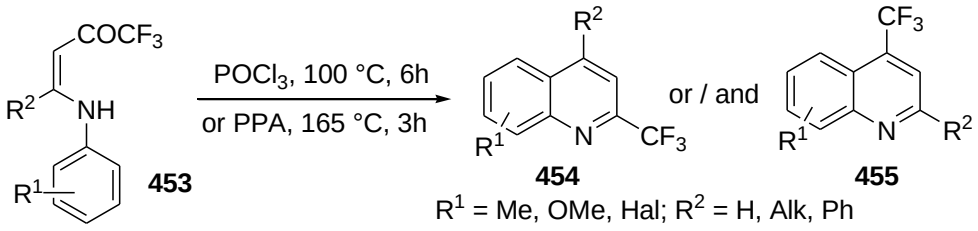
Scheme 126

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]



Scheme 127

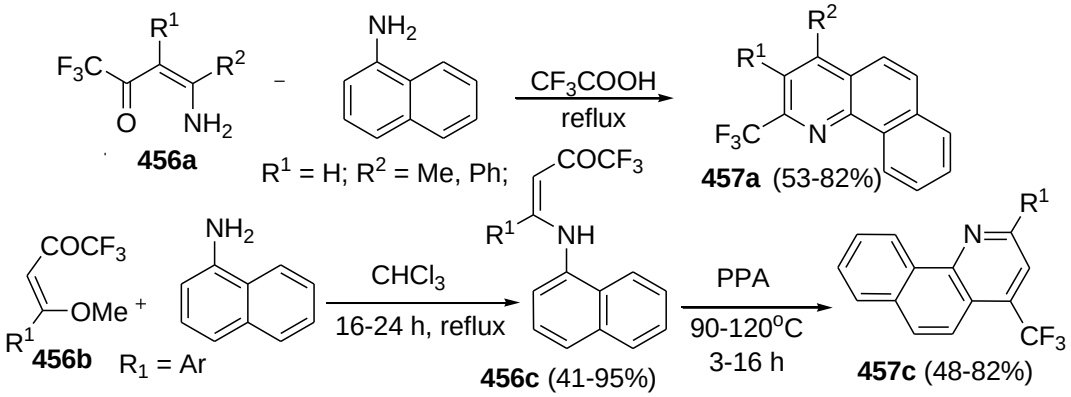
3.2.2 Synthesis of quinolines and benzoquinolines. β-Arylamino-substituted enones **453** were cyclized to 2-trifluoromethyl- **454** and 4-CF_3-quinolines **455** under treatment with acids.[113] $POCl_3$, $ZnCl_2$ and PPA were used as catalysts.[143]



Scheme 128

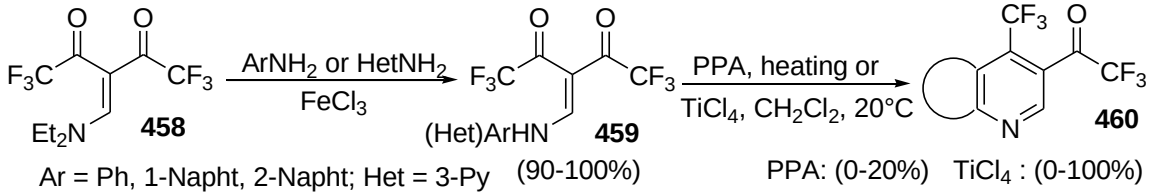
Quinolines **455** are the products of "normal" cyclization, while the mechanism of formation of 2-trifluoromethylquinolines **454** is the question of further investigations. The ratio of the products depends on the nature of acidic catalyst applied and the structure of the enone. Cyclization of enones with R^2 = H gives only 2-trifluoromethylquinolines **454**. When R^2 = 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-CF_3-benzo[*h*]quinolines **457b**. The enaminoketones **456c** prepared from 1-naphthylamine were cyclized with PPA.[145]



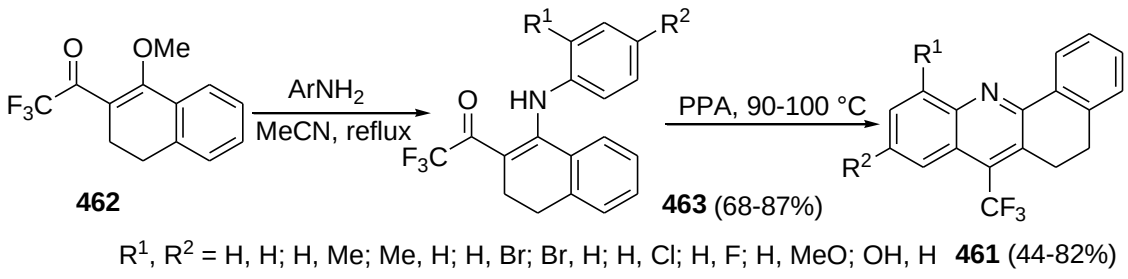
Scheme 129

The enaminodione **458** reacts with aromatic amines in the presence of catalytic amounts of $FeCl_3$ to give N-aryl-substituted enaminodiones **459**, which cyclize on treatment with PPA or $TiCl_4$, the yields of the reaction products **460** being substantially higher in the case of $TiCl_4$.



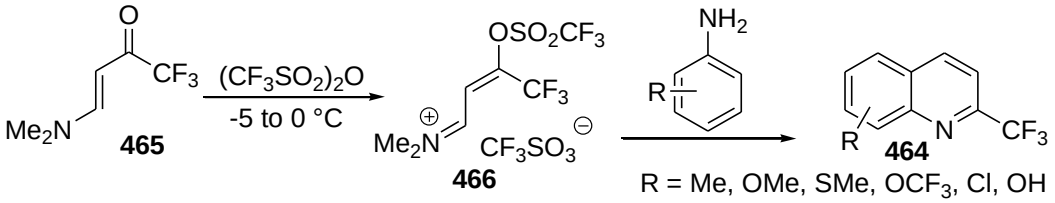
Scheme 130

The synthesis of CF_3-derivatives of dihydrobenzo[*c*]acridine **461** is based on the application of CF_3-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.



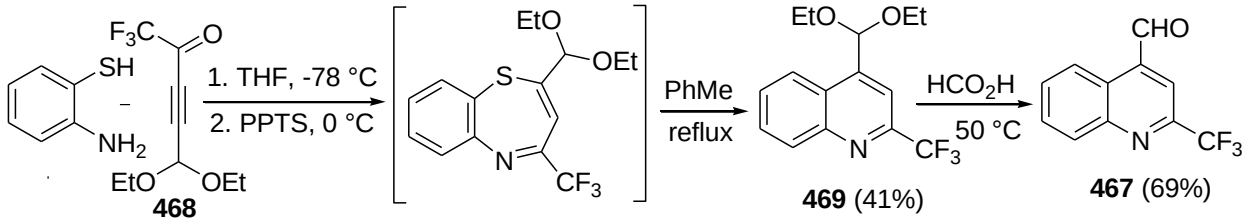
Scheme 131

A simple and general one-pot synthesis of 2-trifluoromethylquinolines **464** from anilines and enaminoketone **465** was elaborated. Treatment of **465** with triflic anhydride caused the formation of 3-trifloxy-3-trifluoromethylpropeniminium triflate **466** which was found to react with electron-rich aromatics to give corresponding CF_3-quinolines **464** in excellent yields.[147]



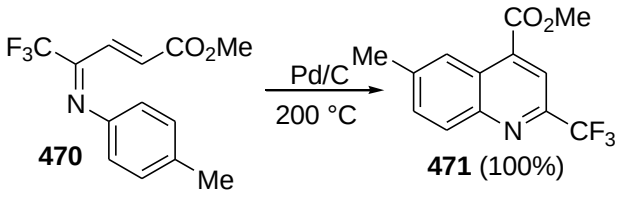
Scheme 132

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



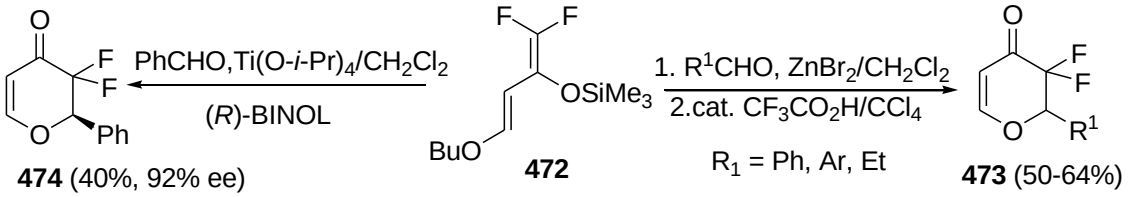
Scheme 133

Imino-derivatives of **470** can be also applied for the synthesis of quinolines derivative **471** in good yield under dehydrogenation (Pd/C).[28]



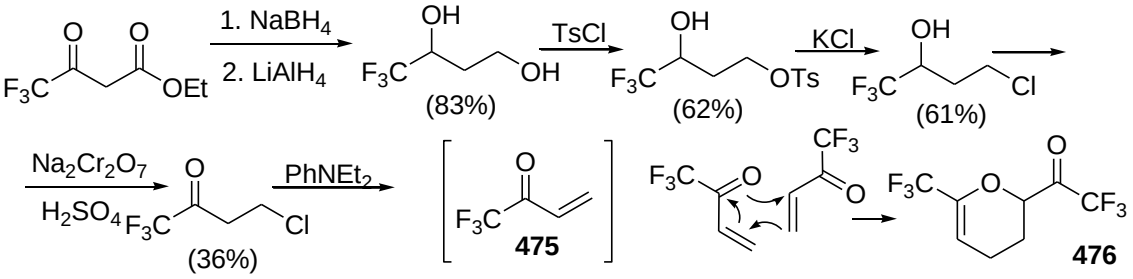
Scheme 134

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



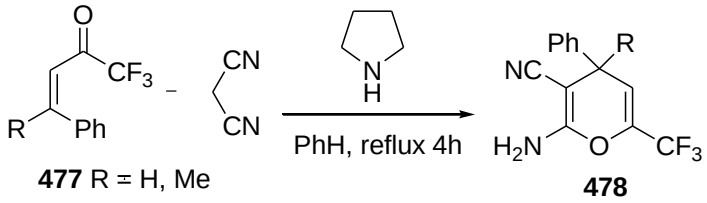
Scheme 135

An attempt to prepare unsubstituted CF_3-enone **475** from ethyl trifluoroacetoacetate have been unsuccessful due to spontaneous dimerization of **475** to give dihydropyran **476**.[149]



