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FLUORINE-CONTAINING 2-FUNCTIONALIZED 1,3-DICARBONYL COMPOUNDS FOR HETEROCYCLIC SYNTHESIS

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Abstract – Data on the synthesis and chemical transformations of 2-functionalized fluoroalkyl-containing 1,3-dicarbonyl compounds are reviewed. Reactions giving fluorinated heterocycles are discussed. The heterocyclization of non-substituted fluoroalkylated 1,3-dicarbonyl compounds with the same dinucleopiles is considered for the sake of comparison.

INTRODUCTION

It is well-known that introduction of fluorine atom or fluoroalkyl group into heterocyclic compounds may have a profound influence on their chemical, physical and biological properties.[1] The incorporation of fluorine atoms into the molecule of organic compound can increase its metabolic stability, allows modulate its volatility, lipophilicity, solubility, acidity, basicity, hydrogen-bonding, steric and electronic effects, facilitate transport *via* cellular membranes.[2] Today undeniable fact is that fluorinated compounds play a substantial part in development of new anticancer and antiviral agents, anti-inflammatory and antihypertensive drugs, contraceptives and other.[3]

To the synthesis of fluorinated heterocyclic compounds, two approaches are mainly applied: the direct fluorination of finished heterocycles and the "block-synthon" method, i.e. using the ready organic substrates that already contain fluorine atoms. We are developing the latter direction based on the usage of fluorinated 1,3-dicarbonyl compounds.

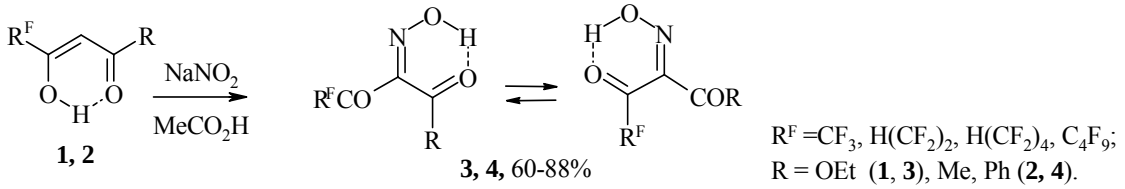
The 1,3-dicarbonyl compounds (3-oxo esters (**1**) and 1,3-diketones (**2**)) including fluorinated ones are the key "block-synthons" to construct the heterocyclic structures.[4-6] The cyclocondensations of 3-oxo esters (**1**) and 1,3-diketones (**2**) with various dinucleophiles at the corresponding β-keto alkoxycarbonyl or β-dicarbonyl fragments lead to the formation of different five-, six-, seven-membered heterocyclic systems and their annelated derivatives. Most heterocyclic compounds derived from 1,3-dicarbonyl

compounds (**1**, **2**) possess various types of biological activities and some from them are used as drugs in medicine.[4,5]

In this context, the development of novel fluorinated 1,3-dicarbonyl compound chemistry is of considerable interest. As far as we are concerned one of the most promising strategies in this area deals with the synthesis and reactions of 2-functionalized fluoroalkylated 1,3-dicarbonyl compounds. In this review the transformations of these versatile building blocks and synthetic strategies towards fluoroheterocycles will be presented taking into account the recent literature data.

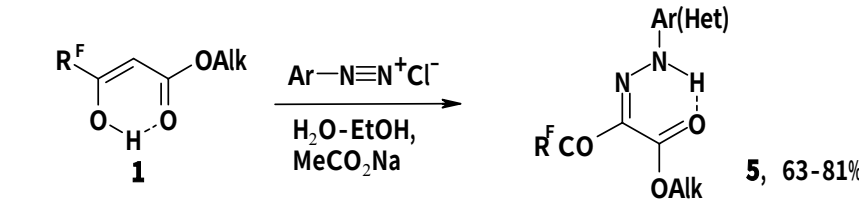
II. SYNTHESIS OF 2-FUNCTIONALIZED FLUORINE-CONTAINING 1,3-DICARBONYL COMPOUNDS

Fluoroalkyl-containing 2-hydroxyimino-3-oxo esters (**3**), 2-hydroxyimino-1,3-diketones (**4**) were obtained by nitrosation of corresponding 1,3-dicarbonyl compounds (**1**, **2**) (Scheme 1).[7-10] According to IR, NMR ^{1}H, ^{19}F and ^{13}C spectroscopy, fluoroalkyl-containing 2-hydroxyimino-1,3-dicarbonyl compounds (**3**, **4**) exist in solutions of $CDCl_3$ and $(CD_3)_2CO$ as a mixture of *Z,E*-isomers of diketohydroxyimino tautomers.[10]



