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Chemistry of fluoro-substituted β-diketones and their derivatives

V G Isakova, T S Khlebnikova, F A Lakhvich

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Abstract. The literature data on the synthesis and chemical properties of fluoro-substituted β-diketones and β-triketones are generalized. The bibliography includes 312 references.

I. Introduction

Incorporation of a strongly electronegative fluorine atom into organic compounds changes substantially their physical and chemical properties. However, this does not lead to significant changes in the size and spatial structure of the molecules; therefore, biologically active compounds retain complementarity to the receptors and preserve or enhance their biological properties.[1] Currently, fluorinated organic derivatives are widely used as medicines or pesticides;[2,3] the presence of fluoro-containing substituents often increases the efficiency and selectivity of the drug action.[4]

Fluoro-containing β-diketones belong to one of the most important families of fluorinated organic compounds. These compounds often surpass non-fluorinated analogues in their useful properties and are widely used as extractants,[5–7] analytical reagents[8] and catalysts for various reactions.[9] The presence of two carbonyl groups in β-diketones allows their efficient application for the synthesis of various heterocyclic structures possessing analgetic,[10] antiparasitic,[11] antimicrobial,[12] antitumour[13] and other kinds of biological activities.

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It is well-known that the most efficient way to chemical modification of such classes of natural compounds as steroids, nucleosides, prostaglandins, some antibiotics, *etc.* is the introduction of the fluorine atom into the molecule. The presence of a strongly electronegative fluorine atom changes the reactivity of the molecule, which is often difficult to predict, and provides additional possibilities for further modification of the structure and investigation of its relationship with biological activity.

The results of the studies in the field of polyfluorinated β-diketones published before 1980 have been reviewed.[14] However, the chemistry of fluoro-substituted dicarbonyl compounds and their derivatives is being intensively developed, which follows from a great number of publications on this subject. In the present review, newer literature data on the synthesis and chemical transformations of fluoro-substituted β-diketones, 3-polyfluoroacyl chromones, 1,3,5- and β,β′-triketones published up to 2009 are generalized. Since the methods for the synthesis and properties of α,β-dioxo acids, their esters, fluoroalkyl- and fluoroaryl-containing β,β′-dioxo esters, β,β′-oxo diesters and their derivatives are considered in a monograph,[15] they are not discussed here.

II. Synthesis and structure of fluoro-substituted β-diketones

The most common method for the synthesis of mono- and difluoro-substituted β-diketones is their direct fluorination. Gaseous fluorine or electrophilic reagents can be used as the fluorinating agents that can be varied to achieve selective mono- or difluorination. Polyfluorinated β-diketones are mostly obtained by the Claisen condensation of fluoro-containing substrates, esters and nitriles of perfluorocarboxylic acids.

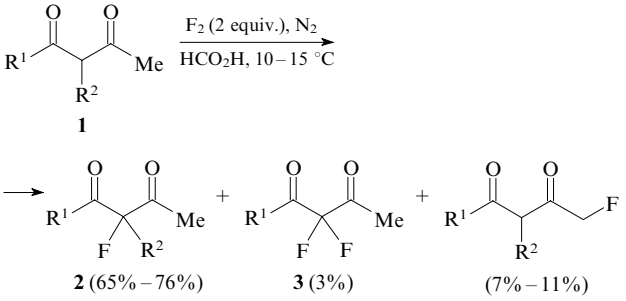
1. 2-Fluoro- and 2,2-difluoro-1,3-diketones

The major method for the synthesis of 2-fluoro- and 2,2-difluoro-1,3-diketones is direct fluorination of the corresponding diketones with gaseous fluorine or various electro-

philic fluorinating agents. The main challenge in the synthesis of these compounds is to perform mono- or difluorination selectively.

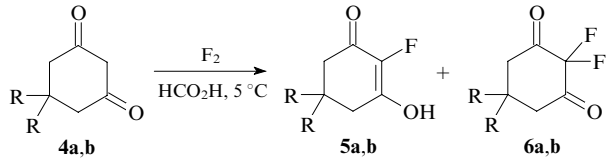
Fluorination with fluorine is the most difficult and low-efficient method compared to fluorination with other reagents described below. Direct fluorination of organic compounds is a strongly exothermic process, which is associated with low dissociation energy of the F–F bond and high strength of the F–C bond formed. Due to high reactivity of fluorine, fluorination is often accompanied by destruction and polymerization processes. Selective and efficient fluorination of organic molecules without the rupture of carbon–carbon bonds in the substrate can be achieved using special procedures that have been developed for the control of high reactivity of elemental fluorine, namely, low temperature, dilution with an inert gas, the use of strong acids as solvents.

Starting from β-diketones **1**, 2-fluoro derivatives **2** were efficiently synthesized using this approach.[16–19] 2,2-Difluoro derivatives **3** and fluorination products of the α-methyl group are the by-products. It is of note that the reaction rate is proportional to the degree of enolization of the starting compound **1**. Since acyclic α-monofluoro-1,3-diketones **2** exist predominantly in the ketone form, the introduction of the second fluorine atom occurs much more slowly: even after several hours of passage of gaseous fluorine, the monofluoro derivative still remained the major product.



R^1 = Me, Ph; R^2 = H, Me, Cl; R^1–R^2 = $(CH_2)_4$.

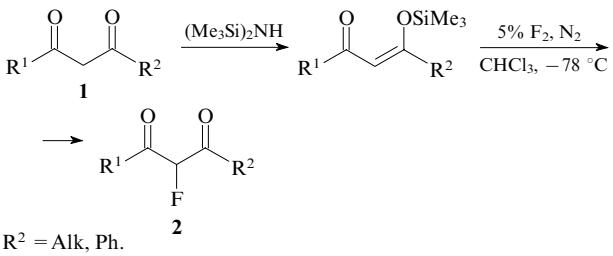
Difluorination of cyclic 1,3-dicarbonyl compounds **4** occurs much easier because the corresponding monoderivatives **5** are predominantly enolized. In this case, the ratio of mono- (**5**) and difluoro-β-diketones (**6**) formed depends on the amount of fluorine used and the reaction time.[16, 18]



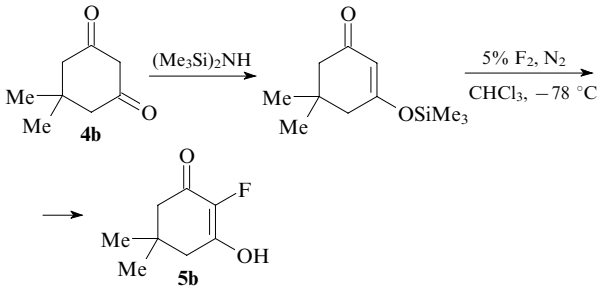
R = H (**a**), Me (**b**).

Conditions	Yield (%)	
	5b	**6b**
2.2 equiv. F_2	0	75
1.1 equiv. F_2	40	33

Regiospecific synthesis of acyclic (**2**) and cyclic (**5b**) monofluoro derivatives of 1,3-diketones was performed by fluorination of enol silyl ethers of the corresponding dicarbonyl compounds **1** and **4b** with elemental fluorine.[19, 20]



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



α-Fluoro derivatives of 1,3-dicarbonyl compounds can be obtained using electrophilic fluorinating agents, which can be divided into three groups: xenon fluorides, oxyfluoride compounds and NF-reagents.[21]

The treatment of acetylacetone with xenon difluoride (XeF_2) in dichloromethane in the presence of catalytic amounts of hydrogen fluoride gives exclusively α,α-difluoro ketone **3**. The highest yield (70%) is achieved using 2 equiv. of the reagent. The α-monofluorinated product **2** was obtained under the conditions of higher dilution and at the ratio substrate : XeF_2 = 2.3 : 1.[22] The result of the reaction of 1,3-diphenylpropane-1,3-dione (**1a**) with XeF_2 depends on the reagent : substrate molar ratio.[23] 5,5-Dimethylcyclohexane-1,3-dione (**4b**) efficiently reacted with xenon difluoride only in the presence of a cross-linked poly(styrene-4-vinylpyridine) and its complex with boron trifluoride, the yield of 2,2-difluoro-5,5-dimethylcyclohexane-1,3-dione (**6b**) being 85%.[22, 24]

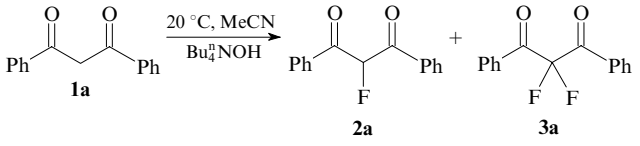
Caesium fluoroxy sulfate [$CsSO_4F$ (Ref. 26)] was used for fluorination of acyclic and cyclic diketones.[19, 23, 25] The reaction with acyclic diketones gave a mixture of mono- and difluorinated products; in some cases, the products of the introduction of the fluorine atom into the α′-position of the substrate were detected.[25] The reactions with cyclic diketones were more selective. Thus treatment of 5,5-dimethylcyclohexane-1,3-dione (**4b**) with an equimolar amount of caesium fluoroxy sulfate gave monofluoro diketone **5b** in 67% yield; the use of 2 equiv. of the reagent resulted in the corresponding difluorinated product **6b** in 48% yield.[23]

Application of acetyl hypofluorite ($MeCO_2F$) as a soft fluorinating agent resulted in mono-α-fluoro derivatives of 1,3-diketones **2** in acceptable yields.[27] Acetyl hypofluorite is readily generated by passing gaseous fluorine through a suspension of sodium acetate in trichlorofluoromethane or in a trichlorofluoromethane–acetic acid mixture, it is brought into the reaction with the substrate without further purification. The yields of the target products significantly increased if diketone sodium enolates were used in this reaction.

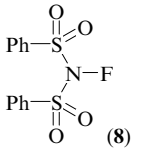
The reaction of equimolar amounts of trifluoroamine oxide (NF_3O) with β-diketones **1** in the presence of tetrabutylammonium hydroxide gives the corresponding α-fluoro derivatives **2** in high yields.[28] With a twofold excess of the reagent, two fluorine atoms can be introduced into the

molecule of unsubstituted 1,3-diketone; however, for the majority of substrates, the formation of a mixture of mono- and difluoro-1,3-dicarbonyl compounds was observed.

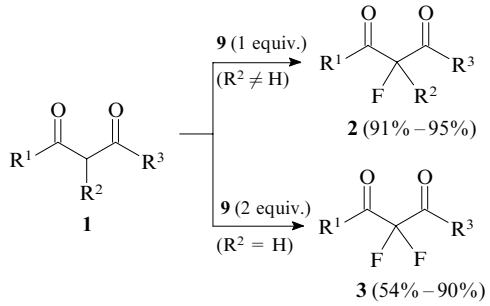
N-Fluoro-*o*-benzenedisulfonimide (**7**)[29] and *N*-fluorodi(benzenesulfonyl)amine (**8**)[30] are readily accessible and stable fluorinating agents. For example, the treatment of 1,3-diketone **1a** with 1.2 equiv. of reagent **7** or **8** results in a mixture of mono- and difluorinated products; with water as a co-solvent, the proportion of monofluoro derivative **2** in the product mixture significantly increased.[29]



1a **2a** **3a**

Reagent	Solvent	**2a** : **3a**	Yield (%)
 (**7**)	CH_2Cl_2	3.5 : 1	52
	$CH_2Cl_2-H_2O$	17 : 1	85
 (**8**)	CH_2Cl_2	3.4 : 1	92
	$CH_2Cl_2-H_2O$	7.2 : 1	41

N-Fluorobis(trifluoromethanesulfonyl)imide (**9**) (the DesMarteau reagent) was also used for the synthesis of α-mono- and α,α′-difluoro derivatives of 1,3-diketones.[31] This reagent appeared the most appropriate for the preparation of difluorinated products **3**. Application of 1 equiv. of fluorinating agent **9** results in α-monofluoro derivative **2** only in the case of α-monosubstited β-diketones ($R^2 \neq H$), in the case of unsubstituted starting compound, a mixture of mono- and difluoro-1,3-diketones is formed.[19,32–35]



1

R^3 = Me: R^1 = Me, Ph; R^1-R^3 = benzo; R^2 = H, Me, Cl, Ph.

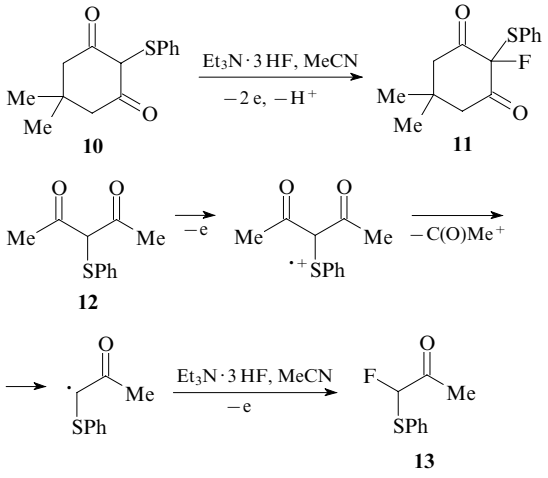
The DesMarteau reagent is an efficient electrophilic fluorinating agent. It is convenient in operation, stable and safe; however, it is expensive and not readily accessible.

Selective synthesis of 2-monofluoro derivative of acyclic and cyclic 1,3-diketones was successfully performed using 1-fluoro-4-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor®).[19,36] Thus the treatment of α-unsubstituted diketones with 2 equiv. of this fluorinating agent results in the corresponding α,α-difluoro diketones only after 8 days.[36] Mono- or di-fluoro β-diketones were obtained in good yields under microwave irradiation (MW) using 1 or 3 equiv. of the fluorinating agent, respectively.[37] With 2-acetylcyclohexanone [**1**, $R^1-R^2 = (CH_2)_4$] and 2-methylcyclohexane-1,3-dione (**4c**) as examples, a possibility of the solvent-free preparation of the target fluorinated compounds was demonstrated.[38] The efficiency of Selectfluor® is comparable with that of the DesMarteau reagent; however, in contrast to the latter, it is cheap, commercially available and convenient in operation.

Umemoto *et al.*[39,40] found that fluorination of 1,3-diketones with 1 or 2 equiv. of *N*-fluoro-2,4,6-trimethylpyridinium triflate selectively furnished mono- or difluoro derivatives, respectively.

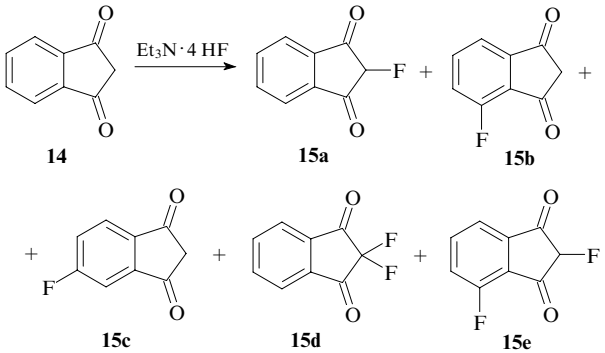
Direct fluorination of 2,2′-bipyridine in the presence of HBF_4 results in *N*,*N*′-difluoro-2,2′-bipyridinium bis(tetrafluoroborate) in high yield, which is a powerful fluorinating agent, each of *N*-fluoropyridinium residues being a source of a fluorine atom.[19,41]

Yet another method for selective α-monofluorination of 1,3-dicarbonyl compounds is electrochemical fluorination. Thus anodic fluorination of α-phenylsulfanyl-substituted cyclic diketone **10** results in monofluoro derivative **11** in a yield of 46%.[42] In the case of α-phenylsulfanylacetylacetone **12**, the corresponding monofluoro-1,3-diketone could not be obtained; under these conditions, elimination of the acetyl group occurred to form 1-fluoro-1-phenylsulfanylpropan-2-one (**13**).[42]



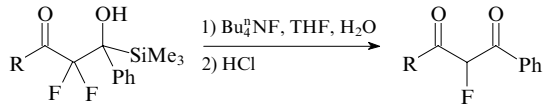
10 **11** **12** **13**

Selective electrochemical α-monofluorination of indan-1,3-dione (**14**) requires potentiostatic conditions.[43] Galvanostatic fluorination of this compound is characterized by low conversion rate and selectivity: in addition to the target 2-fluoroindan-1,3-dione (**15a**), two monofluoro (**15b**,**c**) and two difluoro derivatives (**15d**,**e**) formed.[43]



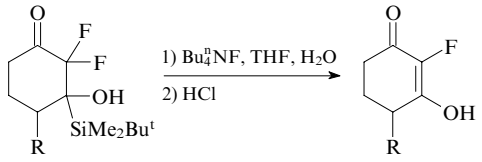
14 **15a** **15b** **15c** **15d** **15e**

The treatment of *gem*-difluoro aldols **16** and **17** with tetrabutylammonium fluoride in aqueous tetrahydrofuran results in defluorosilylation to give the corresponding monofluoro derivatives of acyclic and cyclic diketones.[44]



16 **2**

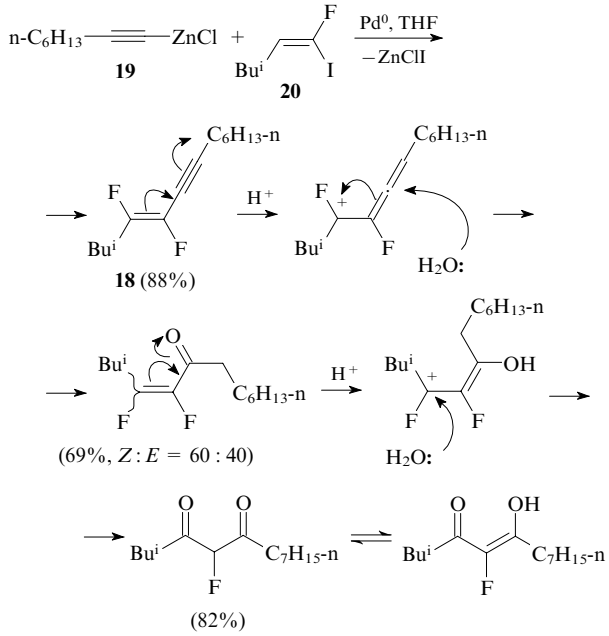
R = Me, Ph.



17

R = H, Me.

The synthesis of α-fluoro-1,3-diketone by hydrolysis of fluoro enyne **18** in the presence of concentrated sulfuric acid is reported.[45] Compound **18** is formed as a result of palladium-catalyzed cross-coupling of zinc derivative **19** and iodide **20**. The mechanism of the transformations can be represented by the following Scheme.

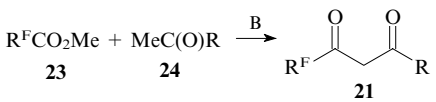


19 **20** **18** (88%)

2. Synthesis of polyfluorinated β-diketones

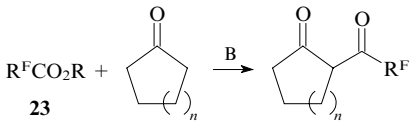
The methods for the synthesis of polyfluorinated β-diketones described below are based on the use of fluoro-containing substrates. The most well-known and versatile method for the synthesis of polyfluorinated acyclic (**21**) and cyclic 1,3-diketones (**22**) is the Claisen condensation. Polyfluoro carboxylates **23** and ketones **24**, **25** containing the hydrogen atom in the α-position are starting compounds for this reaction. Sodium alkoxides,[46–49] sodium amide,[50–52] sodium hydride [53] and lithium hydride serve as condensing agents.[54] The yields of the products vary in the range 57%–90% depending on the nature of the carbonyl and methylene components.†

† Hereinafter R^F denotes fluoro-containing substituent.



23 **24** **21**

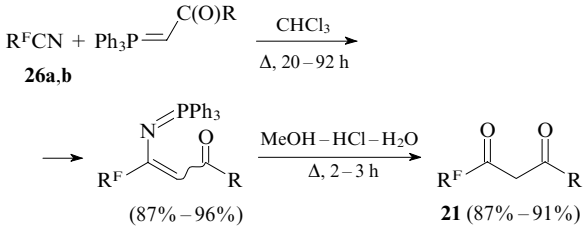
R = Alk, Ar; $R^F = (CF_2)_nH$ (n = 1–6), n-C_mF_{2m+1} (m = 1–8); B is base.



23 **25** **22**

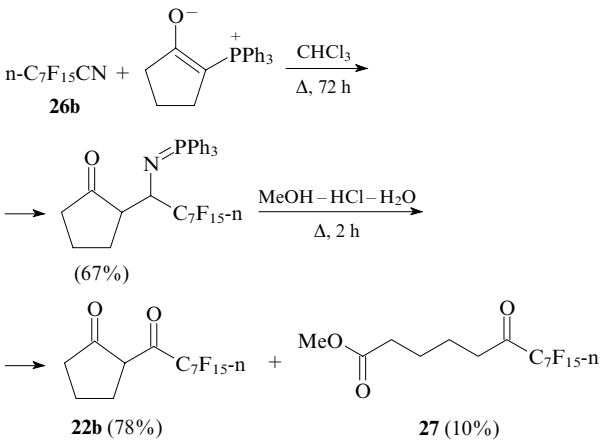
R = Me, Et; R^F = CF_3, C_2F_4H, n-C_4F_9; n = 1, 2.

A series of fluoro-containing 1,3-diketones **21** and **22** was prepared by condensation of perfluoro nitriles **26** and stabilized phosphonium ylides.[48, 55, 56] When cyclic ylides are used, linear diketone **27** is formed as a by-product.