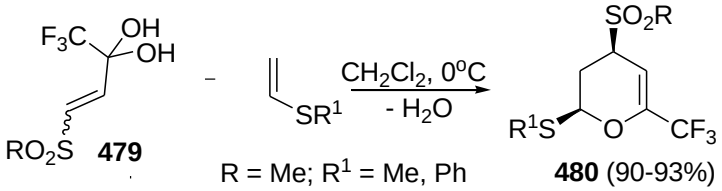
Scheme 136

The reactions of trifluoromethyl enones **477** with malonodinitrile in the presence of pyrrolidine as a catalyst gave the corresponding pyrans **478.** [137]



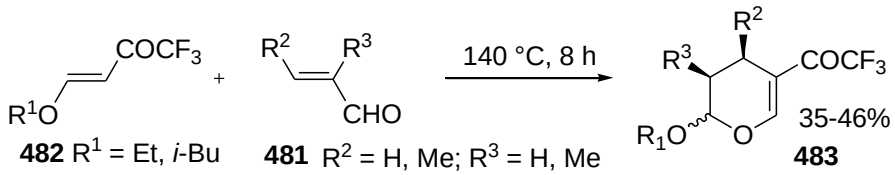
Scheme 137

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]



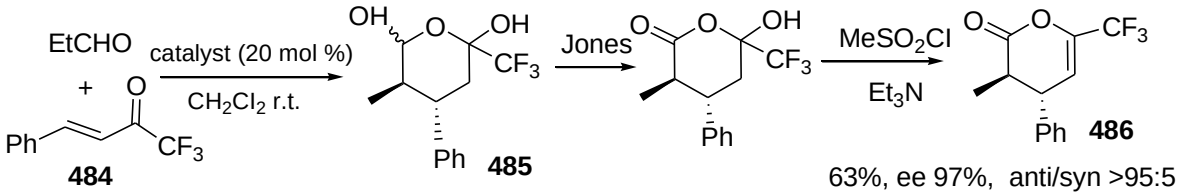
Scheme 138

The cycloaddition of α,β-unsaturated aldehydes **481** with **482** leads to unexpected cycloadducts **483** having alkoxy-group migrated as a mixture of *cis*-/*trans*-isomers.[121]



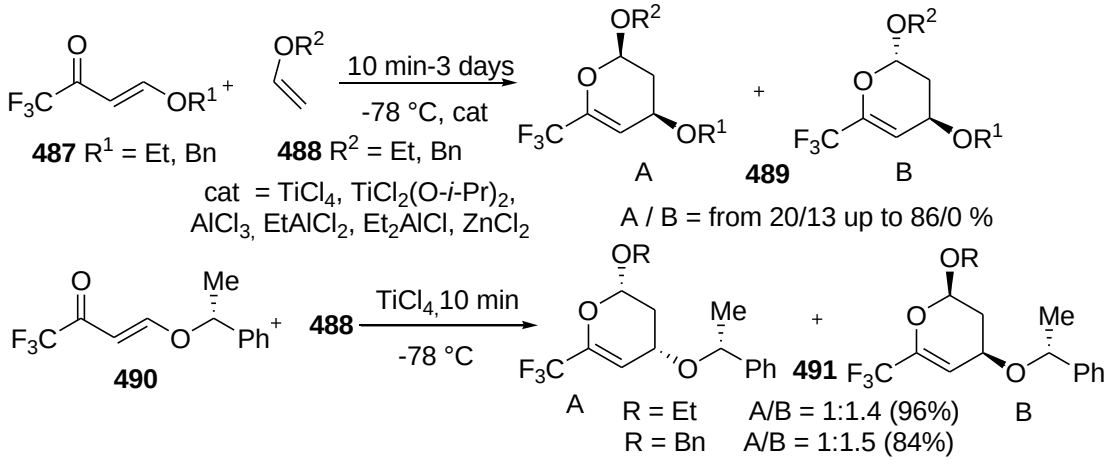
Scheme 139

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-dihydropyan-2-ones **485** were obtained with high ee and transformed to **486**.[150]



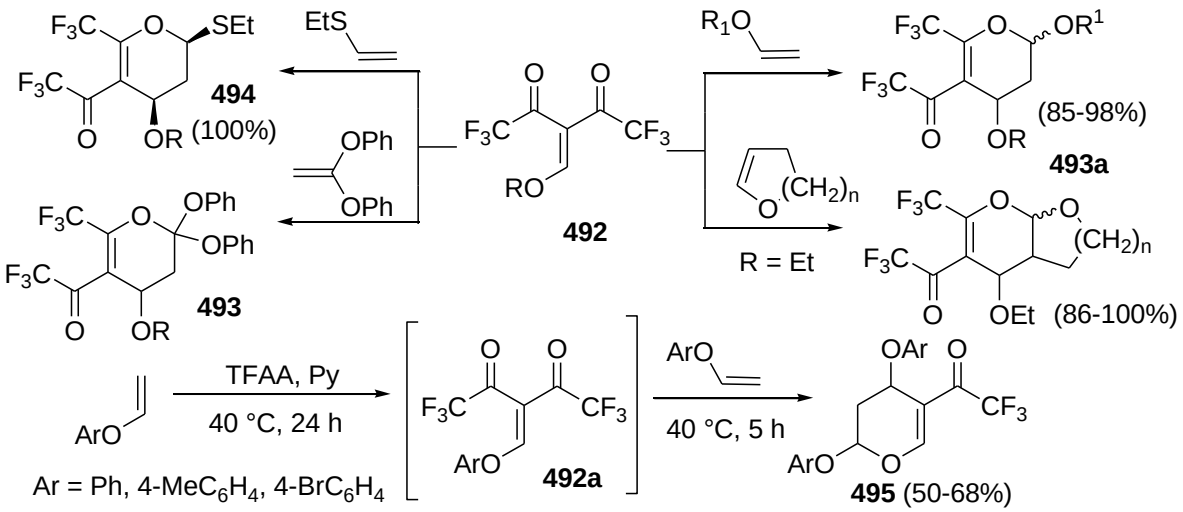
Scheme 140

The influence of various Lewis acids on the cycloaddition reaction of β-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-dihydropyrans **491** was also investigated. In this case the reaction of CF_3-enone **490** containing chiral substituent in β-position was used. The application of $TiCl_4$ gave the target pyrans **491** in high yields but de is very low.[151]



Scheme 141

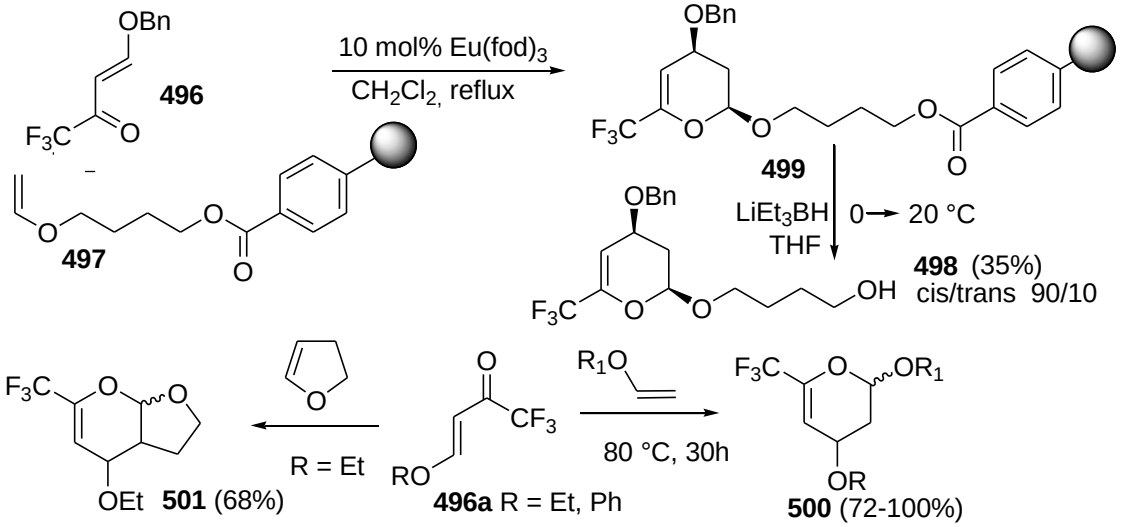
Cycloaddition proceeds especially easily for **492** due to the presence of the second strong EWG increasing the reactivity of trifluoromethylenones **492** as heterodienes.



Scheme 142

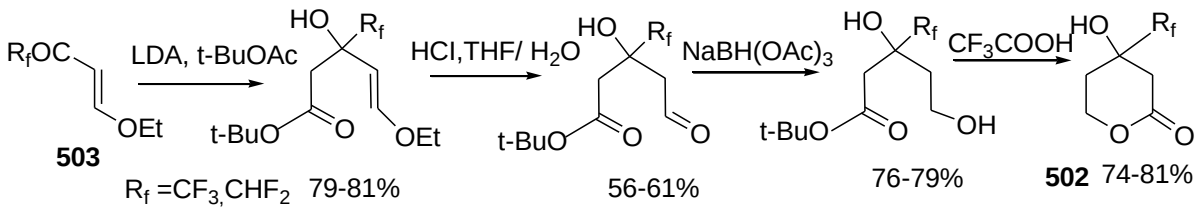
The reaction is carried out at room temperature to give **493** in high yields. Thioethers reacted similarly to give single diastereomers of pyranes **494**. Aryl vinyl ethers react with trifluoroacetic anhydride to give the corresponding bis(trifluoroacetyl) derivatives **492a**. It was found that these 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-CF_3-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 $LiBHEt_3$. The reaction of **496a** with vinyl ethers affords 3,4-dihydro-2H-pyrans **500** and **501** in good yields.[153]



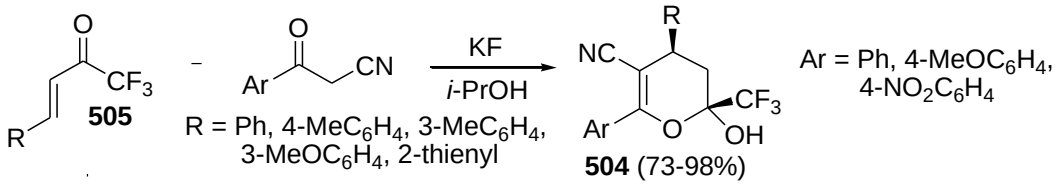
Scheme 143

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]