Scheme 1

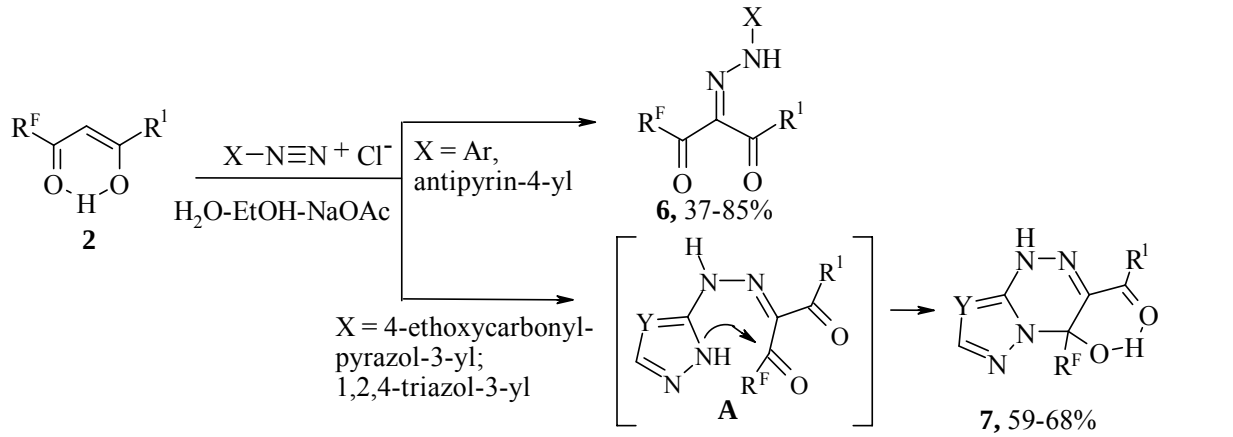
The coupling of fluorinated 3-oxo esters (**1**) with aryldiazonium salts is used for the preparation of 2-arylhydrazono-3-oxo-3-fluoroalkylpropionates (**5**) (Scheme 2).[11-13]



Scheme 2

Polyfluoroalkyl-containing 1,3-diketones (**2**) are coupled with aryl- and (antipyrin-4-yl)diazonium chlorides in the presence of sodium acetate to afford 2-arylhydrazones of 1,2,3-triketones (**6**) (Scheme 3).[11-18] The IR and NMR spectra of compounds (**5, 6**) indicate their presence in the $CHCl_3$ solution and in the crystals as a hydrazono-diketo tautomer, although both keto-enol and azo-hydrazone tautomerisms are possible for these compounds.[11,12,18]

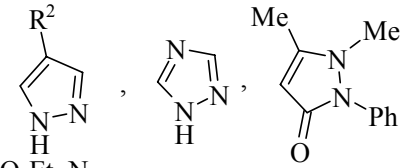
Polyfluoroalkyl-containing 1,2,3-triketones 2-hetarylhydrazones (**A**) were not isolated from the reactions of 1,3-diketones (**2**) with hetarylamine that has *NH*-group at the α-position of heterocycle as the diazonium component (4-ethoxycarbonylpyrazol-3-yl- and 1,2,4-triazol-3-yl diazonium chlorides). Under the reaction conditions they readily cyclized to 4,7-dihydroazolo[5,1-*c*][1,2,4]triazines (**7**) (Scheme 3).[18] The cyclization occurs through nucleophilic addition of the amino group of the azole fragment to the polyfluoromethyl-substituted carbonyl group.



R^F = HCF_2, CF_3, $H(CF_2)_2$, C_3F_7, $H(CF_2)_4$, C_4F_9, C_6F_5, 2,6-$F_2C_6H_3$, 3-FC_6H_4NH, CF_2-OCF_3, CF_2-CF(O)CF_2-CF_2;

R^1 = CF_3, Me, Ph, 2-C_4H_3S, $C(Me)_3$, $CH(Et)_2$;

X = Ph, C_6H_4Me-4, C_6H_4OMe-4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-$SO_2C_6H_4$, 4-$CHF_2C_6H_4$, 2-$(COMe)C_6H_4$, 2,5-$SO_3H(CF_3)C_6H_3$;



R^2 = CO_2Et, Ph; Y = C-CO_2Et, N

Scheme 3

The structure of ethyl 6-benzoyl-7-hydroxy-7-polyfluoromethyl-4,7-dihydroazolo[5,1-*c*]-[1,2,4]triazine-3-carboxylate (**7**) was confirmed also by the single-crystal X-ray diffraction analysis.[18] This cyclic derivative of hetarylhydrazone is stabilized due to the participation of the hydroxyl group in an intramolecular hydrogen bond with the carbonyl group of the benzoyl fragment.