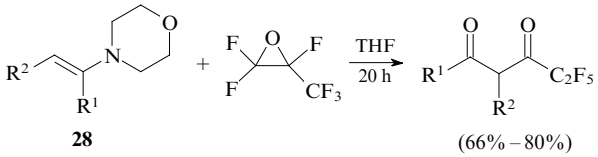
26a,**b** **21** (87%–91%)

R^F = n-C_5F_{11} (**a**), n-C_7F_{15} (**b**); R = Me, Ph.



26b **22b** (78%) **27** (10%)

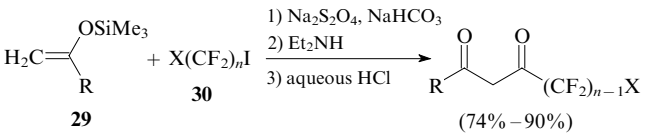
A convenient method for the synthesis of acyclic fluorinated 1,3-diketones is α-pentafluoropropionylation of enamines **28** with hexafluoropropene oxide (reactant ratio 1.6 : 1).[57] Due to mild reaction conditions and neutral medium, high yields of the target products are achieved.



28

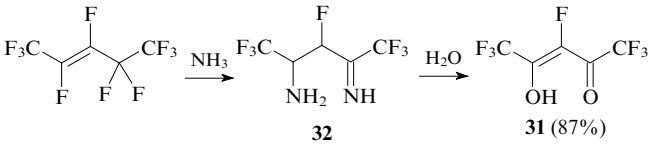
R^2 = H: R^1 = Et, Ph; R^1–R^2 = $(CH_2)_3$, $(CH_2)_4$.

Fluorinated β-diketones were obtained in high yields [58] by one-pot reaction of silyl enolates **29** with perfluoroalkyl iodides **30** in the presence of sodium dithionite and sodium hydrogencarbonate followed by treatment with diethylamine and acid hydrolysis.



R = Me, Bu^t; X = Cl, F; n = 4, 6, 8.

Heptafluoroacetylacetone (**31**) was synthesized in two steps: by the reaction of ammonia with perfluoropent-2-ene followed by hydrolysis of β-amino imine **32** formed.[59]

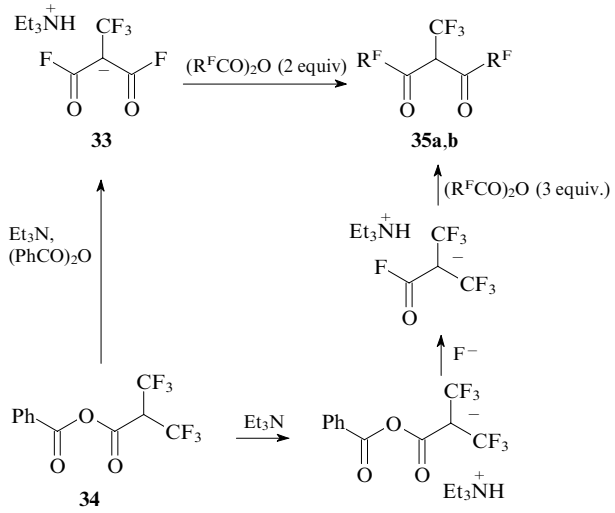


Similar approach was used for the synthesis of homologues of compound **31** starting from other perfluoroalk-2-enes.[60]

3. Synthesis of α-trifluoromethyl-substituted β-diketones

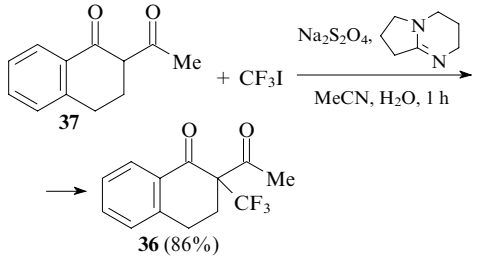
Only segmentary reports are available in the literature concerning the synthesis of α-trifluoromethyl-1,3-diketones.

Thus perfluorocarboxylic anhydrides acylate mesomerically stabilized anions FC(O)C$^-$(CF$_3$)C(O)Y (**33**) generated from benzoic α-hydroperfluoroisobutyric anhydride **34** under the action of Et$_3$N.[61] This reaction is an efficient approach to the synthesis of 1,1-bis(perfluoroacyl)-2,2,2-trifluoroethanes **35a**,**b** and β,β′-tricarbonyl compounds with three perfluoroalkyl substituents (see Section IV.2).

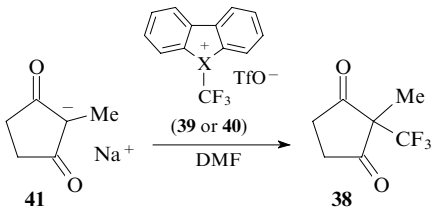


R^F = CF$_3$ (**a**), n-C$_3$F$_7$ (**b**).

Trifluoromethyl derivative **36** was obtained in high yield by free radical trifluoromethylation of 2-acetyl-3,4-dihydronaphthalen-1(2*H*)-one (**37**) with trifluoroiodomethane in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene and sodium dithionite as an initiator of the reaction.[62]

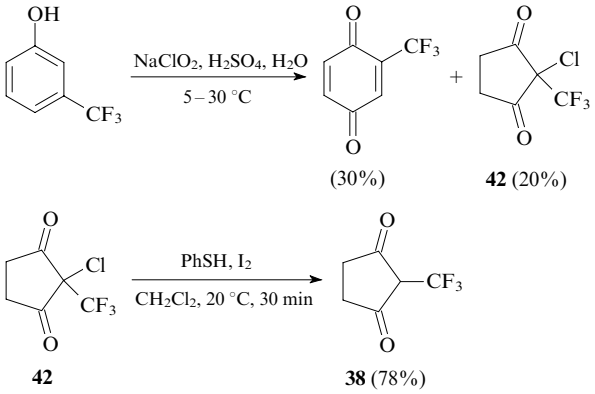


Synthesis of 2-methyl-2-trifluoromethylcyclopentane-1,3-dione (**38**) was performed using triflates **39** and **40** as trifluoromethylating agents. The reaction of compound **39** or **40** with sodium salt **41** gave product **38** in yields 84% or 73%, respectively.[63]



X = S (**39**), Se (**40**).

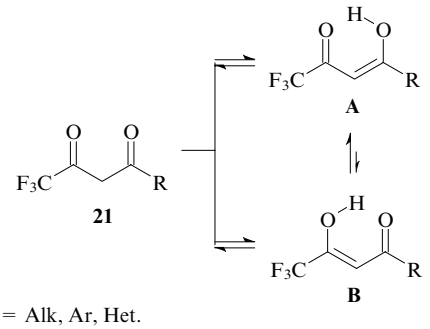
Oxidation of 3-trifluoromethylphenol with a mixture of sodium chlorite and sulfuric acid gave 2-chloro-2-trifluoromethylcyclopentane-1,3-dione (**42**) as a by-product, whereas the corresponding quinone was the major product.[64] Diketone **42** undergoes hydrodechlorination under the action of catalytic amounts of hydroiodic acid generated *in situ* from iodine and benzenethiol to form 2-trifluoromethylcyclopentane-1,3-dione (**38**).



4. Keto–enol tautomerism

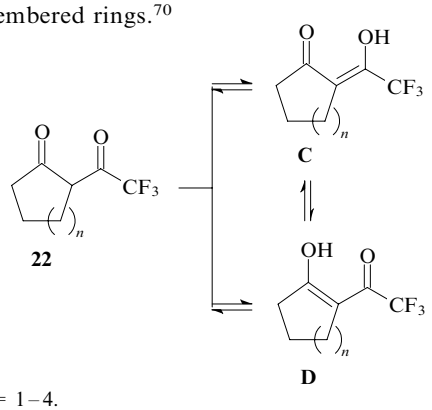
It is known that keto–enol tautomerism is typical of β-dicarbonyl compounds. The presence of additional electron-withdrawing substituents changes the distribution of the electron density in the diketone molecule and favours the increase in the content of enol forms.[14] Thus fluoro-substituted β-diketones are mostly enolized,[65] the proportion of the enol tautomer increasing with an increase in the degree of fluorination.[66,67] However, acyclic 2-fluoro-1,3-diketones with bulky alkyl groups at the C(2) atom exist in deuteriochloroform solution exclusively in the ketone form.[68]

Keto–enol and enol–enol tautomerism of acyclic trifluoromethyl β-diketones **21** was studied by ^{1}H, ^{13}C, ^{19}F NMR, IR and UV spectroscopic methods.[69] It was found that trifluoromethyl-substituted 1,3-diketones **21** exist in non-polar media as mixtures of chelating *cis*-enol forms **A** and **B**, the equilibrium being shifted towards the enol form **A**.[69] For compound **21**, no spatial *cis*–*trans*-isomers are found for forms **A** and **B**.[14]



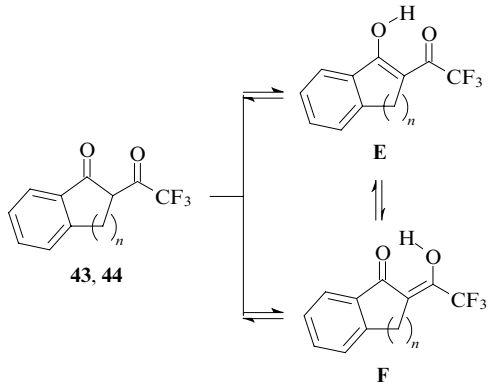
R = Alk, Ar, Het.

The degree of enolization of 2-trifluoroacetylcycloalkanones **22** in deuteriochloroform solution is > 90%. The direction of preferential enolization of these compounds is determined by the size of the carbocycle. Thus the exocyclic enol form **C** dominates in the case of 2-trifluoromethylcyclopentanone (n = 1), whereas the endocyclic form **D** dominates for compounds with six-, seven- and eight-membered rings.[70]



n = 1–4.

Similar regularity is observed for diketones **43** and **44**, which exist in deuteriochloroform solution as a mixture of *cis*-enol forms **E** and **F**. The exocyclic tautomer **F** dominates in the case of indanone **43**, whereas for tetralone **44**, the proportions of endo- and exocyclic forms are comparable.[71]



n = 1 (**43**), 2 (**44**).

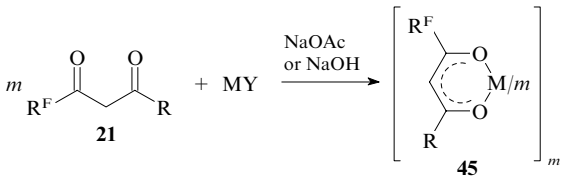
III. Reactions of fluoro-substituted β-diketones

Fluoro-substituted β-diketones are polyfunctional compounds, which undergo chemical transformations with the involvement of such reaction sites as the carbonyl groups and the methylene group between them. These derivatives form coordination compounds with complexing metals, react with N-nucleophiles, N,N-, N,O-dinucleophiles, aldehydes and ketones, the reactions being substantially affected by the fluorine atom or fluoroalkyl substituent.

1. Complexing properties of fluoro-substituted β-diketones

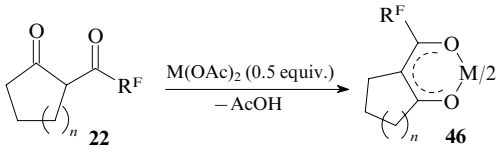
Complexes of β-diketones are mostly obtained by the reaction of different derivatives of complexing metals, mainly salts, with β-diketonate ligands. The data concerning the synthesis and structure of β-diketonates, fluoro-containing among them, published up to 2005 are summarized in reviews,[72,73] hence, in the present review, we give only separate examples of these transformations and some newer data.

The treatment of fluoro-substituted β-diketones **21** with transition metal salts results in the corresponding complexes **45**.[74,75] The structures of fluorinated metal complexes **45** was established by elemental analysis, mass spectrometry, IR and NMR spectroscopy and X-ray diffraction analysis.[74–76]



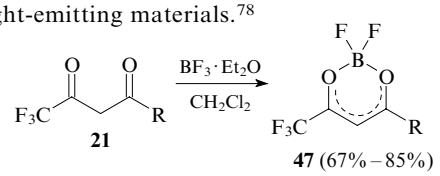
R^F = CF_3, n-C_6F_{13}, n-C_7F_{15}; R = Ph, n-C_6F_{13}, n-C_7F_{15};
M = Zn, Ni, Pd, Cu, Ho, Pr, Er; Y = Cl, OAc.

Similarly, the reactions of Cu(II) and Ni(II) acetates with 2-polyfluoroacylcycloalkanones **22** in diethyl ether afford cyclic fluorinated β-diketonates **46** (yields 42% – 100%).[77]

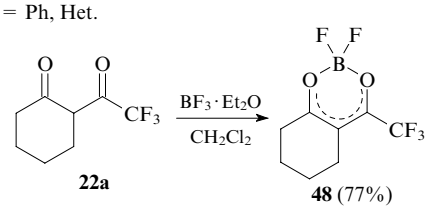


R^F = CF_3, C_2F_4H; M = Cu, Ni; n = 1, 2.

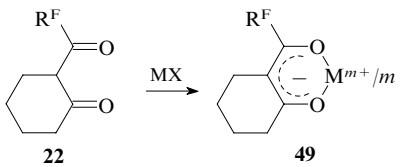
The reactions of boron trifluoride etherate with trifluoromethyl-1,3-diketones **21**[78] and 2-trifluoroacetylcyclohexanone (**22a**)[77] result in BF_2-complexes **47** and **48**. Investigation of optical and electrochemical properties of metallochelates **47** revealed that they can be used as novel light-emitting materials.[78]



R = Ph, Het.

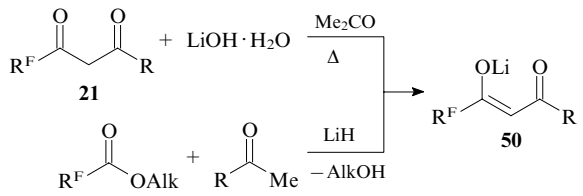


Sodium, lithium and barium 2-polyfluorocyclohexanonates, compounds **49**, are obtained by the reaction of 1,3-dicarbonyl compounds **22** with the corresponding base.[77]



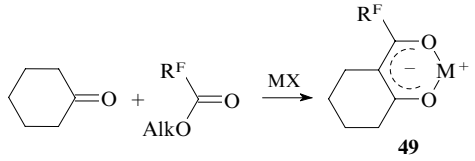
R^F = CF_3, C_2F_4H, n-C_6F_{13};
M = Li, X = H; M = Na, X = OH; M = Ba, X = O; m = 1, 2.

Lithium salts of acyclic fluoro-substituted β-diketones **50** were obtained by both the reaction of lithium hydroxide monohydrate with the corresponding 1,3-diketone **21** [79, 80] and the modified Claisen condensation.



R^F = CF_3, CF_2H, C_2F_4H, n-C_4F_9, n-C_6F_{13}, n-C_8F_{17};
R = Alk, Ar, CF_3.

In the latter case, fluorocarboxylates react in hexane in the presence of LiH as a condensing agent with ketones containing an active methylene group.[81–83] Cyclohexanone also reacts with fluorocarboxylates in the presence of LiH and NaOMe, which is an alternative approach to the synthesis of lithium and sodium 2-polyfluoroacylcyclohexanonates (**49**), respectively.[77, 83] The literature data on the structures and the methods for the synthesis of fluoroalkyl-containing lithium 1,3-diketonates **49** and **50** are summarized in a recent review.[83]



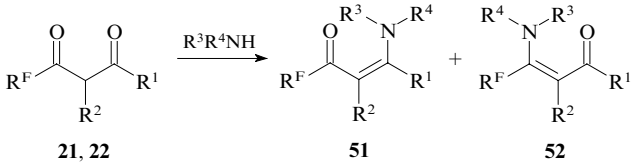
R^F = CF_3, CF_2H, n-C_3F_7;
M = Li, X = H; M = Na, X = OMe.

It is noteworthy that fluorinated lithium 1,3-diketonates are valuable and convenient synthons. The ease of preparation, high reactivity in combination with higher (compared to the corresponding β-diketones) storage stability and high yields of the target products allowed the development of efficient methods for the synthesis of a series of fluoro-containing compounds, heterocyclic among them, from lithium diketonates.[77, 82, 84–91] In addition, lithium complexes of fluoro-substituted β-diketones are not only synthetic equivalents of the corresponding dicarbonyl compounds, but offer wider opportunities to their use.[77, 82, 85, 89]

2. Reactions with N-nucleophiles

Fluorinated β-dicarbonyl compounds react readily with amines. The regioselectivity of these transformations is extremely sensitive to the nature of the amine, the presence of fluorinated and non-fluorinated substituents at the carbonyl groups and the reaction conditions. The reaction can involve one or both carbonyl groups.[92] The main side processes in these transformations are acid cleavage and salt formation.[93]

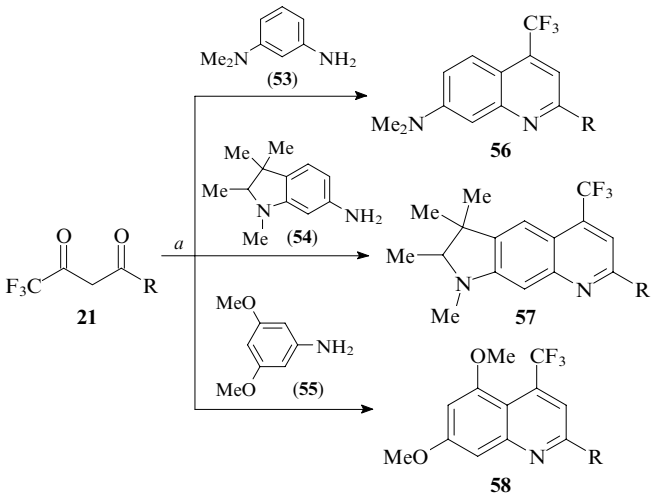
Coupling of primary and secondary amines with non-symmetrical acyclic β-diketones **21** containing alkyl and fluoroalkyl substituents gives exclusively β-aminovinyl ketones **51**.[14, 94] The use of an ionic liquid, 1-methylimidazolium trifluoroacetate, as a solvent enables preparation of enamino ketones **51** at room temperature.[95] Under microwave treatment, β-aminovinyl ketones **51** form in higher yields and in shorter time.[96] Reactions of cyclic β-diketones **22** with anilines involve the carbonyl groups bound to the non-fluorinated substituent.[54] Reactions of non-symmetrical phenyl-substituted acyclic β-diketones **21** with ammonia or methylamine result in mixtures of isomeric β-aminovinyl ketones **51** and **52**.[97]



R^F = CF_3, C_2F_4H, n-C_4F_8H;
R^2 = H: R^1 = Me, Bu^n, Bu^t, Ph; $R^1 - R^2$ = $(CH_2)_3$, $(CH_2)_4$;
R^3 = H: R^4 = H, Me, Ph, 4-MeC_6H_4; R^3 = R^4 = Me.

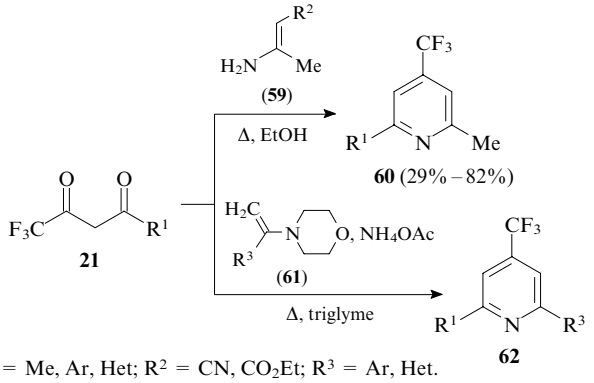
Amination of 1,3-diketones with aromatic amines in the presence of 1 equiv. of $B(OEt)_3$ leads to a significant increase in the reaction rate and the yield of product **51**.[92] Perfluoro-substituted β-diketones **21** form the corresponding salts with cyclic and acyclic secondary [98] and tertiary [99] amines. These salts are characterized by high thermal stability, low melting points, viscosity and density and can be used as ionic liquids.

The reactions of substituted anilines **53**–**55** with trifluoromethyl-1,3-dicarbonyl compounds **21** furnish γ-trifluoromethylquinolines **56**–**58**. Under similar conditions, less nucleophilic amines (3,4,5-trimethoxyaniline, 6-amino-2,3-dihydro-1,4-benzodioxine) do not form the corresponding cyclocondensation products.[100]



R = Me, Ph, CF_3, Het; (*a*) AcOH, Δ, 2–4 h.

The direction of the reaction of trifluoro-substituted β-diketones **21** with enamines depends on the degree of substitution at the nitrogen atom. Thus the reaction of



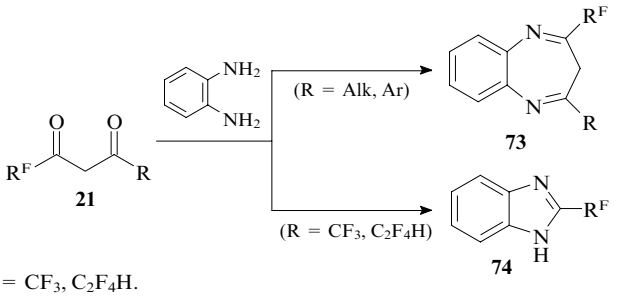
R^1 = Me, Ar, Het; R^2 = CN, CO_2Et; R^3 = Ar, Het.

primary enamines **59** results in 4-trifluoromethylpyridines **60**,[84, 101] whereas tertiary enamines **61** react with compounds **21** in the presence of ammonium acetate to give the corresponding 4-trifluoromethyl-2,6-disubstituted pyridines **62** in high yields.[102]

1,1,1-Trifluoroacetylacetone (**21a**) and 1,1,1,5,5,5-hexafluoroacetylacetone (**21b**) react with different enamines **63** to afford a series of trifluoromethyl- (**64**, **65**)[103] and bis(trifluoromethyl)-substituted benzenes (**66**–**69**),[104] respectively (Scheme 1).