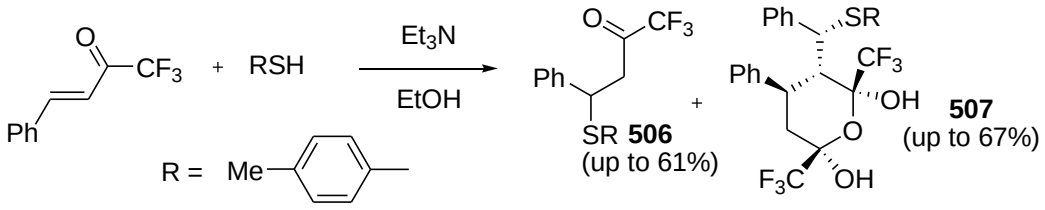
Scheme 144

Cyano substituted dihydropyrans **504** were obtained in the reaction of **505** with α-cyanoketones. The reaction proceeds in the presence of calcinated KF 100% stereoselectively.[155]



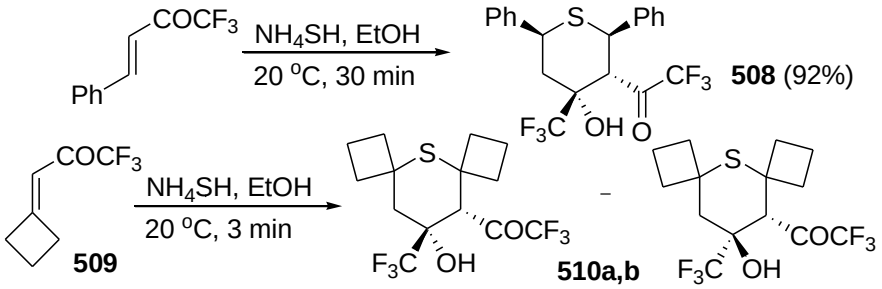
Scheme 145

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]



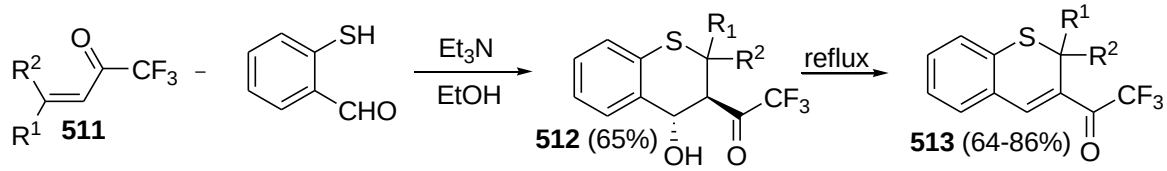
Scheme 146

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

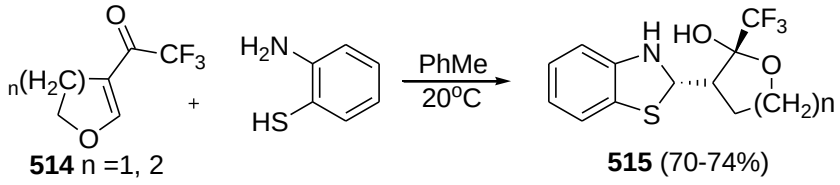
The reaction of **511** with 2-mercaptobenzaldehyde leads to thiochromanes **512** which can be easily transformed into 2H-thiochromenes **513** by heating. The intermediate thiochromane **512** were isolated only in case of CF_3-enone having the phenyl substituent.[156]



R^1 = Ph, R^2 = H; R^1 = 2-Th, R^2 = H; R^1 = N-methylpyrrolyl, R^2 = H; R^1,R^2 = -$(CH_2)_3$-

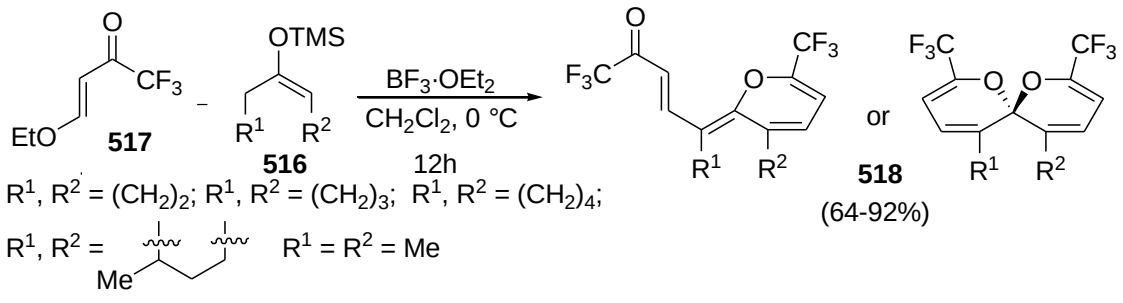
Scheme 148

The reaction of 2-aminothiopenol with cyclic β-alkoxyenones **514** leads to formation of benzothiazolines **515** binding with tetrahydrofuran and tetrahydropyran ring.[158]



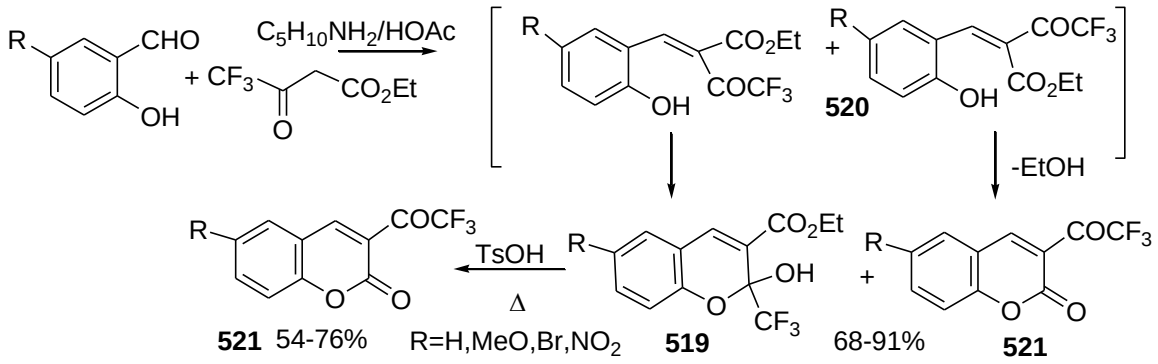
Scheme 149

Spiro-pyrane derivative **518** were obtained in good yields in the reaction of trimethylsilyl ethers **516** with β-ethoxy ketone **517** catalyzed by boron trifluoride-diethyl ether complex.[159]



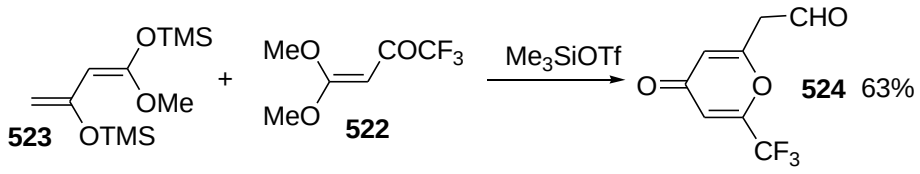
Scheme 150

The Knoevenagel condensation of ethyl trifluoroacetoacetate with salicylaldehydes provides a simple and convenient approach to substituted (trifluoromethyl)-2*H*-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]

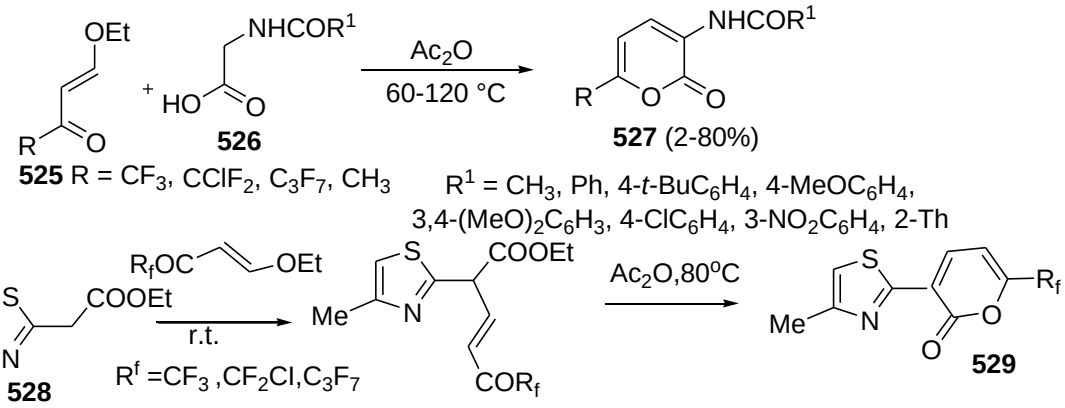


Scheme 151

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]



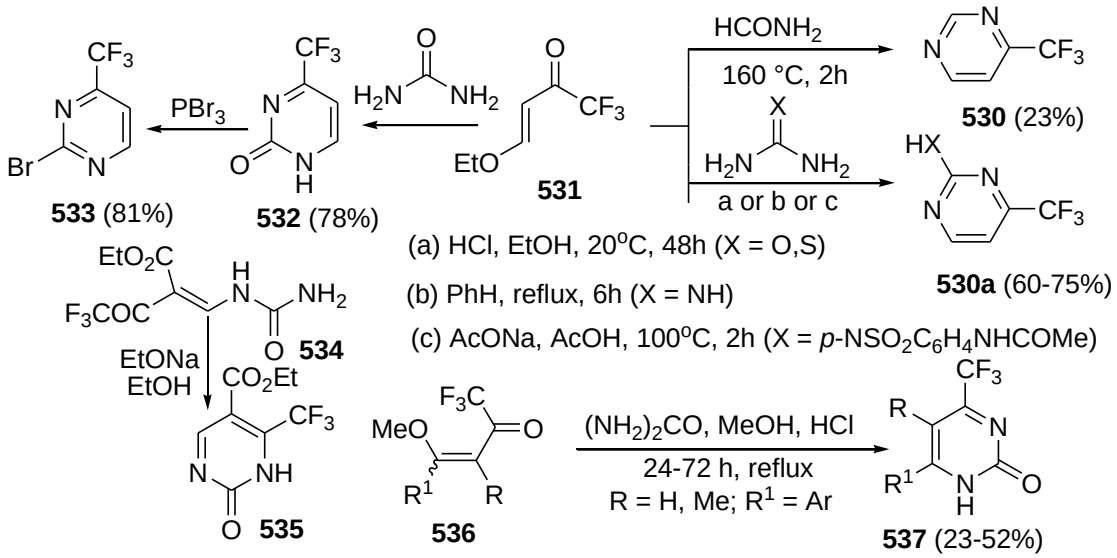
Scheme 152



Scheme 153

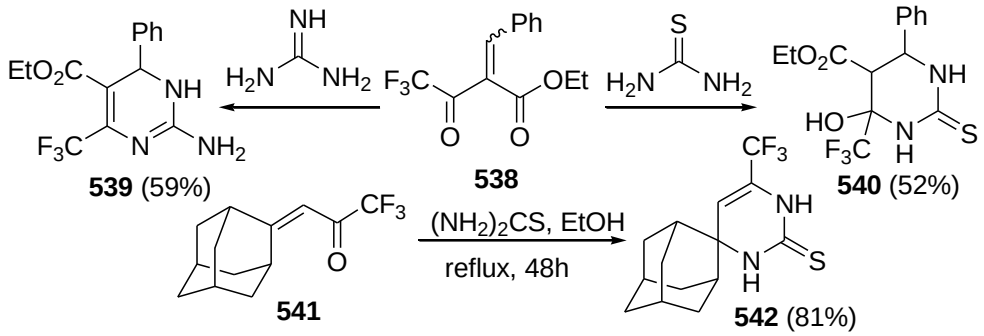
The reaction of **525** with N-aroyl glycines **526** in the presence of Ac_2O leads to 2*H*-pyran-2-ones derivatives **527**. The reaction between enones and thiazole **528** bearing a methylene group activated by an electron-withdrawing substituent leads to formations pyrones **529**.[162]

3.2.4 Synthesis of pyrimidines and their derivatives. Trifluoromethylpyrimidines **530** are formed when β-ethoxyenone **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.