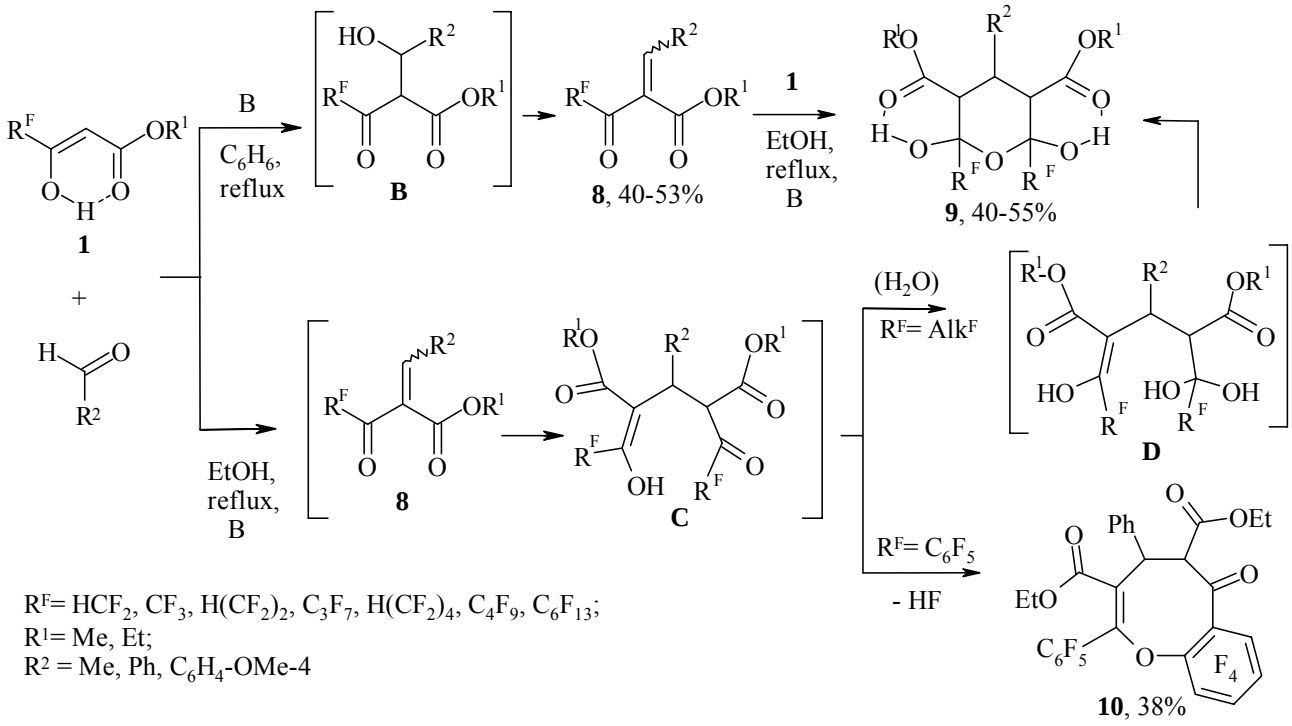
Knoevenagel condensation of fluoroalkyl-containing 3-oxo esters (**1**) with an equimolar amount of arylaldehyde in refluxing toluene in the presence of pyperidine with azeotropic removal of water is used for the synthesis of 2-arylidene-3-flluoroalkylpropionates (**8**)[19-21] (Scheme 4). Data of IR, NMR spectra of esters (**8**) indicate on their existence as an equilibrium mixture of *Z*- and *E*-isomers.

When the reactions of fluoroalkyl-containing 3-oxo esters (**1**) with aldehydes are carried out in refluxing ethanol in the presence of a base (KF or pyperidine), 4-aryl(alkyl)-3,5-dialkoxycarbonyl-2,6-dihydroxy-2,6-di(fluoroalkyl)tetrahydropyranes (**9**)[20-23] were obtained (Scheme 4). Tetrahydropyranes (**9**) can be obtained also from 2-arylidene-3-oxopropionates (**8**) by refluxing in ethanol with 3-oxo esters (**1**) in the

presence of KF (Scheme 4).[20]

The X-ray investigation showed that tetrahydropyranes (**9**) are characterized by the chair conformation with the aryl, alkoxycarbonyl and polyfluoroalkyl groups in equatorial positions and hydroxy groups in axial ones.[21]

The attempts to dehydrate tetrahydropyranes (**9**) upon refluxing in toluene with azeotropic removal of water in the presence of *p*-toluenesulfonic acid were unsuccessful. Evidently, tetrahydropyrane structure of these heterocycles is stable due to the presence of the electron-withdrawing fluoroalkyl substituents. Besides, the participation of hydroxyl groups in the formation of intra- or intermolecular hydrogen bonds with the ester substituent also prevents from dehydration.[20,21]

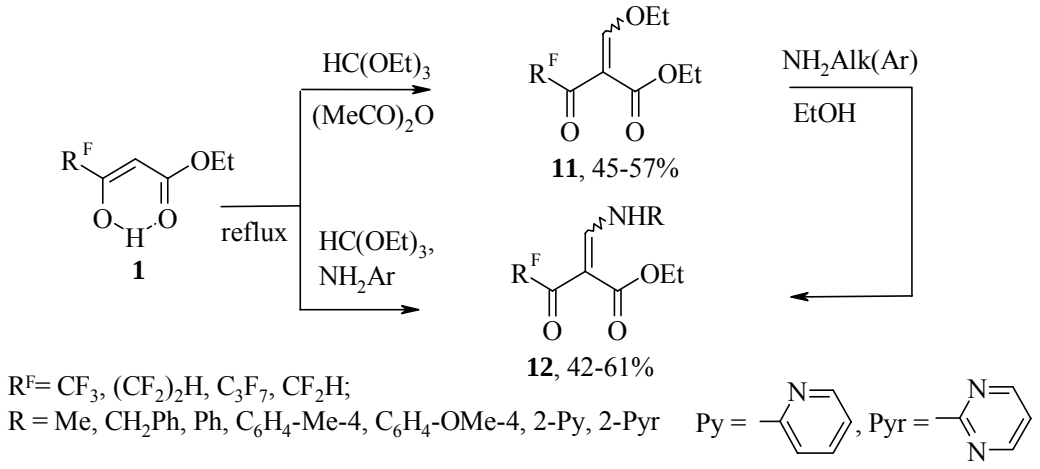


Scheme 4

Ethyl ester of pentafluorobenzoylacetic acid (**1**) with benzaldehyde in refluxing ethanol in the presence of KF provides 3,5-diethoxycarbonyl-2-pentafluorophenyl-4-phenyl-7,8,9,10-tetrafluoro-4,5-dihydro-benzo[*b*]oxacin-6-one (**10**).[23] A possible mechanism of this heterocycle formation is shown in the Scheme 4. Evidently, glutarate (**C**) is formed as an intermediate in each case. Under reaction conditions, the latter undergoes intramolecular cyclyzation to afford heterocycle (**10**). The cyclization occurs through intramolecular substitution of the *ortho*-fluorine atom in the pentafluorophenyl substituent by hydroxyl group and is accomplished by elimination of HF and H_2O.