Reactions of fluoro-containing 1,3-diketones **21a**,**c** with ethylenediamine monohydroperchlorate furnish 2,3-dihydro-1*H*-1,4-diazepines **70** in good yields.[84, 105–107] In the case of diethylenetriamine or triethylenetetramine monohydroperchlorates, acid cleavage of substrates mainly occurs to form the corresponding amides **71** or **72** (Scheme 2).[108] Salts are formed from tertiary diamines.[109]

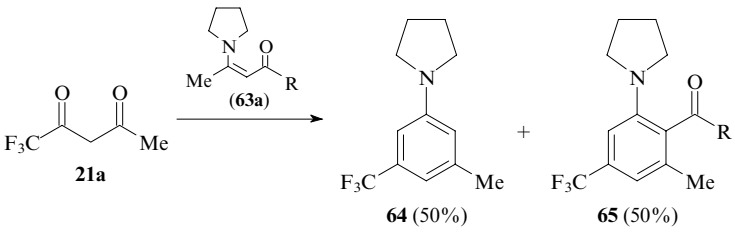
The formation of benzodiazepine **73** is observed only in the reaction of *o*-phenylenediamine with β-diketones **21** containing one fluoroalkyl substituent.[14] Coupling of β-diketones bearing two fluoroalkyl substituents with amines under ambient conditions gives salts, whereas upon boiling in ethanol in the presence of acetic acid, 2-fluoroalkylbenzimidazoles **74** are formed.[14]



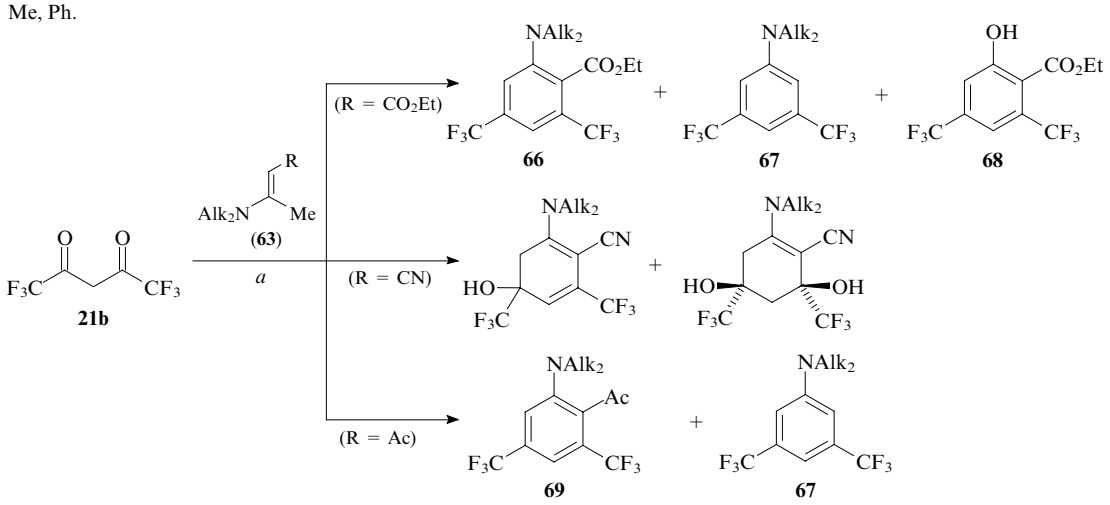
R^F = CF_3, C_2F_4H.

Benzodiazepines are not formed in the reaction of β-diketones **21a**,**d** bearing one fluoroalkyl substituent with *o*-phenylenediamine **75** containing strong electron-withdrawing groups. In this case, the carbonyl group bound to the non-fluorinated substituent is attacked by the amine to form β-aminovinyl ketone **76**.[110] Thus, regioselectivity of the reaction is determined by the mutual arrangement of substituents in diamine **75**, which differentiates the amino

Scheme 1

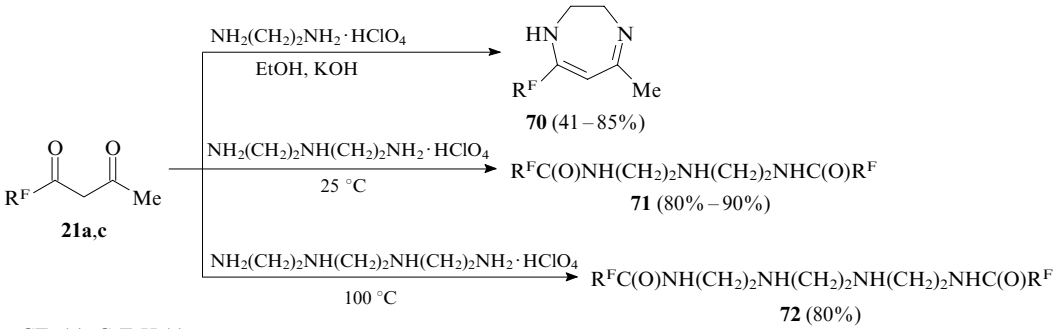


R = Me, Ph.



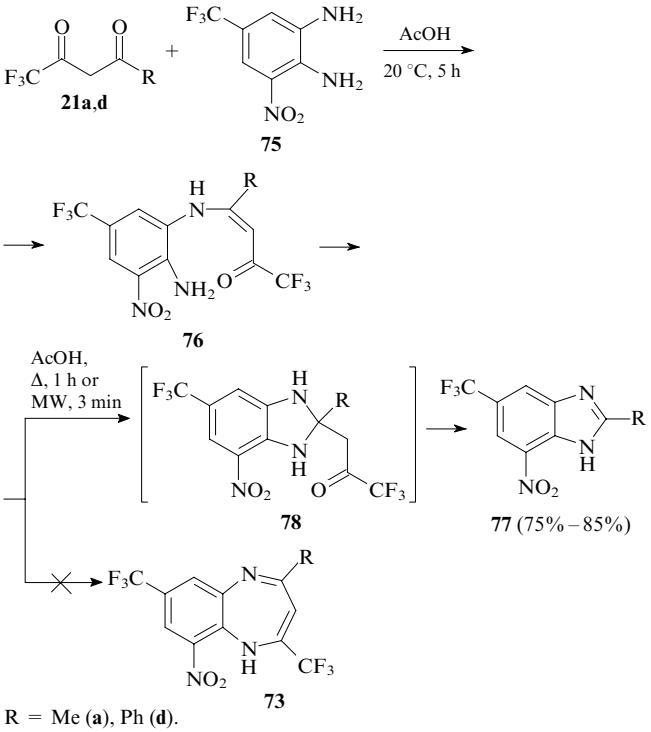
R = CN, CO_2Et, Ac; $NAlk_2$ = $N(CH_2)_4$, $N(CH_2)_5$, $N(CH_2CH_2)_2O$; (*a*) PhH, 20 °C, 3 days.

Scheme 2



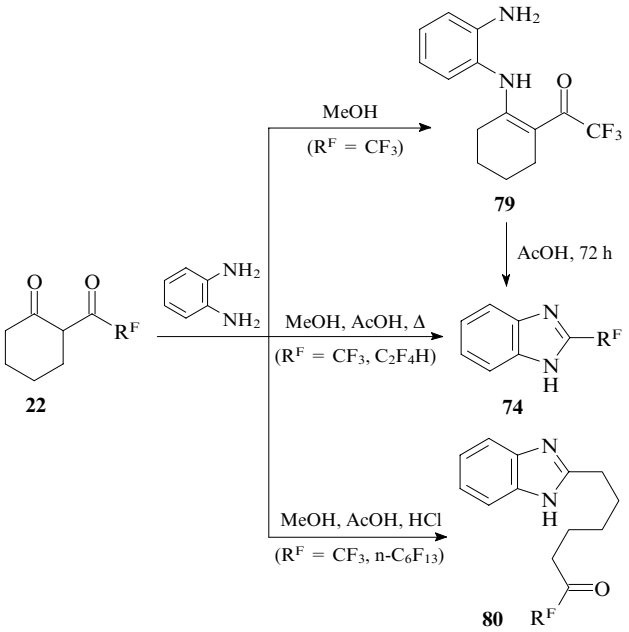
R^F = CF_3 (**a**), C_2F_4H (**c**).

groups according to their ability to nucleophilic attack. Upon heating in acetic acid or under microwave treatment, compound **76** gives benzimidazole **77** rather than the expected benzodiazepine **73** as a result of elimination of the ketone from intermediate **78**.[110]

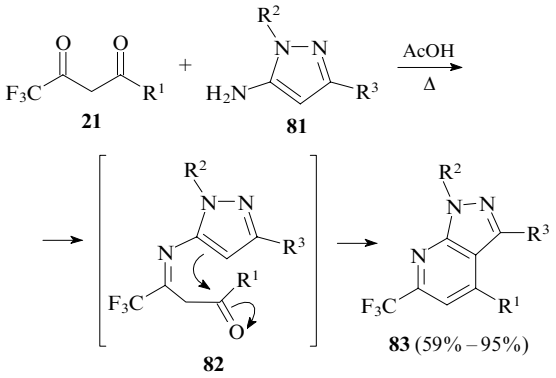


R = Me (**a**), Ph (**d**).

Different products are obtained in the reactions of 2-polyfluoroacylcyclohexanones **22** with *o*-phenylenediamine depending on conditions. Thus in the absence of an acidic catalyst, compound **79** is formed as a result of the amine attack on the carbonyl group of the ring. In the presence of acetic acid additives, enamine **79** undergoes acidic cleavage of the β-diketone fragment to form 2-fluoroalkynebenzimidazole **74**. When a mixture of hydrochloric and acetic acids is used, the C(1)–C(2) bond of the six-membered ring of the ketone is cleaved with subsequent transformation into benzimidazoles **80**.[84, 111, 112]

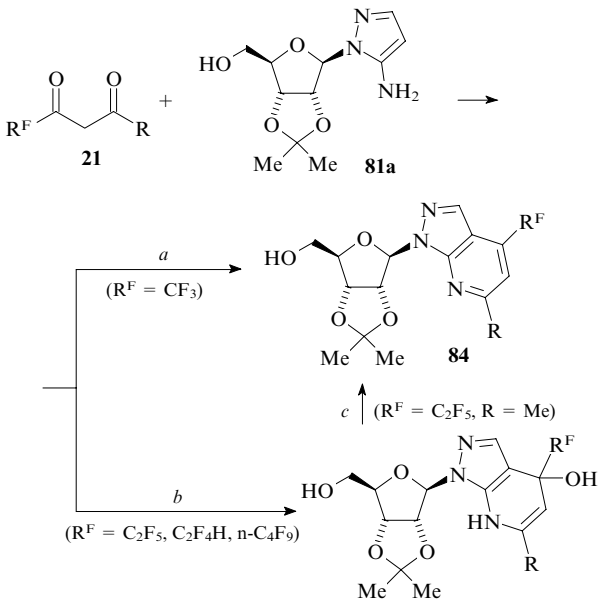


Coupling of trifluoromethyl-1,3-diketones **21** with 5-amino-1,3-disubstituted pyrazoles **81** occurs regioselectively with involvement of the carbonyl group at the fluorinated substituent to form imine **82**. The latter is rapidly cyclized in the presence of acetic acid to the corresponding 1*H*-pyrazolo[3,4-*b*]pyridine **83**.[100, 113–115]



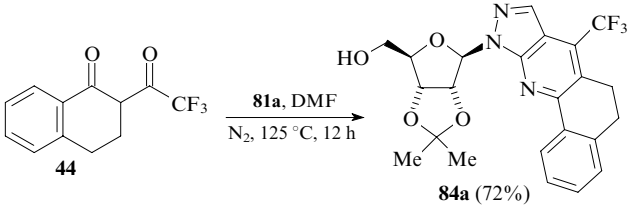
R^1 = CF3, Ph, Het; R^2 = H, Me, Ph; R^3 = Me, Ar.

Reaction of trifluoromethyl-1,3-diketones **21** with aminopyrazole **81a** containing a bulky substituent in position 1 results in pyrazolo[3,4-*b*]pyridines **84** with different arrangement of substituents in the heterocycle.[116]

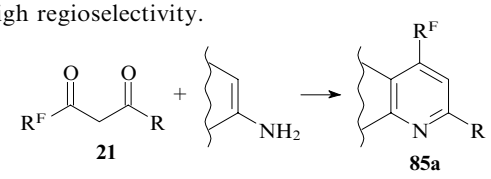


R = CF3, Me, Et, Ph, Het;
(*a*) DMF, N2, 125°C, 12 h; (*b*) DMF, N2, 80 °C, 12 h;
(*c*) without solvent, reduced pressure, 180 °C, 1 h.

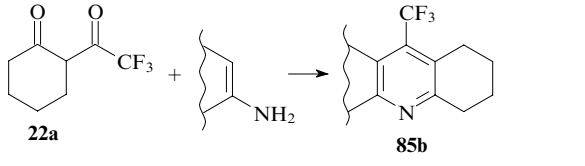
2-Trifluoroacety-3,4-dihydro-2*H*-naphthalen-1-one (**44**) undergoes similar transformation to give product **84a** in good yield.[116]

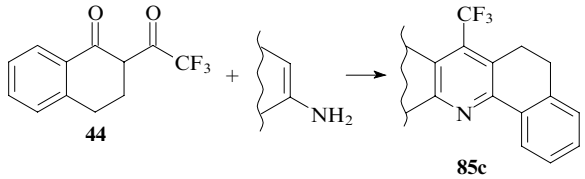


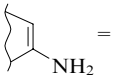
A large series of fused 4-polyfluoroalkyl-substituted pyridines **85a–c** was synthesized from β-diketones **21**, **22**, **44** and aminoheterocyclic compounds: 5-aminoisoxazole,[100] 5-amino-2-ethoxycarbonylfuran,[100] 5-amino-2-methoxycarbonylthiophene,[100] 6-aminouracil,[100] 2-aminobenzofuran,[117] 2-aminoindole,[117] 5-amino-1-*tert*-butyl-1*H*-pyrrole-3-carbonitrile,[118] 5-amino- (Refs 119 and 120) and 4-aminoimidazoles.[120] All reactions are characterized by high regioselectivity.



R^F = CF_3, CF_2H, CF_2Cl, C_2F_5, C_2F_4H, n-C_4F_9;
R = CF_3, Me, Et, Ph, Het.

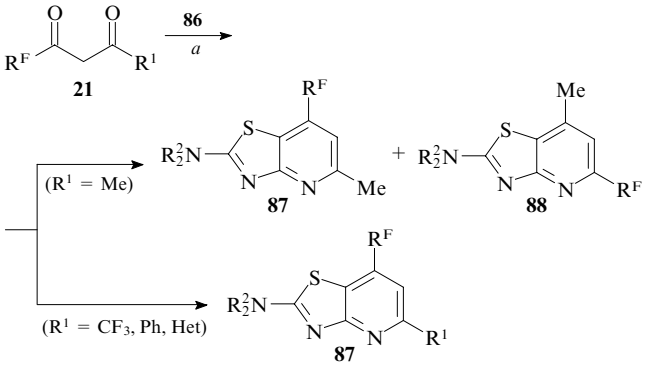


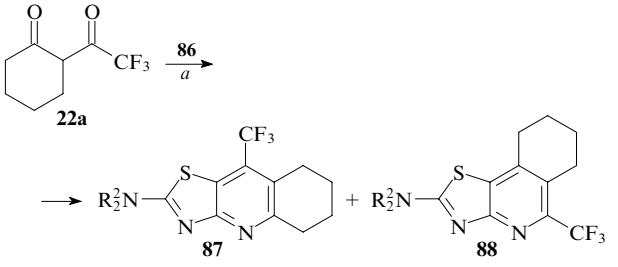




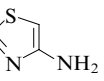
= $HetNH_2$.

It is of note that reactions of non-symmetrical 1,3-diketones **21** containing alkyl and fluoroalkyl substituents and cyclic β-diketone **22a** with aminothiazole derivatives **86** afford mixtures of regioisomers **87** and **88**. However, a similar reaction with phenyl- and hetaryl-substituted compounds **21**, as well as with hexafluoroacetylacetone (**21b**) furnishes exclusively thiazolo[4,5-*d*]pyridines **87**.[121]



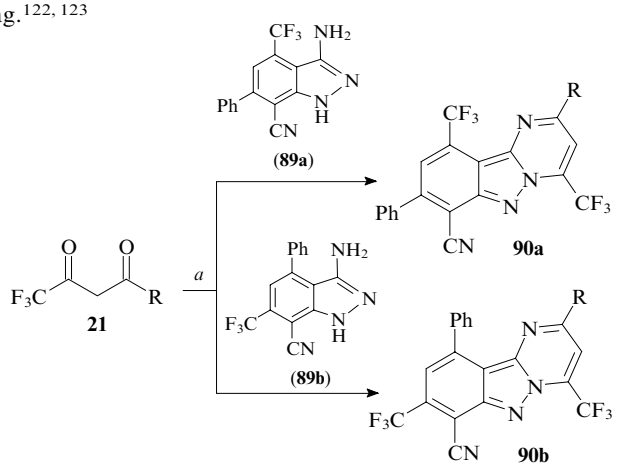


R^F = CF_3, CF_2H, CF_2Cl, C_2F_5;

86 =  (R^2 = H, Alk, Ar);

(*a*) AcONa (1.5 equiv.), AcOH, Δ, 1 h.

Under microwave irradiation, regioisomeric indazoles **89a**,**b** react with trifluoromethyl-β-diketones **21** to form pyrimido[1,2-*b*]indazoles **90a**,**b**. Reaction of non-symmetrical diketones proceeds regiospecifically, the direction of the nucleophilic attack of indazoles **89a**,**b** being opposite. This is rationalized as being due to the difference in relative reactivities of the tertiary nitrogen and the primary amine in compounds **89a**,**b** due to their different positions with respect to the trifluoromethyl group in the benzene ring.[122, 123]



R = CF_3, Me, Ph, 4-MeC_6H_4; (*a*) AcOH, MW, 1.5 min.

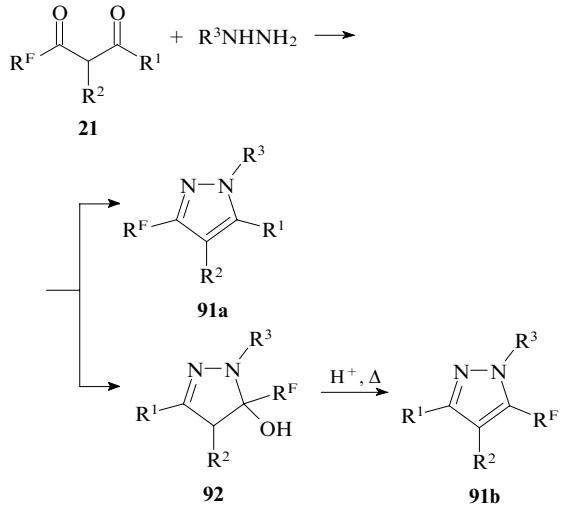
3. Reaction with N,N- and N,O-dinucleophiles

Cyclocondensation of 1,3-dicarbonyl compounds with hydrazines is the simplest and most general approach to the synthesis of pyrazoles. However, in the case of non-symmetrical substrates, regioisomeric pyrazoles are formed in low selectivity.[124–126]

The result of the reaction of fluoro-containing 1,3-diketones with substituted hydrazines depends on such factors as the nature and structure of substituents in the β-diketone and the reagent, reaction conditions.[127] Thus cyclization of monosubstituted hydrazines with non-symmetrical fluoro-containing diketones affords, as a rule, regioisomeric pyrazoles **91a**,**b**.[128, 129] In the reaction of acyclic β-diketones **21**, the product ratio is determined by the contribution of two enol forms. If R^1 is an aliphatic substituent, the $CH_2C(O)R^F$ group is preferably enolized, which results in formation of compounds **92** and **91b**. If R^1 is an aromatic substituent, the alternative enol form is a fully conjugated system and its contribution markedly increases, which results in the presence in the reaction mixture of a significant amount of pyrazole **91a**.[130–137] The direction of cyclocondensation of substituted phenylhydrazines with aryl-1,3-diketones **21** depends on the solvent used.[138–140] Reactions performed in 2,2,2-trifluoroethanol and 1,1,1,3,3,3-hexafluoropropan-2-ol demonstrate a substantial increase in selectivity; the isomer ratio achieves 99 : 1 in favour of 3-trifluoromethyl derivative **91a**.[139, 140]

Regioselective synthesis of pyrazoles **91b** is described.[141, 142] The fluoroalkyl-substituted carbonyl group of a 1,3-diketone was protected by conversion to the pyrrolidine derivative, which reacted with substituted hydrazines to give hydroxypyrazoline **92**. Subsequent dehydration of compound **92** resulted in the target product **91b**.