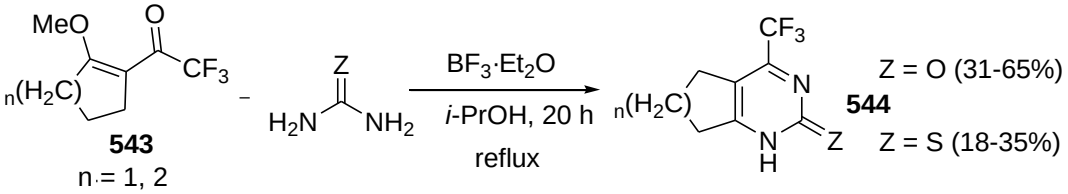
Scheme 154

The reactions of CF_3-enone **538** containing the ethoxycarbonyl group in the α-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]



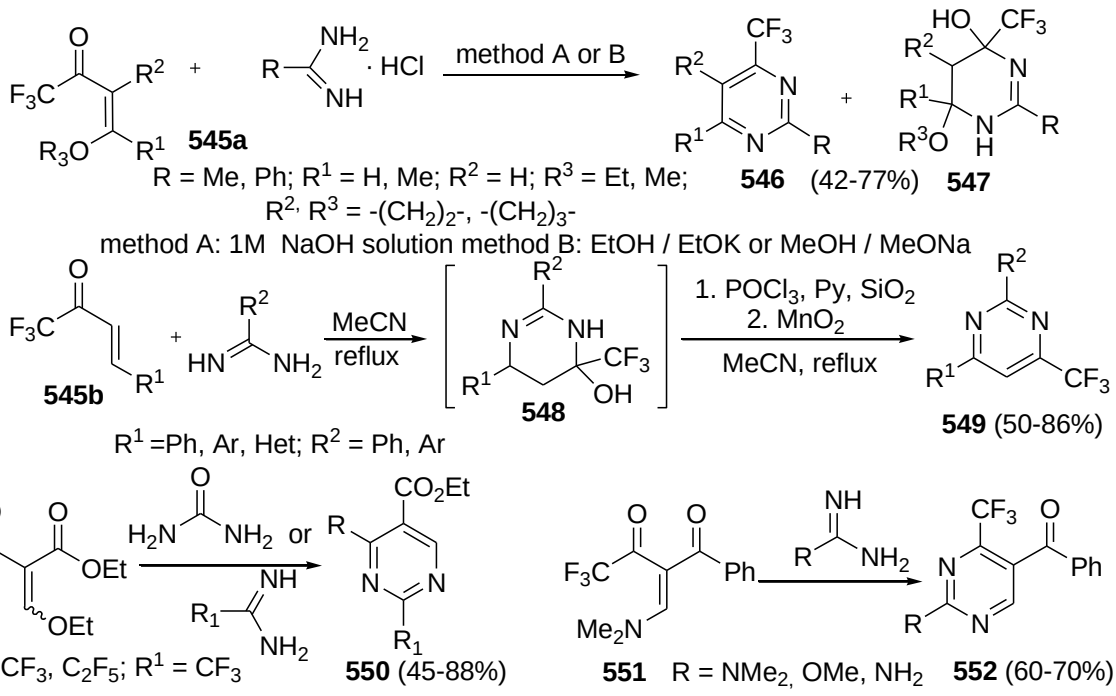
Scheme 155

Cyclic CF_3-enones **543** were applied for the preparation of 2-pyrimidones **544** and their thio-analogous using the reaction with urea and thiourea.[166]



Scheme 156

The reaction of series of CF_3-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 dehydration 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]

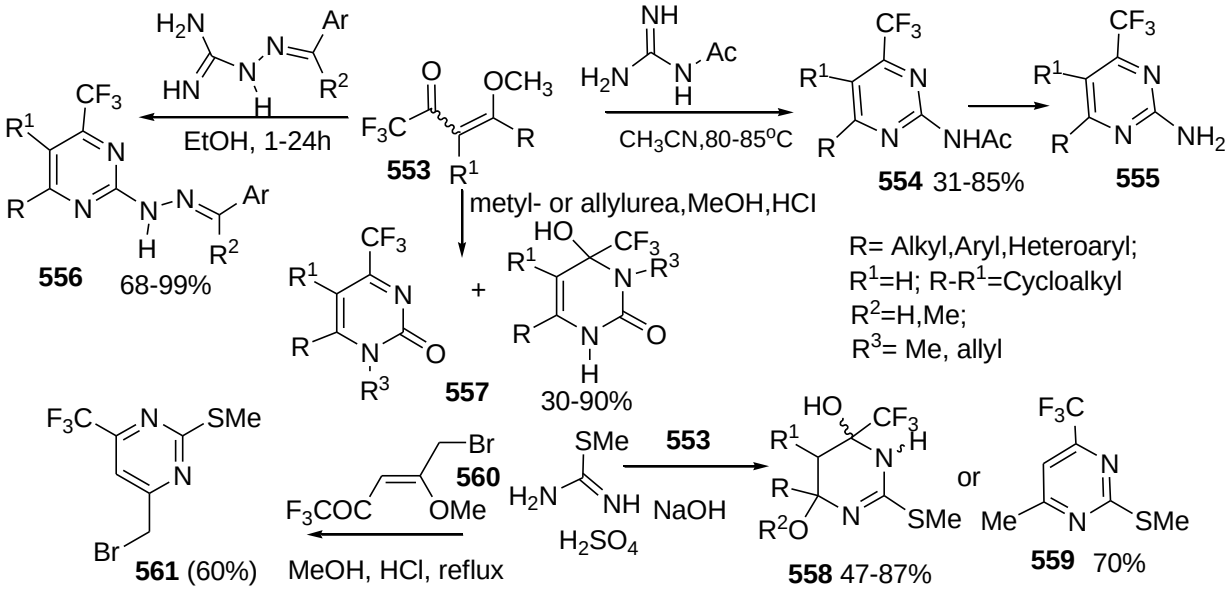


Scheme 157

The one-pot synthesis of substituted 2-acetylaminopyrimidines **554** using the reaction of **553** with 1-acetylguanidine was elaborated. The acetylamino group of 2-acetylaminopyrimidines 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-

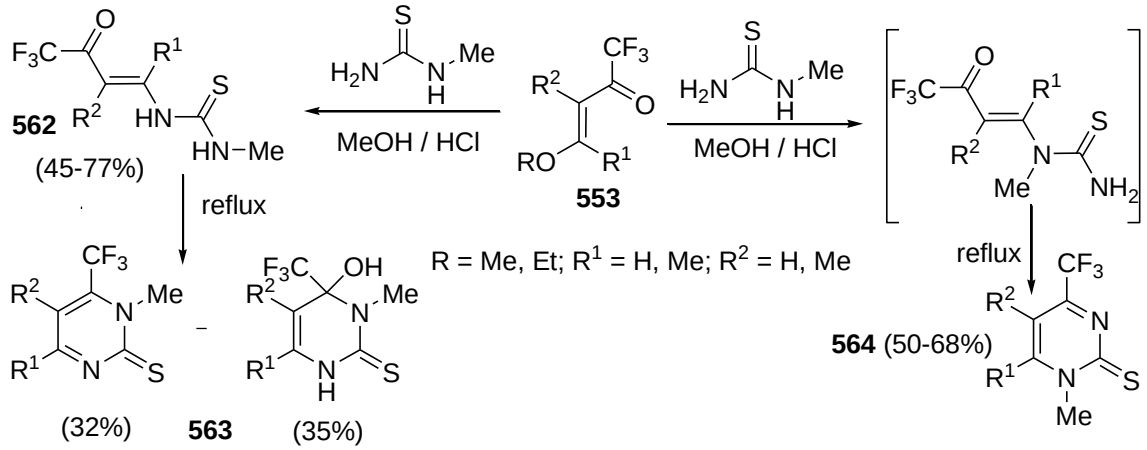
isomers).[170] N-substituted pyrimidinones **557** were synthesized by condensation of enones **553** with excess *N*-methyl- and *N*-allylureas.[171]

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]



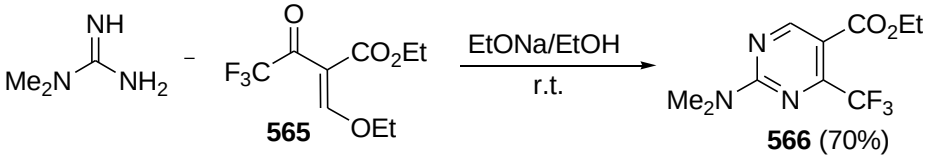
Scheme 158

The cyclocondensation of **553** toward the nonsymmetric dinucleophile - N-methylthiourea was choosen to study its regiochemistry. Depending on the temperature and the reaction time the open-chain products **562** or pyridinethiones **563** were obtained.[173]



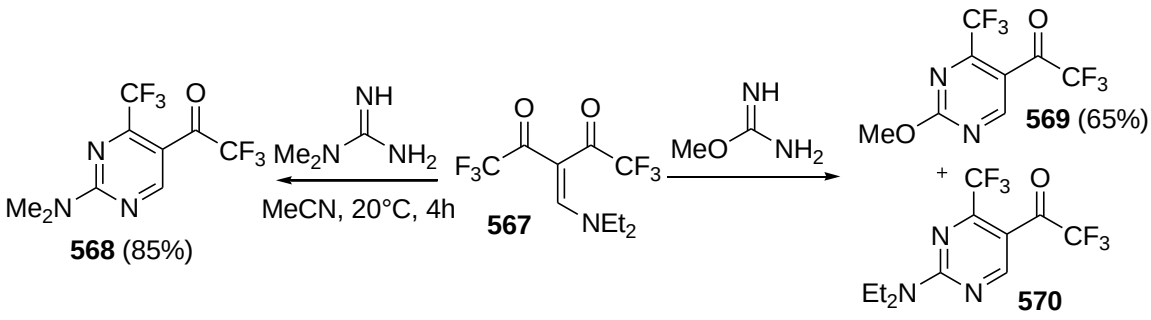
Scheme 159

Analogous reaction was used for synthesis of 2-dimethylamino-derivative **566** showed cardiotonic activity.[174] The target product **566** was obtained in high yield.