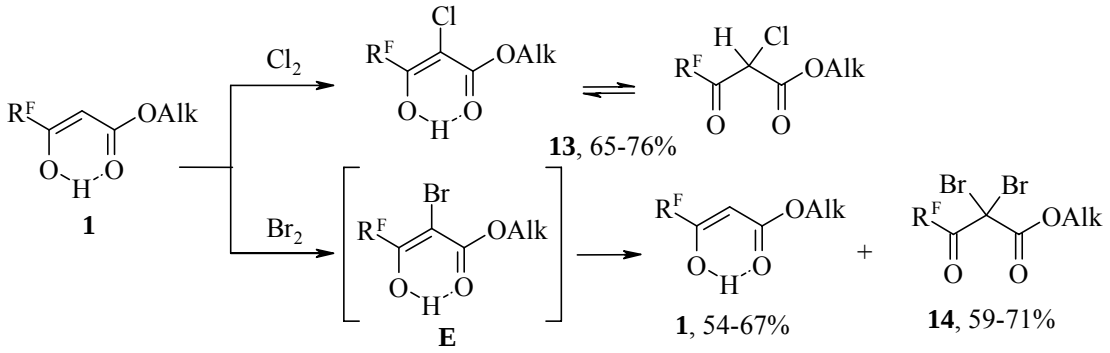
The interaction of fluorinated 3-oxo esters (**1**) with triethylorthoformiate gives 2-ethoxymethylidene-3-oxopropionates (**11**) which can be converted into 2-alkyl(aryl, hetaryl)aminomethylidene-3-oxo esters (**12**) in the reactions with the primary amines (Scheme 5).[20,21] Esters (**12**) can be obtained also by three-component condensation of esters (**1**) with triethylorthoformiate

and amine. The data of the NMR spectroscopy of esters (**11, 12**) indicate on their existence in the solutions as an equilibrium mixture of *Z*- and *E*-isomers.[25]



Scheme 5

Fluoroalkyl-containing 2-halogenated 3-oxo esters were prepared by halogenation of 3-oxo esters (**1**) with molecular chlorine or bromine. Chlorination of 3-oxo esters (**1**) with equimolar amounts of chlorine gives stable 2-chloro-3-fluroalkyl-3-oxopropionates (**13**).[26,27] According to IR and NMR, esters (**13**) exist as a tautomer mixture of keto and enol forms.[27] Opposite to 2-chloro-3-oxo esters (**13**), 2-bromo-3-fluoroalkyl-3-oxopropionates (**E**) obtained by bromination of esters (**1**) are unstable due to the fact that there is a tendency to disproportion to form starting ester (**1**) and 2,2-dibromo-3-fluoroalkyl-3-oxopropionates (**14**)[27,28] (Scheme 6).

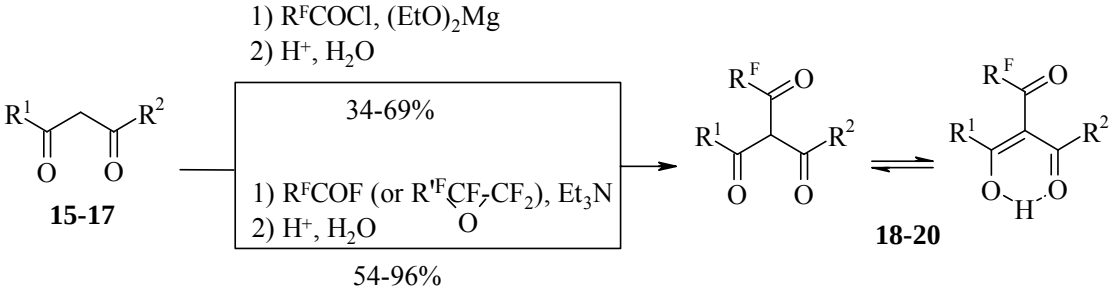


Scheme 6

Acylation of non-fluorinated 1,3-dicarbonyl compounds (diethyl malonate (**15**), ethyl acetoacetate (**16**) and acetylacetone (**17**)) with polyfluorocarbonic halogen-anydrides is used for synthesis of fluoroalkyl-containing 3,3'-tricarbonyl compounds (**18-20**)[29,30] (Scheme 7).