The synthesis of compounds of the type **91b** was also reported.[143–146]

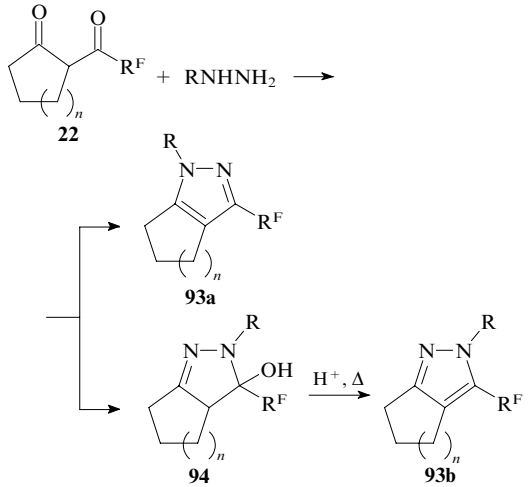


R^F = CF_3, CF_2H, C_2F_5, CF_2Me, CF_2Br, n-C_3F_7; R^1 = Me, Ar, Het; R^2 = H, F; R^3 = H, Me, Ar, Het.

Hetaryl-substituted hydrazines[147–149] and benzylhydrazines with bulky substituents[150] react with the more electrophilic carbonyl group C(O)R^F to form exclusively pyrazole **91a**. However, the reaction of 1,1,1-trifluoropentane-2,4-dione with 4,6-disubstituted 2-hydrazinyl-1,3,5-tetrazines resulted in the corresponding heterocycles **91b**.[151]

Since α-fluoro-substituted β-diketones exist in the ketone form, nucleophilic attack of the terminal amino group of phenylhydrazine occurs on the more electrophilic carbonyl group C(O)CF_3 to form regioisomer **91a**.[68,152]

Reaction of 2-trifluoromethyl-substituted cyclic 1,3-diketones **22** (n = 1, 2) with hydrazine, methyl- and phenylhydrazines occurs regiospecifically to form 3-trifluoromethylpyrazoles **93a**. Regiodirection of the coupling changes with lengthening of the perfluoroalkyl chain. Thus, if R^F = C_2F_4H or n-C_3F_7, a mixture of isomeric pyrazoles **93a**,**b** is obtained, while if R^F = n-C_4F_9 or n-C_6F_{13}, only pyrazoles **93b** are obtained from hydroxy derivatives **94**.[153]

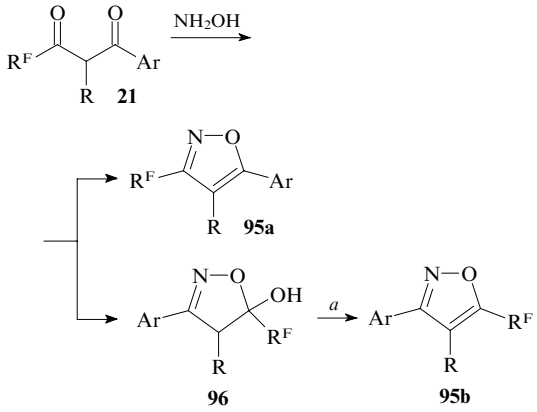


R^F = CF_3, CF_2H, C_2F_4H, n-C_3F_7, n-C_4F_9, n-C_6F_{13}; R = H, Me, Ar, Het; n = 1, 2.

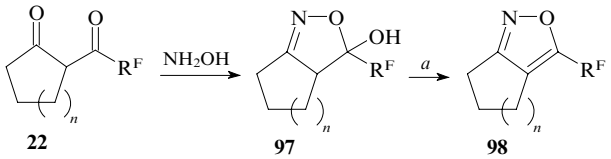
The result of the reaction of cyclic diketones is also determined by nucleophilicity of the terminal nitrogen atom in monosubstituted hydrazines. For example, the reaction of 2-hydrazinopyridine[153] with cyclic fluoroalkyl-substituted 1,3-diketones **22** starts from the nucleophilic attack of the terminal amino group of hydrazine on the carbonyl group of the ring. Cyclocondensation of 2-acetylcyclohexanone with 2,4-difluorophenylhydrazine occurs similarly.[142]

Reaction of 1,3-dicarbonyl compounds with hydroxylamine is considered to be the major method for the synthesis of isoxazole derivatives. In the case of non-symmetrical 1,3-diketones, this reaction can result in regioisomers.[154] Introduction of a polyfluorinated substituent into a 1,3-dicarbonyl compound leads to a substantial change in electron density distribution and, as a consequence, to change in relative reactivity of two carbonyl groups.

Regiodirection of the reactions of 2-fluoro-1,3-diketones **21** (R = F) existing exclusively in the ketone form with hydroxylamine is similar to that of the reaction with hydrazines. In this case, compound **95a**, which is the product of the nucleophilic attack on the carbonyl group bearing the fluoroalkyl substituent, is formed.[152] Opposite direction of the reaction is observed, when aryl β-diketones **21** (R = H)[127,136,155,156] and 2-(perfluoroacyl)cycloalkanones **22** are used as starting compounds.[157,158] Remarkably that hydroxyisoxazolines **96** and **97** formed, in contrast to non-fluorinated analogues, are sufficiently stable; their dehydration to the corresponding isoxazoles **95b** and **98** occurs only upon prolonged boiling of the reactants in the presence of concentrated sulfuric acid.

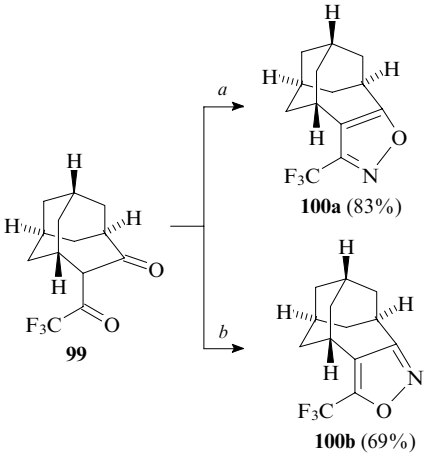


R^F = CF_3, CF_2Br; R = H, F; (*a*) AcOH – conc. H_2SO_4, Δ, 5–16 h.



R^F = CF_3, C_2F_4H, n-C_3F_7, n-C_4F_9, n-C_4F_8H, n-C_6F_{13}; n = 1, 2; (*a*) AcOH – conc. H_2SO_4, Δ, 5–16 h.

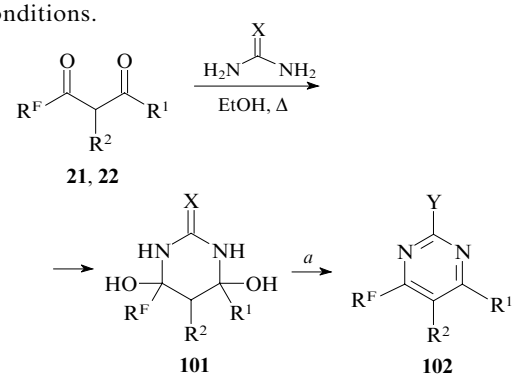
It was found[159] that the reaction of sterically hindered diketone **99** with hydroxylamine results in regioisomer **100a** or **100b** depending on the reaction conditions.



(*a*) $NH_2OH \cdot HCl$, NaOH, EtOH – H_2O, Δ, 5 h;
(*b*) $NH_2OH \cdot HCl$, AcOH, Δ, 2.5 h.

4. Reactions with urea derivatives

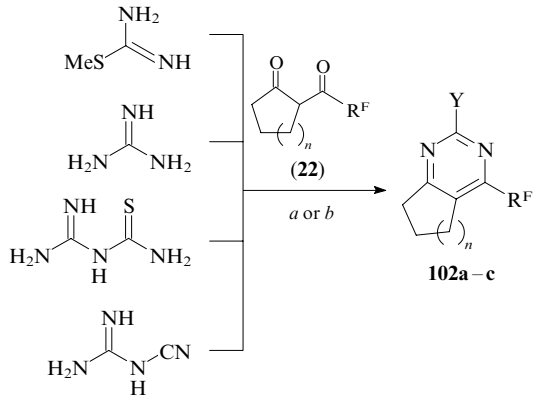
Symmetrical and non-symmetrical β-diketones **21**, **22** containing two fluorinated substituents react with urea or thiourea under reflux in ethanol to form hexahydropyrimidin-2-ones (-thiones) **101**, which are dehydrated in the presence of *p*-toluenesulfonic acid (*p*-TsOH) to form the corresponding pyrimidines **102**.[160, 161] In the case of non-symmetrical acyclic diketones with one perfluorinated substituent [160] and polyfluoroalkyl-substituted 2-acylcycloalkanones,[162] pyrimidines **102** are obtained under milder conditions.



R^F = CF_3, C_2F_4H, C_2F_5, n-C_3F_7, n-C_4F_8H, n-C_4F_9, n-C_6F_{13};
R^2 = H; R^1 = CF_3, Alk, Ar; R^1 – R^2 = $(CH_2)_3$, $(CH_2)_4$;
X = O, Y = OH; X = S, Y = SH; (*a*) *p*-TsOH, PhMe, Δ.

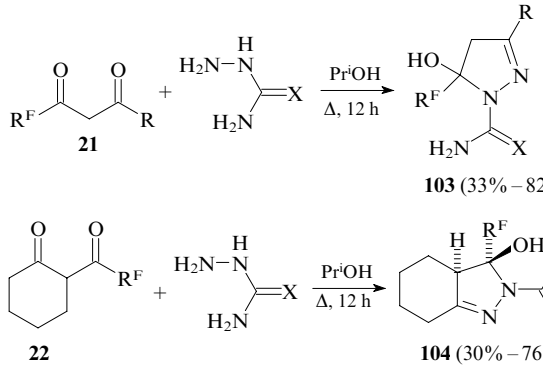
Reactions of 2-polyfluoroacylcycloalkanones **22** with other urea derivatives (*S*-methylisothiourea, guanidine, guanidyl thiourea and dicyanodiamide) were studied.[162] In all cases, the corresponding pyrimidines **102a**–**c** 5,6-annulated with carbocycles were obtained; when reagents with low nucleophilicity (urea, thiourea, dicyanodiamide) were used, the yields of the target products decreased with lengthening of the perfluoroacyl chain.

The formation of pyrimidines containing different substituents in positions 2, 4 and 6 of the ring was also observed for the reaction of trifluoromethyl-substituted diketones **21** with dicyanodiamide [163] and guanidine derivatives.[164–166]



R^F = CF_3, C_2F_4H, C_2F_5, n-C_3F_7, n-C_4F_8H, n-C_4F_9, n-C_6F_{13};
Y = OH (**a**), SH (**b**), $NHC(O)NH_2$ (**c**); (*a*) $BF_3 \cdot OEt_2$, Pr^iOH, Δ;
(*b*) EtOH, Δ.

Reactions of acyclic polyfluoro-containing 1,3-diketones **21** and 2-polyfluoroacylcyclohexanones **22** (n = 2) with semicarbazides result in 5-hydroxy-2-pyrazolines **103** [167] and 3-hydroxy-2-(thio)carbamoyl-3-polyfluoroalkyl-3,3a,4,5,6,7-hexahydro-2*H*-indazoles **104**,[84, 168] respectively, the condensation products with the carbonyl group at the non-fluorinated substituent.

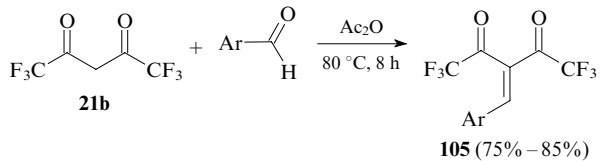


R^F = CF_3, CF_2H, C_2F_5, C_2F_4H, n-C_3F_7, n-C_4F_9;
R = Alk, Ar, Het; X = O, S.

Reactions of semicarbazide and thiosemicarbazide derivatives with non-fluorinated 1,3-diketones (including symmetrical ones) proceed in a complicated way and depend on the structure of starting ketone, the nature of substituents in the nucleophile, reactant ratio and reaction conditions.[169, 170]

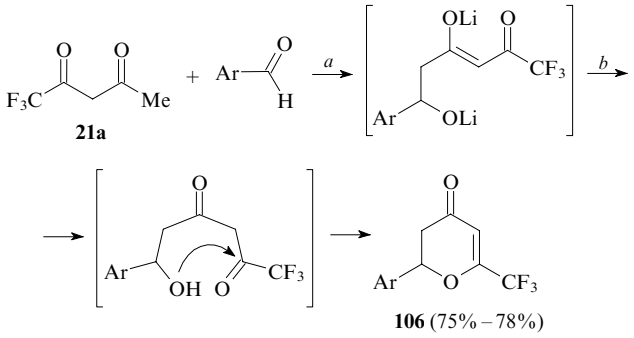
5. Reactions with aldehydes and ketones

Heating of 1,1,1,5,5,5-hexafluoropentane-2,4-dione (**21b**) with an equimolar amount of aromatic aldehydes in acetic anhydride affords the corresponding α,β-unsaturated β-diketones **105** in high yields.[171]



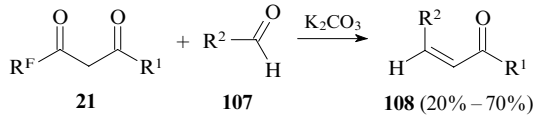
The reaction with formaldehyde furnishes extremely unstable 2-methylidene-1,3-diketone, which undergoes the Diels–Alder reaction with 1,3-dienes to form carbocyclic products.[172]

One-pot reaction of 1,1,1-trifluoropentane-2,4-dione (**21a**) dianion with aromatic aldehydes results in the corresponding 6-aryl-2,3-dihydro-4*H*-pyran-4-ones **106**.[173]



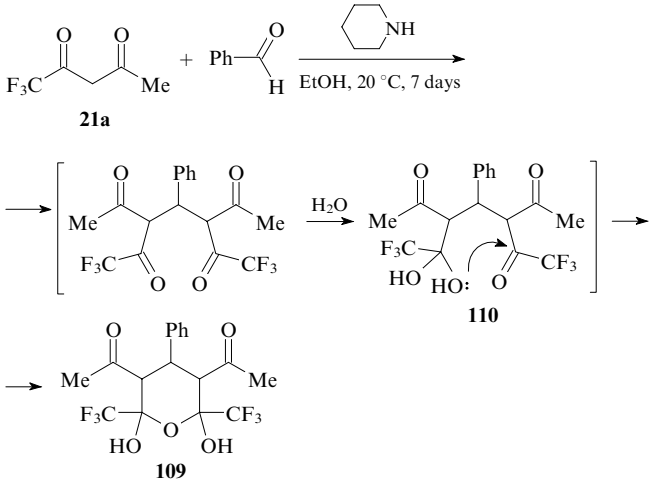
(*a*) 1) LDA (2.5 equiv.), THF, 0 °C, 1 h; 2) −78 °C, diketone, 1 h; 3) aldehyde, −78 °C → 20 °C, 12 h;
(*b*) 10% HCl, extraction with EtOAc.

Reaction of symmetrical and non-symmetrical perfluorinated 1,3-diketones **21** with polyfluorinated aldehydes **107** proceeds in the presence of potassium carbonate to give exclusively α,β-unsaturated ketones **108** in high yields.[174]

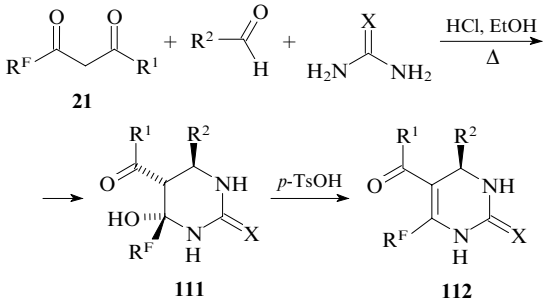


R^1 = Me, Ph, CF_3, C_2F_4H, n-C_4F_8H;
R^F = R^2 = CF_3, C_2F_4H, n-C_4F_8H, n-C_6F_{13}.

Coupling of benzaldehyde with 2 equiv. of trifluoroacetylacetone (**21a**) under the conditions of basic catalysis results in 3,5-diacetyl-2,6-dihydroxy-4-phenyl-2,6-bis(trifluoromethyl)pyran (**109**).[175] Under similar conditions, acetylacetone and alkyl acetoacetates react with aromatic aldehydes to form β-hydroxy ketones.[176–178] The unusual reaction route in the case of fluoro-substituted 1,3-diketone **21a** is explained[175] by hydration of the α-carbonyl groups relative to the electron-withdrawing trifluoromethyl group. As a result, intermediate triketone **110** is cyclized to pyran.

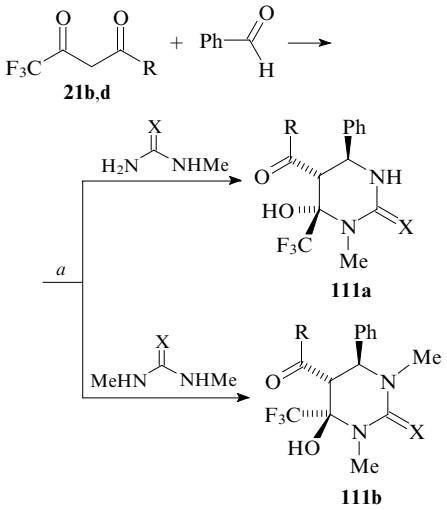


Three-component condensation of fluorinated 1,3-diketones **21** with (hetero)aromatic aldehydes and (thio)urea (the Biginelli reaction) was described.[179] Hexahydropyrimidines **111** formed are converted to the corresponding tetrahydropyrimidines **112** upon heating in toluene in the presence of catalytic amounts of *p*-toluenesulfonic acid. If the reaction was performed under solvent-free conditions in the presence of catalytic amounts of 1-butyl-3-methylimidazolium tetrafluoroborate,[180] $Yb(OTf)_3$ (Ref. 181) and SmI_2,[182] or in dry acetonitrile in the presence of 2% $Bi(OTf)_3$,[183] the yield of compound **112** increased substantially and the reaction time decreased.



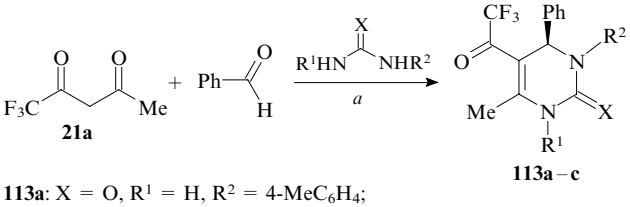
R^F = CF_3, CF_2H, C_2F_4H, n-C_3F_7, n-C_4F_9;
R^1 = Me, Ph, CF_3; R^2 = Ar, Het; X = O, S.

Substituted (thio)ureas were also used in the Biginelli reaction.[184] It was found that in the case of diketones **21b**,**d**, benzaldehyde and *N*-monomethyl-substituted (thio)ureas, hexahydropyrimidines **111a** were formed with the same relative configuration of the steric centres as is the case for unsubstituted reagents. However, the reaction of trifluoromethyl-1,3-diketones with benzaldehydes and *N*,*N*′-dimethyl(thio)ureas gave products **111b** with different configuration.



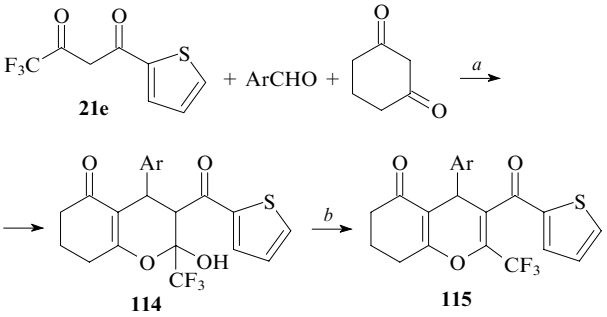
R = CF_3 (**b**), Ph (**d**); X = O, S;
(*a*) Me_3SiCl (4 equiv.), DMF, 20 °C, 48–72 h.

It is of note that cyclization of 1,1,1-trifluoropentane-2,4-dione (**21a**) and benzaldehyde with substituted (thio)ureas occurs unusually to form tetrahydropyrimidines **113a–c**.[184]



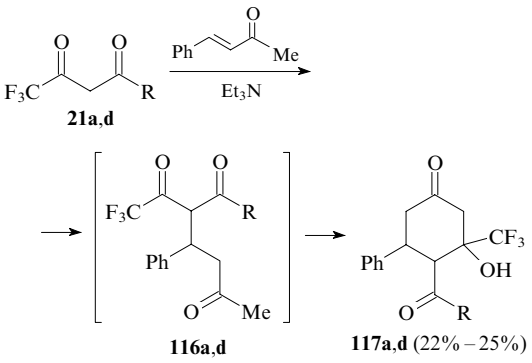
113a: X = O, R^1 = H, R^2 = 4-MeC_6H_4;
113b: X = S, R^1 = R^2 = Me; **113c**: X = S, R^1 = H, R^2 = Ph;
(*a*) Me_3SiCl (4 equiv.), DMF, 20 °C, 48–72 h.

Three-component condensation of 1-(2-thienyl)-4,4,4-trifluoromethylbutane-1,3-dione (**21e**) with aromatic aldehydes and cyclohexane-1,3-dione in the presence of catalytic amounts of triethylamine leads to 2-(trifluoromethyl)-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one derivatives **114**, which are dehydrated to form the corresponding heterocycles **115**.[185]



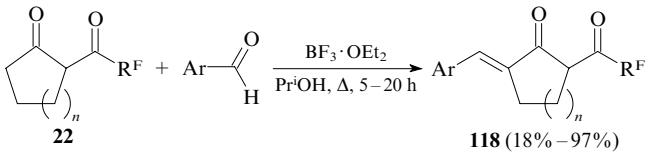
(*a*) Et_3N (25 mol.%), EtOH, Δ; (*b*) *p*-TsOH (4 equiv.), $CHCl_3$, Δ.

