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Methods for the synthesis of α,β-unsaturated trifluoromethyl ketones and their use in organic synthesis

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Abstract. Published data on the methods of synthesis and properties of α,β-unsaturated trifluoromethyl-containing ketones are surveyed and described systematically. Primary attention is devoted to the use of these compounds in organic synthesis as useful building blocks for the preparation of various compounds bearing a trifluoromethyl group. The bibliography includes 133 references.

I. Introduction

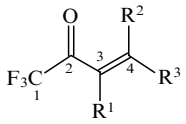
Organofluorine chemistry has been vigorously developing during the last two decades. A large number of studies have been devoted to modification of natural products by introduction of a fluorinated or perfluorinated substituent.[1–3] These fluorinated derivatives often exhibit biological activities; some heterocyclic compounds containing a trifluoromethyl group have already found wide use as medicines (for example, triftazine, trifluorothymidine).[4] α,β-Unsaturated trifluoromethyl ketones (trifluoromethyl α,β-enones) are fairly convenient building blocks for preparing heterocycles with a trifluoromethyl group. Most of the known approaches to the synthesis of these heterocycles suffer from serious drawbacks, associated either with the fact that the initial compounds are rather difficult to obtain or with the fact that they are fairly toxic and inconvenient to work with.[1–3] Thus, development of methods for the synthesis and study of properties of trifluoromethyl α,β-enones present substantial interest and have been in the centre of attention of many researchers in recent years.

In this review, we survey methods for the synthesis of α,β-enones with a trifluoromethyl (perfluoroalkyl) substituent at the carbonyl group, because these enones are used in organic synthesis much more often than those containing a CF_3 group at other positions.[5,6]

II. Methods for the synthesis of α,β-unsaturated trifluoromethyl ketones

Although the first α,β-unsaturated trifluoromethyl ketones were synthesised almost 40 years ago, the vigorous development of the methods for their synthesis has started only in the last decade. As a rule, they cannot be prepared by the same procedures as non-fluorinated α,β-enones.

Five possible approaches to the construction of the carbon skeleton of trifluoromethyl α,β-enones can formally be proposed. Four approaches are based on the formation of C(1) – C(2), C(2) – C(3), C(3) = C(4) and C(4) – R^3 bonds and one is based on transformations resulting in the appearance of a carbonyl group.



Analysis of published data shows that the following principal methods for the synthesis of trifluoromethyl α,β-enones exist.

— Trifluoroacetylation (for example, of alkenes, their organometallic derivatives or compounds generating alkenes *in situ*) to give a C(2) – C(3) bond.

— Condensation of 1,1,1-trifluoroacetone and its derivatives with aldehydes and the formation of the C(3) – C(4) double bond in an elimination reaction.

— Addition to alkynyl ketones (α,β-ynones) or to enones containing a β-substituent capable of being replaced (most often, an alkoxy group), and replacement of one carbonyl group in β-diketones containing a perfluoroalkyl substituent [formation of the C(4) – R^3 bond]. In this case, examples described in the literature include formation of both C – C and C – heteroatom bonds.

— Addition of perfluoroalkyl organolithium compounds to esters of acrylic acid to give the C(1) – C(2) bond. This method is scarcely documented and has never been used for the preparation of trifluoromethyl α,β-enones. Apparently, this is due to the fact that synthesis of perfluorinated organolithium compounds requires the use of perfluoroalkyl iodides, which are toxic and difficult to work with (especially, trifluoromethyl iodide).[3]

— Oxidation of allyl alcohols, which are synthesised using perfluorinated or vinylic organometallic compounds, yielding a C = O group. This approach also has not found wide use.

Below, we consider all the above methods for the synthesis of α,β-unsaturated trifluoromethyl ketones in the same order.

1. Trifluoroacetylation of alkenes

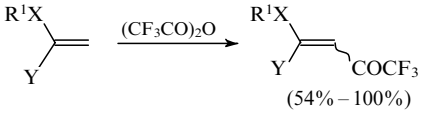
a. Trifluoroacetylation of electron-rich alkenes by trifluoroacetic anhydride

Trifluoromethyl α,β-enones are formed upon trifluoroacetylation of activated alkenes by trifluoroacetic anhydride (or other derivatives of trifluoroacetic acid) at room temperature or on

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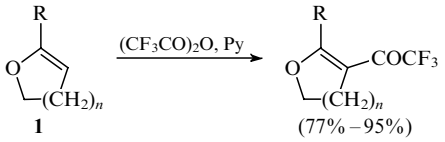
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cooling. The reaction is often carried out in the presence of pyridine, which increases the yield.



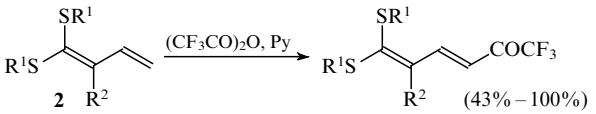
Y = H, Alk, Ar, SAr; X = O, S, Te, NSO_2R^2, $NCOR^3$;
R^1, R^2, R^3 = Alk, Ar.

Activated alkenes can be represented by vinyl ethers [7] (including cyclic ones such as **1**),[8,9] vinyl sulfides,[10] ketene dithioacetals,[10] vinyl tellurides,[11] vinylamides,[7] cyclic enamines [12,13] and activated dienes such as 1,1-bis(alkylthio)alka-1,3-dienes **2** or *N*-acetyl-*N*-isopropyl-1-aminobuta-1,3-diene **3**.[14]



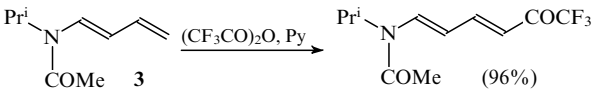
1

R = H, Me; n = 1, 2.



2

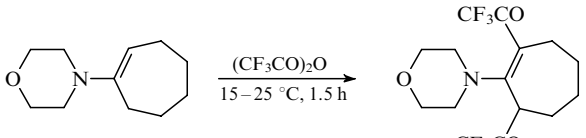
R^1 = Alk; R^2 = H, Et.



3

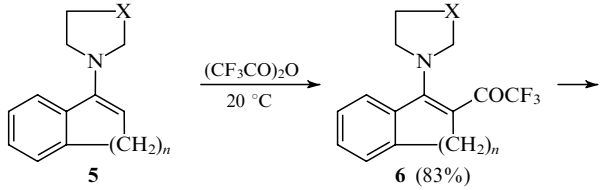
Trifluoroacetylation of vinyl ethers, vinylamides and 1,1-bis(alkylthio)alka-1,3-dienes **2** occurs stereospecifically yielding thermodynamically more favourable *E*-isomers of trifluoromethyl α,β-enones. Trifluoroacetylation of vinyl tellurides gives rise to *Z*-isomers, because they are stabilised by an O – Te coordinate bond (X-ray diffraction data [11]). Vinyl sulfides are trifluoroacetylated non-stereoselectively. According to the ^{1}H NMR spectra and data on the reaction kinetics,[15,16] this process follows an addition – elimination mechanism. Trifluoroacetylation of vinyl ethyl ether gives polymers as side products.[16] In the absence of pyridine, the highest yield (59%) was attained when the reaction was carried out in chloroform.

Trifluoroacetylation of cyclic enamines, for example, 1-morpholinocyclopent-1-ene (or 1-morpholinocyclohex-1-ene), affords a complex mixture of products. In the case of less reactive 1-morpholinocyclohept-1-ene, doubly trifluoroacetylated product **4** was isolated.[12]

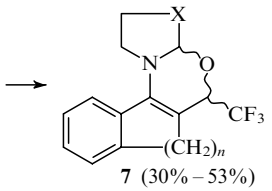


4 (57%)

Enamines **5**, derived from indene, dihydronaphthalene and benzocycloheptene, react ambiguously with trifluoroacetic anhydride. Depending on the structure of the initial enamine, either trifluoromethyl enamino ketones **6** or products of their cyclisation, oxazine derivatives **7**, can be isolated.



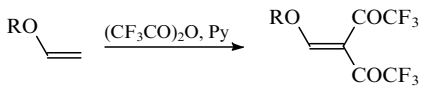
5 **6** (83%)



7 (30% – 53%)

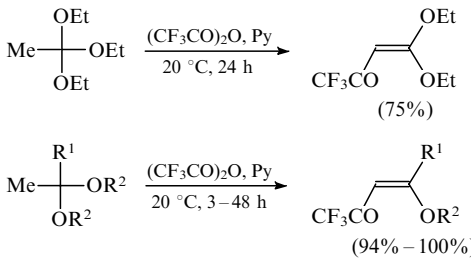
X = CH_2, $(CH_2)_2$, OCH_2; n = 1 – 3.

The reactions of vinyl ethers with a threefold excess of trifluoroacetic anhydride in the presence of pyridine result in the formation of 3-(alkoxymethylidene)-1,1,1,5,5,5-hexafluoropentane-1,3-diones in high yields.[17]

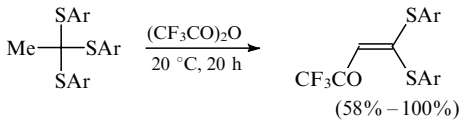


R = Et, Bu^i.

Orthoacetates, acetals [18] and trithioorthoacetates [19] react with excess trifluoroacetic anhydride with elimination of alkyl or aryl trifluoroacetate (thioacetate) to give trifluoromethyl enones, *i.e.*, they are precursors of the corresponding activated alkenes. It should be noted that only trifluoroacetic and trichloroacetic anhydrides enter into this reaction, whereas acetic anhydride does not.

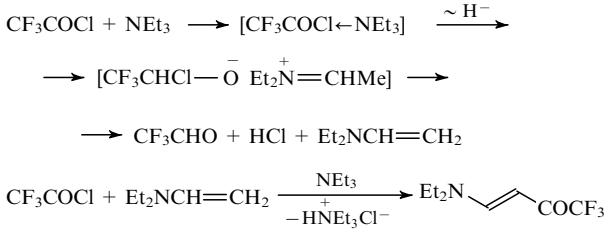


R^1 = Me, Ph; R^2 = Me, Et.



b. Trifluoroacetylation of tertiary amines

When trialkylamines are made to react with trifluoroacetic anhydride or trifluoroacetyl halides, β-dialkylamino-substituted trifluoromethyl enones are formed. The reaction of two equivalents of triethylamine with trifluoroacetyl chloride at −30 °C gives rise to 4-diethylamino-1,1,1-trifluorobut-3-en-2-one (in 18% yield based on the initial trifluoroacetyl chloride).[20] The reaction mechanism proposed in the study cited [20] includes oxidation of triethylamine by one equivalent of trifluoroacetyl chloride to give diethyl(vinyl)amine. Trifluoroacetyl chloride is reduced simultaneously to fluoral. The subsequent interaction of diethyl(vinyl)-amine with a second equivalent of trifluoroacetyl chloride results in the formation of the corresponding enaminone.



It has been found [21] that the reaction of triethylamine or ethyldiisopropylamine with an equimolar amount of trifluoroacetic anhydride at 0 °C gives rise to doubly trifluoroacetylated

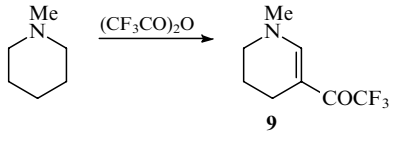
products **8a**,**b** (yield ~25%), in conformity with the reaction stoichiometry

$$4\,R_2NEt + 4\,(CF_3CO)_2O \longrightarrow$$

$$\longrightarrow R_2N\!\!=\!\!C(COCF_3)_2 \;(\mathbf{8a,b}) + CF_3CH(OCOCF_3)_2 + 3\,R_2Et\overset{+}{N}HCF_3CO_2^-$$

R = Et (**a**), Pr^i (**b**).

Cyclic amines react in a similar way. For example, *N*-methylpiperidine is converted into the corresponding enaminone **9** in 96% yield (with allowance for the degree of conversion of the starting amine).



9

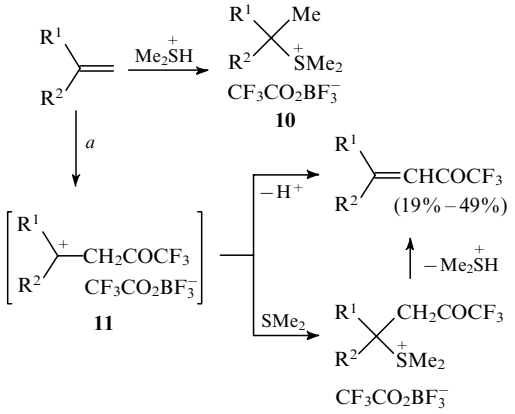
Some alkaloids containing tertiary nitrogen atoms enter into similar reactions with trifluoroacetic anhydride. They are oxidised and the resulting enamine fragment is then trifluoroacetylated.[22]

c. Trifluoroacetylation of non-activated alkenes

The electrophilicity of trifluoroacetic anhydride and other derivatives of trifluoroacetic acid is insufficient for trifluoroacetylation of non-activated alkenes. The attempts to increase the reactivity of these reagents by complex formation with Lewis acids prove successful only for acylation of aromatic compounds. Unsaturated substrates undergo cationic polymerisation under these conditions. The use of acylium salts for the acylation of unsaturated compounds would permit conducting the reaction at low temperatures and thus diminish the probability of polymerisation and other side processes. Unfortunately, acylium salts with a perfluoroalkyl radical are unstable and decompose with decarbonylation during their attempted synthesis.[23,24]

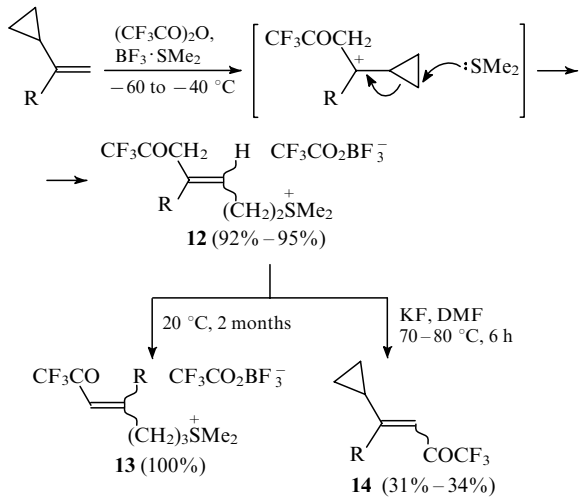
$$R_FCOF + AgSbF_6 \longrightarrow [R_FCO^+SbF_6^-] \longrightarrow R_FF + SbF_5 + CO$$

A new method for direct electrophilic trifluoroacetylation of non-activated alkenes has been proposed.[25] The method is based on the use of trifluoroacetic anhydride in the presence of a complex of dimethyl sulfide with boron trifluoride. This reagent is more electrophilic than trifluoroacetic anhydride, which reacts only with alkenes activated by a heteroatom at the double bond. However, the use of the complex $BF_3\cdot SMe_2$ has a drawback; acylation of an equivalent of an alkene results in the liberation of protonated dimethyl sulfide, which then reacts with at least one more equivalent of the alkene to give sulfonium salt **10**. Consequently, the yield of vinyl trifluoromethyl ketones does not exceed 50%. This reaction proceeds with alkenes able to form benzylic, allylic or tertiary cations (of the type **11**); however, in the last-mentioned case, mixtures of α,β- and β,γ-enones are formed.[26,27]



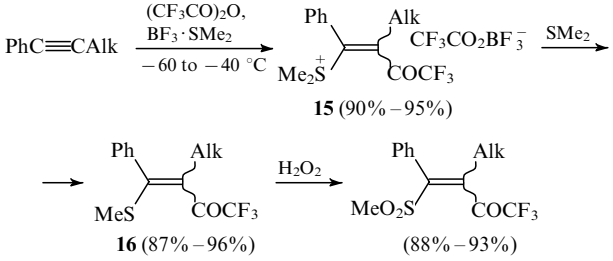
(*a*) $(CF_3CO)_2O$, $BF_3\cdot SMe_2$, −60 to −30 °C.

Cyclopropyl-substituted alkenes enter into a similar reaction.[28,29] The reaction of 2-cyclopropylpropene and 1,1-dicyclopropylethene with trifluoroacetic anhydride in the presence of $BF_3\cdot SMe_2$ follows an unusual route and results in cyclopropane ring opening to give sulfonium salts **12**.[29] The salts **12**, which are β,γ-unsaturated ketones, rearrange spontaneously into α,β-enones **13** (2 months, ~20 °C) in a quantitative yield. In the presence of a base (KF, DMF), the sulfonium salts **12** undergo cyclisation in which the dimethylsulfonium group is intramolecularly substituted to give α,β-enones with a cyclopropyl substituent **14**.

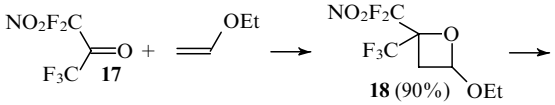


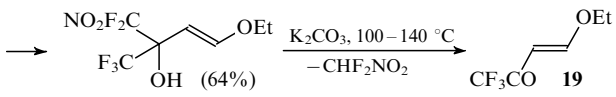
R = Me, cyclo-C_3H_5.