Instead of halogen-anhydrides, terminal fluoroolefins α-oxides can be applied.[31] 2-Acetyl-3-polyfluoroalkyl-3-oxopropionates (**19**) and 3-acetyl-4-polyfluoroalkylbutan-2,4-dione (**20**) in $CDCl_3$ and CCl_4 solutions are enols, while diethyl-2-polyfluoroacylmalonates (**18**) are the mixture of keto

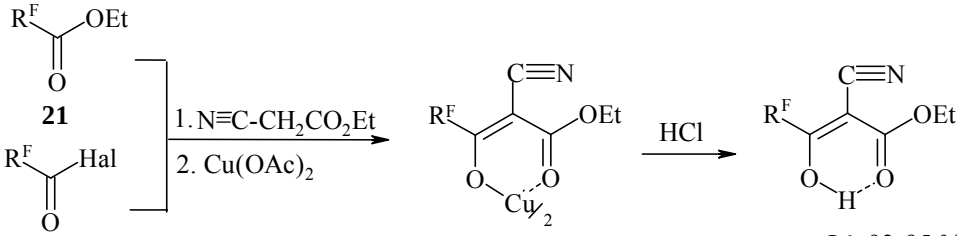
and enol forms.[30]



$R^1 = R^2 =$ Me (**15, 18**), $R^1 =$ Me, $R^2 =$ OEt (**16, 19**), $R^1 = R^2 =$ OEt (**17, 20**);
$R^F = H(CF_2)_2$, C_2F_5, C_3F_7, $CF(CF_3)_2$, $H(CF_2)_4$, C_4F_9, $H(CF_2)_5$, C_6F_{13};
$R'^F = CF_3$, HCF_2

Scheme 7

3-Fluoroalkyl-2-cyano esters (**24**) can be obtained by condensation of fluorocarbonic esters (**21**) with cyanoacetate in the presence of metallic sodium as a condensing agent or by acylation of cyanoacetate with fluorocarbonic acid halogenanhydrides (**22**) in the presence of triethylamine.[32] The last method is convenient for ethyl 2-cyano-3-hydroxy-3-pentafluorophenylbut-2-enoate (**24**) ($R^F = C_6F_5$). However, magnesium ethylate is used as acylating agent in this case. 2-Cyano esters (**24**) are isolated *via* their cupric chelates (**23**).



$R^F = CF_3$, C_4F_9, C_6F_5

Scheme 8

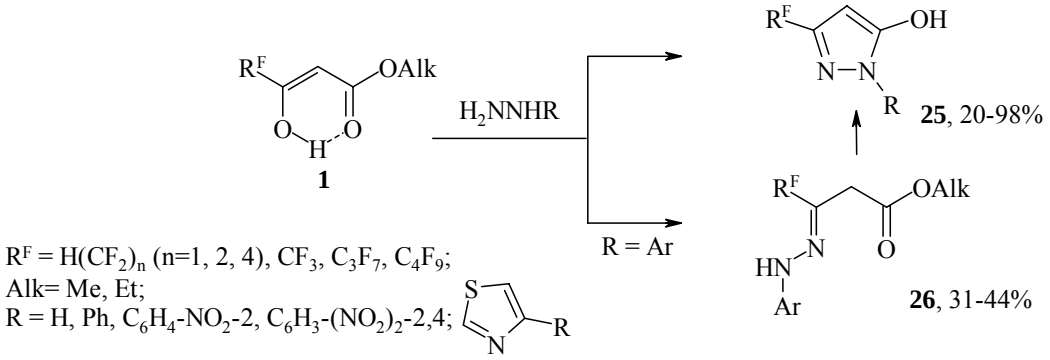
According to IR and NMR spectroscopy fluorinated 2-cyano-3-oxo esters (**24**) are enolized practically completely.

III. SYNTHESIS OF HETEROCYCLES ON THE BASE OF FLUORINE-CONTAINING 2-FUNCTIONALIZED 1,3-DICARBONYL COMPOUNDS

1. Reactions with α-dinucleophiles

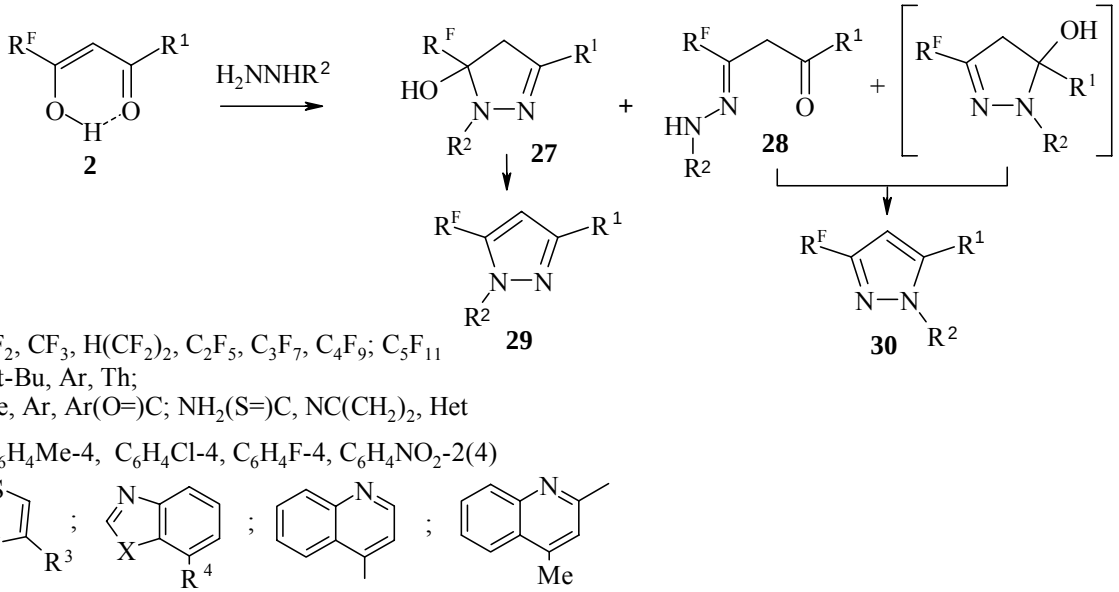
Cyclocondensation at β-dicarbonyl fragment is known to be typical for non-fluorinated and fluoroalkyl-containing 1,3-dicarbonyl compounds (**1, 2**) in the reactions with hydrazines. It is the most common method for construction of pyrazoles derivatives. The use of substituted hydrazines can lead to the formation of individual *regio*-isomeric 3-R^F and 5-R^F-pyrazoles or a mixture of these isomers.[4,33,34] The reactions of fluoroalkyl-containing 3-oxo esters (**1**) result in mainly one *regio*-isomer, *viz*