Reaction of trifluoromethyl-1,3-diketones **21a**,**d** with benzylideneacetone in the presence of a base results in the monoaddition products **116a**,**d**, which further cyclized with involvement of the carbonyl group bearing the trifluoromethyl substituent. This reaction affords compounds **117a**,**d** in low yields.[186]

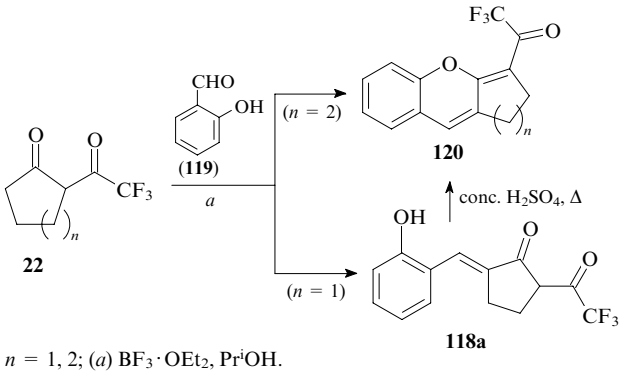


R = Me (**a**), Ph (**d**).

2-Polyfluoroacylcycloalkanones **22** react with aromatic aldehydes in the presence of catalytic amounts of boron trifluoride etherate to give enediones **118** in high yields. However, diketones of the cyclohexane and cyclopentane series react with salicylaldehyde (**119**) differently. The former give compounds **120** upon condensation and heterocyclization, while *o*-hydroxyphenyl-substituted enedione **118a** was obtained from the latter. It is converted to the corresponding heterocyclic product **120** when heated with concentrated H_2SO_4.[187]



R^F = CF_3, C_2F_4H, C_2F_5, n-C_3F_7, n-C_4F_9; *n* = 1, 2.

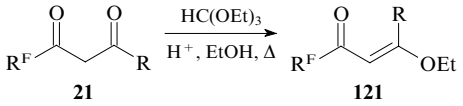


n = 1, 2; (*a*) $BF_3 \cdot OEt_2$, Pr^iOH.

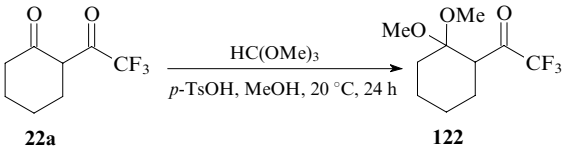
Non-fluorinated 2-acetylcycloalkanones react readily with aromatic aldehydes to form the double condensation products with involvement of the activated methyl and methylene groups.[188]

6. Miscellaneous reactions

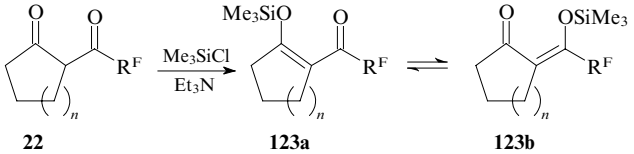
Reaction of perfluoroalkyl-containing diketones **21** with triethyl orthoformate in ethanol in the presence of strong mineral acids is a regioselective method for the synthesis of β-ethoxy enones **121**.[189] On the other hand, the reaction of 2-trifluoroacetylcyclohexanone **22a** with trimethyl orthoformate results in the corresponding ketal **122**.[190]



R^F = CF_3, n-C_4F_9, n-C_6H_{13}; R = Me, Et, Pr^i.

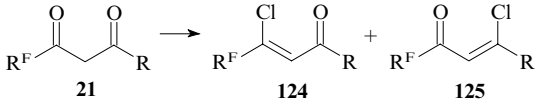


Enol silyl ethers **123** were obtained from cyclic 1,3-diketones **22** and chlorotrimethylsilane in the presence of twofold excess of triethylamine. Compounds **123** have the *Z*-configuration and exist in deuteriochloroform solution as mixtures of endo- (**123a**) and exocyclic enol forms (**123b**) in different proportions depending on the size of the carbocycle and the length of the perfluoroalkyl chain.[191]



R^F = CF_3, n-C_3F_7; *n* = 1, 2.

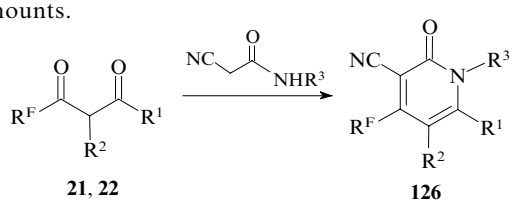
Mixtures of β-chlorovinyl ketones **124** and **125** are formed from acyclic fluoro-containing β-diketones **21** under the action of different chlorinating agents ($SOCl_2$,[192, 193] $POCl_3$, $COCl_2$ [194]), the regioselectivity of the



R^F = CF_3, C_2F_5, C_2F_4H, n-C_3F_7; R = Alk, Ar, Het.

process depending on the reagent used, reaction conditions and the structure of substituent R.

Polyfluorinated 1,3-diketones **21**, **22** are also used for the regiospecific synthesis of 4-fluoroalkyl-2-pyridones **126**.[195,196] The highest yields of the target products **126** are obtained upon reaction of β-diketones **21**, **22** with 2-cyanoacetamide in isopropyl alcohol in the presence of freshly calcined potassium fluoride.[196] It is of note that this method can only be applied for the preparative synthesis of 3-cyano-2-pyridones **126** with short polyfluoroalkyl substituents. In the case of cyclic substrates **22** with long fluorohydrocarbon chain, the yield of the target product is sharply decreased; no compounds of this type are formed from analogous acyclic β-diketones **21** even in trace amounts.

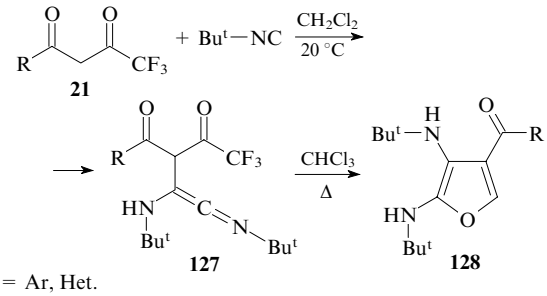


21, **22** **126**

$R^F = CF_3, CF_2H$; $R^2 = H$: $R^1 = Me, Ar, Het$; $R^1 - R^2 = (CH_2)_3, (CH_2)_4$; $R^3 = H, Me$.

Condensation of two malononitrile molecules with one molecule of trifluoromethyl-1,3-diketone **21** also results in 2-pyridones **126**.[197]

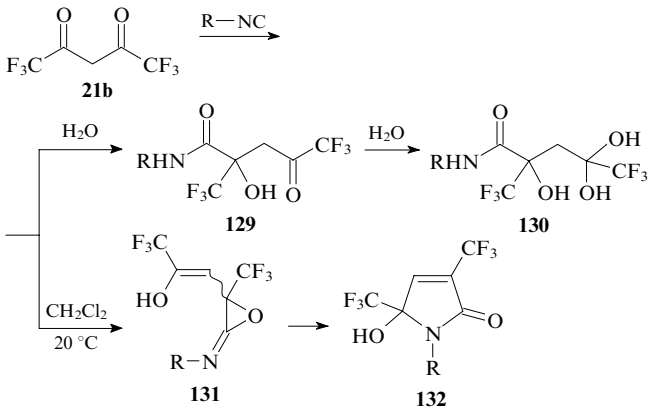
Reaction of aryl trifluoromethyl-β-diketones **21** with 2 equiv. of *tert*-butyl isocyanide furnishes ketene imine **127**, which transforms quantitatively into the corresponding furan derivative **128** upon boiling in chloroform.[198]



21 **127** **128**

R = Ar, Het.

The reaction of equimolar amounts of alkyl isocyanides and 1,1,1,5,5,5-hexafluoropentane-2,4-dione (**21b**) in water results in a mixture of fluorinated amides **129** and **130**.[199] However, in the similar reaction in dichloromethane, alkyl isocyanide attacks first the β-carbon atom of the diketone

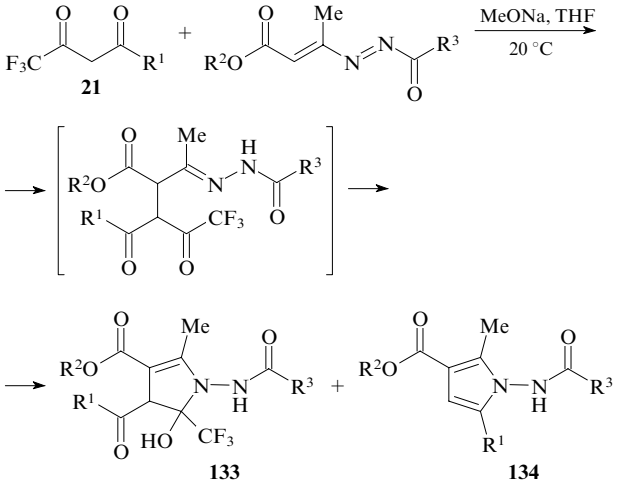


21b **129** **130** **131** **132**

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

to form imino oxirane **131**, which undergoes the Cope–Claisen rearrangement to the corresponding unsaturated lactam **132**.[200]

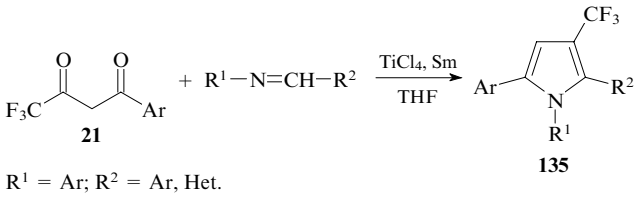
A series of diverse heterocyclic compounds was obtained from trifluoromethyl-substituted diketones **21**, namely: derivatives of 1*H*-pyrrole **133**–**135**,[201,202] 2-pyrone **136**[203] and γ-lactone **137**.[204] Thus 1,2-diazabuta-1,3-dienes react regioselectively with 1,3-diketones **21** to form stable derivatives of 2-hydroxy-2-trifluoromethyl-2,3-dihydro-1*H*-pyrrole **133**, the yield of by-products **134** being only 4%–6%; in the case of hetaryl-substituted diketones **21**, the reaction is regiospecific.[201]



21 **133** **134**

R^1 = Me, CF_3, Ar, Het; R^2 = Me, Et; $R^3 = NH_2$, NHPh, OBu^t, OMe.

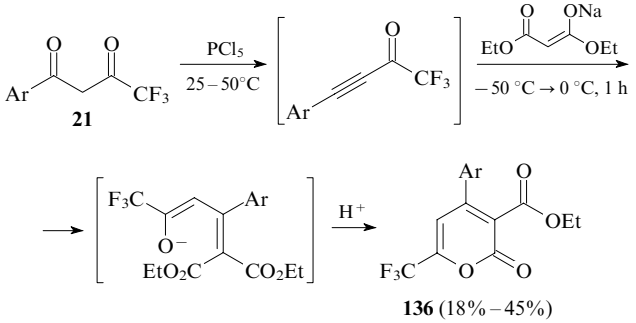
Aroyl trifluoromethyl ketones **21** react with imines catalyzed by low-valence titanium compounds leading to 3-trifluoromethyl-substituted pyrroles **135** in high yields.[202]



21 **135**

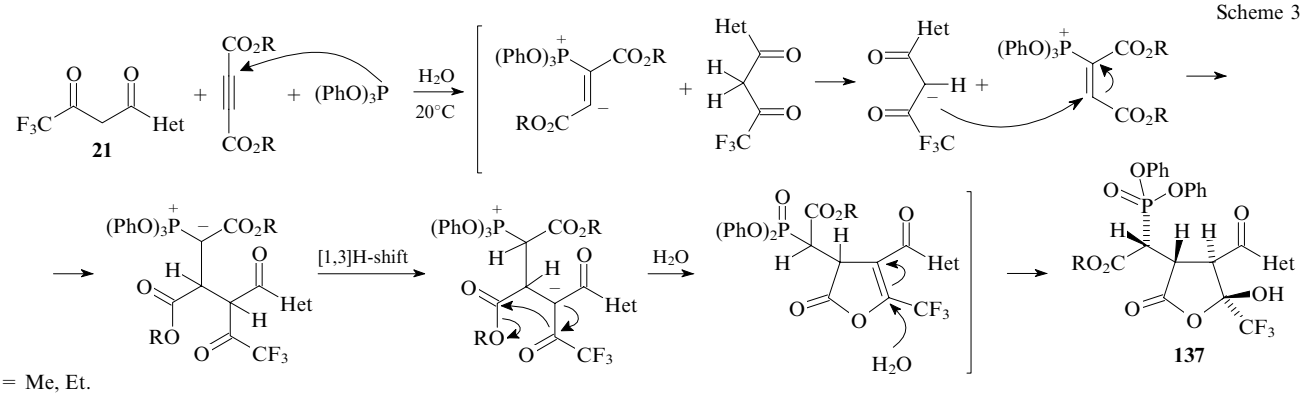
R^1 = Ar; R^2 = Ar, Het.

The treatment of aryl-1,3-diketone **21** with phosphorus pentachloride followed by the introduction of sodium diethyl malonate into the reaction mixture afforded the corresponding 2*H*-pyran-2-ones **136** in moderate yields.[203] The reaction rate depended strongly on the nature of aryl substituent. Electron-donating substituents in the *para*-position of the aromatic ring accelerate the process substantially, whereas electron-withdrawing substituents slow it down.



21 **136** (18%–45%)

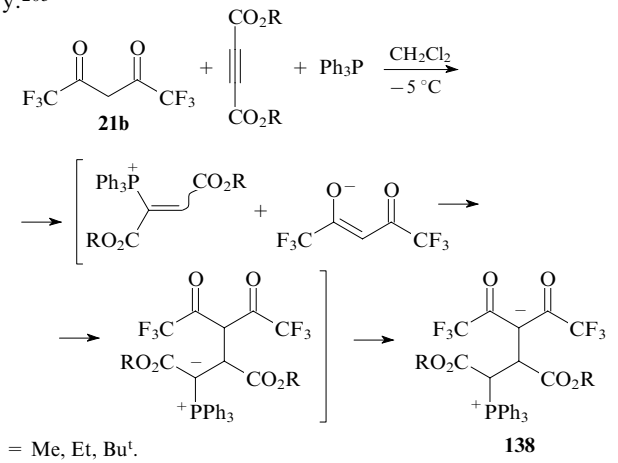
Scheme 3



R = Me, Et.

Synthesis of γ-lactones **137** was performed by mixing the equimolar amounts of triphenyl phosphite, diketone **21** and dialkyl acetylenedicarboxylate in aqueous medium. This reaction is diastereoselective, characterized by simplicity of experiment and high yields of the target products (Scheme 3).[204]

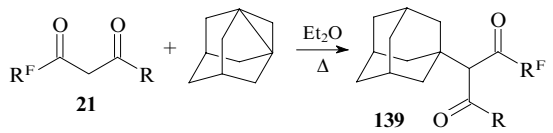
However, the reaction of hexafluoroacetylacetone (**21b**) with dialkyl acetylenedicarboxylates in the presence of triphenylphosphine in dichloromethane results in trifluoromethylated zwitterions **138** in the yields of 85%–88%. Compounds **138** are stable crystalline substances, their structures were confirmed by elemental analysis, IR, ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectroscopy and mass spectrometry.[205]



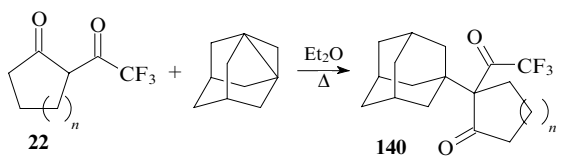
R = Me, Et, Bu^{t}.

For reactions of trifluoromethylated 1,3-diketones **21** and 2-polyfluoroacylcycloalkanones **22** with different phosphorus derivatives see Refs 206 (a review) and 207.

The reactions of 1,3-dehydroadamantane with polyfluorinated acyclic β-diketones **21**[208] and 2-trifluoroacetylcycloalkanones **22**[209] gave for the first time the corresponding fluoro-substituted α-adamantyl-1,3-diketones **139** and **140** in the yields of 83%–98%. C-Adamantylation was performed in boiling diethyl ether in dry oxygen-free nitrogen atmosphere with 1.5–2-fold excess of a diketone for 1–2 h, it required no catalyst.[208, 209]

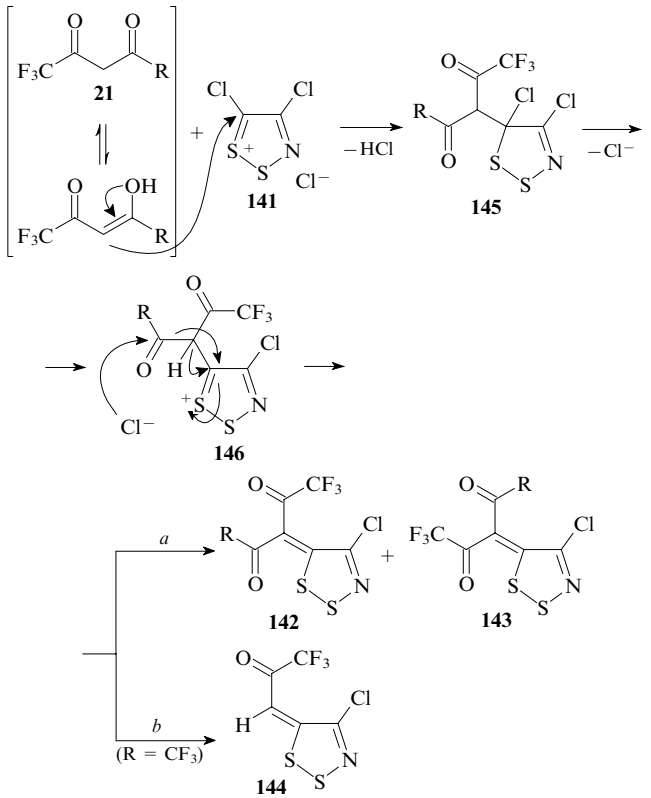


R^{F} = CF_3, CF_2H; R = CF_3, Bu^{t}, Ar, Het.



n = 1, 2.

The reactions of trifluoromethyl-substituted β-diketones **21** with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt, **141**) in the presence of pyridine in dichloromethane at room temperature resulted in the corresponding 5-alkylidene-1,2,3-dithiazoles **142**–**144**.[210] In the case of hexafluoroacetylacetone (**21b**, R = CF_3), products **142** and **144** were isolated in the yields of 18% and 44%, respectively. 1,1,1-Trifluoropentane-2,4-dione (**21a**, R = Me) gives an inseparable mixture of stereoisomers **142** and **143** in an overall yield of 21% (the ratio **142** : **143** = 85 : 15). Remarkably, the reactions of aroyltrifluoroacetylmethanes **21** (R = Ph, 2-naphthyl) afford under similar conditions the only stereoisomer **143** in the yields of 34% and 18%, respectively. The proposed mechanism of this reaction includes the nucleophilic attack of a carbon atom of the enol on the C(5) atom of Appel's salt to form intermediate **145**, which further extrudes the Cl atom to form a new dithiazolium ion **146**. Deprotonation with subsequent elec-



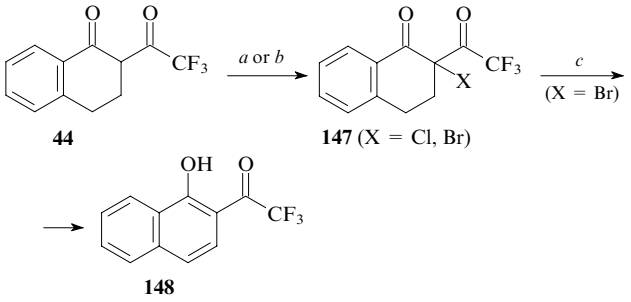
R = CF_3, Me, Ph, 2-naphthyl; (*a*) Δ; (*b*) base.

tron migration (pathway *a*) give compounds **142** and/or **143**. Nucleophilic attack of the chloride ion on the more electrophilic [due to interaction with the electrophilic S(1) atom] carbonyl carbon atom (pathway *b*) and subsequent elimination of trifluoroacetyl chloride result in compound **144** with *syn* arrangement of the trifluoroacetyl group and Cl atom.[210]

Hydrogenation of acyclic β-diketones **21** over Pt/Al_2O_3 in the presence of chiral amino alcohols or amines[211] and reduction with baker's yeast[212] occur regioselectively to form the corresponding β-hydroxy ketones with the hydroxyl group in the α-position with respect to the trifluoroalkyl substituent.