In the presence of the complex $BF_3\cdot SMe_2$, trifluoroacetic anhydride trifluoroacylates alkynes with a phenyl substituent at the triple bond. The reactions afford sulfonium salts **15** as a result of conjugate addition of the CF_3CO group and dimethyl sulfide to the alkyne molecule.[30] The demethylation of these salts upon the reaction with dimethyl sulfide results in the formation of trifluoromethyl α,β-enones **16**. Oxidation of the enones **16** by hydrogen peroxide makes it possible to synthesise unsaturated compounds with two electron-withdrawing substituents at the double bond, namely, sulfonyl and CF_3CO groups.

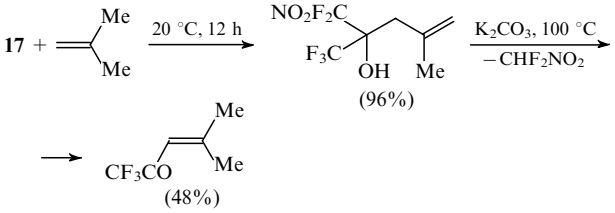


The reactions of pentafluoronitroacetone **17** with vinyl ethyl ether,[31] ketene diethyl acetal[32] or isobutylene[33] give rise to products similar to those formed upon trifluoroacetylation of alkenes with trifluoroacetic anhydride. The reaction with activated alkenes follows a cycloaddition pathway. Thus the compound **17** and vinyl ethyl ether react at 0–5 °C to give oxetane **18**. Opening of the oxetane ring and subsequent thermolysis of the resulting alcohols in the presence of catalytic amounts of K_2CO_3 affords 4-ethoxy-1,1,1-trifluorobut-3-en-2-one **19** (yield 96%). Ketene diethyl acetal enters into a similar reaction with the compound **17** (at −30 °C), 4,4-diethoxy-1,1,1-trifluorobut-3-en-2-one being formed in 90% yield.



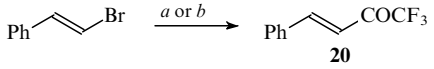


The reaction of pentafluoronitroacetone **17** with isobutylene yields an alcohol, which eliminates difluoronitromethane to give 4-methyl-1,1,1-trifluoropent-3-en-2-one.



d. Trifluoroacetylation of vinylic and allylic organometallic compounds

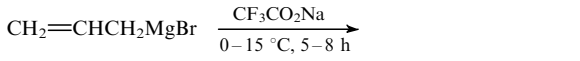
Trifluoroacetylated derivatives of non-activated alkenes can be prepared by acylation of vinylic organometallic compounds. The first trifluoromethyl-containing enone, 1,1,1-trifluoro-4-phenylbut-3-en-2-one **20**, was synthesised by the reaction of styrylmagnesium bromide with trifluoroacetic acid in 1959; however, the yield of the product was relatively low.[34] The subsequent studies showed that organolithium derivatives are better suited for the synthesis of trifluoromethyl enones; in this case, higher yields of the target products can be attained.[35] However, only one example of this type of synthesis is known to date; apparently, this is due to the fact that the corresponding vinyllithium derivatives are difficult to obtain.



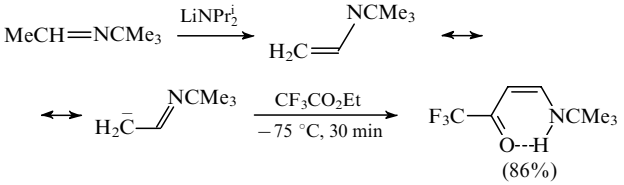
(*a*) Mg, Et_2O; CF_3COOH (yield 11%);

(*b*) Li, Et_2O; CF_3CON⟨⟩ (yield 63%).

Trifluoromethyl α,β-enones can also be prepared from allylic organometallic compounds. For example, the reaction of allylmagnesium bromide with sodium trifluoroacetate gives a mixture of the corresponding α,β- and β,γ-enones (ratio ~1 : 1) in an overall yield of 37%.[36]



When lithium diisopropylamide is made to react with *N*-ethylidene-*tert*-butylamine, a heteroallylic anion is formed; subsequent treatment of the anion with ethyl trifluoroacetate gives rise to 4-(*tert*-butylamino)-1,1,1-trifluorobut-3-en-2-one.[37]

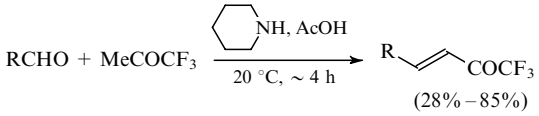


Reactions of other vinylic or allylic organometallic compounds with trifluoroacetic acid or its derivatives have not been studied.

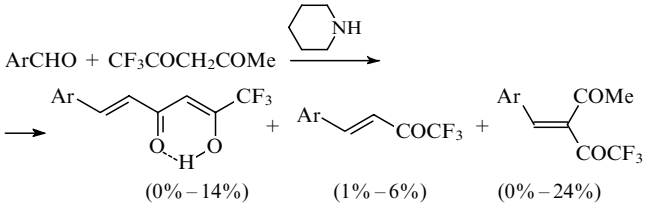
Thus, trifluoroacetylation of alkenes is a convenient method for the synthesis of trifluoromethyl enones; however, it is applicable only to alkenes containing either an activating group (*e.g.*, OR, SR, TeR, NR_2) or, at least, a phenyl, vinyl or cyclopropyl substituent or two alkyl substituents (trifluoroacetylation in the presence of $Me_2S \cdot BF_3$).

2. Condensation of 1,1,1-trifluoroacetone and its derivatives; construction of a double bond upon an elimination reaction

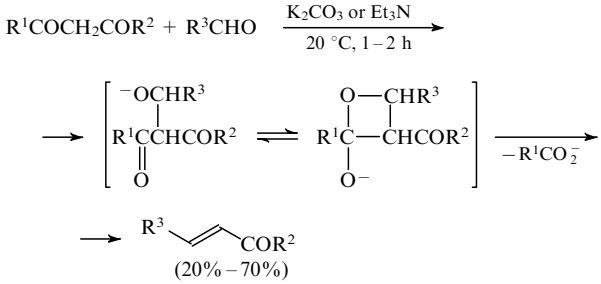
The condensation of 1,1,1-trifluoroacetone with aromatic or α,β-unsaturated aldehydes catalysed by the piperidine–acetic acid system in THF makes it possible to prepare trifluoromethyl-containing conjugated enones, dienones and polyenones (retinoids).[38,39] The reaction is stereospecific and gives *E*-isomers of enones. A drawback of this method is self-condensation of 1,1,1-trifluoroacetone during the reaction; therefore, it should be taken in more than 10-fold excess.



α,β-Unsaturated ketones are often prepared by condensation of β-dicarbonyl compounds with aldehydes and ketones (Knoevenagel condensation). However, β-dicarbonyl compounds containing a perfluoroalkyl substituent enter into this reaction with difficulty. Thus the reaction of aromatic aldehydes with 1,1,1-trifluoroacetylacetone yields a mixture of products resulting from condensation at the methyl and methylene groups in a relatively low yield.[40] This fact was explained by assuming that the addition of amine, used as the catalyst, to the initial 1,1,1-trifluoroacetylacetone is the predominant reaction route.

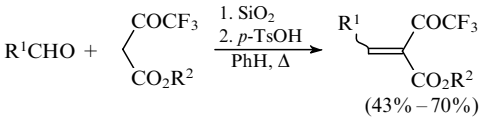


The reactions of β-diketones having one or two perfluoroalkyl groups with polyfluorinated aldehydes have also been studied.[41] In the case of β-diketones with one perfluoroalkyl group, the carbonyl group adjacent to the perfluoroalkyl substituent, being more active, participates in the formation of the cyclic intermediate. As a consequence, the elimination of a carboxylate anion gives rise to β-unsaturated ketones with a non-fluorinated substituent at the carbonyl group.



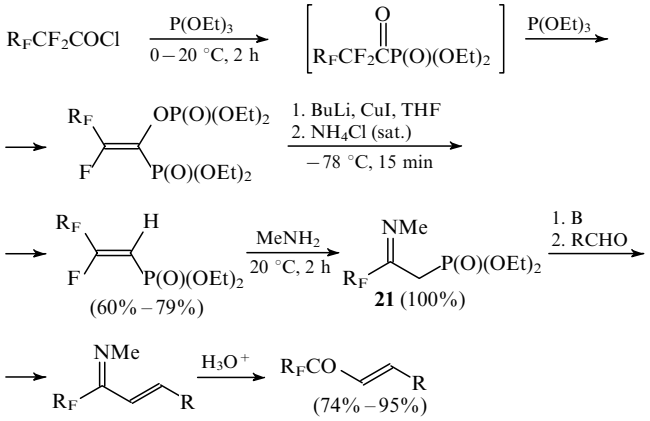
$R^1 = CF_3, H(CF_2)_n$; R^2 = Me, Ph, CF_3, $H(CF_2)_n$; $R^3 = H(CF_2)_n$.

When esters of trifluoroacetic acid are made to condense with aldehydes in the presence of traditional catalysts such as piperidine–AcOH, the target products are formed in fairly low yields.[42] Recently, it has been proposed to use functionalised silica gel [silica gel treated with (3-aminopropyl)triethoxysilane] as the catalyst with toluene-*p*-sulfonic acid being added subsequently to the reaction mixture. A mixture of *Z*- and *E*-isomers of alkoxycarbonyl-substituted trifluoromethyl α,β-enones was obtained in this way in a good yield.[42]



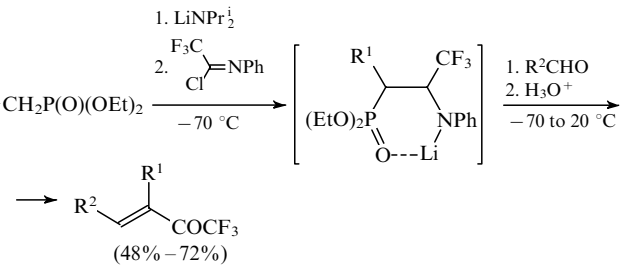
R^1 = Alk, Ar; R^2 = Et, Pr^i.

The Knoevenagel condensation of pefluoroalkyl-containing β-dicarbonyl compounds is often accompanied by side reactions (*e.g.*, self-condensation, in the case of 1,1,1-trifluoroacetone), the yields of the target products being relatively low. This fact has stimulated the search for new methods for their synthesis. For example, the reaction of β-iminophosphonate anions with aldehydes (the Horner–Emmons reaction), which yields perfluoroalkylated enones as the final products after acid hydrolysis, has been used for this purpose. Two approaches to the synthesis of β-iminophosphonates have been proposed. Perfluorocarboxylic acid chlorides can be converted *via* a four-stage procedure into compounds **21**, which are then treated with a base (*n*-butyllithium, lithium diisopropylamide or sodium hydride) and with an aldehyde.[43] Ketones do not enter into this reaction.



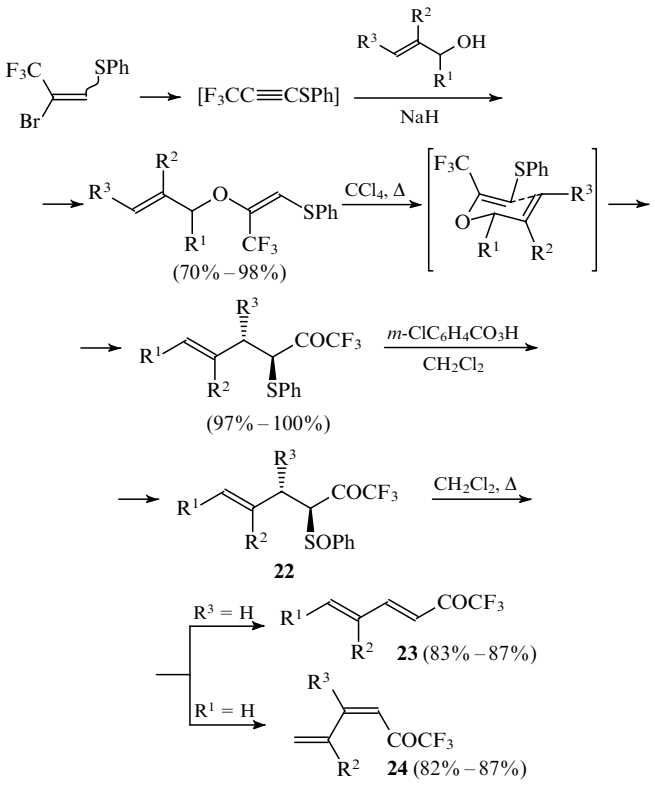
R_F = CF_3, C_2F_5, n-C_6F_{13}; R = Alk, Ph; B = Bu^nLi, $LiNPr^i_2$, NaH.

β-Iminophosphonate anions can also be obtained from diethyl alkylphosphonates and trifluoroacetoimidoyl chloride. The synthesis is carried out as a one-pot procedure; first, diethyl alkylphosphonates are treated with two equivalents of lithium diisopropylamide and then with trifluoroacetoimidoyl chloride; after that, the required aldehyde is added to the resulting β-iminophosphonate anion.[44]



R^1 = H, Me; R^2 = Alk, Ar.

A method for the synthesis of substituted trifluoromethyl dienyl ketones with a particular configuration at the double bond has been reported.[45] Thus sulfoxides **22** were prepared from 1-trifluoromethyl-2-phenylthioacetylene *via* a four-stage procedure (Claisen rearrangement is the key stage of the process). Subsequent elimination of sulfinic acid from the sulfoxides **22** gave trifluoromethyl dienyl ketones **23** and **24** in high yields.



R^1, R^2, R^3 = H, Alk, Ph.

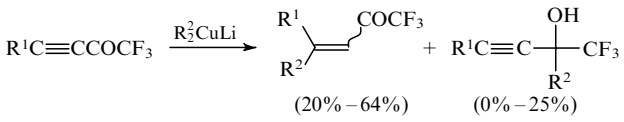
3. Addition to alkynyl ketones

Alkynyl trifluoromethyl ketones are easily available compounds, readily formed upon acylation of lithium or magnesium acetylides (Iotsitch reagents) with trifluoroacetic acid or its derivatives.[46–50] The best yields were attained in the reaction of lithium acetylides with ethyl trifluoroacetate in the presence of boron trifluoride etherate.[50]



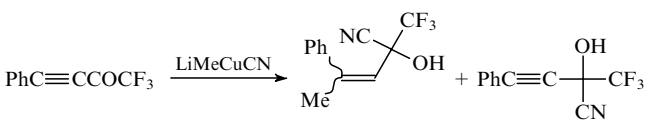
R = Alk, Ph.

A method for the synthesis of trifluoromethyl α,β-enones is based on 1,4-addition of dialkylcuprates to acetylenic ketones. This reaction is highly regioselective but it is not stereoselective and gives products in moderate yields.[50, 51]

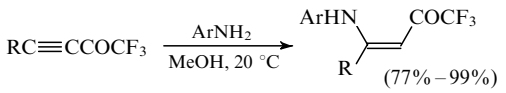


R^1 = Ph, Bu^n; R^2 = Me, Bu^n, Bu^t.

The use of cyanocuprates results in higher yields and in a nearly 100% regioselectivity of the reaction. However, in some cases (for example, in the case of 1,1,1-trifluoro-4-phenylbut-3-yn-2-one), cyanohydrins are produced.[51]

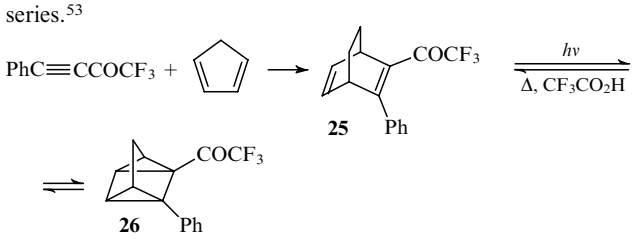


The reactions of alkynyl trifluoromethyl ketones with aromatic amines afford β-amino-substituted trifluoromethyl enones in good yields.[52]



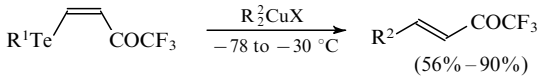
R = Alk, Ar.

Alkynyl trifluoromethyl ketones can act as dienophiles in the Diels–Alder reaction. 1,1,1-Trifluoro-4-phenylbut-3-yn-2-one reacts with cyclopentadiene to give bicyclic trifluoromethyl enone **25**, a norbornadiene derivative, which undergoes a reversible rearrangement to give compound **26** of the quadricyclane series.[53]



4. Addition to enones containing a replaceable group in the β-position

A method for the synthesis of trifluoromethyl enones based on the reactions of various zinc dialkyl- and diaryl-cuprates with β-trifluoroacetylvinyl tellurides has been proposed.[54]

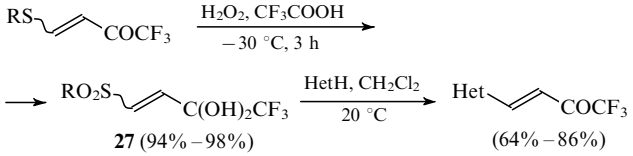


R^1 = Bu^n, Bu^i, Ph; R^2 = Ar, Alk; X = $(CN)(ZnCl)_2$, ZnCl.