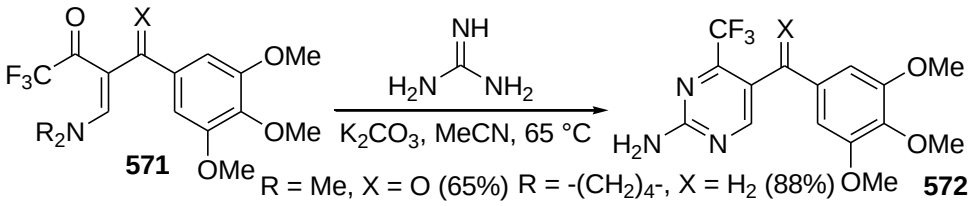
Scheme 160

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



Scheme 161

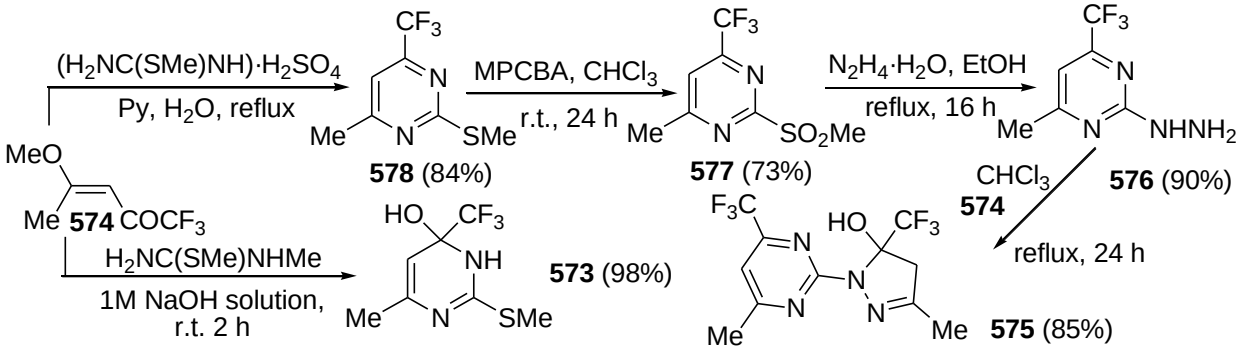
The work was undertaken to apply the methodology of the synthesis of fluorinated aminopyrimidines analogous to trimethoprim (TMP)[175] - the reference drug for prophylaxis and treatment of opportunistic infections due to *Pneumocystis carinii* and *Toxoplasmagondii*. Enaminoketones **571** were reacted with guanidine to give **572**.



Scheme 162

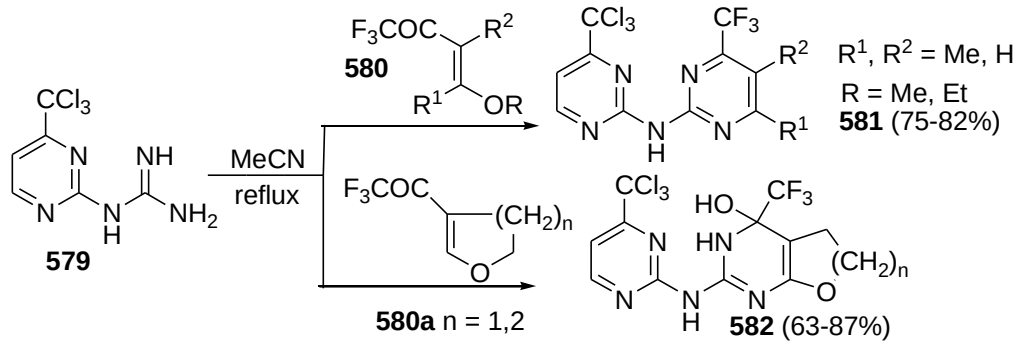
Four novel pyrimidines were prepared to investigate the effects of on NTPDase activity in a synaptosomal fraction obtained from rat cerebral cortex.[176] The pyrimidine **573** was prepared by the cyclocondensation reaction of **574** with 1,2-dimethyl-isothiourea. The synthesis of **575** was

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.



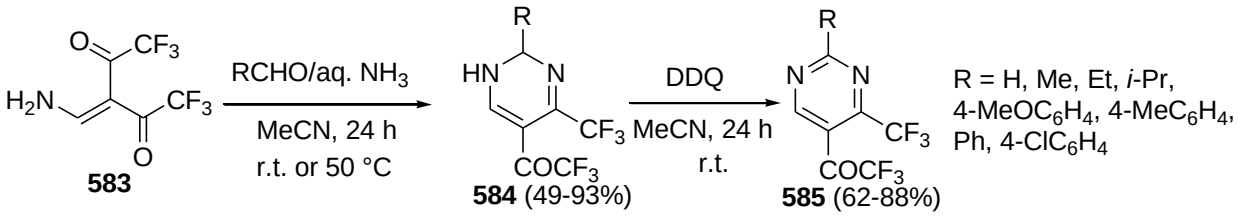
Scheme 163

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]



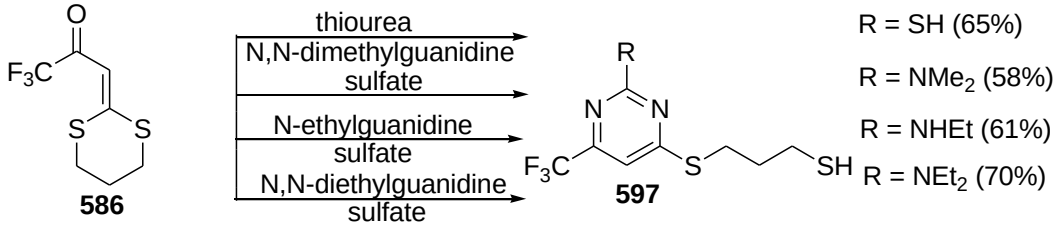
Scheme 164

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]



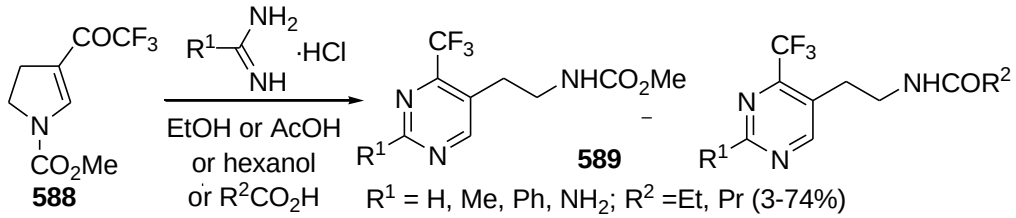
Scheme 165

The reactions of CF_3-enone **586** with several N,N-binucleophiles gave various 2-substituted pyrimidines **587** containing 1,3-dithiopropyl substituent.[104]



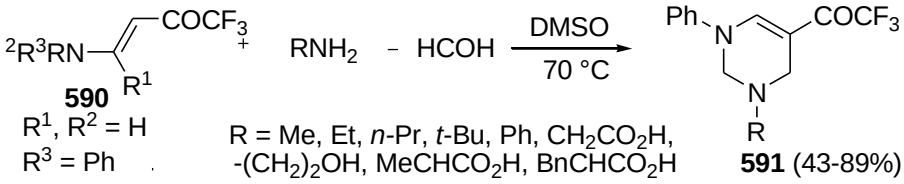
Scheme 166

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]



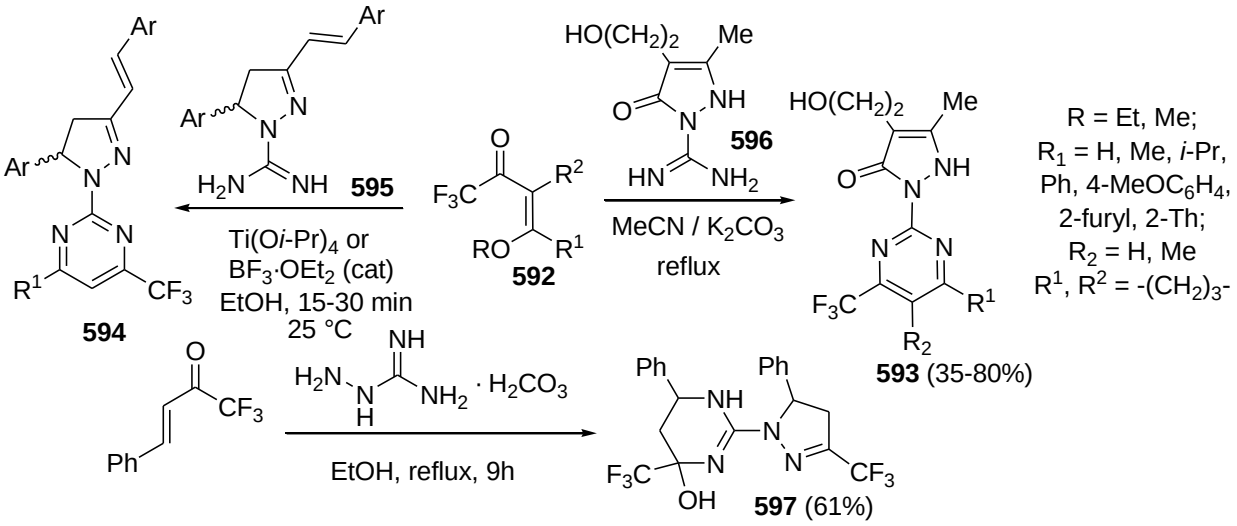
Scheme 167

The multicomponent reaction of CF_3-enone **590**, primary amine and formaldehyde was used for the synthesis of tetrahydropyrimidines **591** in moderate to high yields.[179]