A series of reductive systems was investigated in reactions of enantio- and diastereoselective hydrogenolysis of 1,3-diphenyl-2,2-difluoropropane-1,3-dione. The best result was obtained in the case of Ru-catalyzed process using chiral diphosphine ligands as additives.[213]

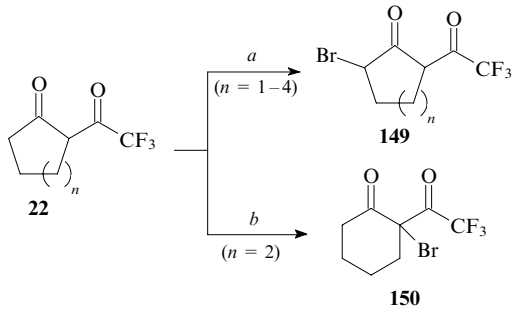
Direct halogenation of 1,3-diketone **44** occurs readily to form α-chloro and α-bromo dicarbonyl compounds **147**.[214] Dehydrobromination of 2-bromo-2-trifluoroacetyl-1-tetralone **147** on boiling in a nitrogen atmosphere for 5 h results in aromatization to afford 2-trifluoroacetyl-1-naphthol (**148**) in a yield of 67%.[214]



44 **147** (X = Cl, Br) **148**

(*a*) SO_2Cl_2 (1.1 – 1.2 equiv.), $CHCl_3$; (*b*) Br_2 (1.1 equiv.), $CHCl_3$; (*c*) *o*-dichlorobenzene, Δ, 5 h.

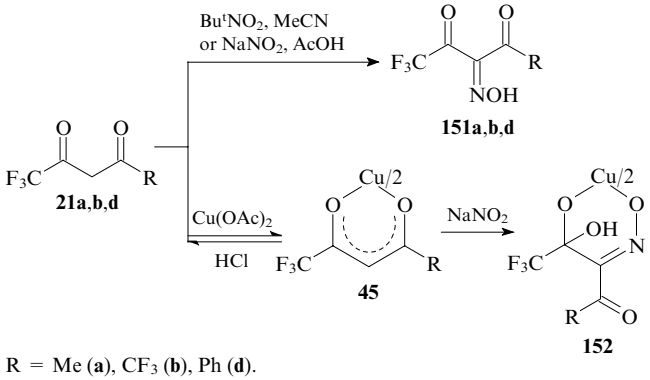
There are contradictions in the literature concerning halogenation on non-fused analogues, compounds **22**. Thus the treatment of 2-trifluoroacetylcycloalkanones **22** with bromine and pyridine (1 equiv. each) was reported[215] to result in high yields of the ω-substitution products **149**. However, under similar conditions 2-trifluoroacetylcyclohexanone **22a** gave a complex mixture where only the starting 1,3-diketone and trace amounts of compound **149** could be identified by NMR spectroscopy.[214] However, bromination of cyclic β-diketone **22a** with 1 equiv. of Br_2 in chloroform gives α-bromo-β-diketone **150** as the major product.[214] When 2-trifluoroacetylcyclohexanone **22a** was replaced by its lithium salt and elemental bromine was replaced by *N*-bromosuccinimide, α-bromo derivative **150** was obtained in high yield as the only product.[214]



22 **149** **150**

(*a*) 1) Br_2, $CHCl_3$, 25 °C, 2 h; 2) Py, $CHCl_3$, 25 °C, 1 h; (*b*) Br_2, $CHCl_3$, 20°C.

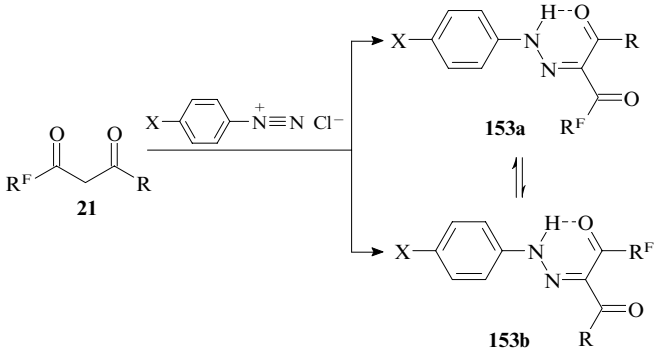
The reaction of fluoro-containing β-diketones **21** with *tert*-butyl nitrite[216] or sodium nitrite[217,218] in acidic medium furnishes the corresponding 2-hydroxyimino 1,3-dicarbonyl compounds **151**, which can be used as 'building blocks' for the synthesis of different heterocycles containing the hydroxyimine fragment.[217–220] Compounds **151** are unstable; only 3-hydroxyimino-4-phenyl-1,1,1-trifluorobutane-2,4-dione (**151d**) was isolated in the individual state. However, the reaction of copper bis(1,3-diketonates) **45** with sodium nitrite in acetic acid leads to stable hydroxy-substituted ketooximates **152**, which is a clear example of the role of copper ion in formation and isolation of isonitroso-derivatives of fluoroalkyl-containing 1,3-diketones.[217,218]



21a,b,d **151a,b,d** **45** **152**

R = Me (**a**), CF_3 (**b**), Ph (**d**).

Coupling of fluoro-substituted β-diketones **21** with aryldiazonium chlorides in the presence of sodium acetate gives 2-arylhydrazones of 1,2,3-triketones **153**.[221–225] The data from NMR spectroscopy and X-ray diffraction analysis demonstrated that 2-arylhydrazono-1,3-diketones exist in crystal and in deuteriochloroform solution predominantly as isomer **153a** where the carbonyl group at the non-fluorinated substituent is involved in intramolecular hydrogen bonding.[225,226]



21 **153a** **153b**

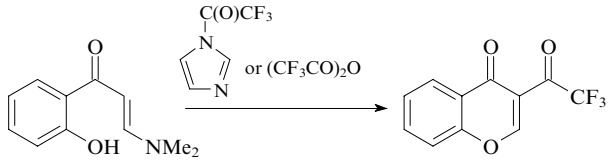
R^F = C_2F_4H, CF_2OCF_3, n-C_3F_7; R = Me, Ph, Bu^t; X = H, Me, OMe, NO_2.

Like unsubstituted 1,3-diketones, compounds **153** react with amines, hydrazine, phenylhydrazine, thiosemicarbazide and hydroxylamine to form the corresponding derivatives.[221–225,227–230] The literature data on the synthesis, structures and chemical transformations of fluoro-substituted 2-(het)arylhydrazono-1,3-dicarbonyl compounds are generalized in a review.[225]

7. Reactions of 3-polyfluoroacylchromones

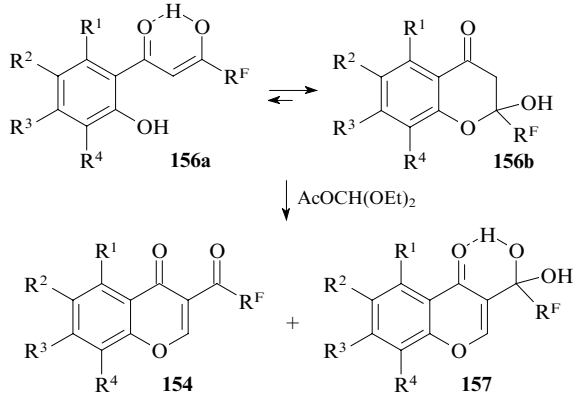
3-Polyfluoroacylchromones **154** containing a β-dicarbonyl fragment are highly reactive compounds. Due to the presence of three electrophilic centres, C(2), C(4) and $R^FC(O)$, these derivatives are often used for the synthesis of novel fluoro-containing heterocycles.

For the first time, 3-trifluoroacetylchromone **154a** was synthesized by the reaction of enamino ketone **155** with trifluoroacetic anhydride or *N*-trifluoroacetylimidazole (yield 89% or 93%).[231]



155 **154a**

In a general method for the synthesis of 3-polyfluoroacylchromones **154**, an excess (6 equiv.) of diethoxymethyl acetate was used as a formylating agent and a solvent and the coupling products of 2-hydroxyacetophenones with ethyl perfluorocarboxylates **156** as substrates.[232–234] Compounds **156** in deuteriochloroform solution exist as a mixture of cyclic (**156b**) and open-chain (**156a**) tautomers with domination of the cyclic semiketal form.[235–237] Spectral characteristics of the reaction mixture indicate that the reaction results in a mixture of 3-polyfluoroacylchromones **154** and their hydrated forms **157**, the ratio **154** : **157** being dependent on the number of fluorine atoms (~1% of compound **157** in the case of $R^F = CF_2H$, ~6% in the case of $R^F = C_2F_4H$, ~15% in the case of $R^F = C_2F_5$, ~50% in the case of $R^F = CF_3$).[232–234]

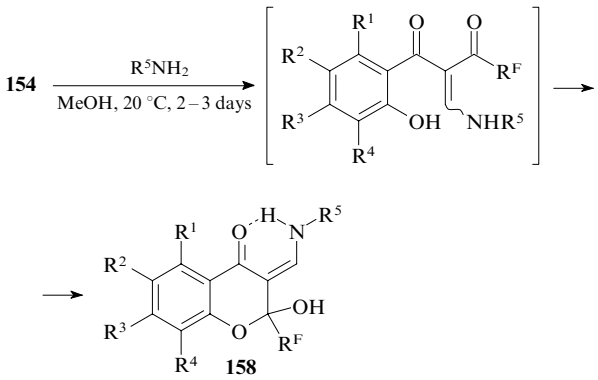


156a **156b** **154** **157**

R^F = CF_3, CF_2H, C_2F_4H, C_2F_5; R^1 = H, Me, OMe; R^2 = H, Me, NO_2, Cl, Br; R^3 = H, Me, OMe; R^2–R^3 = OCH=CH; R^4 = H, Br, OMe.

Reactions of 3-polyfluoroacylchromones **154** with primary aliphatic and aromatic amines occur as 1,4-addition followed by opening of the pyran ring and cyclization to 3-alkyl(aryl)aminomethylidene-2-hydroxy-2-polyfluoroalkylchroman-4-ones **158**.[233, 234, 238]

6-Polyfluoroacylnor-kellins **154** (R^2–R^3 = OCH=CH) react with aliphatic amines (cyclohexylamine and benzylamine) to form only mixtures of unidentified products.[233] The reaction of 3-formylchromones with primary aromatic amines results in a mixture of 3-aryliminomethylchromone and 2-arylamino-3-arylaminomethylidenechroman-4-one that was difficult to separate.[239]

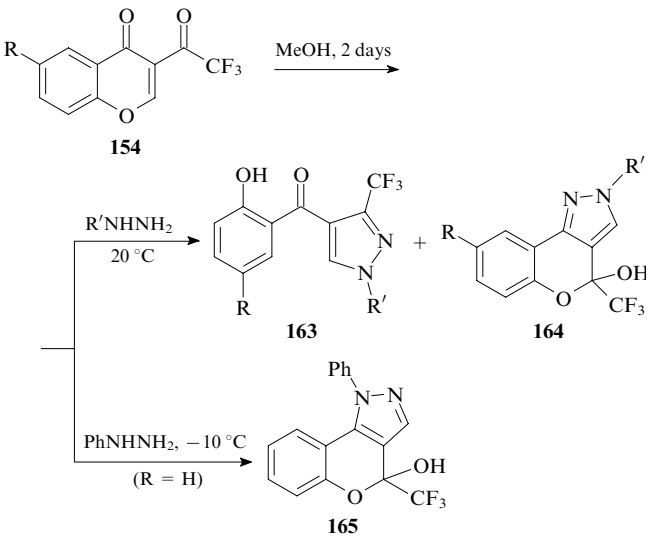


158

R^F = CF_3, CF_2H, C_2F_4H, C_2F_5; R^1, R^3 = H, Me, OMe;
R^2 = H, Me, NO_2, Cl, Br; R^4 = H, Br, OMe;
R^5 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$O_2NC_6H_4$, cyclo-C_6H_{11}, Bn.

The result of the reaction of 3-trifluoroacetylchromones **154** with ethylenediamine and *o*-phenylenediamine depends on the reaction conditions and the nature of the substituent in the benzene ring of chromone.[240] Chromones containing electron-withdrawing groups react with more basic ethylenediamine to give only monoadducts **159**, whereas unsubstituted chromone and 6-chlorochromone give only bisadducts **160** under similar conditions. The direction of the reaction of chromones with less basic *o*-phenylenediamine is easily controlled by reaction conditions. Thus the reaction with an excess of *o*-phenylenediamine at ~20 °C in methanol gives monoadducts **161**, while boiling with an excess of chromone in methanol results in bisadducts **162** (Scheme 4).[240]

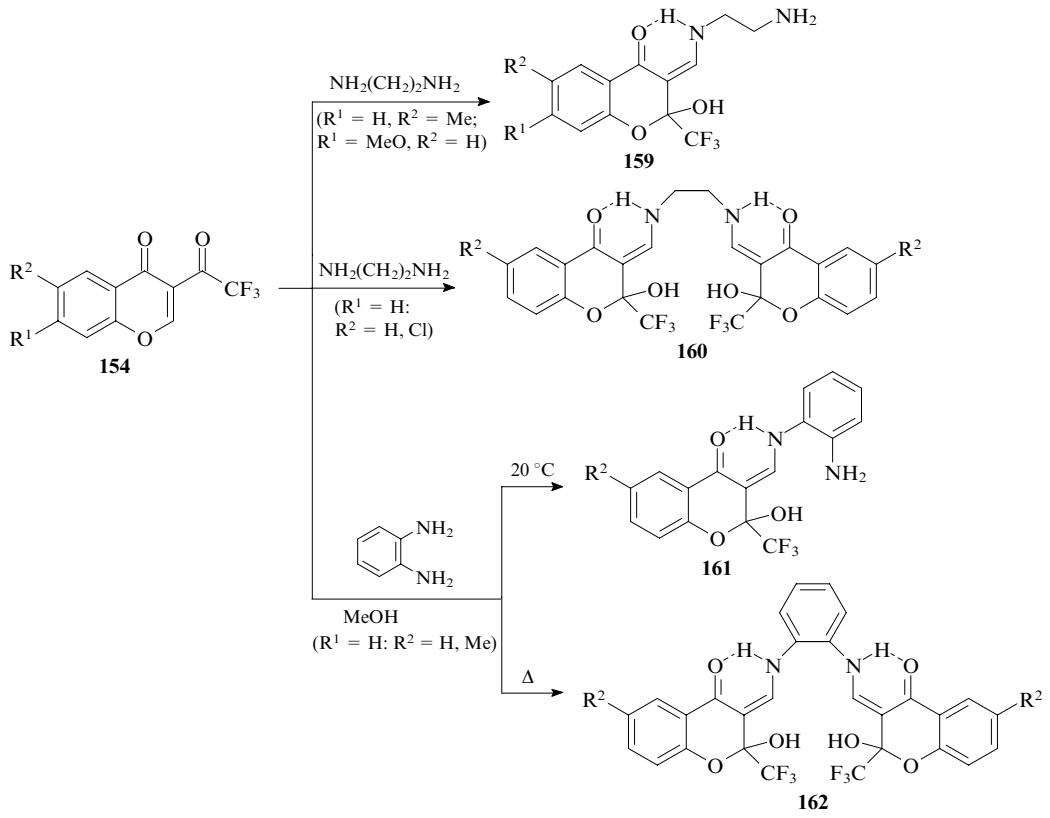
Reactions of 3-trifluoroacetylchromones **154** with hydrazine and methylhydrazine proceed as nucleophilic 1,4-addition with concomitant opening of the pyran ring and heterocyclization involving the polyfluoroacyl group to 4-(2-hydroxyaroyl)-3-polyfluoroalkylpyrazoles **163** or involving the aroyl group to 4-polyfluoroalkyl-2,4-dihydrochromeno[4,3-*c*]pyrazol-4-ols **164**. The product ratio **163** : **164** depends markedly on the nature of substituents in the chromone system and on the reaction conditions.[241] However, 1,4-addition of phenylhydrazine to unsubstituted trifluoroacylchromone **154a** proceeds with subsequent re-



154 **163** **164** **165**

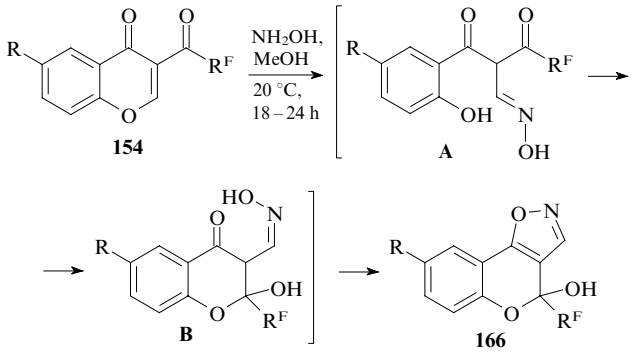
R = H, Me, Cl, NO_2; R′ = H, Me.

Scheme 4



cyclization to 4-hydroxy-1-phenyl-4-trifluoromethyl-1,4-dihydrochromeno[3,4-*d*]pyrazole (**165**).[241]

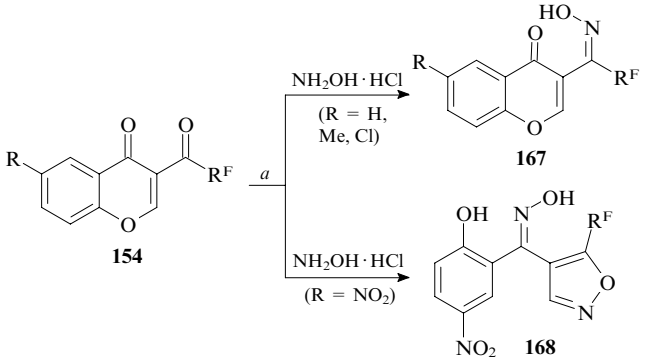
3-Polyfluoroacylchromones **154** react with hydroxylamine to form the corresponding chromeno[3,4-*d*]isoxazoles **166** in high yields.[242, 243]



R = H, Me, Cl, NO_2; R^F = CF_3, C_2F_4H.

At first, hydroxylamine attacks the chromone molecule on the electrophilic C(2) atom with ring opening and formation of intermediate **A**, which transforms to intermediate **B** through cyclization of the phenolic hydroxyl with perfluoroacyl group. Cyclodehydration of intermediate **B** leads finally to the target isoxazoles **166**.

In dependence of the substituent, oximation of 3-polyfluoroacylchromones **154** with hydroxylamine hydrochloride occurs at either the carbonyl group of the polyfluoroacyl residue or the C(2) atom to form chromone oximes **167**[242, 243] or 4-salicyloylisoxazole oximes **168**,[243] respectively.



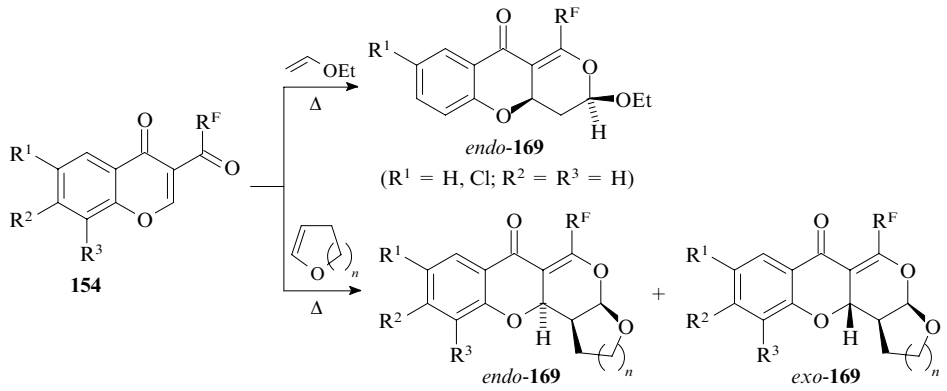
R^F = CF_3, C_2F_4H; (*a*) MeOH, Δ, 5 h.

Reactions of non-fluorinated 3-formyl- and 3-acylchromones with hydroxylamine and hydrazines starts predominantly from the attack on the unsubstituted C(2) atom (1,4-addition) and is accompanied by opening of the pyran ring to give β-dicarbonyl intermediates that can undergo intramolecular heterocyclizations.[244–247] In addition, the primary attack can proceed also on the 3-RC(O) group (1,2-addition), which explains the diversity of products obtained.[248, 249]

In contrast to the reaction of 3-formylchromone with 3,4-dihydro-2*H*-pyran, which proceeds under drastic conditions and in low stereoselectivity,[250] the hetero-Diels–Alder reaction of 3-polyfluoroacylchromones **154** with 3,4-dihydro-2*H*-pyran, 2,3-dihydrofuran and ethyl vinyl ether proceeds under mild conditions. As a result, fused pyrans **169** are obtained in high yields (Scheme 5).[251, 252]

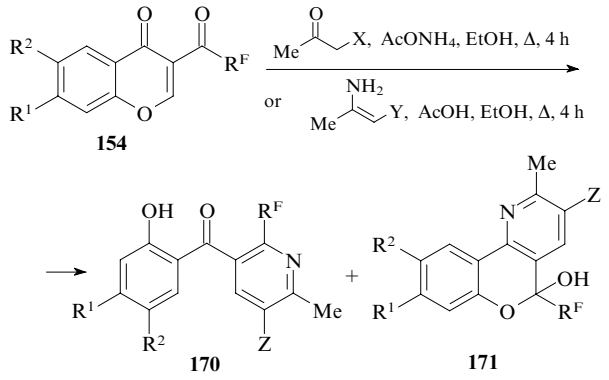
Depending on the nature and the length of polyfluoroalkyl chain, chromones **154** react with active methylene

Scheme 5



R^1 = H, Me, Cl, NO_2; R^2 = H, OMe; R^3 = H, Br; R^F = CF_3, CF_2H, C_2F_4H; n = 1, 2.

compounds (acetoacetamide, ethyl acetoacetate, ethyl β-aminocrotonate, β-aminocrotononitrile) and ammonium acetate to form substituted pyridines **170** or chromeno[4,3-*b*]pyridines **171**.[253]



R^1 = H, OMe; R^2 = H, Me, Cl; R^F = CF_3, CF_2H, C_2F_4H;
X = $C(O)NH_2$, CO_2Et; Y, Z = CO_2Et, CN.