However, in the case of zinc dialkylcuprates, the reaction is accompanied by side formation of the double addition products, $Alk_2CHCH_2COCF_3$, in 11%–19% yields. The necessity of using organotellurium compounds is also an obvious drawback of this method.

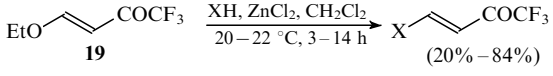
A new procedure for the synthesis of trifluoromethyl enones from β-trifluoroacetylvinyl sulfones **27** has been reported quite recently. The compounds **27** are formed as stable diols upon oxidation of trifluoroacetylated vinyl sulfides.[55]

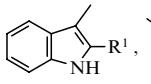
Thus β-trifluoroacetylvinyl sulfone **27** (R = Ph) reacts with electron-rich aromatic compounds (furans, indoles and pyrroles) to liberate sulfinic acid and to give aryl- and hetaryl-substituted trifluoromethyl α,β-enones.[55] The reaction is stereospecific yielding *E*-isomers of the enones.



R = Me, Ph.

β-Alkoxy-substituted trifluoromethyl enones (most often, 4-ethoxy-1,1,1-trifluorobut-3-en-2-one) are used as the starting compounds in a large number of syntheses. These compounds can be readily prepared by trifluoroacetylation of vinyl ethers.[56] Several studies consider the reactions of the enone **19** with diverse nucleophiles — electron-rich aromatic compounds, organometallic and organoboron compounds and amines. This reaction in the presence of zinc chloride can be carried out only for reactive aromatic compounds such as indoles, pyrroles[57,58] and *N*,*N*-dimethylaniline.[57]

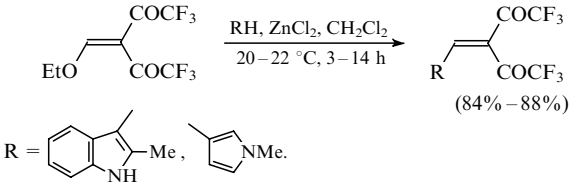


X = , , 4-$Me_2NC_6H_4$; R^1 = H, Me, Ph;

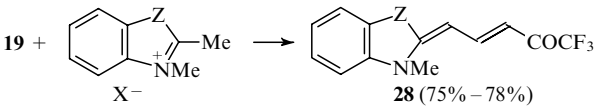
R^2 = H, Me.

Less reactive compounds such as anisole do not enter into this reaction, and the use of other Lewis acids (BF_3 or $TiCl_4$) results in resinification.[57] The reactions of the enone **19** with other heterocyclic compounds such as furan, 2-methylfuran and thiophene under the same conditions do not lead to the desired result either.[58]

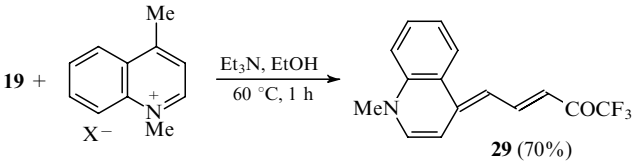
The reaction of 3-ethoxymethylidene-1,1,1,5,5,5-hexafluoropentane-1,3-dione with indoles and pyrroles occurs faster and gives products in higher yields.[58]



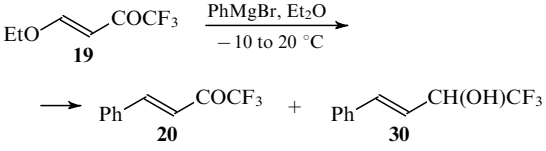
The enone **19** reacts with quaternary salts derived from nitrogenous heterocycles to give dienones — δ-trifluoromethylbutadienylmerocyanines **28** or **29**.[59]



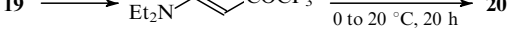
Z = S, Me_2C, CH=CH.



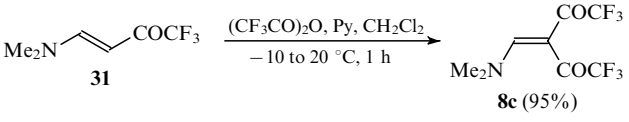
4-Butoxy-1,1,1-trifluorobut-3-en-2-one enters into a similar reaction. The enone **19** reacts with the phenylmagnesium bromide to give a mixture of β-trifluoroacetylstyrene **20** and allylic alcohol **30**, resulting from its reduction, in an overall yield of 40%–60%, the proportion of the alcohol **30** increasing with an increase in the reaction time.[57] The reaction of phenylmagnesium bromide with 4-diethylamino-1,1,1-trifluorobut-3-en-2-one, prepared from the enone **19**, occurs more unambiguously;[57] it gives only β-trifluoroacetylstyrene **20** in 53% yield.



Reaction time /h	2	20
The **20** : **30** ratio	1 : 1	1 : 7

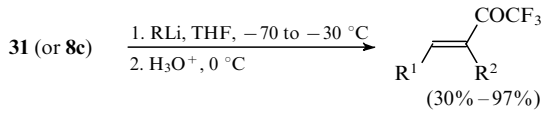


Recently, a new convenient and fairly versatile method for the synthesis of unsaturated trifluoromethyl ketones has been developed; this method is based on the reactions of various organolithium compounds with 4-dimethylamino-1,1,1-trifluorobut-3-en-2-one **31** and 3-(*N*,*N*-dimethylaminomethylidene)-1,1,1,5,5,5-hexafluoropentane-2,4-dione **8c**. The compound **8c** can be easily prepared by acylation of the enaminone **31** with trifluoroacetic anhydride in the presence of pyridine.[60]



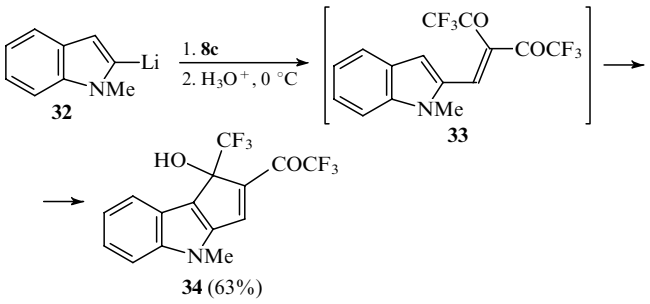
The reactions of the trifluoromethyl enaminones **31** and **8c** with organolithium compounds afford trifluoromethyl enones; in

the case of the enaminone **31**, the reactions are stereospecific and give only *E*-isomers of the enones.[60]

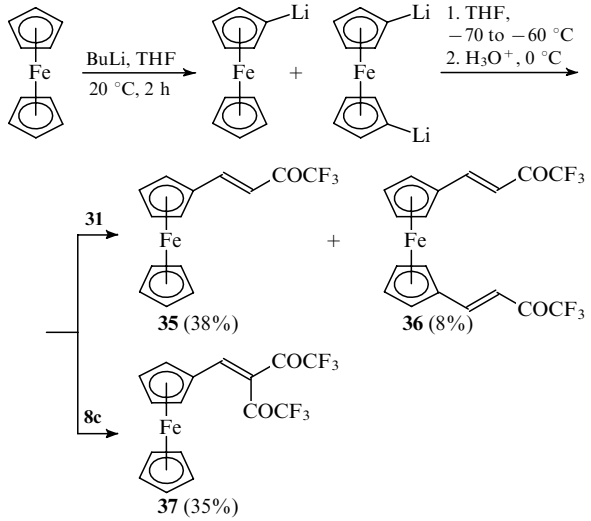


R^1 = Ar, Het; R^2 = H, $COCF_3$.

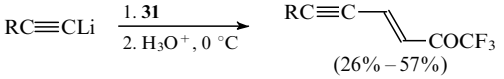
The reaction of enaminodione **8c** with 1-methyl-1*H*-2-indolyllithium **32** gives rise to the corresponding enedione **33** but does not stop at this stage; the subsequent cyclisation yields cyclopenta[*b*]indole derivative **34**.[60]



The same study [60] describes the reaction of the enaminone **31** with a mixture of lithiated ferrocenes, resulting in the formation of the corresponding mono- **35** and bis-enones **36**. In the case of the enaminodione **8c**, only the product of its interaction with monolithioferrocene, enedione **37**, was isolated.

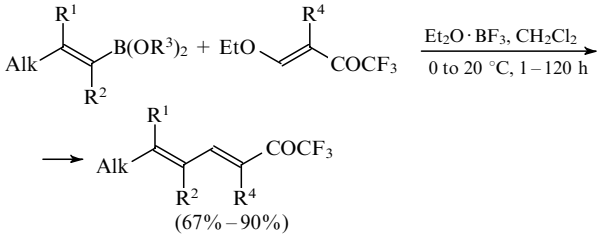


In order to synthesise conjugated trifluoromethyl enones containing an acetylenic fragment (enynones), which are promising from the synthetic point of view, a method based on the reaction of lithium acetylides with the enone **31** has been developed.[61] The reaction is stereospecific giving *E*-isomers of substituted trifluoromethyl enynones.

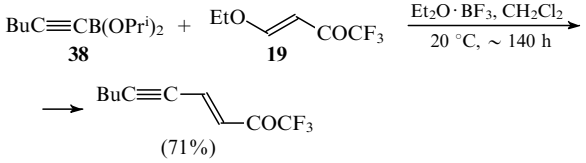


R = Alk, Ar, Me_3Si.

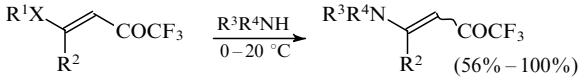
The reactions of various trifluoroacetylated vinyl ethers with organoboron compounds, which occur with high stereoselectivity (92%–98%) to give the *E*-isomers of the corresponding dienones, have been studied.[62,63] Thus the reaction of alkenyldialkoxyboranes with substituted vinylic ethers in the presence of boron trifluoride etherate affords the corresponding trifluoromethyl dienones.[62] Similarly, 6-butyl-1,1,1-trifluorohex-3-en-5-yn-2-one is formed in the reaction of alkynyldialkoxyborane **38** with the enone **19**.[63]



R^1 = H, Me, Ph, Br; R^2 = H, Br; R^3 = Et, Pr^i; R^4 = H, Me, Ph.

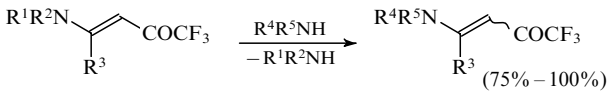


β-(Thio)alkoxy-substituted trifluoromethyl enones react with ammonia and primary and secondary amines (including aromatic ones) at room temperature to give β-amino-substituted enones (enaminones) in high (sometimes quantitative) yields.[64,65]



X = O, S; R^1 = Alk; R^2 = H, Me, Ph; R^3 = H, Alk; R^4 = H, Alk, Ar.

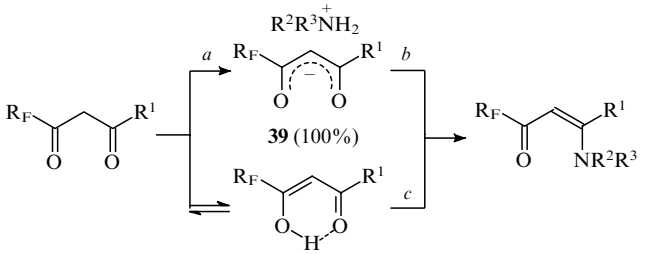
Diamines enter into a similar reaction. Thus symmetrical enaminones have been synthesised by the reaction of ethylenediamine and *o*-phenylenediamine with two molecules of β-ethoxy trifluoromethyl enone **19**.[64] The route of transamination in the series of β-amino-substituted enones does not depend on the nature of the solvent, being determined by the ratio of the initial reactants and the basicities of both the entering and leaving amines. The highest yields are attained when the amine entering into the reaction is more basic than the leaving one (for example, an amino group can easily be replaced by a dimethylamino or methylamino group but not *vice versa*). The reactions occur at room temperature and do not require a large excess of the amine used.[65,66]



R^1 = H, Alk; R^2, R^3 = H, Alk, Ph; R^4 = H, Alk; R^5 = Alk.

5. Preparation of trifluoromethyl ketones from β-diketones

Trifluoromethyl enaminones can be synthesised by the reaction of amines with β-diketones. When fluorinated β-diketones are made to react with ammonia,[67] ammonium acetate, ammonium hydrogen carbonate,[68] alkylamines or dialkylamines, stable salts **39** are initially formed. Refluxing of the salts **39** obtained from β-diketones having one trifluoromethyl (or perfluoroalkyl) substituent in benzene or toluene with azeotropic distillation of water affords β-amino-substituted enones in 12%–76% yields.[67]

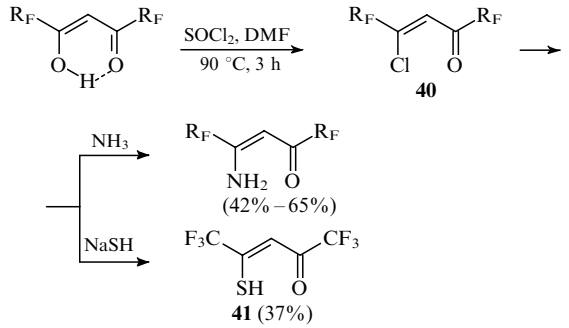


R_F = $H(CF_2)_n$ (*n* = 2, 4); R^1 = Alk, Ar;
(*a*) R^2R^3NH (R^2, R^3 = H, Alk), 20 °C; (*b*) PhH or PhMe, Δ;
(*c*) R^2R^3NH (R^2 = Ph, R^3 = H), MeOH, 20 °C.

In the case of low-basicity aromatic amines (*e.g.,* aniline), salts are not formed and the corresponding enamines are obtained by prolonged keeping of the initial compounds in polar solvents such as methanol at room temperature (yields 70% – 90%).[67]

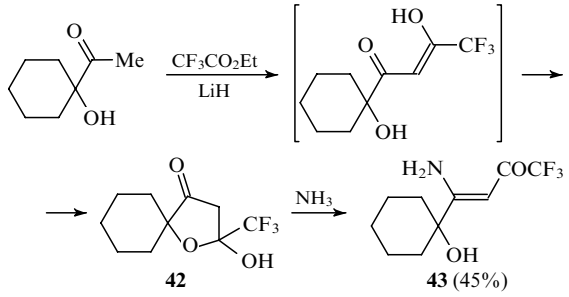
As a rule (or always if R^1 = Alk), this reaction gives enaminones in which the amino group is removed from the perfluoroalkyl substituent. Apparently, the electron-withdrawing influence of this group stabilises the *gem*-amino-alcoholic fragment and hampers elimination of water in the case where the amine has added at the carbonyl group adjacent to the perfluoroalkyl substituent.

β-Diketones having two perfluoroalkyl substituents react with amines, including aromatic ones, to give stable salts, which cannot be converted into the corresponding amino-substituted enones.[69] However, these enones can be obtained by the reaction of ammonia or aliphatic amines with fluorine-containing β-chlorovinyl ketones **40**.[70,71] The compounds **40** are formed in the 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 – $(COCl)_2$].[71–74] This approach has also been used to synthesise hexafluoromonothioacetylacetone **41**, which exists in the enol form.[72]

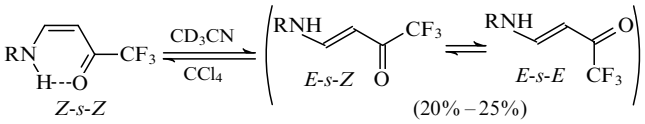


$R_F = H(CF_2)_n$.

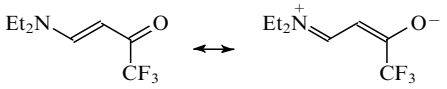
Similarly, treatment of hydroxytetrahydrofuranone **42** — the hemiketal form of a diketone — with ammonia is accompanied by opening of the furan ring and gives rise to the corresponding hydroxy enamino ketone **43**.[75]



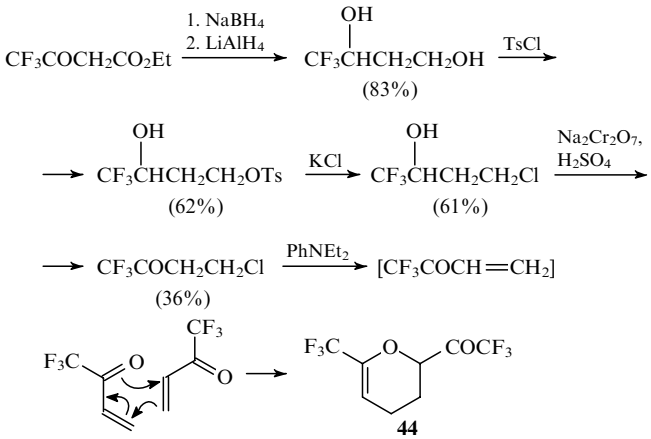
The structure and the stereochemistry of β-amino-substituted trifluoromethyl enones were studied by NMR and IR spectroscopy.[64,76] The configuration of their molecules was found to depend on the nature of the amino substituent. Trifluoromethyl enaminones with NH_2, AlkNH or ArNH groups in non-polar solvents or neat exist entirely as *Z*-isomers, which is apparently due to the presence of an intramolecular hydrogen bond. In polar solvents such as acetonitrile, an equilibrium between the *Z*- and *E*-isomers is established.