3-fluoroalkyl-5-hydroxypyrazoles (**25**). Diamine is likely to attack initially at β-keto group (Scheme 9). The possibility of the isolation of hydrazones (**26**) from the reactions with (het)arylhydrazines confirms this.



Scheme 9

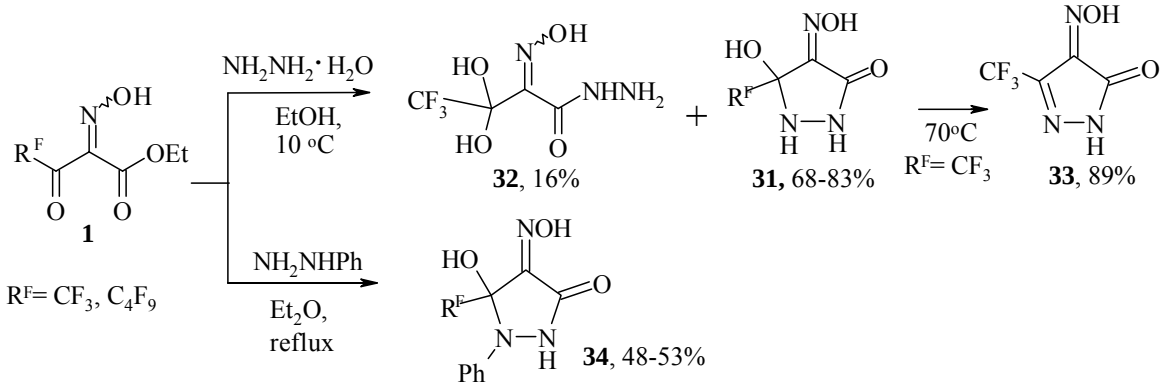
In the reaction with the substituted hydrazines non-symmetrical monofluoroalkyl-containing 1,3-diketones (**2**) can form isomeric 3-R^F or/ and 5-R^F-pyrazoles (**29**, **30**) or/ and their precursors 5-hydroxy-5-fluoroalkylpyrazolines (**27**) or hydrazones (**30**) depending on non-fluorinated substituent, the reaction conditions and hydrazine type (Scheme 10).[5, 6, 35]



Scheme 10

2-Hydroxyimino-1,3-dicarbonyl compounds (**3, 4**) react with hydrazines at the 1,3-dicarbonyl fragment to retain hydroxyimino substituent and to give the pyrazole derivatives.[9, 36] 2-Hydroxyimino-3-oxo esters (**3**) in the reaction with hydrazine-hydrate form 5-hydroxy-4-hydroximino-5-fluoroalkylpyrazolidin-3-ones (**31**) (Scheme 11). Besides, hydrazide of 2-hydroxyimino-3,3-dihydroxy-4,4,4-trifluorobutanoate (**32**) was isolated from the reaction of ester (**3**) that has trifluoromethyl substituent. Pyrazolidin-3-one (**31**) with the trifluoromethyl residue is dehydrated easily on heating to give

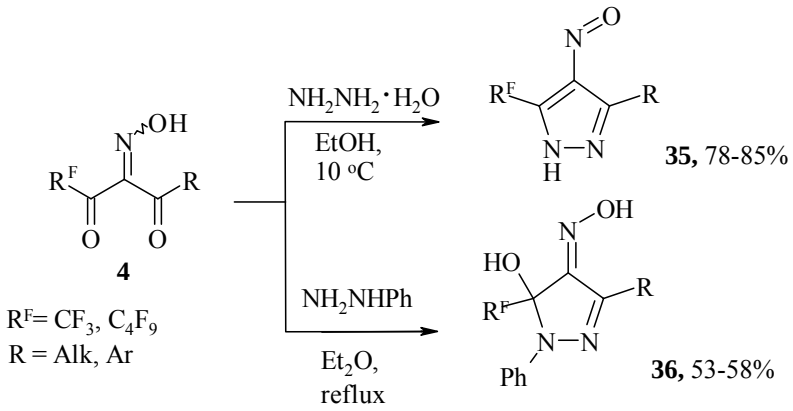
4-hydroxyimino-3-trifluoromethylpyrazolin-5-one (**33**). On the contrary pyrazolidin-3-one (**31**) having nonafluorobutyl substituent is more stable to dehydration. It is obviously due to the formation of hydrogen bond between hydroxyl group and β-fluorine atoms of nonafluorobutyl substituent.