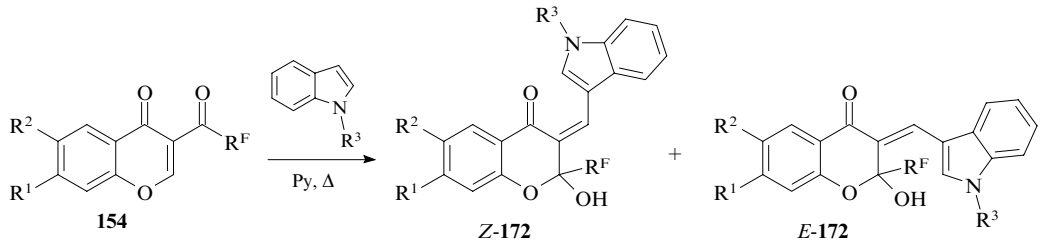
Refluxing a mixture of chromones **154** with indole and *N*-methylindole in pyridine results in a mixture of *Z*- and *E*-isomers of the corresponding 2-hydroxy-3-(indol-3-ylmethylidene)-2-(polyfluoroalkyl)chroman-4-ones **172** [*Z* : *E* = (83 : 17) – (96 : 4)] in the yields of 42% – 68% (Scheme 6).[254, 255] Attempted reaction of 2-methylindole under various conditions was unrewarded by success. In this case, only polymerization took place, which is probably associated with steric effect of the substituent in position 2 of the indole ring.[255] *N*-Methylpyrrole as a substrate required change in the experimental conditions, because in boiling pyridine resinification occurred. The target pyrrole derivatives **173** are formed upon heating of chromones **154** in *N*-methylpyrrole for 1 h at 85 °C (Scheme 6).[255]

IV. Synthesis and properties of fluoro-substituted acyclic β-triketones

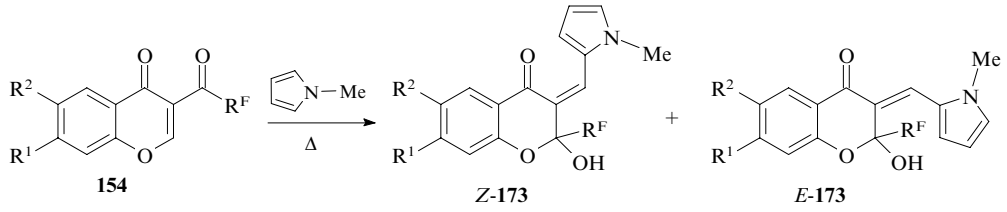
1. Fluoroalkyl-1,3,5-triketones

A preparative method for the synthesis of polyfluoroalkyl-1,3,5-triketones **174** is coupling of acetone[256, 257] or fluorinated β-diketones **21**[258] with methyl perfluorocarboxylates in the presence of lithium hydride. In the case of R^F = R = CF_3, a mixture of triketone **174** and its cyclic hydrate **175** is formed.

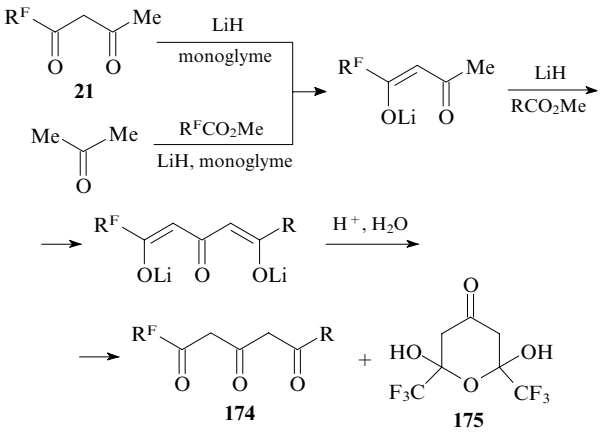
Scheme 6



R^F = CF_3, CF_2H, C_2F_4H; R^1 = H, OMe; R^2 = H, Me, Cl; R^3 = H, Me.



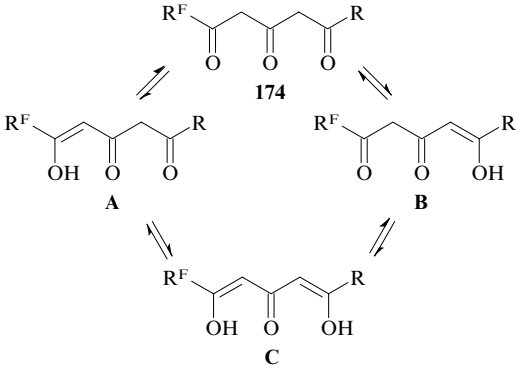
R^F = CF_3, CF_2H; R^1 = H, Br; R^2 = H, Cl, Br.



R^F = CF_3, C_2F_4H, n-C_3F_7, n-C_4F_9, n-C_6F_{13};
R = CF_3, C_2F_4H, n-C_4F_9, n-C_6F_{13}.

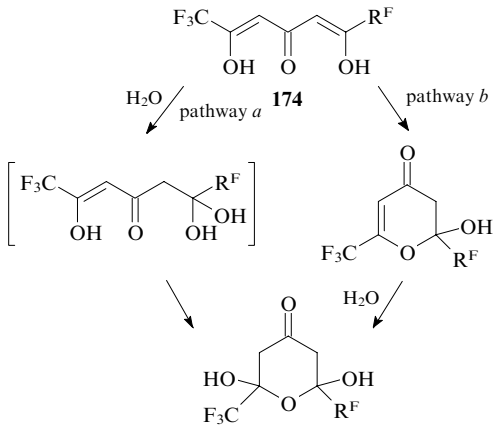
The yield of the target compounds **174** varies in the range of 50%–90% and depends on the length of the perfluoroalkyl substituent chain: it is higher for R^F = C_2F_4H, n-C_3F_7, n-C_4F_9. The yields of non-symmetrical triketones ($R^F \neq R$) are not significantly affected by substituents in the diketone or perfluorocarboxylate.

In theory, 1,3,5-triketones **174** can exist as several tautomeric forms. The most probable forms (by analogy with non-fluorinated triketones) are triketone form, monoenols **A** and **B** (if $R^F \neq R$) and bisenol **C**. An analysis of spectroscopic data revealed [256] that for triketones **174** the equilibrium is virtually totally shifted towards the dienediol structure **C**.



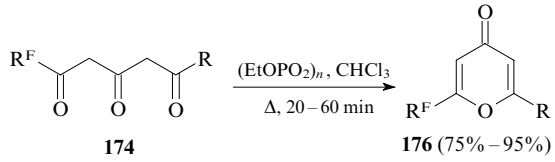
R^F, R = C_2F_4H, n-C_3F_7, n-C_4F_9, n-C_6F_{13}.

For compound **174** with trifluoromethyl substituents, ring–chain transformations occur as intramolecular cyclization with subsequent hydration (pathway *b*) or *vice versa* (pathway *a*).



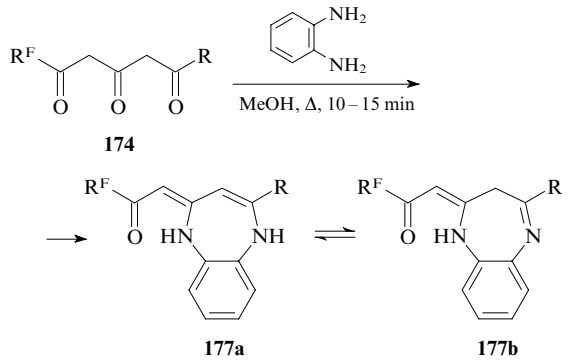
R^F = CF_3, C_2F_4H, n-C_4F_9, n-C_6F_{13}.

Heating of symmetrical and non-symmetrical bis(polyfluoroalkyl)-1,3,5-triketones **174** in the presence of ethyl polyphosphate furnishes the corresponding 2,6-bis(polyfluoroalkyl)-4*H*-pyran-4-ones **176** (γ-pyrones), the precursors of polyfluorinated heterocyclic compounds.[259]



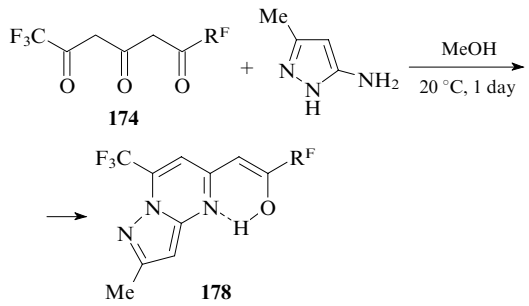
R^F, R = CF_3, CF_2H, C_2F_4H, n-C_3F_7, n-C_4F_9, n-C_6F_{13}.

The reaction of bis(polyfluoroalkyl)-1,3,5-triketones **174** with *o*-phenylenediamine occurs regioselectively at the less sterically hindered carbonyl group to form the corresponding 1,5-benzodiazepines **177**, which can exist in both ketodienamine (**177a**) and ketoenaminoimine (**177b**) tautomeric forms. It was found [260] that the tautomer ratio depends substantially on the solvent polarity and basicity and, to a lesser degree, on the bulkiness of the fluoroalkyl substituent. Thus tautomer **177a** is thermodynamically more stable in non-polar solvents, whereas in polar aprotic solvents, tautomer **177b** dominates.



R^F = CF_3, CF_2H, C_2F_4H, n-C_3F_7, n-C_4F_9, n-C_6F_{13};
R = CF_3, CF_2H, C_2F_4H, n-C_4F_9.

Regioselective addition of a bifunctional nucleophile, 3-methyl-5-aminopyrazole, to the trifluoromethyldicarbonyl fragment of triketone **174** results in polyfluoroalkylpyrazolo[1,5-*a*]pyrimidines **178**.[261]

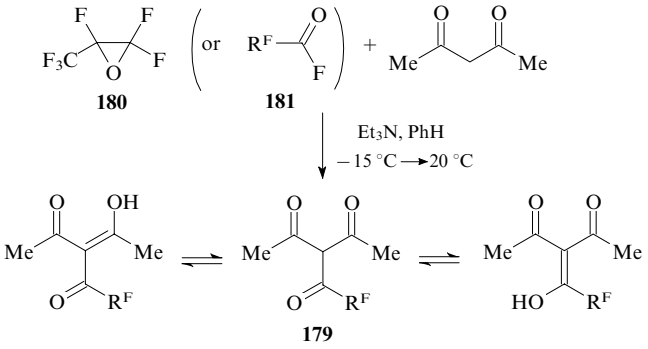


R^F = CF_3, n-C_4F_9.

2. Acyclic fluoro-containing β,β′-triketones

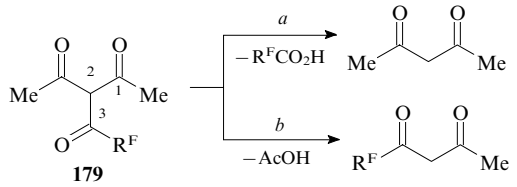
Synthesis of acyclic fluoroalkyl-containing β,β′-triketones **179** was performed in good yields by acylation of acetylacetone with fluoroalkene epoxides **180** [262] or perfluoroacyl fluorides **181**.[263] The spectral characteristics of the products

obtained indicate that β,β′-triketones **179** exist exclusively in the enol form.



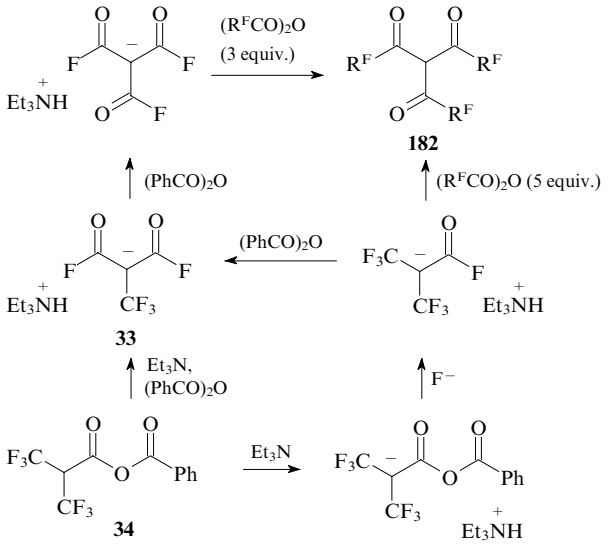
R^F = C_2F_5, C_2F_4H, n-C_4F_9.

The direction of hydrolysis of compounds **179** strongly depends on the reaction conditions. Thus in the presence of bases, the cleavage of the C(2)−C(3) bond is preferably observed (pathway *a*), whereas the action of dilute hydrochloric acid leads to the regioselective cleavage of the C(1)−C(2) bond (pathway *b*). The latter approach is used as a preparative method for the synthesis of fluoro-containing β-diketones.[264]



Acylation of mesomerically stabilized anions $FC(O)C^-(CF_3)C(O)F$ (**33**) (generated from mixed of α-hydroperfluoroisobutyric benzoic anhydride **34**) with perfluorocarboxylic anhydrides is an efficient method for the synthesis of tris(perfluoroacyl)methanes **182**.[61]

Tris(perfluoroacyl)methanes **182** [$R^F = CF_3$ (**a**) and C_2F_5 (**b**)] are enolized to a lesser extent: the degree of enolization is 8% and 10%, respectively, which is believed [61] to be connected with steric hindrance created by an α-substituent. The trifluoroacetyl group in compound **182a** appeared to be highly labile, its reaction with water readily yields hexafluoroacetylacetone and trifluoroacetic acid.



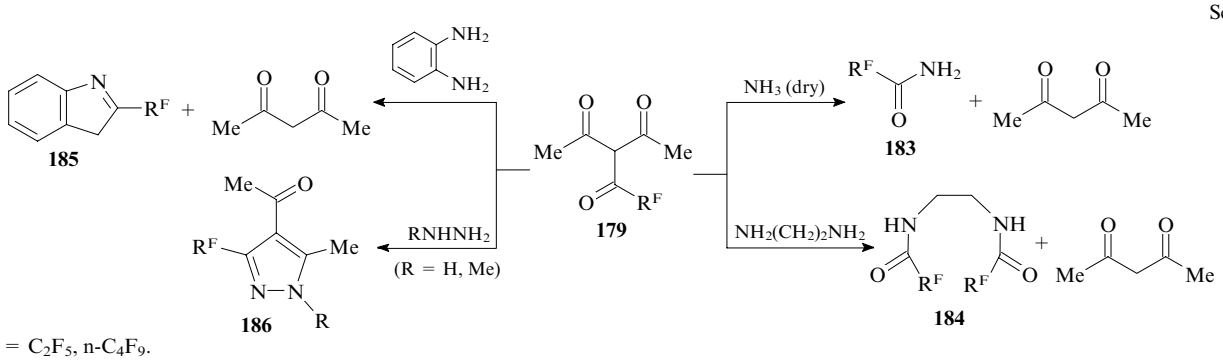
In reactions with N-nucleophiles (ammonia, 1,2-ethylenediamine, *o*-phenylenediamine), β,β′-triketones **179** undergo acid cleavage to give perfluorocarboxamides **183**, *N*,*N*′-bis(polyfluoroacyl)ethylenediamines **184** or 2-perfluoroalkylbenzimidazoles **185**. In reactions with hydrazines, acetylacetone derivatives **179** cyclized to substituted pyrazoles **186**. Hence, in all trasformations of compounds **179** discussed above, N-nucleophile attacks the perfluoro-substituted carbonyl group (Scheme 7).[263]

V. Synthesis and properties of fluoro-substituted cyclic β-triketones

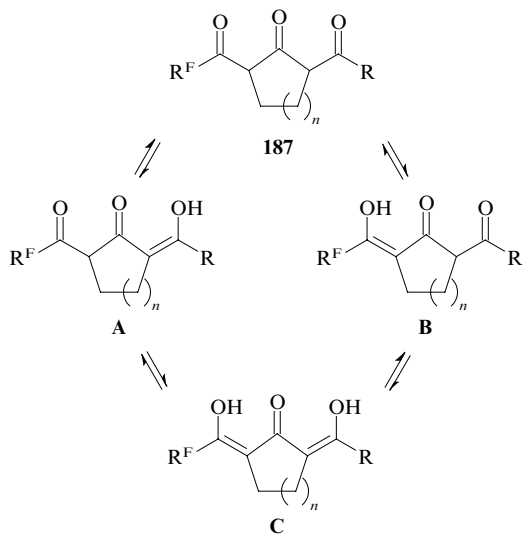
1. Bis(fluoroacyl)cycloalkanones

Bis(fluoroacyl)cycloalkanones **187** are synthesized by the reaction of cycloalkanones [265, 266] or 1,3-diketones [265, 267] with alkyl perfluorocarboxylates in the presence of lithium hydride. All 1,3,5-triketones **187** of the cyclopentane series ($n = 1$) exist in deuteriochloroform solution predominantly in the bis(enol) form **C**, while monoenol forms **A**, **B** and the ketone form are present in insignificant amounts (< 3%). However, cyclohexanone derivatives **187** ($n = 2$) exist in solution as a mixture of all possible tautomers. According to the Brown rule, the exocyclic double bond in the six-membered ring is unfavourable, which is rationale for the presence of the monoenol forms **A** and **B** in solution.

Scheme 7

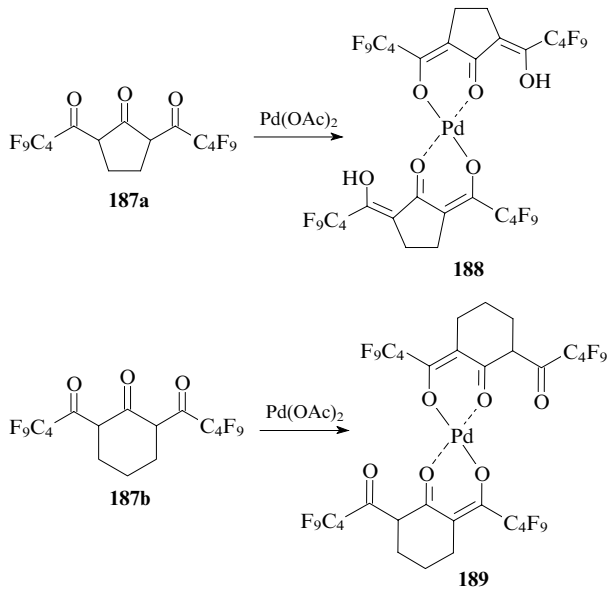


R^F = C_2F_5, n-C_4F_9.

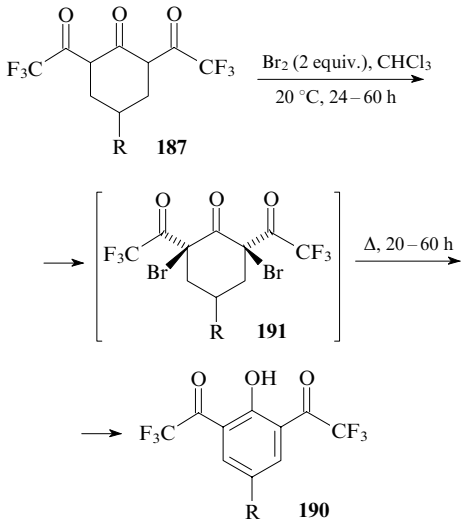


R^F, R = CF_3, n-C_4F_9; n = 1, 2.

Bis(fluoroacyl)cycloalkanones **187** react with $Pd(OAc)_2$ at a molar ratio 2 : 1 to form mononuclear Pd(II) complexes **188**, **189**.[268] The product yields depend on the length of the 2,4-oligomethylene bridge. Thus bis(perfluorobutanoyl)cyclopentanone **187a** gives triketonate **188** in a yield of 72%, whereas in the case of the triketone of the cyclohexane series **187b**, the yield of product **189** is only 45%. In addition, the NMR data revealed that the size of the triketone ring influences tautomerism of non-bound carbonyl groups in triketonates obtained. These groups in complex **188** are enolized, while for complex **189**, no enolization was observed.[268] Since the reaction of triketonates **188**, **189** with the second equivalent of $Pd(OAc)_2$ does not result in binuclear complexes, as is the case for non-fluorinated *trans*-mononuclear Pd(II) complexes of 1,3,5-triketones,[269] compounds **188**, **189** were classified as *trans*-structures. Besides, the *trans* configuration of triketonate **189** follows from X-ray diffraction data.[268]



An efficient method for the synthesis of 2,6-bis(trifluoroacetyl)phenols **190** from 1,3,5-triketones **187** (n = 2, R^F = R = CF_3) was developed;[270] these phenols are hardly accessibly by other methods.

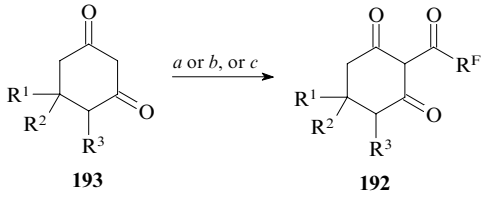


R = H, Me, Pr^n, Ph, CO_2Et.