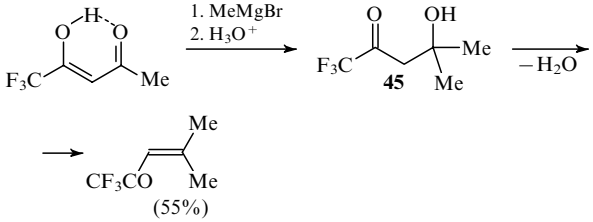
β-Dialkylamino-substituted enones always exist as *E*-isomers. Their ^{1}H NMR spectra exhibit two pairs of signals corresponding to the diethylamino group, which seems to be due to the hindrance of its rotation around the C(4) – N bond caused by conjugation.[64]



An attempt has been made[77] to prepare unsubstituted perfluoroalkyl enone — trifluoromethyl vinyl ketone — from ethyl trifluoroacetoacetate. The researchers found that this enone (like other unsubstituted perfluoroalkyl vinyl ketones) dimerises spontaneously at temperatures above −30 °C to give dihydropyran derivative **44**.

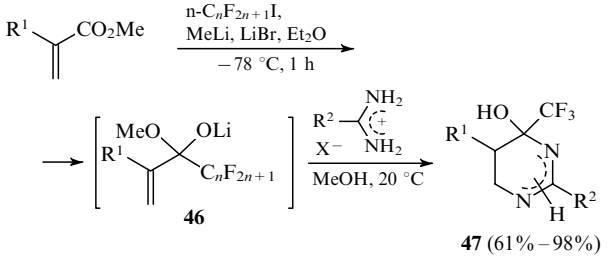


When two moles of methylmagnesium bromide are made to react with one mole of trifluoroacetylacetone, methylmagnesium bromide adds to the trifluoroacetylacetone anion formed initially (mostly at the carbonyl group further removed from the CF_3 substituent). The resulting tertiary alcohol **45** is readily dehydrated (to a large extent, during the hydrolysis) to give 1,1,1-trifluoro-4,4-dimethylbut-3-en-2-one.[78]



6. Addition of perfluoroalkyl organolithium compounds to acrylic esters

Perfluoroalkyl organolithium compounds, generated by the reaction of perfluoroalkyl iodides with methyllithium (transmetallation reaction), react with methyl acrylate or methyl methacrylate to give perfluoroalkyl enones, which exist in the reaction medium as anions of the corresponding hemiacetals **46**. Pefluoroalkyl α,β-enones having no substituents at the β-position are unstable and readily dimerise to give dihydropyran derivatives. Therefore, the hemiacetals **46** were introduced without isolation in reactions with isothiouronium salts or amidines, giving 4-perfluoroalkyltetrahydropyrimidines **47** in good yields.[79]

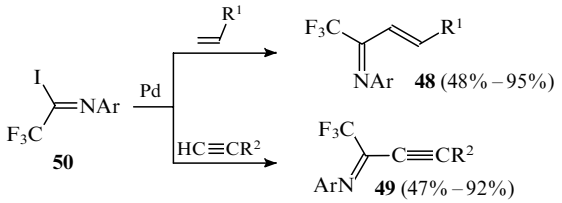


R^1 = H, Me; R^2 = AlkS, Me, Ph; X = I, Cl; n = 2, 4, 6, 8.

This method has not been used to prepare trifluoromethyl enones, probably, because trifluoromethyl iodide is a toxic gaseous compound, inconvenient to work with.[3]

7. Palladium-catalysed reactions

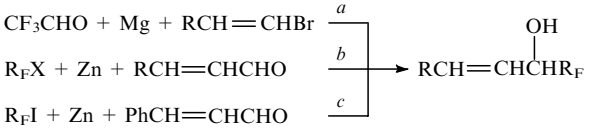
Imino-derivatives of alkenyl (**48**) and alkynyl (**49**) trifluoromethyl ketones can be synthesised by condensation of trifluoroacetimidoyl iodides **50** with various alkenes and alkynes in the presence of a palladium catalyst; no elimination of fluorine, typical of this type of reaction, occurs.[80] The reaction is carried out under mild conditions, alkynes reacting much faster and at lower temperatures than alkenes.



R^1 = CO_2Me, Ph, CN, SO_2Ph, C_6H_{13};
R^2 = Ph, CO_2Me, CO_2Et, C_6H_{13}, CH_2OCOPh.

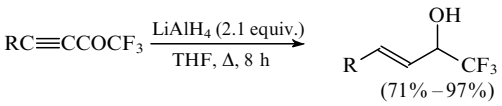
8. Oxidation of allyl alcohols

Perfluoroalkyl-containing allyl alcohols can be synthesised in two ways, namely, by the addition of vinyl-containing organometallic reagents to fluoral[81] or to another perfluorinated aldehyde or by the addition of perfluoroalkyl organometallic compounds to α,β-unsaturated aldehydes.[82,83] In both cases, the corresponding halide and the metal are directly introduced in the reaction, because perfluoroalkyl organometallic compounds are unstable and vinyl organometallic compounds are usually formed in low yields. To increase the yield of perfluoroalkyl-containing allylic alcohols, ultrasonic treatment (yield 40% – 70%)[82,83] and catalysis by palladium or nickel complexes (yield 19% – 62%)[83] have been employed.



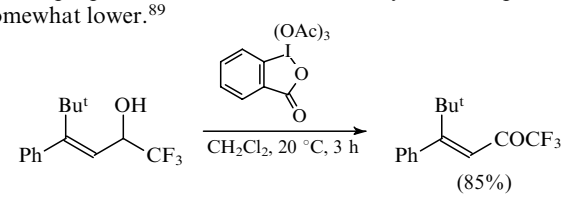
R = H, Me, Ph, Me_3Si; R_F = CF_3, C_2F_5, C_3F_7; X = Br, I;
(*a*) ultrasound, THF, 20 °C, 3 h; (*b*) ultrasound, DMF, 100 °C, 1 h;
(*c*) $(Ph_3P)_2PdCl_2$ or $(Ph_3P)_2NiCl_2$, DMF, 20 °C, 3 – 4 h.

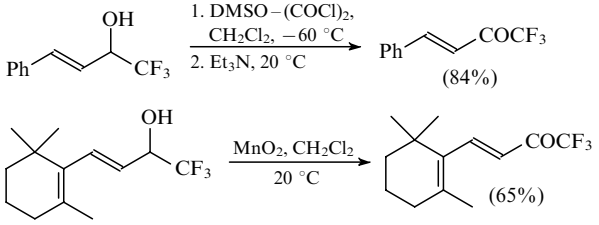
In addition, trifluoromethyl-containing allylic alcohols have been prepared by the reduction of alkynyl ketones with lithium tetrahydroaluminate.[84] The reaction is stereospecific and gives the alcohols as *E*-isomers.



R = C_nH_{2n+1} (n = 4 – 16), $Ph(CH_2)_2CH(OSiMe_2Bu^t)$.

Trifluoromethyl-containing allylic alcohols can be oxidised into the corresponding enones on treatment with the Dess – Martin reagent[84 – 87] or Swern reagent[88] (DMSO – oxalyl chloride – triethylamine). Manganese dioxide in CH_2Cl_2 was also used for this purpose; however, in this case, the yield of the product was somewhat lower.[89]





Thus, despite the high yields of the target enones, this method is limited due to the poor accessibility of the initial allylic alcohols and has not found wide use.

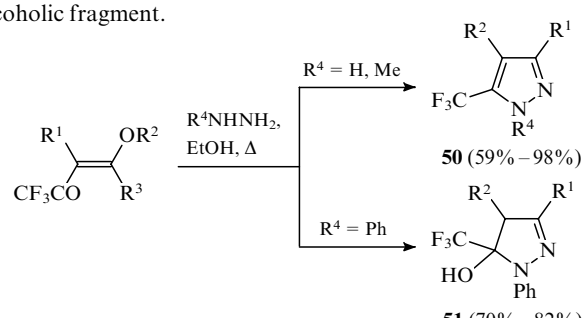
III. The use of α,β-unsaturated trifluoromethyl ketones in organic synthesis

The first example of using a trifluoromethyl enone (β-trifluoroacetylstyrene) for the synthesis of pyrazolines dates back to 1959;[34] however, vigorous studies along this line started in the last decade. Trifluoromethyl α,β-enones are usually employed to prepare heterocyclic compounds. Attempts to use them for other purposes, for example, as protective reagents in peptide synthesis, have also been made (see below). All trifluoromethyl enones can be divided into two main types: (a) enones containing a group capable of being substituted (*e.g.*, OR, SR, NR_2) in the β-position and (b) enones without such group. β-Alkoxy- and β-amino-substituted trifluoromethyl enones as well as alkynyl trifluoromethyl ketones (α,β-ynones) have found the widest application. Below we consider the use of these compounds in organic synthesis, except for their use to prepare trifluoromethyl-containing enones from acetylenic ketones and enones of type (a), which is described in Section II.3.

1. Reactions of β-alkoxy-substituted enones and acetylenic ketones

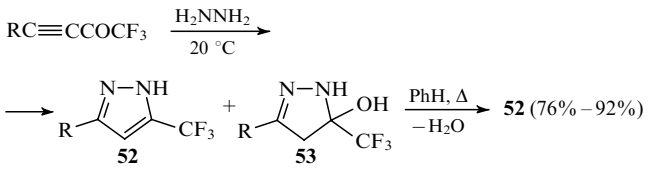
Enones containing a β-alkoxy group (trifluoroacetylated vinyl ethers) and alkynyl trifluoromethyl ketones are readily available reagents (see Sections II.1 and II.3). Their reactions with various nucleophiles are widely used to synthesise five-, six- and seven-membered heterocycles and other compounds containing a CF_3 group.

Hydrazine and methylhydrazine react with β-alkoxy-substituted trifluoromethyl enones to give trifluoromethyl-containing pyrazoles **50**.[61,90] The reaction of trifluoromethyl enones with phenylhydrazine affords pyrazolines **51**. On treatment with sulfuric acid, the compounds **51** are not dehydrated.[90] Apparently, the conjugation of the nitrogen lone electron pair with the benzene ring hampers aromatisation. In addition, the electron-withdrawing influence of the CF_3 group stabilises the *gem*-amino-alcoholic fragment.

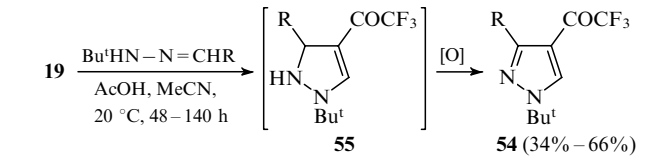


R^1, R^3 = H, Me; R^2 = Me, Et.

The reaction of alkynyl trifluoromethyl ketones with hydrazine at room temperature gives rise to a mixture of pyrazoles **52** and pyrazolines **53**. Subsequent refluxing of the reaction mixture in benzene with azeotropic distillation of water affords only pyrazoles **52** in good yields.[91]



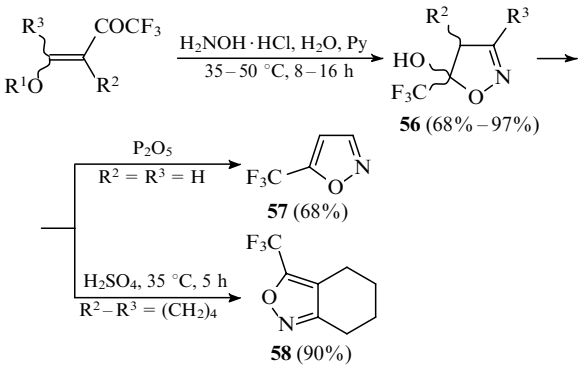
tert-Butylhydrazones of aldehydes react with β-ethoxy enone **19** giving rise to 4-trifluoroacetylpyrazoles **54**. A possible mechanism of this reaction includes replacement of the ethoxy group by the hydrazone. The subsequent cyclisation affords pyrazolines **55**, which are oxidised to pyrazoles by atmospheric oxygen.[92]



R = Et, Ar.

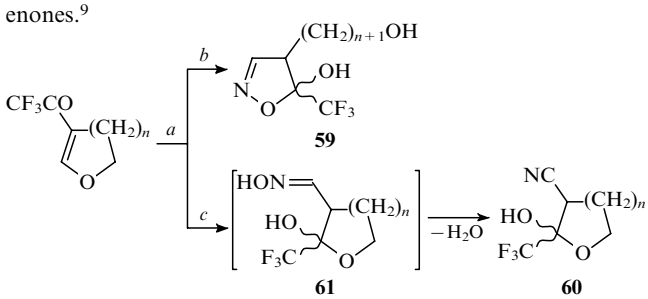
It is noteworthy that the reactions of aldehyde methylhydrazones do not give the corresponding pyrazoles. In all probability, the bulky *tert*-butyl group favours cyclisation resulting in the formation of intermediate **55**. When the pyrazoles **54** are heated with 90% sulfuric acid, the *tert*-butyl group is removed, which gives *N*-unsubstituted 4-trifluoroacetylpyrazoles in high yields.

The reactions of β-alkoxy-substituted enones with hydroxylamine follow different pathways, depending on the structure of the initial enone. Thus acyclic enones and enones containing no oxygen atom in the ring are converted into isoxazolines **56**,[9, 64, 93] which are dehydrated on treatment with P_2O_5 (followed by distillation of the reaction mixture)[64] or concentrated H_2SO_4[93] to give the corresponding isoxazoles **57** or **58**.



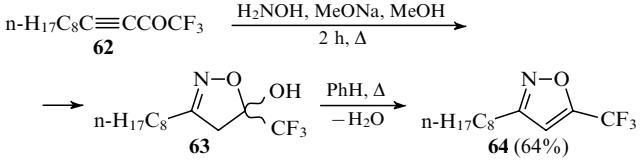
R^1 = Me, Et; R^2, R^3 = H, Me; $R^2 - R^3 = (CH_2)_4$.

Cyclic enones prepared by trifluoroacetylation of 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran are converted in a similar way at 0–20 °C into isoxazolines **59**, 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 **60**, formed apparently upon dehydration of aldehyde oximes **61**, resulting from recyclisation of the starting enones.[9]

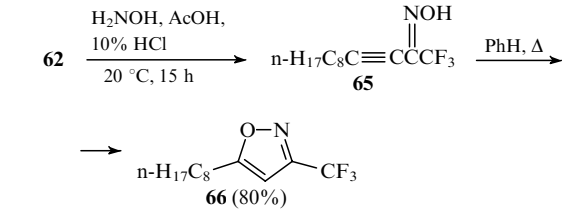


n = 1, 2; (*a*) $H_2NOH \cdot HCl$, H_2O, Py; (*b*) 0–20 °C, 5–170 h; (*c*) 65–85 °C, 30–170 h.

Isoxazolines and isoxazoles were also obtained in good yields in the reaction of alkynyl ketones with hydroxylamine, the regiodirectivity of the reaction being dependent on the reaction conditions.[91] Thus ketone **62** reacts with hydroxylamine in an alkaline medium to give isoxazoline **63**; on refluxing in benzene with azeotropic distillation of water, this product undergoes dehydration to give the corresponding isoxazole **64**.

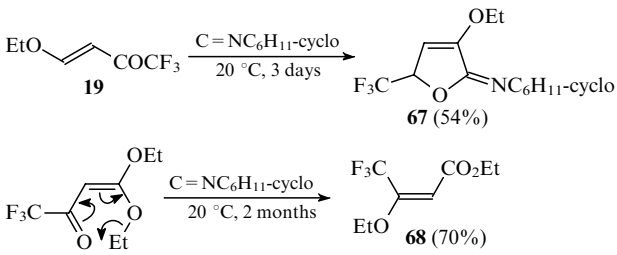


This reaction performed in an acid medium gives initially oxime **65**, which cyclises on refluxing in benzene giving rise to isoxazole **66**, isomeric to the isoxazole **64**.

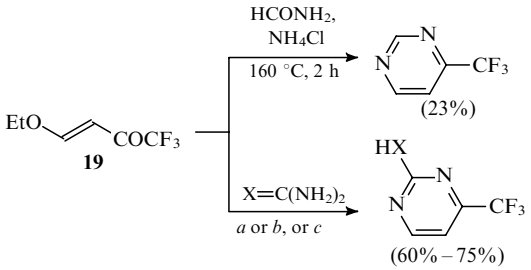


This reaction pathway may be due to the fact that in an acid medium, dehydration is possible, which shifts the equilibrium towards the oxime. In an alkaline medium, the formation of isoxazoline, which exists as the anion under these conditions, appears to be thermodynamically more favourable.