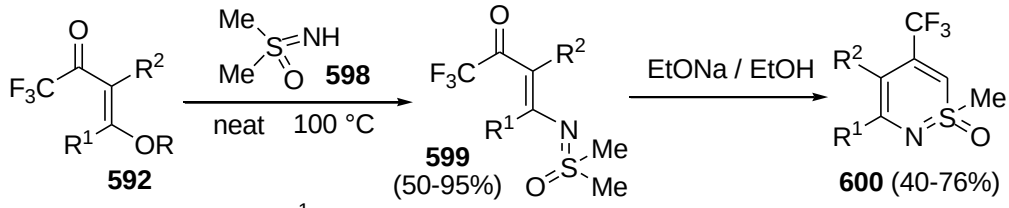
Scheme 168

β-Alkoxy-CF_3-enones **592** were also used for preparation of various CF_3-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.[110a]



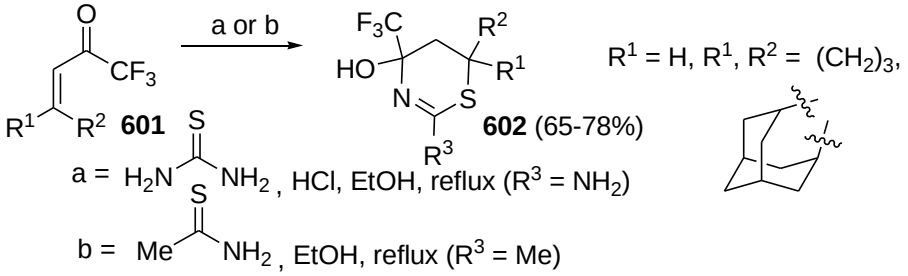
Scheme 169

3.2.5 Synthesis of 1,2-, 1,3- and 1,4-thiazines. The reaction of β-alkoxy-CF_3-enones **592** with *S*,*S*-dimethylsulfoximine **598** gave **599** cyclized into the derivatives of 1,2-thiazine-1-oxide **600** in high yields.[182]



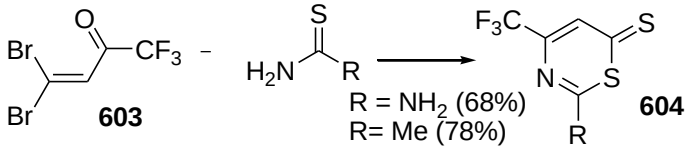
Scheme 170

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]



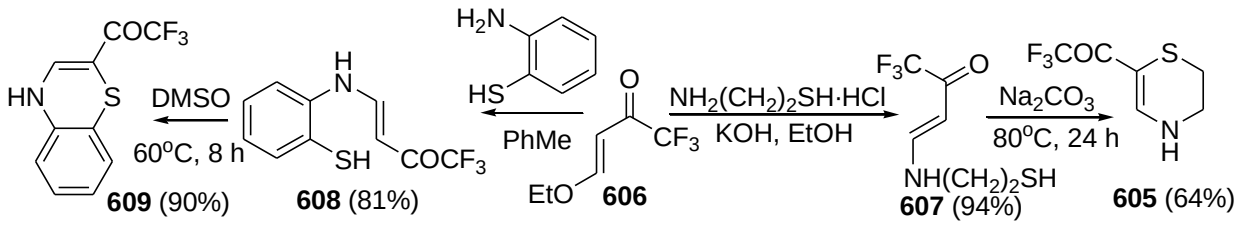
Scheme 171

The reaction of β,β-dibromo-CF_3-ketone **603** with thioacetamide and thiourea lead regioselectively to the corresponding 1,3-thiazine derivatives **604** in good yields.[15e]



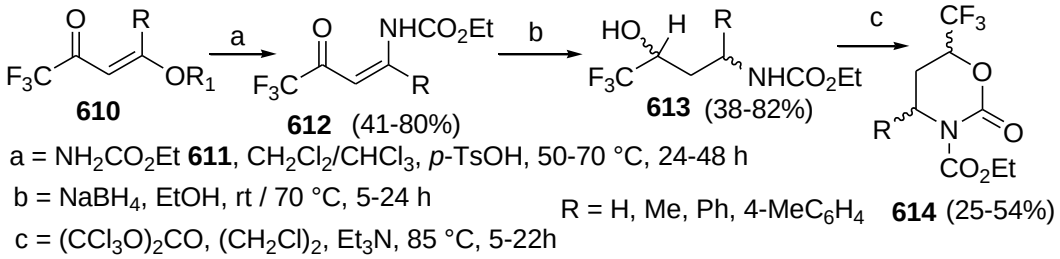
Scheme 172

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

3.2.6 Synthesis of 1,3-oxazines and 1,2,3-oxathiazines. The reaction of β-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]

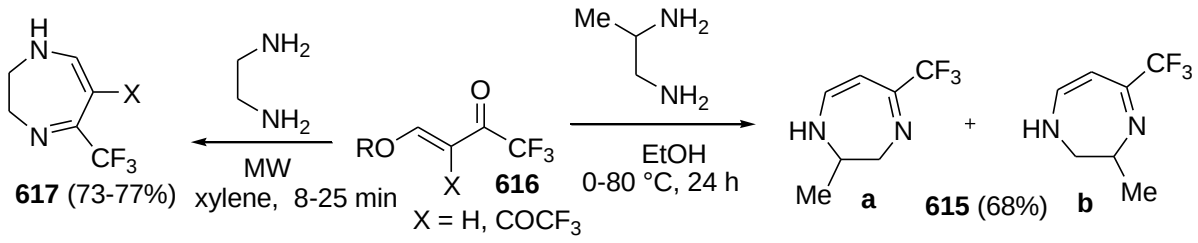


Scheme 174

3.2. Synthesis of seven-membered heterocycles

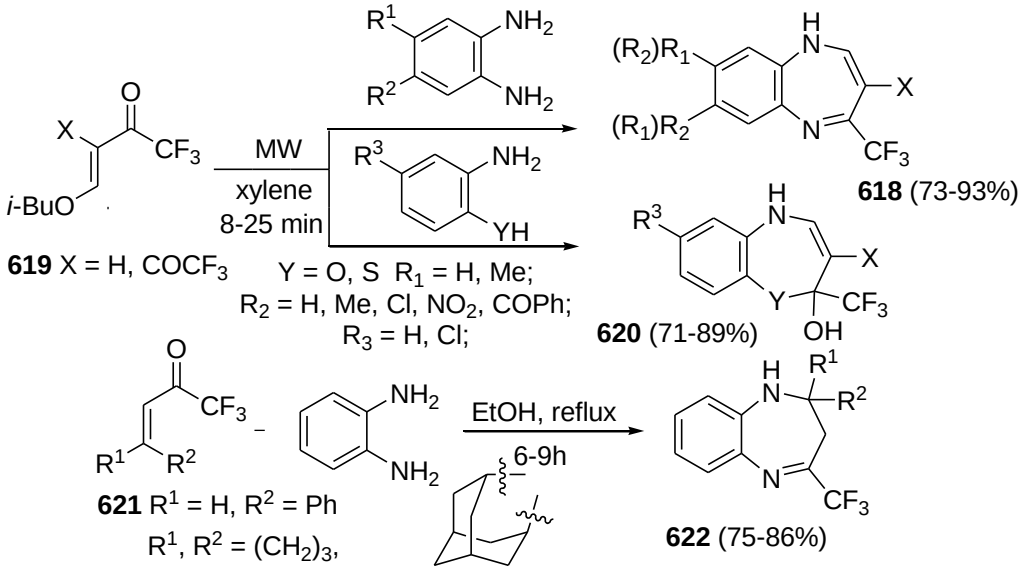
3.2.1 Synthesis of 1,4-diazepines (benzoanalogues) and 1,5-benzoxazepines. 5-Trifluoromethyl-2,3-dihydro-1,4-diazepines **615** were prepared by the reaction of CF_3-enone **616** with 1,2-propylenediamine.[43b] The reaction gave two isomeric products **615a,b** in a nearly 1:1 ratio. Similarly 1,4-diazepines **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.[185] Benzodiazepines have been considered the most extensively consumed psychoactive drugs worldwide due to their anxiolytic and anticonvulsant activity.



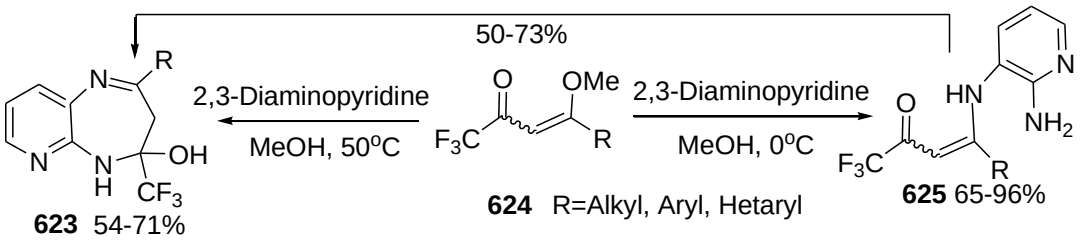
Scheme 175

The high yield preparation of benzodiazepines **618** by one-step reaction of **619** with o-phenylendiamines 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**.[186]



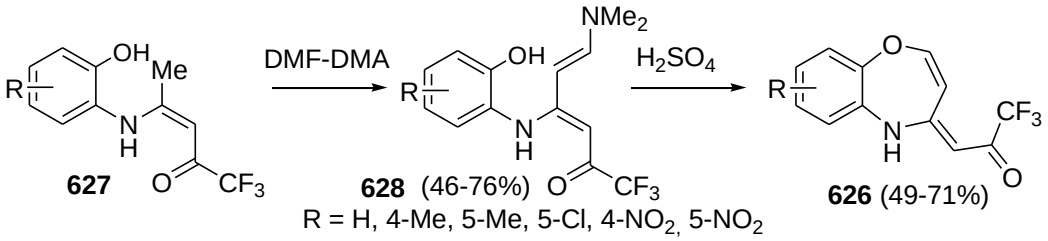
Scheme 176

The trifluoromethyl-4,5-dihydro-3H-pyrido[2,3-b][1,4]diazepin-4-ols **623** were obtained by cyclocondensation of 4-methoxy-CF_3-enones **624** with 2,3-diaminopyridine. The reactions proceed regiospecifically in a moderate to good yields.[187] The compounds **623** were also obtained from intramolecular cyclization reaction of the respective trifluoroacetyl enamines **625**.