The sequence of transformations includes dibromination[270, 271] and double dehydrobromination without isolation of intermediate dibromo derivatives **191**.[270]

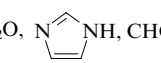
2. 2-Perfluoroacylcyclohexane-1,3-diones

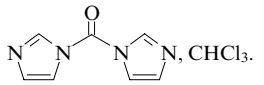
2-Perfluoroacylcyclohexane-1,3-diones **192** are synthesized by the imidazolide method. The reaction of cyclohexane-1,3-diones **193** with a small excess of *N*-perfluoroacylimidazole at room temperature results in selective C-acylation of β-diketones to the corresponding fluoro-containing β,β′-triketones **192**.[272, 273]



R^1 = H, Me, Ph, 4-$MeOC_6H_4$; R^2 = H, Me; R^3 = H, CO_2Me;
R^F = CF_3, C_2F_5, C_3F_7;

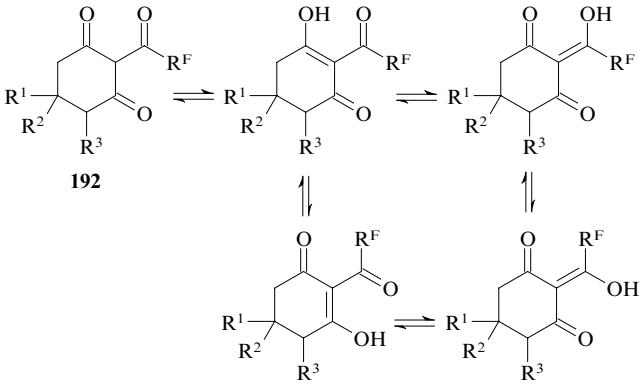
(*a*) 

(*b*) $(R^FCO)_2O$, 

(*c*) R^FCO_2H, 

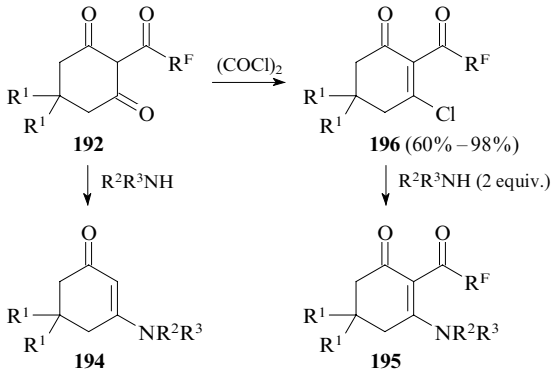
This transformation can be performed with both pure *N*-trifluoroacetylimidazole (method *a*)[272, 273] and *N*-perfluoroacylimidazoles obtained *in situ* by the reaction of perfluorocarboxylic anhydrides with imidazole (method *b*) or by the reaction of perfluorocarboxylic acids with 1,1′-carbonyldiimidazole (method *c*).[273]

2-Perfluoroalkanoylcyclohexane-1,3-diones, as well as other cyclic β,β′-tricarbonyl compounds,[274] can exist as tautomeric endo- and/or exocyclic enols with strong intramolecular hydrogen bond.



192

R^1 = H, Me, Ph, 4-$MeOC_6H_4$; R^2 = H, Me; R^3 = H, CO_2Me; R^F = CF_3, C_2F_5, C_3F_7.



192 **196** (60% – 98%) **194** **195**

R^F = CF_3, C_2F_5, C_3F_7; R^1 = H, Me; R^2 = H: R^3 = Ph, 4-FC_6H_4, Bn, 4-$FC_6H_4CH_2$; $R^2 - R^3$ = $(CH_2)_4$, $(CH_2)_5$.

Using IR and one- and two-dimensional NMR spectroscopy, it was found that 2-perfluoroacylcyclohexane-1,3-diones **192** are fully enolized in solution, the exocyclic tautomer dominating.[273]

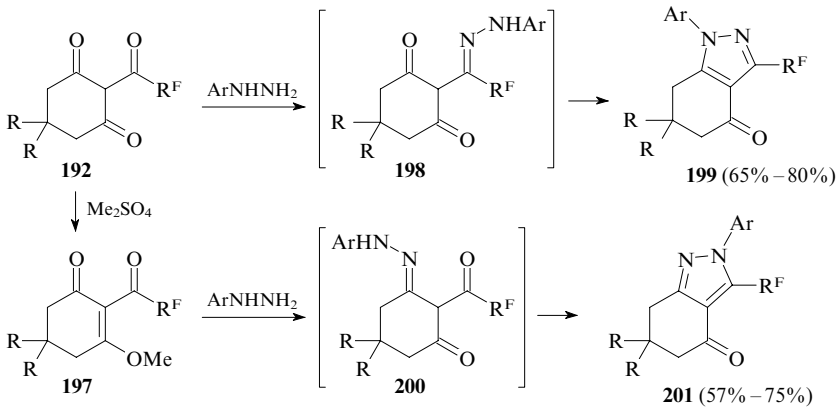
Different reaction centres of the fluoro-containing cyclic β,β′-triketones existing in the enol form, *i.e.*, exo- and endocyclic carbonyl groups, methylene groups, can be involved in chemical reactions. Due to the presence of three electrophilic centres, these compounds can be used for the synthesis of diverse structures, including heterocycles.

2-Perfluoroalkanoylcyclohexane-1,3-diones **192** are unstable in the presence of both acidic and basic substances. For this reason, the reactions with primary and secondary amines lead to acid cleavage of compounds **192** to give enamino ketones **194**.[275] Regioisomeric endocyclic enamino derivatives **195** readily formed upon the treatment of the corresponding vinylogous carbonyl chlorides **196** with a twofold excess of an amine at room temperature.[275] Enol derivatives **196**, in turn, are obtained by the reaction of an excess of oxalyl chloride with parent β,β′-triketones **192**.[275]

Regioselective synthesis of perfluoroalkylated tetrahydroindazolones and isoindazolones was performed by the reaction of 2-perfluoroalkanoylcyclohexane-1,3-diones **192** and enol methyl ethers **197** with phenylhydrazines (Scheme 8).[276,277] Coupling of 2-perfluoroalkanoylcyclohexane-1,3-diones **192** with phenylhydrazines occurs selectively at the exocyclic carbonyl group with subsequent intramolecular cyclization of intermediate hydrazones **198** and formation of tetrahydroindazolones **199**.[276,277] The corresponding enol methyl ethers **197** were obtained by alkylation of tetrabutylammonium salts of 2-acylcyclohexane-1,3-diones **192** with dimethyl sulfate in benzene at room temperature. They were brought into reaction with phenylhydrazines without purification to avoid losses associated with instability. The reaction occurred according to the mechanism of vinylogous substitution to form hydrazones **200**, their subsequent intramolecular cyclisation resulted in tetrahydroindazolones **201**.[276,277]

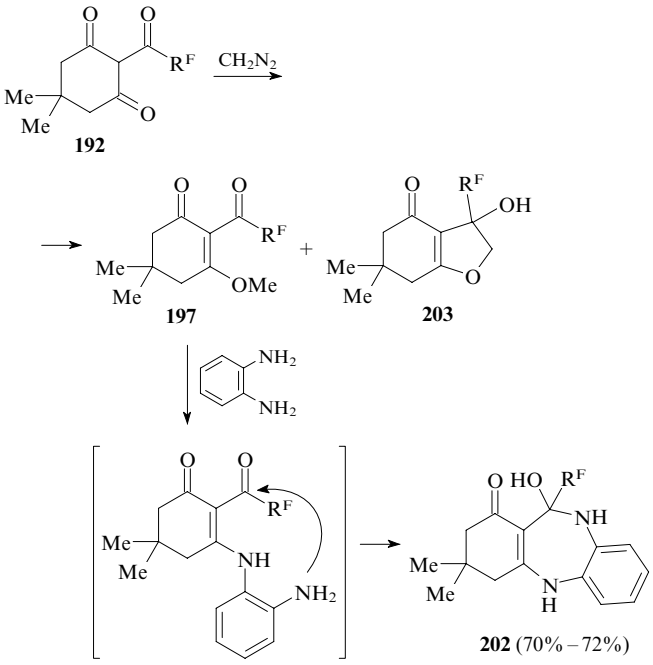
The reaction of 2-perfluoroacylcyclohexane-1,3-diones **192** with *o*-phenylenediamine afforded a mixture of the products of acid cleavage,[278] as was the case for their acyclic analogues **179**.[263] At the same time, the treatment of the corresponding enol methyl ethers **197** with the equimolar amount of *o*-phenylenediamine results in 11-perfluoroalkyl-11-hydroxy-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-ones **202**.[278]

Scheme 8



192 **198** **199** (65% – 80%) **197** **200** **201** (57% – 75%)

R^F = CF_3, C_2F_5, C_3F_7; R = H, Me; Ar = Ph, 4-FC_6H_4, C_6F_5.



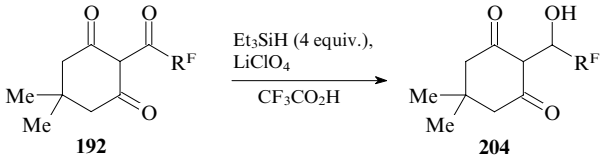
192 → **197** + **203** → **202** (70%–72%)

R^F = CF_3, C_2F_5, C_3F_7.

The reaction of diazomethane (ethereal solution) with fluoro-containing β,β′-triketones **192** gave enol ethers **197**, 3-hydroxy-6,6-dimethyl-3-perfluoroalkyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-ones **203** being by-products of this transformation.[278,279] Further reaction of vinylogous substitution of one amino group of *o*-phenylenediamine for the methoxy group in compounds **197** and subsequent intramolecular cyclization result in dibenzo[*b*,*e*][1,4]diazepinones **202**. Cyclic products **202** are stabilized by intramolecular hydrogen bonding between the hydroxyl group and the carbonyl group of the cyclohexene fragment and by the presence of strong electron-withdrawing group inhibiting elimination of a water molecule.[278]

It was found that under the action of triethylsilane in trifluoroacetic acid in the presence of lithium perchlorate, the exocyclic carbonyl group of β,β′-triketones **192** is reduced to hydroxyl group to form hydroxyalkyldiketones **204**.[280]

In contrast to parent 2-perfluoroacylcyclohexane-1,3-diones **192**, which are characterized by low stability, hydroxy derivatives **204** are stable on prolonged storage. This fact is explained by stabilization of hydroxyalkyldiketones **204** due to the presence of strong electron-withdrawing perfluoroalkyl substituent.[280]

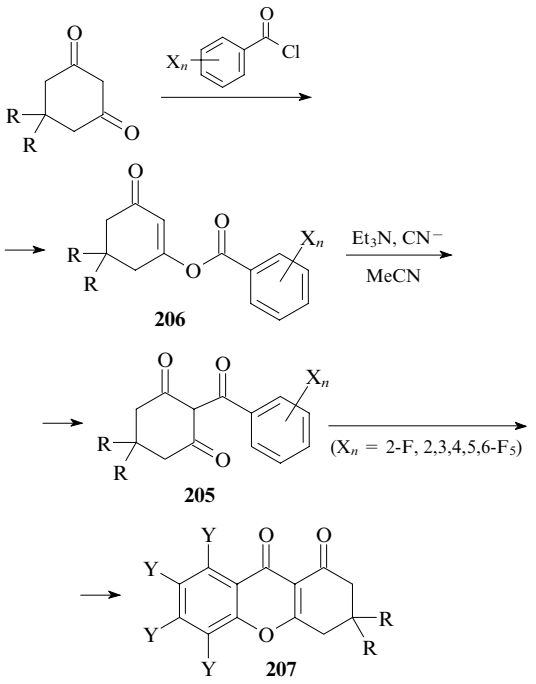


192 → **204**

R^F = CF_3, C_2F_5.

3. Fluorinated 2-benzoylcyclohexane-1,3-diones

2-Benzoylcyclohexane-1,3-diones with fluorinated aromatic ring (**205**) are obtained by O–C-isomerization of the corresponding enol ethers **206** in the presence of different catalysts.[281–284] Under isomerization conditions of 3-benzoyloxycyclohex-2-enones **206** containing the fluorine atom in the *ortho*-position of the benzene ring to β,β′-triketones **205** in the presence of aluminium chloride in dichloroethane[281] or potassium cyanide and triethylamine in

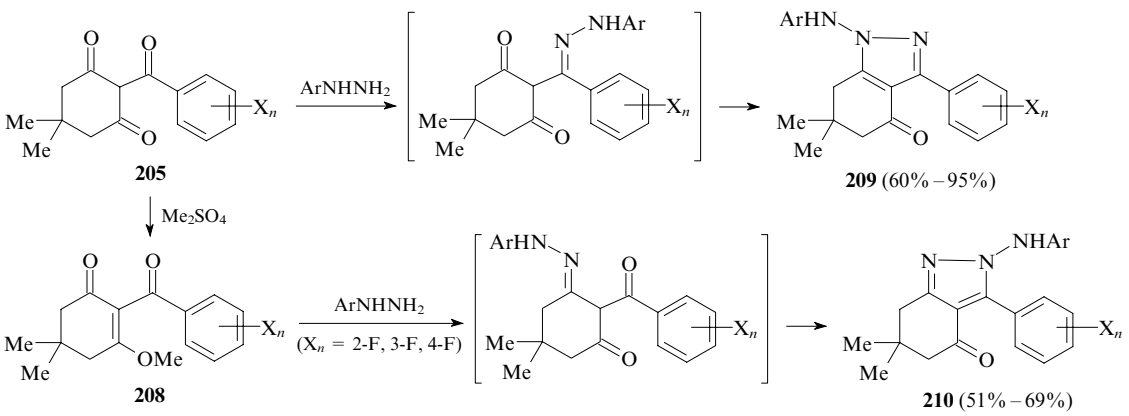


206 → **205** → **207**

R = H, Me; Y = H, F;

X_n = 2-F, 4-F, 2-CF_3, 4-CF_3, 2,3,4-F_3, 2,3,4,5,6-F_5.

Scheme 9



205 → **209** (60%–95%)

205 → **208** → **210** (51%–69%)

X_n = 2-F, 3-F, 4-F, 2,3,4,5,6-F_5; Ar = Ph, 4-FC_6H_4, C_6F_5.

dichloromethane,[282] β,β′-triketones **205** undergo nucleophilic intramolecular heterocyclization with elimination of HF to form 2,3,4,9-tetrahydro-1*H*-xanthene-1,9-diones **207**. However, under the action of catalytic amounts of acetonecyanohydrin in the presence or triethylamine in dry acetonitrile, subsequent intramolecular heterocyclization of β,β′-triketones **205** containing the fluorine atom in the *ortho*-position of the benzene ring was not observed.[283,284]

The direction of enolization of fluoro-containing 2-benzoylcyclohexane-1,3-diones was established from spectral data and quantum chemical calculations.[284,285] It was found that in deuteriochloroform solution these compounds exist predominantly in the endocyclic enol form.

Regularities of the reaction of fluoro-containing 2-benzoylcyclohexane-1,3-diones **205** and enol methyl ethers **208** with phenylhydrazines are similar to those observed for perfluoroalkyl cyclic β,β′-triketones **192**. In this case, the corresponding tetrahydroindazolones **209** and -isoindazolones **210** were obtained (Scheme 9).[286]

VI. Application of fluoro-substituted β-diketones

The ability of β-diketones[72,73,287] to form complexes with the majority of metals of the Periodic Table is the most valuable characteristic from the practical viewpoint. The presence of electron-withdrawing fluoro-containing groups in the ligands and the corresponding complexes is the reason for the appearance of unique properties of these compounds, which are not typical of non-fluorinated structures. In particular, solubility in polar and non-polar organic solvents allows variation of pH within wide limits, which is useful for extraction of metal cations.

Application of polyfluorinated β-diketones as chelating agents in supercritical liquid extraction is discussed in reviews.[5,6] For example, trifluoroacetylacetone, hexafluoroacetylacetone, thenoyltrifluoroacetone are used for efficient extraction of heavy toxic metals (As, Cd, Cr, Cu, Pd) from solid samples including sand, filter paper and soil. Hexafluoroacetylacetone, thenoyltrifluoroacetone and (heptafluorobutanoyl)pivaloylmethane are more efficient, compared to acetylacetone, for supercritical liquid extraction of lanthanides and actinides from solid and liquid media. Synergism of thenoyltrifluoroacetone with tributyl phosphate allows one to perform quantitative extraction of lanthanides and uranyl ions (UO_2^{2+}) from solid samples.

Phenyl and α-thienyl derivatives of acetylacetone containing the oxygen atom in the fluorinated substituent[288] as well as long-chain perfluoro derivatives of acetylacetone[289] are used for highly sensitive luminescent determination of Nd, Sm, Eu, Yb in high-purity La, Gd, Lu and Y oxides.

In gas-phase methods for preparation of coatings and films, metal β-diketonates are widely used as starting compounds, if they possess the following practically important properties: volatility, relatively high thermal stability in condensed and gaseous states, air stability, solubility in organic solvents, *etc*. Complex investigation of physicochemical properties of lithium trifluoroacetylacetonate, hexafluoroacetylacetonate and pivaloyltrifluoroacetonate revealed that these substances possess all the above properties.[290] In addition, it was noted in the reviews[291,292] that the introduction of the trifluoromethyl group into the ligand results in an increase in volatility and a decrease in thermal stability. Thus fluorinated metal β-diketonates can be used for the introduction of metals into high-temperature superconductive films by chemical vapour deposition.

Binuclear complexes formed in solution from Ln(III) and Ag(I) polyfluorinated β-diketonates are used as shift reagents for alkenes, aromatic and halogen-containing compounds.[293]

Due to high volatility and thermodynamic stability, europium tris{1-phenyl(4,4,4-trifluorobutane-1,3-dionato)}bipyridine can easily be obtained as a thin film. Investigation of its optical chracteristics revealed that this substance is a promising material for the production of optical devices.[294]

Adducts of fluoro-substituted β-diketonates with biradical bases represent a new family of molecular magnets.[295–297]

Palladium(II) perfluorooctanoate is a catalyst for oxidation of different polyfunctional alkenes to the corresponding methyl ketones.[46] Selective dimerization of propylene to 2,3-dimethylbutenes[9] and hetero-Diels–Alder addition of crotonaldehyde to ethyl vinyl ether[298] proceed in the presence of catalytic amounts of Ni(II) and Ln(III) complexes of perfluorinated β-diketones, respectively. In the presence of a Pd(II) complex containing 6,6,6-trifluoro-1-phenylhexane-1,3,5-trione and chiral diphosphines or diamines, the enantioselectivity of oxidation of α-alkenes to chlorhydrines is > 50%.[299]

1,1,1-Trifluoroheptane-2,4,6-trione, 1,1,1,7,7,7-hexafluoroheptane-2,4,6-trione and bis(trifluoroacetyl)cyclopentanone are used as the starting ligands for the synthesis of coordination clusters and supramolecular structures.[300]

The literature data on the application of fluoro-substituted β-diketones as starting materials for the synthesis of compounds exhibiting a wide spectrum of biological activity are abundant and worth separate publication. For this reason, within the frame of this review, we present only several examples. Insecticide activity was revealed for polyfluorinated aryl-1,3-diketones with different length of the perfluoroacyl chain and with substituents in the aromatic ring.[47] Bis- and tris(trifluoromethyl)-substituted pyrimido[1,2-*b*]indazoles possess antitumour activity.[123] 4-Phenyl- and 3-alkyl(aryl)-5-hydroxy-1-tosyl-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles manifested antibacterial activity.[12]

Pronounced pesticide properties were found for 3-aryl-5-trifluoromethylisoxazoles,[301] 3-aryl-5-(chlorodifluoromethyl)-4-isoxazolecarboxamides and their derivatives[302,303] Antibacterial activity was found for 3-aryl-5-trifluoromethylpyrazoles.[137]

1,5-Diaryl-3-difluoromethyl- and -3-trifluoromethylpyrazoles containing substituted benzenesulfonamide or azidophenyl residues as pharmacophores comprise a family of selective inhibitors of cyclooxygenase-2 (Refs 129, 304–306). 3,5-Bis(trifluoromethyl)pyrazoles belong to a new family of regulators of the transcription factor NFAT.[307] A series of aryl-3-trifluoromethylpyrazoles serves as inhibitors of CRA-calcium channels.[134,308] Some 3-trifluoromethylpyrazoles are selective inhibitors of blood coagulation factor Xa.[309]

2-[2-Nitro-4-(trifluoromethyl)]benzoylcyclohexane-1,3-dione is successfully used for the treatment of type I tyrosinemia.[310] One of the possible mechanisms of the action of this compound as a herbicide and a drug is inhibition of 4-hydroxyphenylpyruvate oxygenase likely due to chelation of the enzyme-bound Fe(III) ion with the enol form of β,β′-triketone.[311,312]

VII. Conclusion

Thus, the presented material shows that over recent 30 years, significant attention has been paid to the development of the methods for the synthesis and subsequent modification of fluorinated β-diketones. This is associated with the fact that fluorinated diketones and their derivatives are convenient precursors of acyclic, carbocyclic and heterocyclic fluoroorganic compounds manifesting a wide spectrum of biologicalal activity. Since it is known that numerous cyclic β,β′-tricarbonyl compounds isolated from natural sources (plants, microorganisms) and their synthetic analogues exhibit different kinds of biological activity, preparation of fluorinated derivatives seems promising. The latter can find application as efficient drugs and pesticides. In this regard, the topicality and validity of studies focused on the development of the methods for the synthesis of novel fluoro-containing 2-acylcyclohexane-1,3-diones aimed at search for new biologically active compounds is doubtless.

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