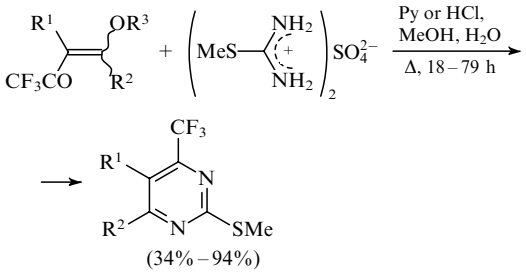
The reactions of some β-alkoxy-substituted trifluoromethyl enones with isocyanides have been studied.[94] β-Ethoxyvinyl trifluoromethyl ketone **19** reacts with cycohexyl isocyanide to give 2,5-dihydrofuran derivative **67**, whereas β,β-diethoxyvinyl trifluoromethyl ketone isomerises under the same conditions to ester **68**.



When β-alkoxy-substituted enones are made to react with formamide in the presence of NH_4Cl, with compounds of the urea series[95] or with isothiouronium salts,[96] trifluoromethylpyrimidines are formed. In the last-named case, the reaction is carried out in the presence of an acid or a base.

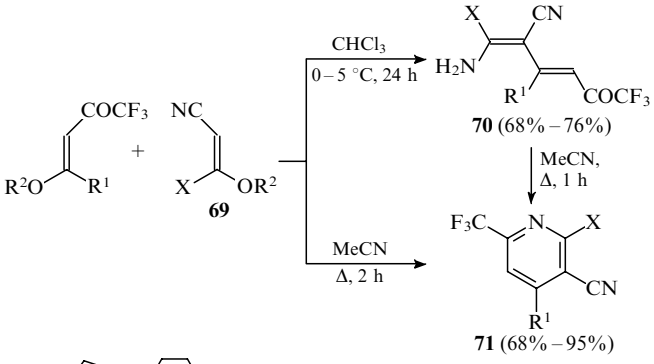


(*a*) HCl, EtOH, 20 °C, 48 h (X = O, S); (*b*) PhH, Δ, 6 h (X = NH); (*c*) AcONa, AcOH, 100 °C, 2 h (X = *p*-$NSO_2C_6H_4NHCOMe$).



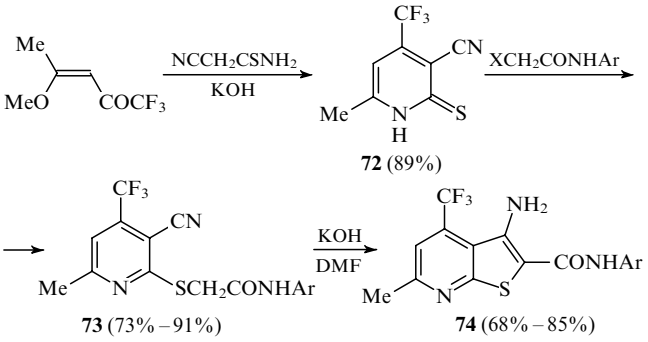
R^1, R^2 = H, Me; R^3 = Me, Et; R^1–R^2 = $(CH_2)_2$, $(CH_2)_3$.

The reactions of β-alkoxy-substituted enones with enamino nitriles **69** result in the formation of pyridine derivatives containing a CF_3 group. Acyclic adducts **70** are formed as intermediates. For R^1 = H, they can be isolated in good yields on cooling. At room temperature, mixtures of the adducts **70** and cyanopyridines **71** are formed; refluxing of initial compounds in acetonitrile leads to pyridines **71** in high yields.[97]



X = –N, –N Y (Y = O, NMe, NCOOEt).

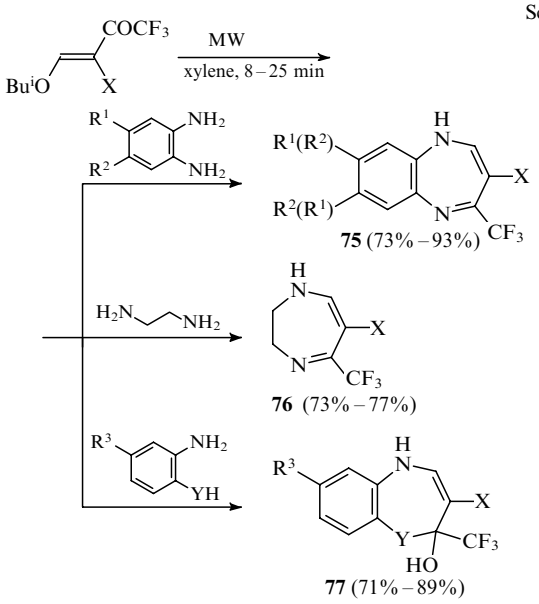
Unlike reactions of enamino nitriles with alkoxyenones, which give 2-trifluoromethylpyridines, the reaction of 1,1,1-trifluoro-4-methoxypent-3-en-2-one with cyanothioacetamide results in the regioselective formation of 4-trifluoromethylpyridinethione **72**, the structure of which was proved by X-ray diffraction analysis.[98] The alkylation of the pyridinethiones **72** obtained by *N*-arylchloro(iodo)acetamides followed by cyclisation of the resulting compounds **73** in an alkaline medium affords 3-amino-4-trifluoromethylthieno[2,3-*b*]pyridinecarboxamides **74**.



X = Cl, I; Ar = Ph, 4-MeC_6H_4, 3-$BuOC_6H_4$.

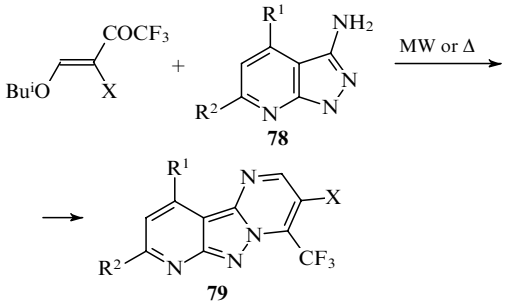
The reaction of the butoxy-substituted trifluoromethyl enone, prepared by trifluoroacetylation of vinyl isobutyl ether, with 1,2-diamines (*o*-phenylenediamine or 1,2-ethylenediamine) gives rise to 1,5-diazepine **75** or **76**, while the reactions with *o*-aminophenols or *o*-aminothiophenol yield 1,5-oxazepines or 1,5-thiazepines **77**, respectively. The bis(trifluoroacetyl) derivative was also introduced into this reaction. Good yields were attained by using microwave (MW) radiation, whereas conducting the reaction in boiling xylene resulted in a complex mixture of products (Scheme 1).[99, 100]

Scheme 1



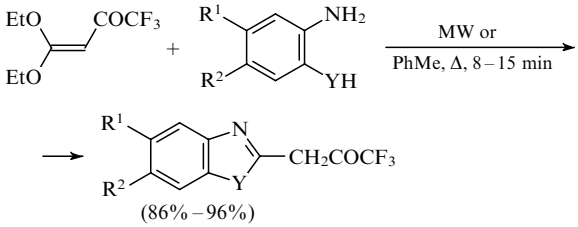
X = H, $COCF_3$; R^1 = H, Me; R^2 = H, Me, Cl, NO_2, COPh; R^3 = H, Cl; Y = O, S.

3-Aminopyrazolo[3,4-*b*]pyridine derivatives **78** enter into a similar reaction as nucleophiles. On exposure to microwave radiation, trifluoromethyl-substituted derivatives of pyrido-[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine **79** are formed in 62%–78% yields (the yield in the thermal reaction is only 20%).[101]



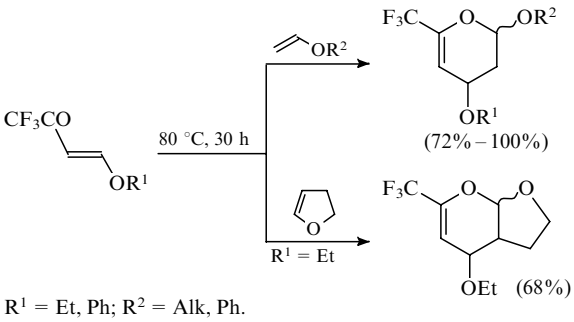
X = H, $COCF_3$; R^1 = Me, CF_3; R^2 = Me, Ar.

4,4-Diethoxy-1,1,1-trifluorobut-3-en-2-one reacts with *o*-phenylenediamines, *o*-aminophenols and *o*-aminothiophenol to give five-membered heterocycles — benzoimidazoles, benzooxazoles and benzothiazoles — in high yields, the reaction occurring both on refluxing in toluene and on exposure to microwave radiation.[100]



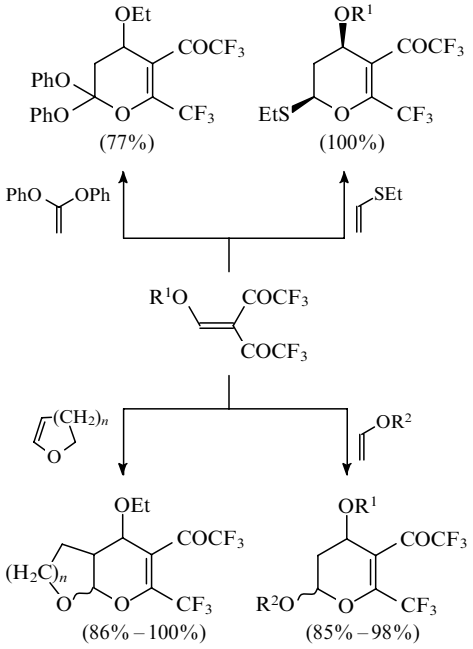
Y = O, S: R^1 = H, Cl; R^2 = H; Y = NH: R^1, R^2 = H, Me.

The reaction of β-ethoxy(phenoxy)-substituted enones with vinyl ethers affords 3,4-dihydro-2*H*-pyrans in good yields; thus, these enones are efficient heterodienes in the hetero-Diels–Alder reaction.[102]



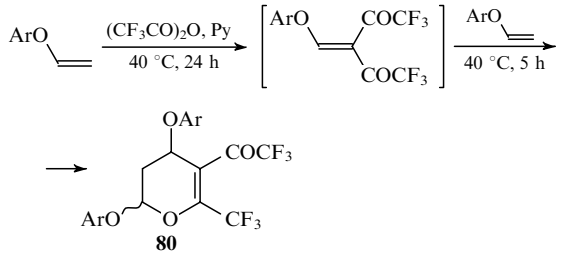
R^1 = Et, Ph; R^2 = Alk, Ph.

This reaction proceeds especially easily for β-alkoxy-substituted bis(trifluoromethyl) enones. The presence of the second strong electron-withdrawing group, $COCF_3$, increases the reactivity of trifluoromethyl enones as heterodienes. The reaction occurs at room temperature to give 5-trifluoroacetyl-3,4-dihydro-2*H*-pyrans in high yields.[17]



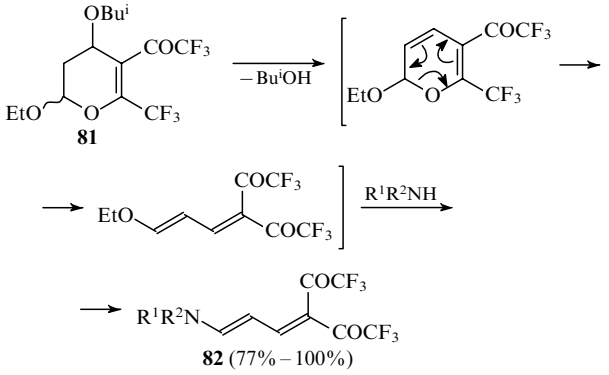
R^1 = Et, Bu^i; R^2 = Et, Ph; n = 1, 2.

Aryl vinyl ethers react with trifluoroacetic anhydride to give the corresponding bis(trifluoroacetyl) derivatives. It was found [17] that these compounds are unstable and cannot be isolated in a pure state; however, they can be introduced without isolation in the reaction with a second equivalent of aryl vinyl ether. Aryloxy-substituted 5-trifluoroacetyl-3,4-dihydro-2*H*-pyrans **80** were obtained in this way in 50% – 68% yields. In some cases, these products are formed directly in trifluoroacetylation of aryl vinyl ethers.[17]



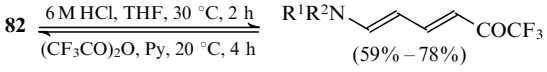
Ar = Ph, 4-MeC_6H_4, 4-BrC_6H_4.

Ring opening in 5-trifluoroacetyl-3,4-dihydro-2*H*-pyrans **81** induced by secondary amines in acetonitrile gives rise to 1-amino-4,4-bis(trifluoroacetyl)buta-1,3-dienes **82**. The mechanism proposed for this reaction includes elimination of isobutanol, electrocyclic ring opening and nucleophilic substitution of the amine for the ethoxy group. It is of interest that no reaction of this type occurs in the series of non-fluorinated analogues of pyrans **81**.[103]

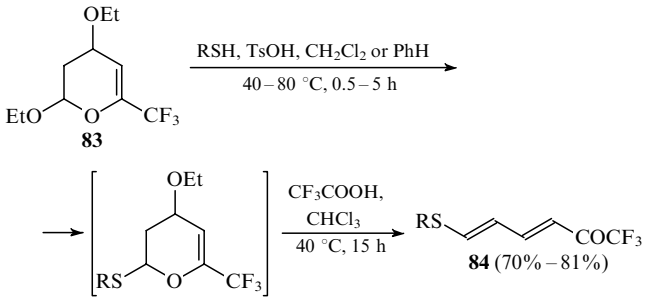


R^1 = Alk, Ph; R^2 = Alk.

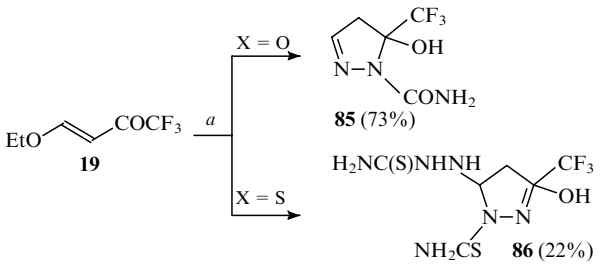
One trifluoroacetyl group in bis(trifluoroacetyl)-substituted dienes **82** can be eliminated in an acid medium; this gives 1-amino-4-trifluoroacetylbuta-1,3-dienes, which can be acylated by trifluoroacetic anhydride in the presence of pyridine to give the initial compounds **82**.[103]



3,4-Dihydro-2*H*-pyran **83**, prepared by hetero-Diels – Alder reaction of β-ethoxy trifluoromethyl enone with vinyl ethyl ether, enters into a similar reaction. The dihydropyran ring opening induced by thiols in an acid medium is stereospecific and gives (*E*)-1-alkylthio-4-trifluoroacetylbuta-1,3-dienes **84** in good yields.[104]



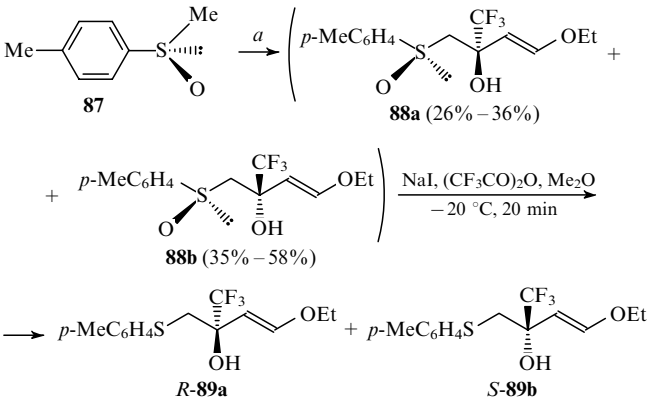
The reactions of β-ethoxy enone **19** with semicarbazide and thiosemicarbazide result in the formation of 2-pyrazoline-1-carboxamide **85** and 5-(1-thiosemicarbazido)-2-pyrazoline-1-thiocarboxamide **86**, respectively.[105]



(*a*) $H_2NCXNHNH_2$, EtONa, EtOH; NH_4Cl, H_2O.

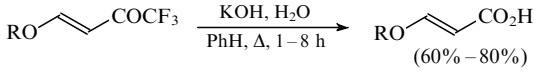
Apart from the synthesis of heterocycles, β-alkoxy-substituted enones have been used to prepare acyclic compounds. Thus the reaction of the lithium salt of (*R*)-methyl 4-tolyl sulfoxide **87** with the enone **19** (or some other perfluoroalkyl-containing enone) gives a mixture of two diastereoisomers of β-hydroxy sulfoxides **88a**,**b** in a ratio of ~1 : 1. These diastereoisomers were separated by chromatography; their configurations were determined by

X-ray diffraction analysis. The subsequent reduction of the sulfoxide group permits the preparation of two enantiomers of chiral allylic alcohols **89a**,**b** with known absolute configurations in a pure state (overall yield 40% – 94%).[106]

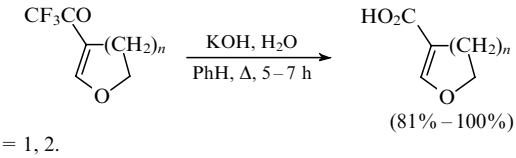


(*a*) $LiNPr^i_2$, −78 °C; EtOCH = $CHCOCF_3$ (**19**).