Scheme 11

The interaction of 2-hydroxyimino-3-oxo esters (**3**) with phenylhydrazine result in the 5-hydroxy-5-fluoroalkylpyrazolidin-3-ones (**34**)[36] (Scheme 11). The formation of different *regio*-isomeric pyrazoles as compared to 2-unsubstituted 3-oxo esters (**1**) (Scheme 9) is the distinctive feature of 2-hydroxyimino-3-oxo esters (**3**) in these reactions. The presence of three conjugated electrophilic reactionary centers in esters (**3**) is likely to result in the change of primary attack of phenylhydrazine at ester fragment and not at β-keto group as in the case of other 3-oxo esters (**1**).

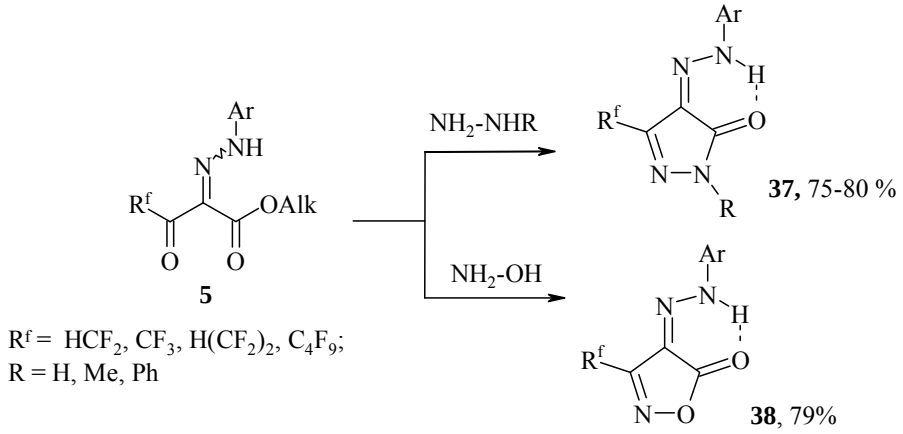
The condensations of 2-hydroxyimino-1,3-diketones (**3**) with hydrazines produce 4-nitrosopyrazoles (**35**) and with phenylhydrazine furnish 5-hydroxy-4-hydroxyimino-1-phenyl-5-fluoroalkylpyrazolines (**36**) (Scheme 12).[9] The stabilization of pyrazolines (**36**) is the result of the presence of the electron-withdrawing fluoroalkyl substituents.



Scheme 12

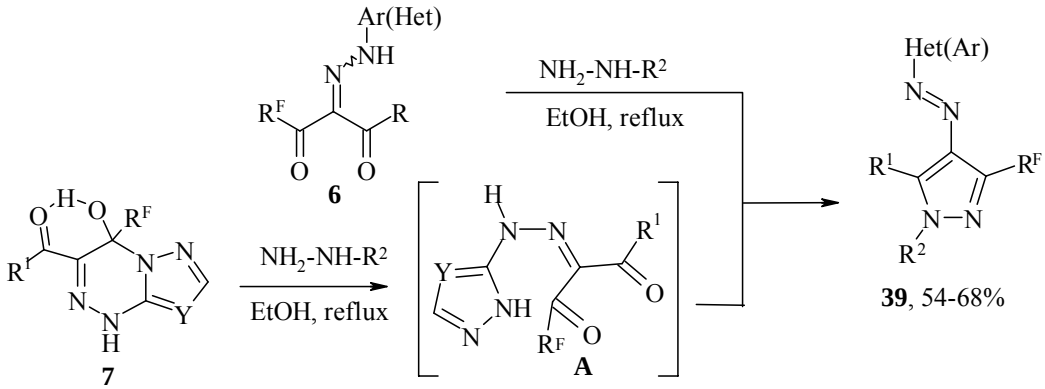
Fluoroalkyl-containing 2-arylhydrazono-1,3-dicarbonyl compounds (**5, 6**) condense with α–*N,N*- and *N,O*-dinucleopiles at β–dicarbonyl fragment to produce the five-membered heterocycles. So condensation of 2-arylhydrazono-3-oxo esters (**5**) with hydrazine hydrate, methylhydrizine and phenylhydrazine results in 4-arylydrazono-3-fluoroalkylpyrazolin-5-ones (**37**) and with hydroxylamine leads to 4-

arylhydrazono-3-fluoroalkylisoxazol-5-ones (**38**) (Scheme 13).[12,13] In these reactions the primary amino group of dinucleophile condenses at polyfluoroacyl fragment.



Scheme 13

Polyfluoroalkylated 1,2,3-triketones 2-(het)arylhydrazones (**6**) and their cyclic derivatives (**7**) were used as the starting building blocks for the synthesis of polyfluoromethyl-containing pyrazoles.[12,13,17,18] The compounds (**6**) react with hydrazine hydrate, methylhydrazine, phenylhydrazine and 2-hydroxyehtyl-hydrazine at the 1,3-dicarbonyl fragment to result in pyrazoles (**39**) (Scheme 14). The pyrazoles (**39**) were the final products also in the reactions of 4,7-dihydrotriazolo[5,1-*c*]triazines (**7**) with methylhydrazine and phenylhydrazine. It is likely that the azolo[5,1-*c*]triazines (**7**) undergo ring opening in refluxing ethanol to give 1,2,3-triketones 2-hetarylhydrazones (**A**), which further react with these hydrazines on 1,3-dicarbonyl fragment.