Scheme 177

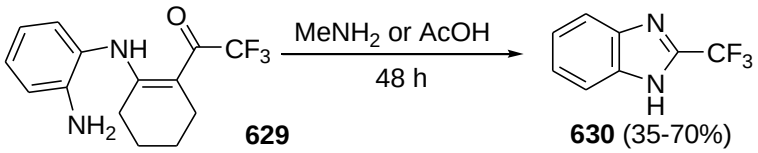
Useful approach to the preparation of new CF_3-containing 1,5-benzoxazepines **626** was presented. The reaction of enaminoketones **627** with DMF-DMA results in the corresponding dienamines **628**. Its cyclization with H_2SO_4 give the fluorinated 1,5-benzoxazepines **626**.[188]



Scheme 178

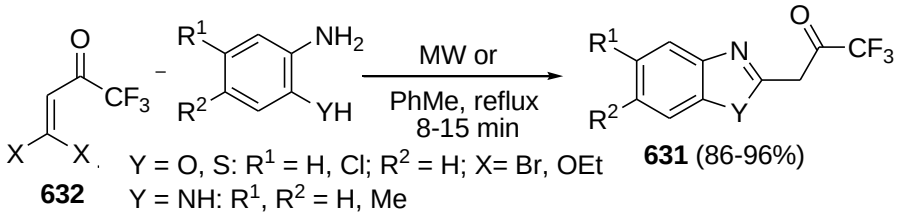
3.3 Synthesis of other condensed heterocycles

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]



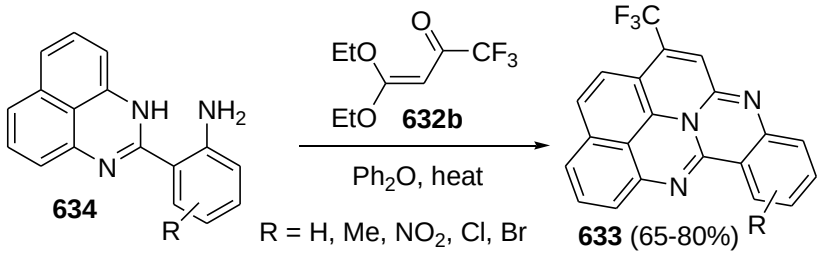
Scheme 179

The benzimidazolyl- and benzoxazolyl CF_3-ketones **631** were obtained in high yields in the reaction of *o*-phenylendiamine and *o*-aminophenol with β,β-dibromoketone **632a** and diethoxyketone **632b**.[101]



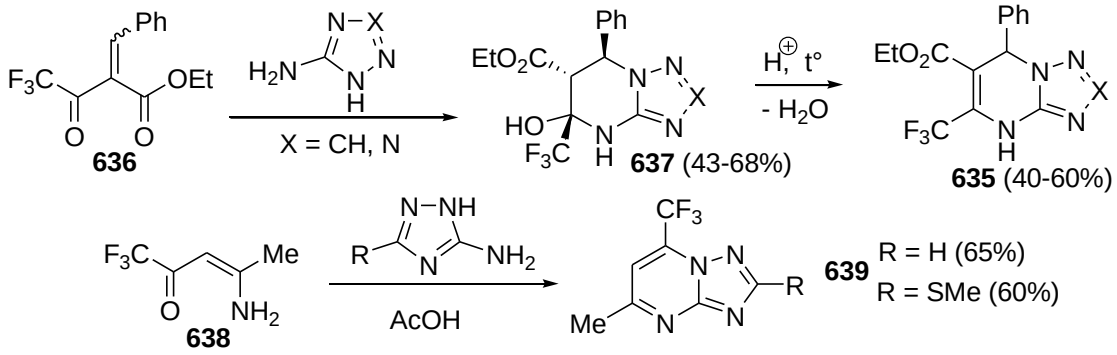
Scheme 180

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]



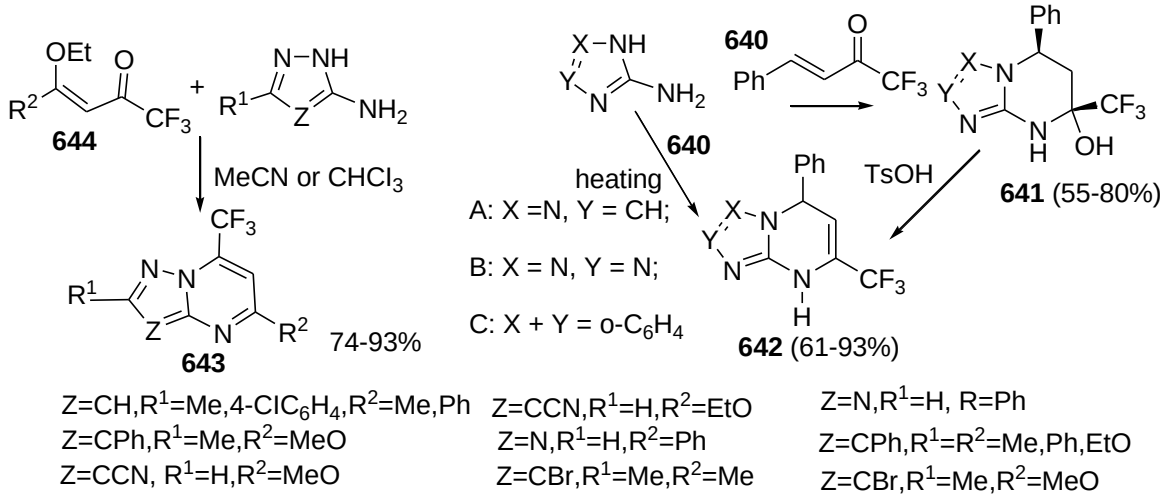
Scheme 181

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]



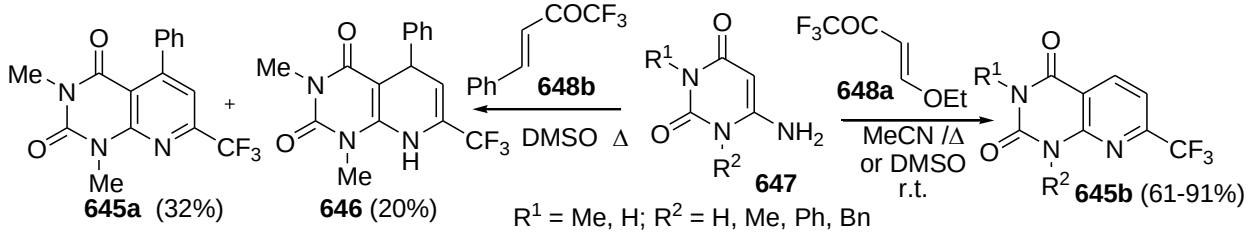
Scheme 182

The reaction of CF_3-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 CF_3- and Ph- groups.[192] An effective and regioselective method for the synthesis of 7-CF_3 substituted azolopyrimidines **643** from CF_3-ketones **644** with 5(3)-aminoazoles was proposed.[193]



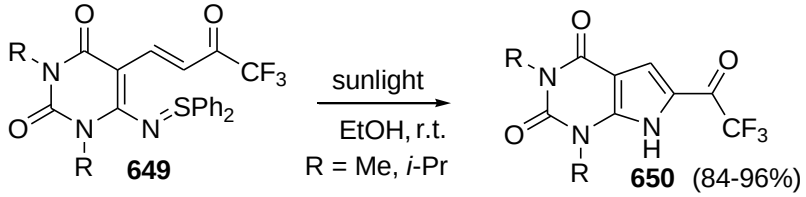
Scheme 183

The condensation of 6-aminouracil derivatives **647** and CF_3-enones **648** provides preparation of CF_3-derivatives of pyrido[2,3-d]pyrimidine **645a,b** and dihydro-derivative **646**.[194]



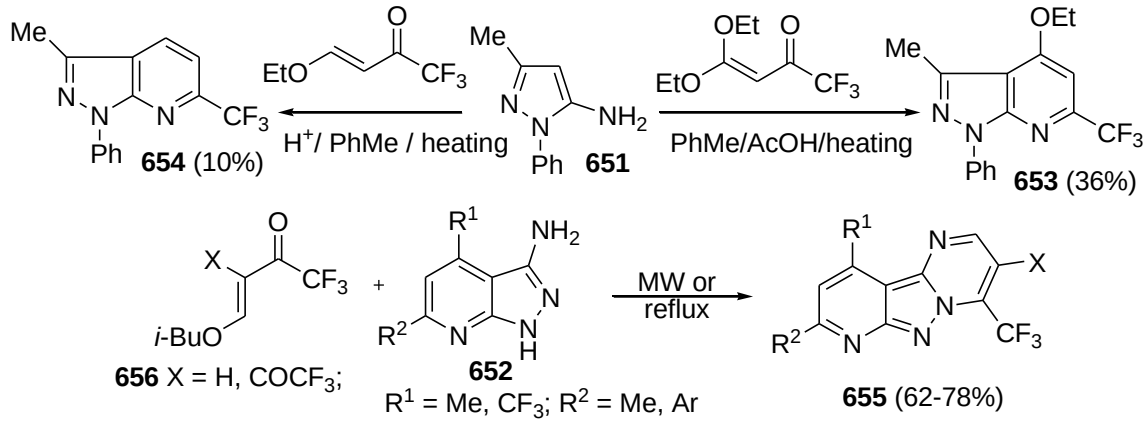
Scheme 184

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 CF_3-group.[53]



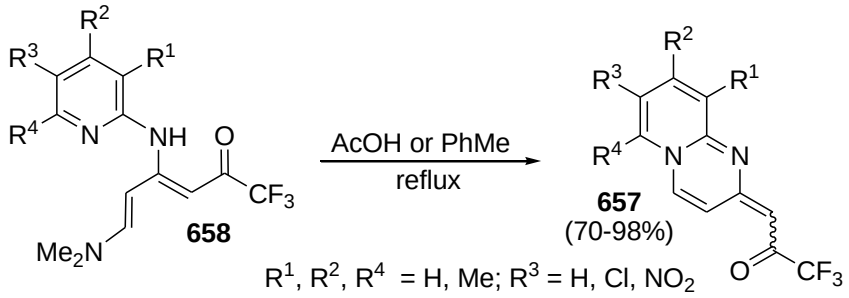
Scheme 185

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]