Trifluoroacetylated vinyl ethers (including cyclic ones) readily undergo haloform cleavage induced by KOH in boiling benzene in the presence of a small quantity of water to give α,β-unsaturated acids.[8]

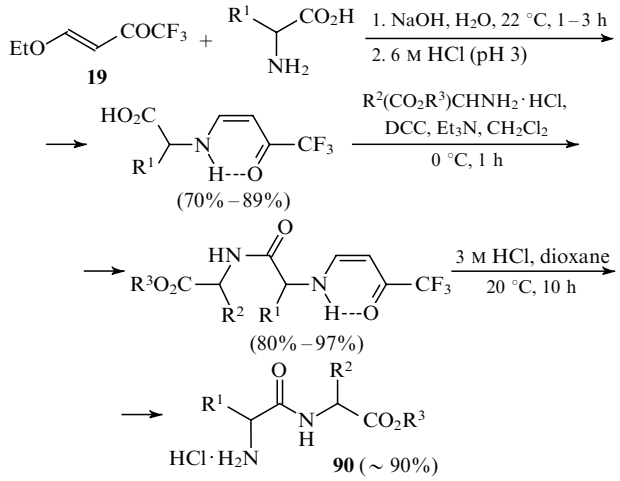


R = Et, Bu^n, Bu^i, Ph.



n = 1, 2.

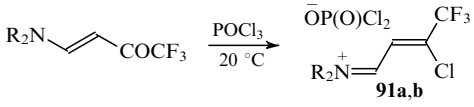
The replacement of the alkoxy group in β-alkoxy enones on treatment with amines occurs with high yields and the resulting enaminones are readily hydrolysed. Therefore, these enones can be used as protective reagents in peptide synthesis. Thus the β-ethoxy enone **19** reacts with amino acids in the presence of an equivalent of a base at room temperature to give the corresponding enaminones. The amino acids protected in this way were used to synthesise dipeptides **90**. The protective group can be easily removed on treatment with 3 M HCl in dioxane at room temperature.[107]



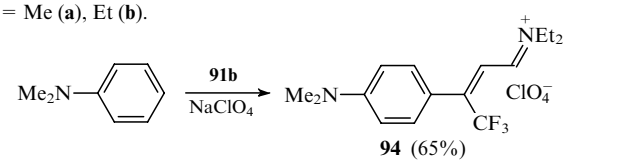
R^1 = Me, Pr^i, $(CH_2)_2CO_2Me$, $(CH_2)_2CO_2Bu^t$, $PhCH_2$; R^2 = H, Pr^i, $PhCH_2$; R^3 = Et, Bu^t, Me; DCC is dicyclohexylcarbodiimide.

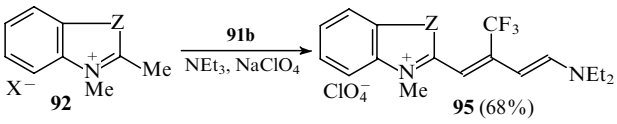
2. Reactions of β-amino-substituted trifluoromethyl enones

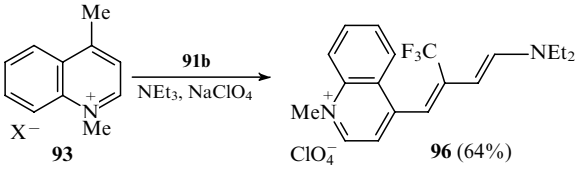
In addition to β-alkoxy-substituted trifluoromethyl enones, their β-dialkylamino-substituted analogues, readily prepared by treatment of β-alkoxy enones with dialkylamines, are also used for the synthesis of various trifluoromethyl-containing heterocyclic compounds. Since enaminones are less reactive in nucleophilic substitution than β-alkoxy enones, they are activated by virtue of $POCl_3$ or trifluoromethanesulfonic anhydride. Thus the reactions of enaminones with $POCl_3$ afford iminium salts **91a**,**b**, vinylogues of the Vilsmeier complexes. Despite the fact that these salts are less reactive than the complex DMF · $POCl_3$, they are still able to aminoformylate (~20 °C, 1 h), *e.g.*, *N*,*N*-dimethylaniline or quaternary salts of nitrogenous heterocycles **92** and **93**. These reactions yield hemicyanines **94** – **96**, respectively, which are valuable intermediates in the synthesis of cyanine dyes.[59]



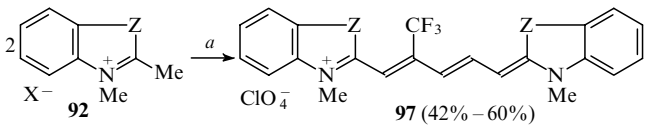
R = Me (**a**), Et (**b**).





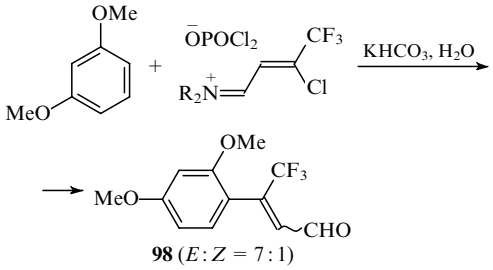


When two equivalents of the quaternary salt **92** react with one equivalent of triethylamine and with the iminium salt **91**, dicarbocyanines **97** are formed.[59]



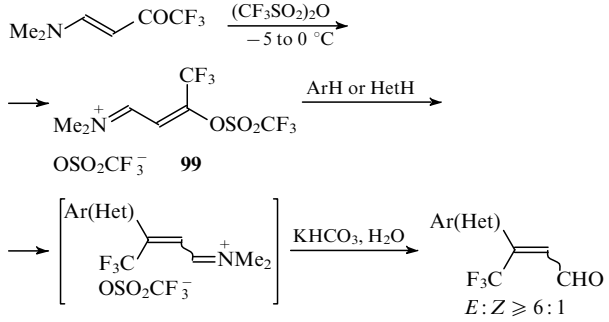
Z = S, CMe_2, CH = CH; (*a*) **91**, NEt_3, $NaClO_4$, 20 °C, 30 min.

The electrophilicity of iminium salts proves to be insufficient for them to react with aromatic compounds less reactive than *N*,*N*-dimethylaniline. Thus quenching with a solution of $KHCO_3$ of the reaction mixture obtained upon the reaction between the complex of 4-dimethylamino-1,1,1-trifluorobut-3-en-2-one with $POCl_3$ and 1,3-dimethoxybenzene gave α,β-unsaturated aldehyde **98** in 7% – 12% yield,[108] more than 80% of the initial 1,3-dimethoxybenzene being recovered unchanged.

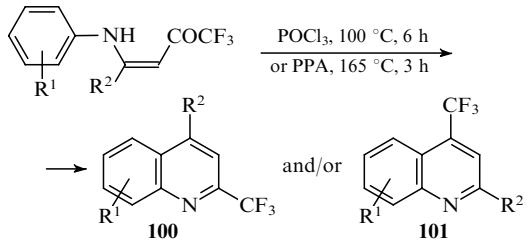


Due to the low electrophilicity of the iminium salts obtained by the reaction of enaminones with $POCl_3$ it has been proposed to

use more reactive salt **99**, formed from enaminone and trifluoromethanesulfonic anhydride and containing a better leaving group (OSO_2CF_3). The reactions of this compound with electron-donating aromatic or heteroaromatic compounds under mild conditions give rise to α,β-unsaturated trifluoromethyl-containing aldehydes.[108] The reaction is stereoselective giving mainly *E*-isomers of the aldehydes; it occurs for relatively reactive compounds such as indoles, pyrroles, furans and 1,3-dimethoxybenzene, whereas thiophene and anisole do not enter into this reaction, even when it is carried out under more rigorous conditions.

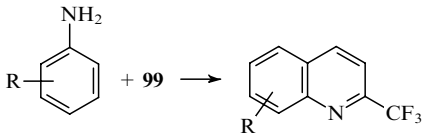


β-Arylamino-substituted trifluoromethyl enones cyclise on treatment with acids giving rise to 2-trifluoromethyl- (**100**) and 4-trifluoromethylquinolines (**101**).[37, 52, 109, 110] As catalysts, $POCl_3$, $ZnCl_2$ and polyphosphoric acid (PPA) were used. Quinolines **101** are the products of 'normal' cyclisation, while the mechanism of formation of 2-trifluoromethylquinolines **100** needs to be further investigated. The ratio of the reaction products depends on the acidic catalyst used and the structure of the initial enone. Cyclisation of enones with R^2 = H gives only 2-trifluoromethylquinolines **100**,[37, 52] and when R^2 = Alk or Ph, 4-trifluoromethylquinolines **101** are formed predominantly.[52] The presence of electron-donating substituents in the *meta*-positions of the aromatic amine substantially facilitates cyclisation and increases the total yield.



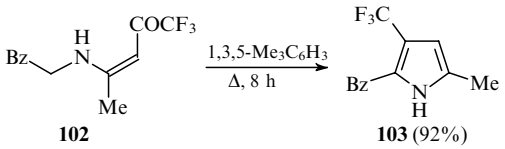
R^1 = Me, OMe, Hal; R^2 = H, Alk, Ph; PPA is polyphosphoric acid.

The reactions of aniline derivatives with the iminium salt **99** afford 2-trifluoromethylquinolines and no 4-trifluoromethyl-derivatives.[111]



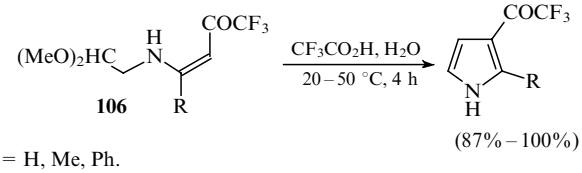
R = Me, OMe, SMe, OCF_3, Cl, OH.

Enaminone **102** cyclises on refluxing in a high-boiling solvent to give substituted 3-fluoromethylpyrrole **103**.[112]



A detailed study of the mechanism of cyclisation of such enamino ketones in the presence of a base demonstrated that the transformations of trifluoromethyl-containing ketones include not only 5-*exo*-trigonal cyclisation to give 3-trifluoromethylpyrroles **104** but also previously unknown 3-*exo*-trigonal cyclisation, giving 2-trifluoromethylpyrroles **105**. Similarly, in the case of sulfide derivatives of enones, 3-trifluoromethylthiophenes were isolated in addition to 2-trifluoromethylthiophenes (Scheme 2).[113]

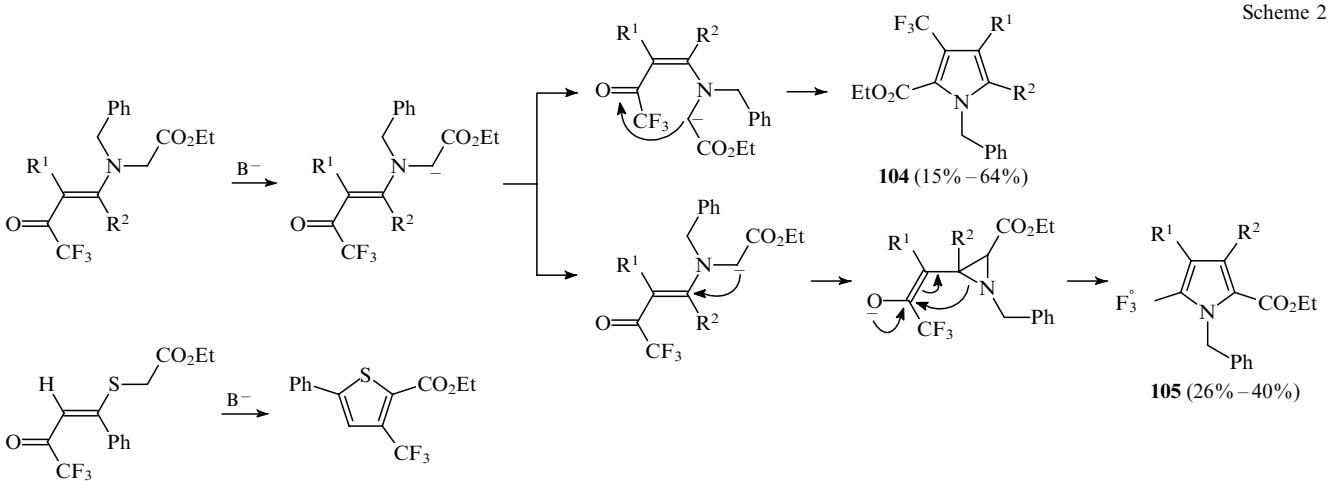
Meanwhile, enaminones **106** cyclise in the presence of trifluoroacetic acid to yield 3-trifluoroacetylpyrroles.[112, 114]

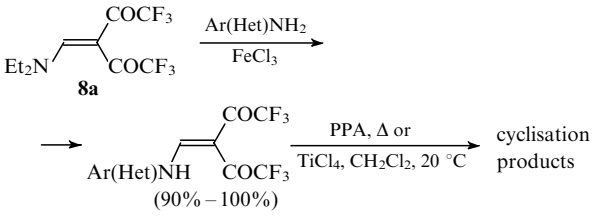


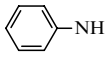
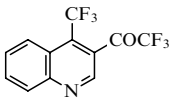
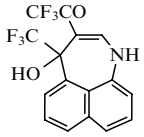
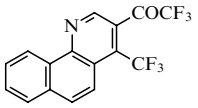
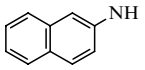
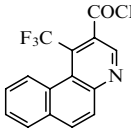
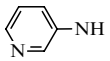
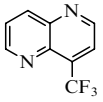
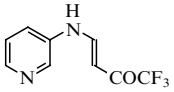
R = H, Me, Ph.

Reactions of 3-(diethylaminomethylidene)-1,1,1,5,5,5-hexafluoropenta-2,5-dione **8a** (enaminodione, whose electrophilicity is enhanced by the presence of the second trifluoroacetyl group) with various nucleophiles have been studied.[115] When the enaminodione **8a** reacts with aromatic amines in the presence of catalytic amounts of $FeCl_3$, the diethylamino group is substituted to give *N*-aryl-substituted enaminodiones, which cyclise on treatment with PPA or $TiCl_4$, the yields of the reaction products being substantially higher in the case of $TiCl_4$.

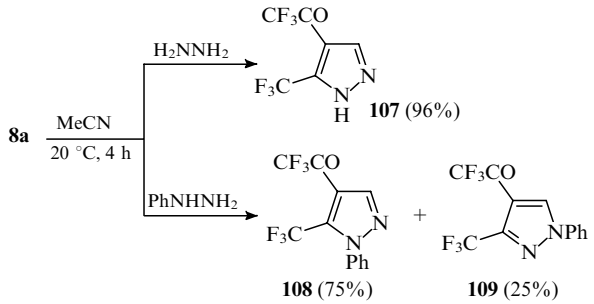
Scheme 2



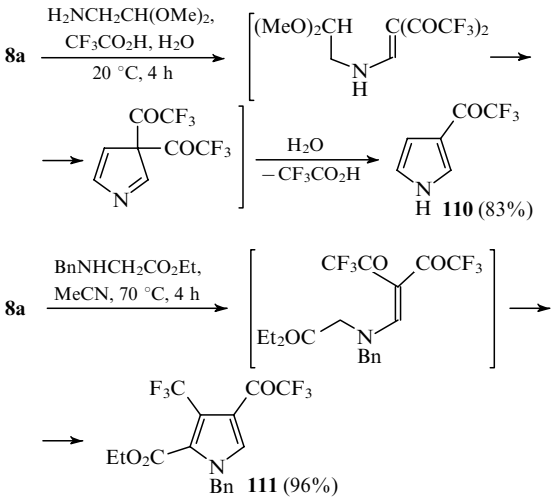


Ar(Het)NH	Cyclisation product	Yield (%)	
		PPA	$TiCl_4$
		10	96
		0	90
		15	0
		–	100
		25	60
		0	25

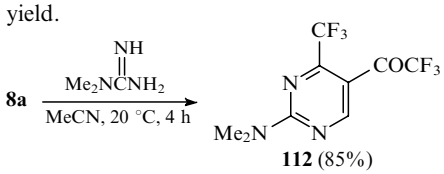
The reactions of the enaminodione **8a** with bifunctional nucleophiles occur similarly to the reactions of β-alkoxy-substituted enones. Thus the reaction of the compound **8a** with hydrazine gives rise to trifluoromethyl-substituted pyrazole **107**, while its reaction with phenylhydrazine yields a mixture of regioisomers **108** and **109** in 1 : 3 ratio.[115]

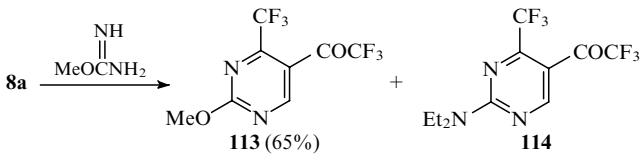


The reactions of the enaminodione **8a** with α-aminocarbonyl compounds (or their acetals) — 2,2-dimethoxyethylamine or ethyl *N*-benzylglycinate — result in the corresponding pyrroles **110** and **111**.[115] In the reaction with 2,2-dimethoxyethylamine, for aromatisation to occur one molecule of CF_3CO_2H is eliminated; this is the pathway to 3-trifluoroacetylpyrrole **110**.[114]



The enaminodione **8a** has also been introduced in reactions with compounds of the urea series. The reaction of **8a** with guanidine affords pyrimidine **112** in a good yield.[115] The reaction with *O*-methylisourea affords two products — 1-methoxypyrimidine **113** and 1-diethylaminopyrimidine **114** — because diethylamine formed in the reaction reacts with methoxypyrimidine **113**. Optimisation of the reaction conditions (MeCN, 65 °C, 4 h) makes it possible to prepare the target compound **113** in 65% yield.



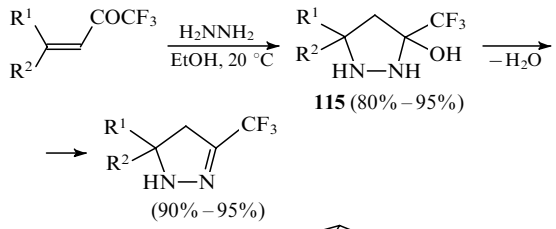


Thus, the enaminodione **8a** is a readily available reagent, widely used for the synthesis of various heterocyclic compounds containing both trifluoromethyl and trifluoroacetyl groups.

3. Reactions of trifluoromethyl enones containing no replaceable group

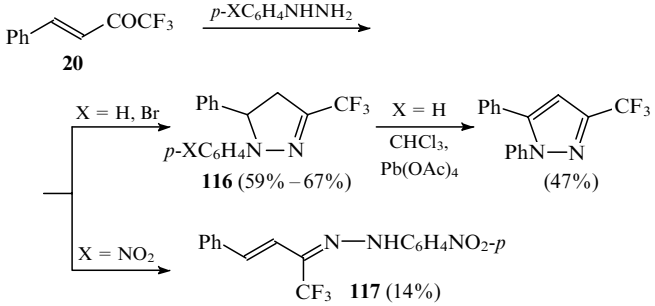
Trifluoromethyl enones containing no β-substituents able to be replaced are less available compounds than β-alkoxy- or β-amino-substituted enones; therefore, their reactions have not been studied so extensively. However, in the early 1990s, new methods for the synthesis of these compounds were developed (*e.g.*, trifluoroacetylation of alkenes in the presence of the complex of dimethyl sulfide with boron trifluoride[25,26]). This stimulated vigorous studies of their synthetic potential.

Trifluoromethyl enones containing no replaceable substituents readily react with various bifunctional nucleophiles. Thus the reactions of phenyl-, cyclobutyl- or adamantyl-substituted enones with hydrazine result in the formation of pyrazolidines **115**, which contain a *gem*-amino-alcoholic fragment, stabilised by the electron-withdrawing influence of the CF_3 group. Dehydration of the pyrazolidines **115**, which occurs either during the reaction, or on prolonged storage, or on refluxing in benzene in the presence of a catalytic amount of toluene-*p*-sulfonic acid (depending on the nature of substituents R^1 and R^2) gives the corresponding pyrazolines.[116]

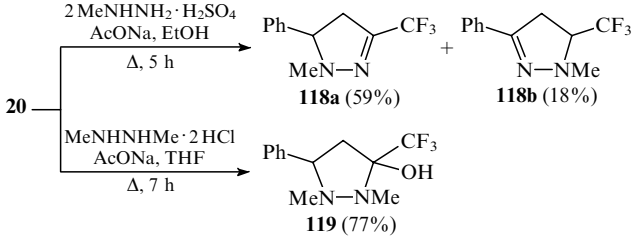


R^1 = H, R^2 = Ph; $R^1 - R^2$ = $(CH_2)_3$, .

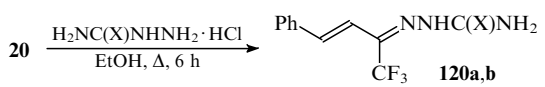
β-Trifluoroacetylstyrene **20** reacts with substituted aryl- or alkyl-hydrazines. Thus the reaction with *p*-bromophenyl- and phenyl-hydrazine affords pyrazolines **116**. Oxidation of the compound **116** with X = H by lead tetraacetate affords the corresponding pyrazole in a moderate yield.[31] The reaction with *p*-nitrophenylhydrazine does not give pyrazoline; in this case, β-trifluoroacetylstyrene *p*-nitrophenylhydrazone **117** is formed in a low yield.



When β-trifluoroacetylstyrene **20** is made to react with methylhydrazine, a mixture of isomeric pyrazolines **118a**,**b** (in ~1 : 3 ratio) is formed, which is apparently due to the fact that the nucleophilicities of the nitrogen atoms in methyl hydrazine are close. The reaction with 1,2-dimethylhydrazine gives pyrazolidine **119**, apparently due to the fact that elimination of water yielding a C=C bond is substantially hampered.[116]

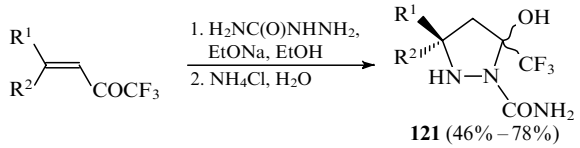


The enone **20** reacts with semicarbazide or thiosemicarbazide in an acid medium to afford semicarbazone **120a** or thiosemicarbazone **120b**. These compounds are stable both in acid and alkaline media and do not tend to cyclise.[105]



X = O (**120a**, 91%), S (**120b**, 93%).

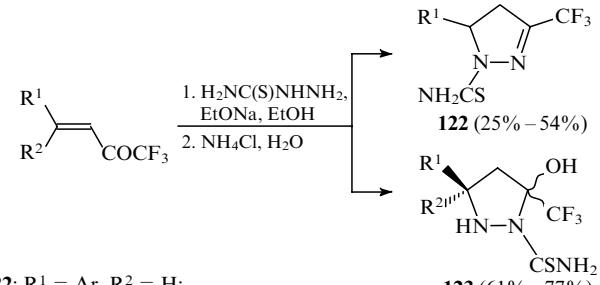
Conversely, the reaction with semicarbazide carried out in the presence of an equimolar amount of sodium ethoxide gives a cyclic compound, 5-trifluoromethylpyrazolidine-1-carboxamide **121**.[105]



R^1 = Ar, R^2 = H; $R^1 - R^2$ = $(CH_2)_3$, .

The reaction occurs regio- and stereoselectively, yielding predominantly one diastereoisomer. The bulky substituents R^1 and R^2 occupy pseudo-equatorial positions, *i.e.* thermodynamically the most favourable isomers are produced.[105]

When trifluoromethyl-containing enones react with thiosemicarbazide under the same conditions, either 3-trifluoromethyl-2-pyrazolinethiocarboxamides **122** or 5-trifluoromethyl-2-pyrazolinethiocarboxamides **123** are obtained, depending on the structure of the starting enone.[105]

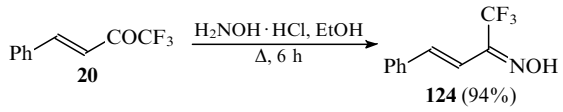


122: R^1 = Ar, R^2 = H;

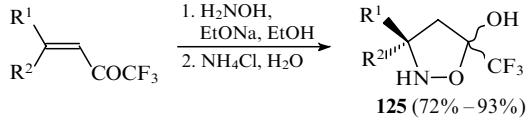
123: R^1 = Ph, R^2 = Me; $R^1 - R^2$ = $(CH_2)_3$, .

Unlike pyrazolidines **115**, pyrazolidine-1-carboxamides and -thiocarboxamides cannot be converted into the corresponding pyrazolines.[105]

The reaction of β-trifluoroacetylstyrene **20** with hydroxylamine in an acid medium gives rise to oxime **124**, which does not tend to cyclise in either acid or alkaline medium.[117]



Meanwhile, the reactions of trifluoromethyl enones with hydroxylamine in the presence of an equimolar amount of sodium ethoxide give isoxazolidines **125** in good yields.[117]



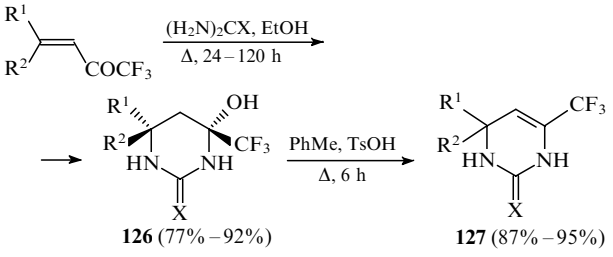
R^1, R^2 = Ar, Het, Alk.

The attempts to carry out dehydration of isoxazolidines **125** to isoxazolines were unsuccessful. Refluxing of these compounds in toluene with azeotropic distillation of water in the presence of toluene-*p*-sulfonic acid gives rise to the corresponding oxime, the initial enone being formed as a side product. At the same time, β-alkoxy enones or alkynyl ketones are converted into isoxazolines, which are dehydrated in an acid medium to give isoxazoles.[63,93] Thus, the possibility of aromatisation has the crucial influence on the reaction route.

The isoxazolidines **125** are fairly interesting from the stereochemical viewpoint. They exist in solutions at room temperature as equilibrium mixtures (~1 : 1) of diastereoisomers. The energy barrier to nitrogen inversion in the compound **125** is almost a half that in the isoxazolidines described previously by Kostyanovsky *et al.*;[118,119] however, it is still high enough (51 – 55 kJ mol^{-1})[117] to retard nitrogen inversion. Therefore, the signals in the ^1H and ^{13}C NMR spectra recorded at room temperature are broadened, and when the temperature decreases, the conformation becomes 'frozen' and signals for four diastereoisomers are observed (due to the chirality of the nitrogen atom).

The reactions of trifluoromethyl enones with compounds of the urea series afford tetrahydropyrimidines **126** in high yields.[120] The compounds **126** are easily dehydrated on refluxing in toluene in the presence of catalytic amounts of toluene-*p*-sulfonic acid

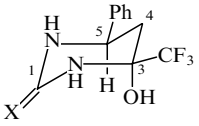
[unlike cyclohexane derivatives containing a $C(OH)CF_3$ fragment][121] giving rise to dihydropyrimidines **127**.[120]



126 (77%–92%) **127** (87%–95%)

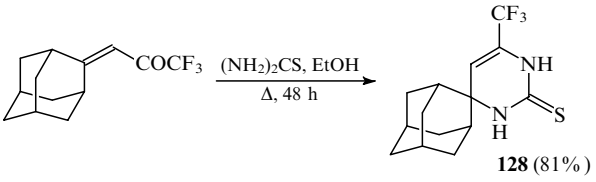
R^1 = H, R^2 = Ph; R^1–R^2 = $(CH_2)_3$; X = O, S.

In the case of β-trifluoroacetylstyrene **20**, the reaction occurs stereoselectively, yielding predominantly (⩾95%) one of the two possible diastereoisomers of **126**. The configuration of the major diastereoisomer was established by X-ray diffraction analysis. This was found to be the thermodynamically more favourable *trans*-isomer (regarding the arrangement of the Ph and OH groups), in which the bulkiest substituents, Ph and CF_3, occupy equatorial positions.



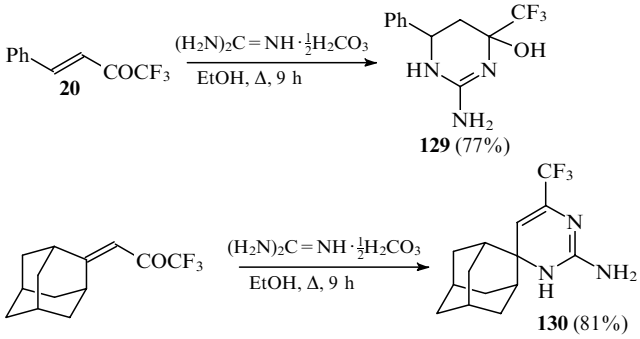
It should be noted that such stereochemistry has also been observed for cyclohexane derivatives with the same substituents at the 3- and 5-positions;[121] this may be due to the relatively large effective size of the trifluoromethyl group † and to the high electron density on this group.

The reaction of a sterically hindered trifluoromethyl enone having an adamantane fragment with thiourea gives dihydropyrimidine **128**.[120]



128 (81%)

The reactions of phenyl- and adamantyl-substituted trifluoromethyl enones with guanidine occur in a similar way giving rise to the corresponding aminopyrimidines **129** and **130**.



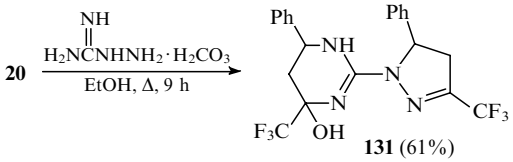
129 (77%)

130 (81%)

β-Trifluoroacetylstyrene **20** reacts with aminoguanidine to give compound **131**, resulting from addition of two enone molecules to an aminoguanidine molecule and containing two heterocyclic moieties (tetrahydropyrimidine and pyrazoline).[120]

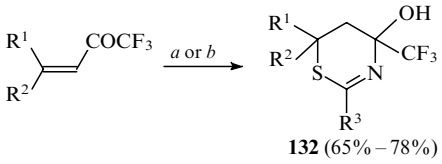
† The energy required for substituents to pass from an equatorial to an axial position (conformational energy) was reported [122] to increase in the sequence Me < Pr^i < CF_3 < Bu^t.

In this case, water is eliminated only from the five-membered ring, which is consistent with the general rule according to which trifluoro-substituted pyrazolidines are dehydrated more readily than tetrahydropyrimidines.[116, 120]



131 (61%)

The reactions of trifluoromethyl enones with thiourea and thioacetamide in an acid medium afford dihydrothiazines **132**.[123] Both reactions are regiospecific and give one isomer, formed upon the addition of sulfur at the double bond and nitrogen at the carbonyl group. This reaction route was interpreted [123] in terms of the principle of hard and soft acids and bases.

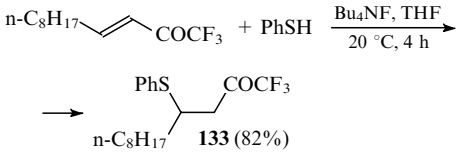


132 (65%–78%)

R^1 = H, R^2 = Ph; R^1–R^2 = $(CH_2)_3$, ;

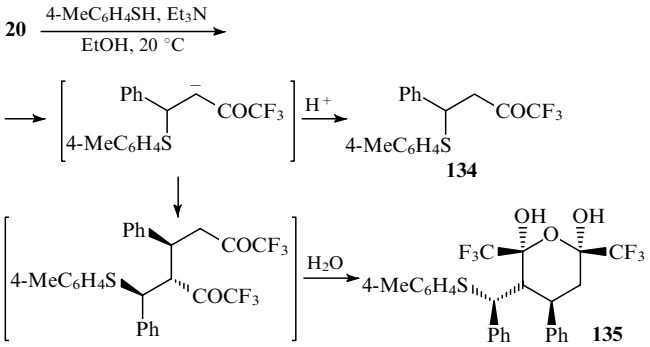
(*a*) $(H_2N)_2CS$, HCl, EtOH, Δ (R^3 = NH_2);
(*b*) $MeC(S)NH_2$, EtOH, Δ (R^3 = Me).

The reactions of some trifluoromethyl enones with thiols have been studied. Thus 1,1,1-trifluorodec-3-en-2-one reacts with benzenethiol to give β-oxo sulfide **133**.[86, 124]



133 (82%)

As opposed to this, the reaction of the enone **20** with 4-methylthiophenol gives rise to two products, β-oxo sulfide **134** and pyran **135**. The compound **134** results from Michael addition, while the pyran **135** is formed upon interaction of two molecules of the ketone with one molecule of the thiol and one water molecule.[124]



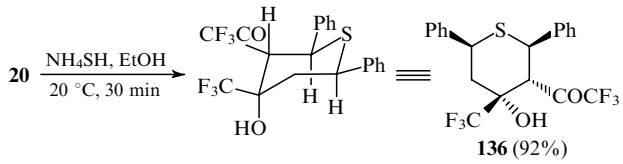
134

135

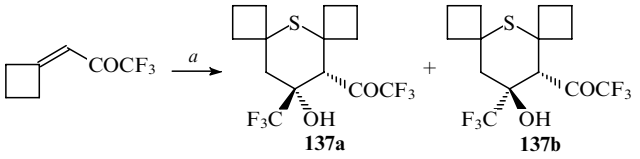
The reaction is stereospecific, the compound **135** being formed as one diastereoisomer of the 16 possible isomers (the molecule has five asymmetric centres); the bulkiest phenyl, trifluoromethyl, and (4-methylphenylthio)phenylmethyl substituents occupy equatorial positions. The relative configuration of the carbon atom located outside the ring and bearing the phenyl and 4-methylphenylthio substituents is also fixed. Thus, effective asymmetric 1,2-induction takes place.[124]

The reactions of trifluoromethyl enones with ammonium hydrogen sufide have been studied.[125] The reaction pathway depends on the structure of the initial enone. For instance, the

enone **20** reacts stereospecifically yielding tetrahydropyran **136** as one diastereoisomer of the eight possible isomers.[125]

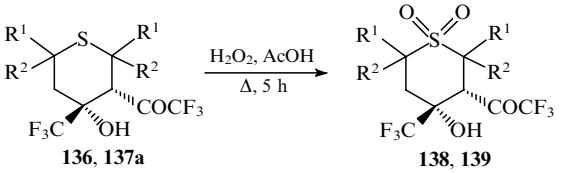


The reaction of ammonium hydrogen sulfide with cyclobutyl-substituted enone affords a mixture of *cis*- and *trans*-diastereoisomers of tetrahydrothiopyran **137a**,**b** (total yield 90%) in 1 : 1 ratio.[125]



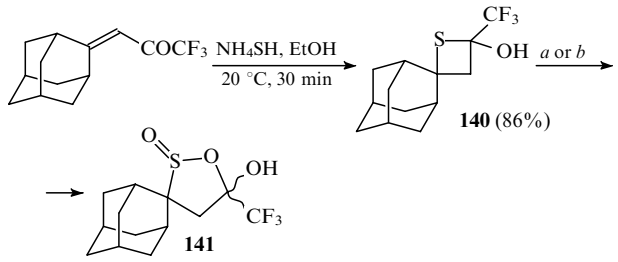
(*a*) NH_4SH, EtOH, 20 °C, 3 min.