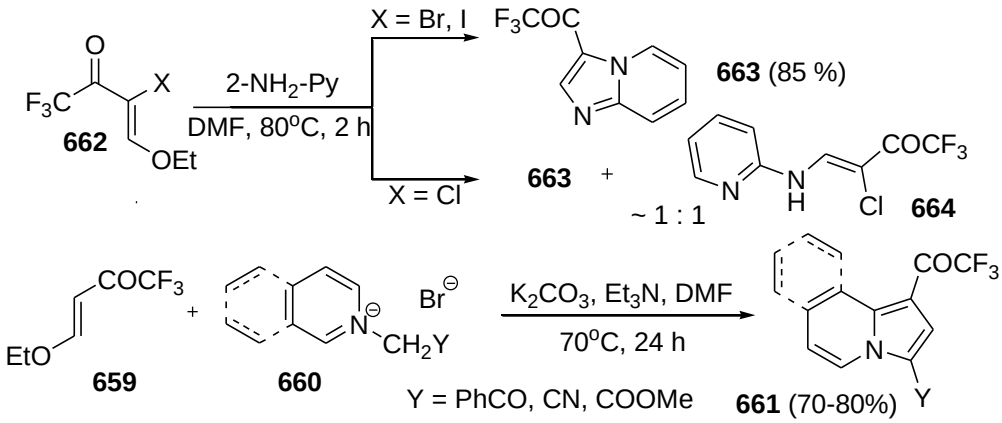
Scheme 186

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.[131b]



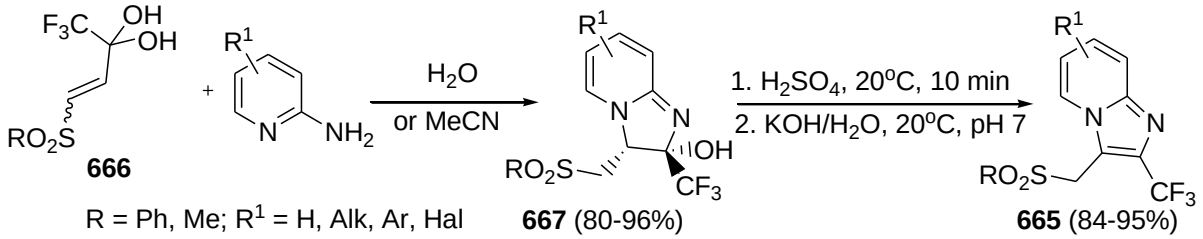
Scheme 187

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.[196]



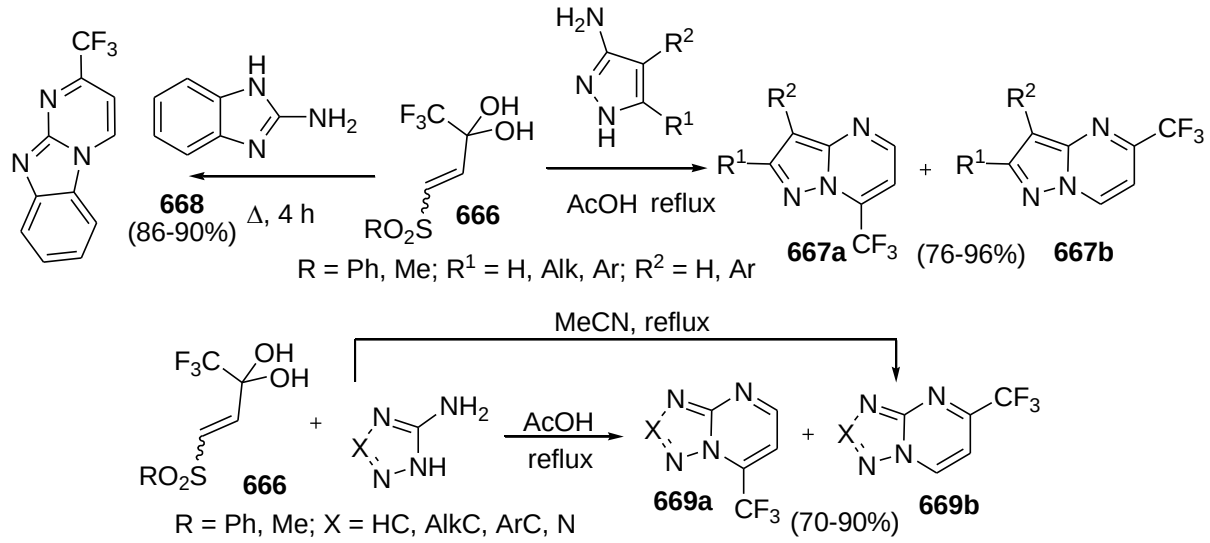
Scheme 188

The synthesis of imidazopyridines **665** using the reaction of **666** with several 2-aminopyridines was described. The reaction proceeds regio- and stereoselectively (the intermediate dihydro-derivatives **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]



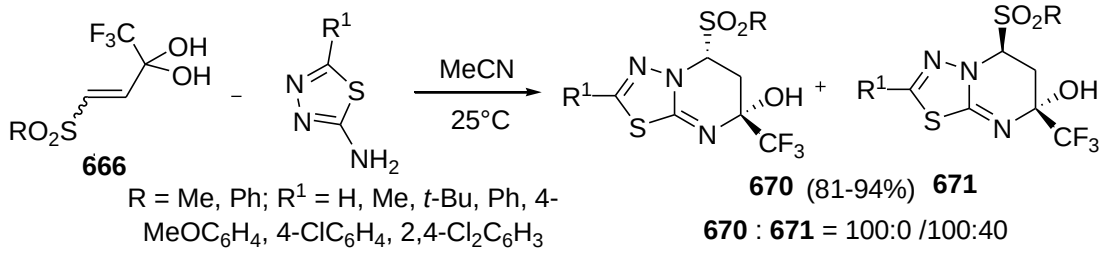
Scheme 189

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 **667**a. In several cases, the isomeric pyrazolopyrimidines **667b** were formed as the second product. Using aryl-substituted aminopyrazoles the reaction proceeded stereoselectively forming **667**a 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]



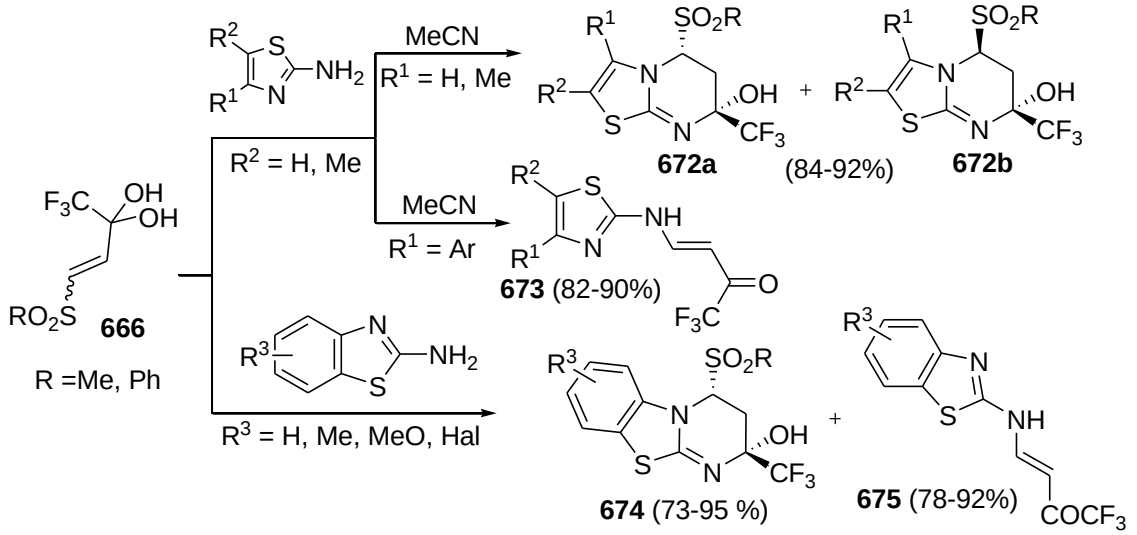
Scheme 190

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]



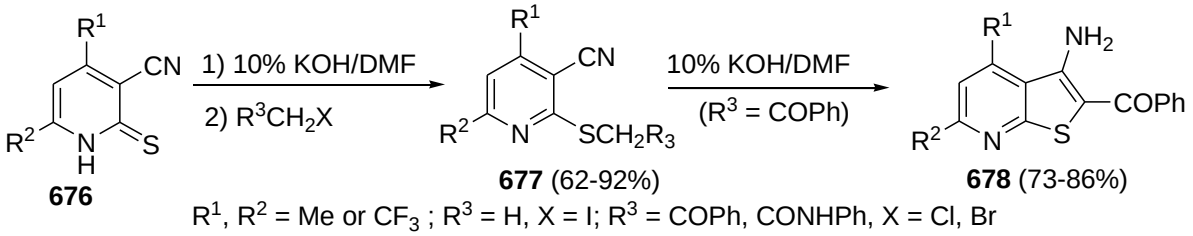
Scheme 192

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]



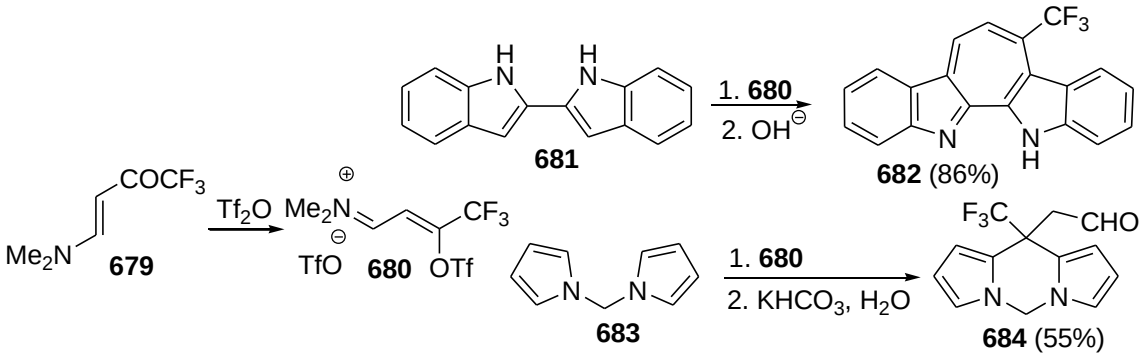
Scheme 193

The alkylation of pyridinethiones **676** with methyl iodide and ω-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'-dipyrylmethane **683** with **680** leads to aldehyde **684** formation.[202]



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

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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.