The tetrahydrothiopyrans **136** and **137a** are oxidised with retention of configuration, giving the corresponding sulfones **138** and **139** in almost quantitative yields.



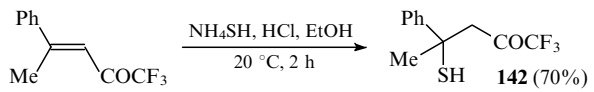
R^1 = Ph, R^2 = H (**136**, **138**); $R^1 - R^2 = (CH_2)_3$ (**137a**, **139**).

The reaction of ammonium hydrogen sulfide with adamantylidenemethyl ketone follows an unusual route and affords compound **140**, containing a four-membered thietane ring, as the only product. On treatment with hydrogen peroxide in acetone or acetic acid, this product is oxidised to give 1,3-sultine **141** as a mixture of diastereoisomers.[125]

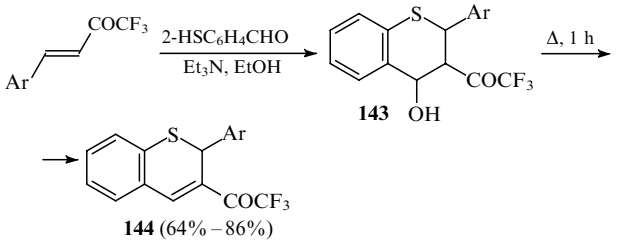


(*a*) H_2O_2, Me_2CO, Δ, 24 h (92%); (*b*) H_2O_2, AcOH, Δ, 1 min (61%).

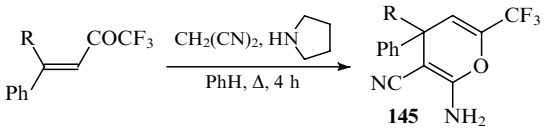
1,1,1-Trifluoro-4-phenylpent-3-en-2-one with three substituents at the double bond reacts with ammonium hydrogen sulfide to yield β-sulfanyl ketone **142**.[125]



Aryl-substituted trifluoromethyl enones were found to react with 2-sulfanylbenzaldehyde at room temperature in ethanol in the presence of a basic catalyst (triethylamine). This gives a mixture of two compounds, thiochromanes **143** and 2*H*-thiochromenes **144**, resulting from dehydration of **143**. When the reaction mixture is refluxed for 1 h, the compounds **144** are formed in good yields. The intermediate thiochromane **143** (Ar = Ph) can be isolated in 65% yield only when the starting enone is β-trifluoroacetylstyrene **20**.[124]

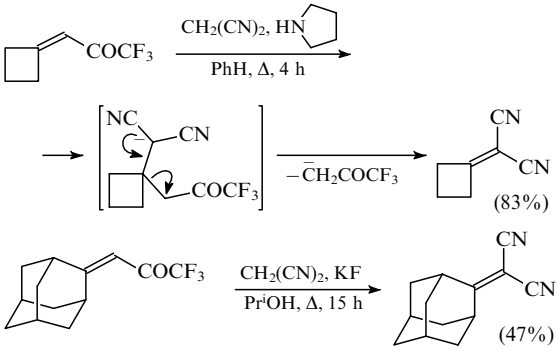


The reactions of trifluoromethyl enones with malonodinitrile and cyanoacetamide in protic (ethanol, propan-2-ol) and aprotic (benzene) solvents in the presence of various basic catalysts (triethylamine, pyrrolidine, calcined potassium fluoride) have been studied.[126] The reaction route depends on the reaction conditions and on the structure of the initial ketone.[126] On refluxing in benzene with malonodinitrile in the presence of pyrrolidine as a catalyst, β-aryl-substituted enones are converted into pyrans **145**.[126]

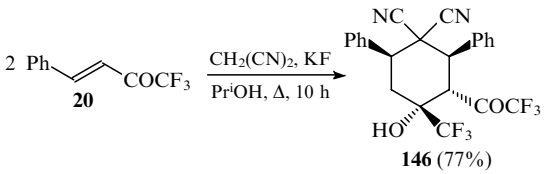


R = H, Me.

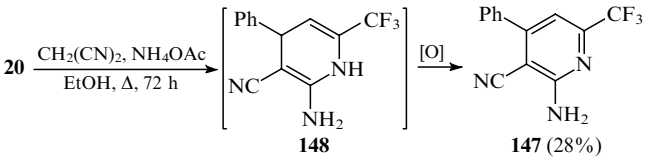
Under the same conditions, cyclobutylidenemethyl trifluoromethyl ketone is converted into cyclobutylidenemalonodinitrile, while adamantylidenemethyl trifluoromethyl ketone reacts in the presence of a stronger base (calcined potassium fluoride) to give adamantylidenemalonodinitrile. Apparently, in the case of ketones with an exocyclic double bond, the initial Michael addition of malononitrile is not followed by cyclisation to give pyran derivatives; instead, elimination of trifluoroacetone enolate occurs. The researchers cited suggest [126] that otherwise, cyclisation products would contain a spiro-fused fragment and, as a consequence, the ring would be more strained.



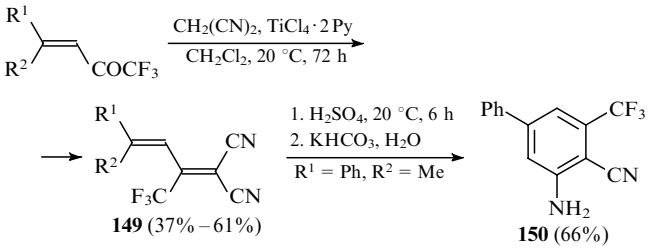
The reaction of malonodinitrile with two equivalents of β-trifluoroacetylstyrene **20** in the presence of potassium fluoride in isopropanol affords substituted cyclohexanol **146**, the product of addition of two molecules of the ketone to malonodinitrile and the subsequent intramolecular aldol condensation. The compound **146** is formed in a good yield as a single diastereoisomer of the eight possible isomers; the bulky substituents (Ph, CF_3, $COCF_3$) occupy energetically more favourable equatorial positions.[126]



The reactions of trifluoromethyl enones with malonodinitrile in the presence of ammonium acetate occur ambiguously. Only in the case of the enone **20**, was pyridine derivative **147**, resulting from oxidation of the corresponding dihydropyridine **148** with atmospheric oxygen, isolated in a low yield.



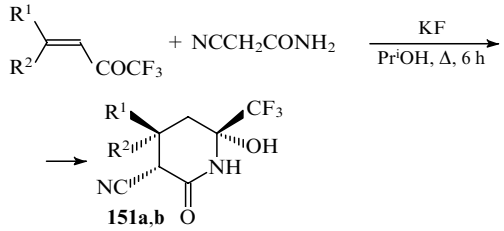
1,1-Dicyanobuta-1,3-dienes **149** [126] were synthesised by Knoevenagel condensation of trifluoromethyl enones with malonodinitrile in the presence of the complex $TiCl_4 \cdot 2Py$ in dichloromethane.



R^1 = Ph; R^2 = H, Me; $R^1 - R^2 = (CH_2)_3$, .

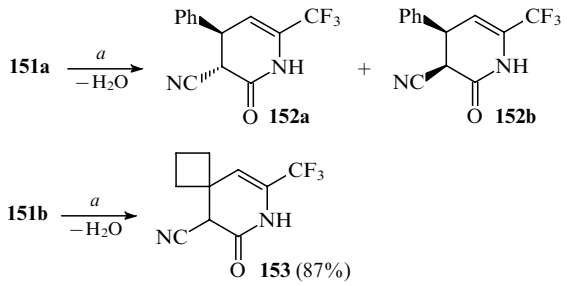
An attempt to carry out cyclisation of the compounds **149** in an acid medium was undertaken. When 1,1-dicyano-4-phenyl-2-trifluoromethylpenta-1,3-diene was treated with concentrated sulfuric acid, substituted benzonitrile **150** was obtained; in other cases, such cyclisation did not occur.

It was found that on refluxing of benzylidene- and cyclobutylidene-methyl trifluoromethyl ketones with cyanoacetamide in isopropanol in the presence of calcined KF, a stereospecific reaction occurs, giving piperidines **151a**,**b** in high yields.[126]



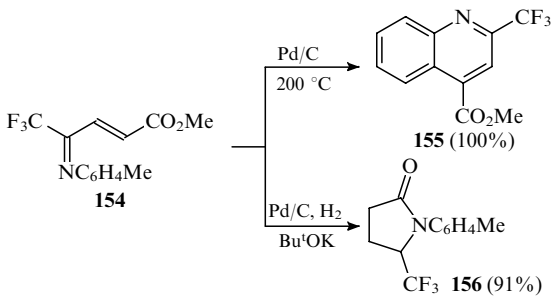
R^1 = Ph, R^2 = H (**a**); $R^1 - R^2 = (CH_2)_3$ (**b**).

Dehydration of the piperidines **151a** and **151b** gives dihydropyridines **152a**,**b** (a mixture of diastereoisomers in ~2 : 1 ratio) and spiro compound **153**, respectively.

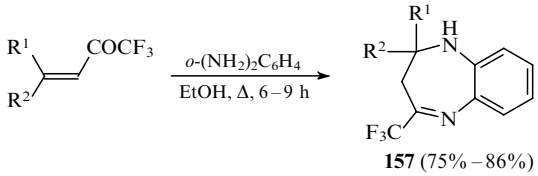


(*a*) PhMe, TsOH, Δ, 48 h.

Imino-derivatives of unsaturated trifluoromethyl-containing ketones **154** cyclise in the presence of palladium supported on carbon to give, depending on the reaction conditions, either 2-trifluoromethylquinoline derivative **155** or 5-trifluoromethylpyrrolidone derivatives **156**.[80]

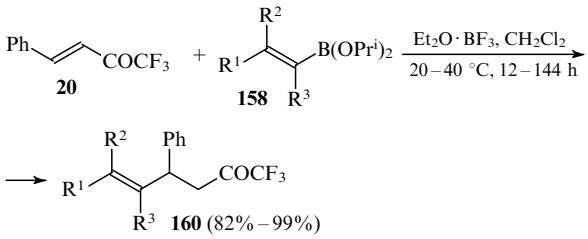


The reactions of trifluoromethyl enones with *o*-phenylenediamine afford 2,3-dihydro-1,5-benzodiazepines **157**.[127] The compounds **157** undergo spontaneous dehydration, apparently, due to the fact that this enables the energetically favourable conjugation of the resulting C=N bond with the benzene ring.

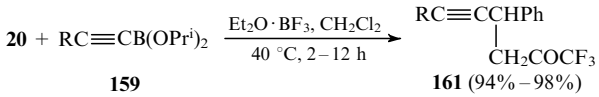


R^1 = H, R^2 = Ph; $R^1 - R^2 = (CH_2)_3$, .

γ,δ-Unsaturated trifluoromethyl-containing ketones **160** and **161** have been prepared by the reactions of β-trifluoromethylstyrene **20** with alk-1-enyl- (**158**) [128] and alk-1-ynyl-diisopropoxyboranes (**159**) [62] in the presence of boron trifluoride etherate.

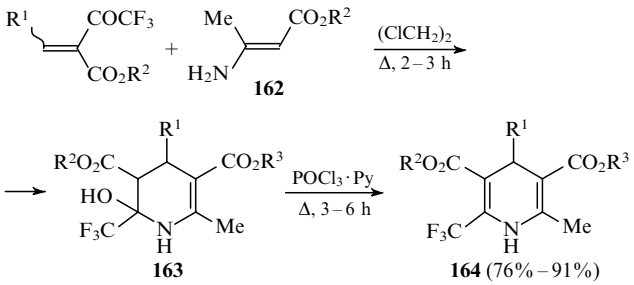


R^1 = Bu^n, Me; R^2 = H, Br; R^3 = H, Me.



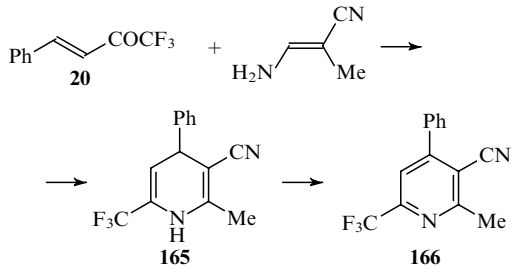
R = Bu^n, Ph.

α-Alkoxycarbonyl-substituted trifluoromethyl α,β-enones, prepared by condensation of ethyl trifluoroacetoacetate with aldehydes, react with enamino esters **162** to afford fairly stable hydroxypyridines **163**, whereas their non-fluorinated analogues are converted directly into 1,4-dihydropyridines. The hydroxypyridines **163** were dehydrated in the presence of a number of catalysts; best yields were attained when the complex $POCl_3 \cdot Py$ adsorbed on silica gel was used.[129]

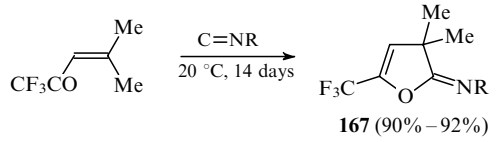


The reaction of the enone **20** with β-aminocrotononitrile results in the formation of 6-trifluoromethylpyridine **165** in a low

yield; oxidation of this product leads to the corresponding aromatic derivative **166**.[130]



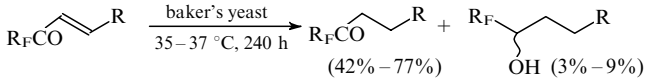
The reactions of 1,1,1-trifluoro-4-methylpent-3-en-2-one with isocyanides occur at room temperature without catalysts to give stable 1,4-cycloaddition products, namely, substituted dihydrofurans **167**.[131]



167 (90% – 92%)

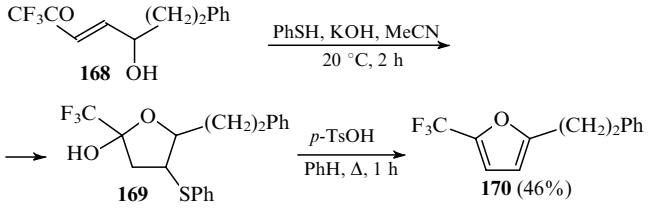
R = Bu^t, cyclo-C_6H_{11}.

Treatment of perfluoroalkyl α,β-enones with reagents that are widely used for asymmetric reduction of non-fluorinated ketones (*e.g.*, Binal-H, Darvon-red) [132] results in racemic alcohols.[133] The microbial reduction of perfluoroalkyl enones by baker's yeast was studied; however, the corresponding saturated ketones rather than alcohols were formed as the major reaction products. The alcohols were formed with high enantioselectivities (*ee* 77% – 85%) but in very low yields.



R_F = CF_3, C_2F_5, n-C_4F_9; R = Me, Ph.

The reaction of γ-hydroxy enone **168**, synthesised by oxidation of the corresponding protected allyl alcohol by the Dess – Martin reagent, with benzenethiol affords a tetrahydrofuran derivative — hemiacetal **169**. On refluxing in benzene in the presence of sulfuric acid with azeotropic distillation of water, the compound **169** eliminates water and benzenethiol being thus converted into the corresponding furan **170**.[84]



IV. Conclusion

The data presented in this review can be summarised by stating that development of facile methods for the synthesis of trifluoromethyl α,β-enones remains a topical task. Trifluoromethyl enones containing no RO, RS or R_2N groups are not very easy to synthesise; nevertheless, they are highly reactive compounds possessing great synthetic potential.

A remarkable feature of trifluoromethyl enones is their high reactivity towards nucleophiles combined with regio- and stereoselectivity of the corresponding reactions. Similar reactions of their non-fluorinated analogues with nucleophiles occur non-selectively giving products in low yields or do not occur at all. Another significant feature that distinguishes trifluoromethyl α,β-enones from non-fluorinated enones is their ability to form compounds incorporating a stable hemiacetal or hemiaminal fragment, $CF_3C(OH)O$ or $CF_3C(OH)NH$.

Thus, α,β-unsaturated trifluoromethyl-containing ketones are fairly convenient 'building blocks' for the synthesis of diverse CF_3-derivatives; further research into their properties and the ways of using them in organic synthesis appears quite promising.

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