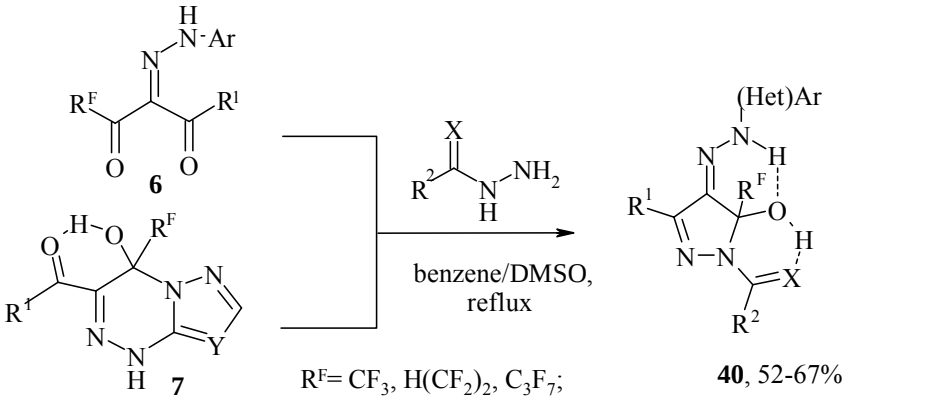


Scheme 14

The cyclocondensation of non-symmetrical *mono*(polyfluoromethyl)-containing 1,2,3-triketones 2-(het)arylhydrazones (**6**) with substituted hydrazines can afford 3-R^F-*regio*-isomeric pyrazoles (**39**) that was determined by the X-ray diffraction analysis.[18]

In contrast 1,2,3-triketones 2-arylhydrazones (**6**) and 7-fluoroalkyl-4,7-dihydroazolo[5,1-*c*]triazines (**7**) react with hydrazides of benzoic and isonicotinic acids and thiosemicarbazide to form

4-(het)arylazo-5-hydroxy-5-polyfluoroalkyl-2-pyrazolines (**40**) (Scheme 15) as a result of initial addition of the hydrazide primary group to the carbonyl group connected with non-fluorinated substituent.[13]

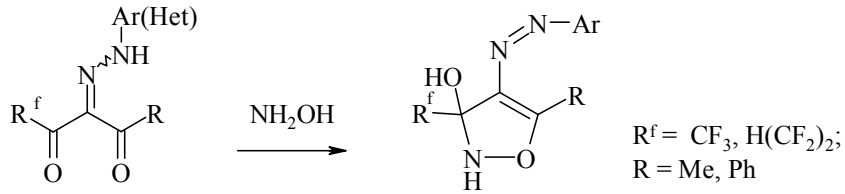


6 **7** **40**, 52-67%

R^F= CF_3, $H(CF_2)_2$, C_3F_7;
R^1 = Me, Ph;
Y = N, C-CO_2Et,
X= O, R^2 = Ph, Py; X= S, R^2 = NH_2;
Het = 1,2,4-triazol-3-yl, 1H-4-ethoxycarbonylpyrazol-3-yl

Scheme 15

The reactions of 1,2,3-triketones 2-arylhydrazones (**6**) with hydroxylamine furnish the stable 4-arylazo-3-hydroxy-3-fluoroalkylisoxazoles (**41**) (Scheme 16).[12,13]

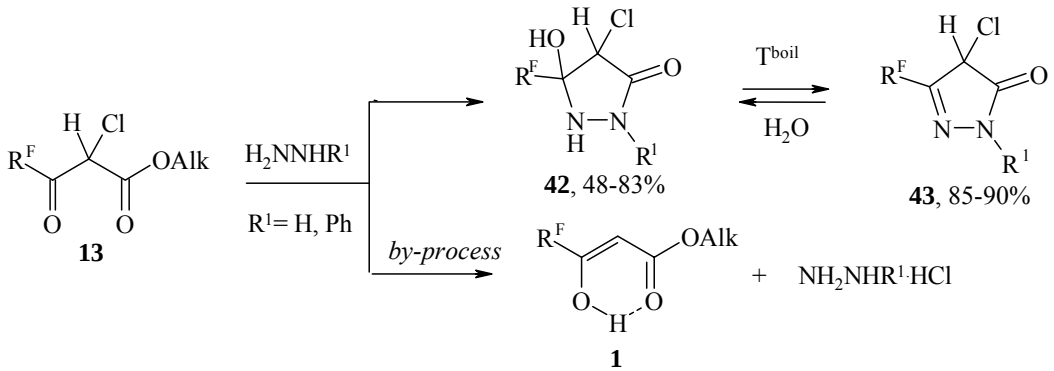


6 **41**, 63-79%

R^f = CF_3, $H(CF_2)_2$;
R = Me, Ph

Scheme 16

2-Chloro-3-fluoroalkyl-3-oxopropionates (**13**) in the reactions with hydrazine and phenylhydrazine furnish 3-polyfluoroalkyl-4-chloro-3-hydroxypyrazolidin-5-ones (**42**) which can eliminate hardly a water molecule to afford 3-polyfluoroalkyl-4-chloropyrazolin-5-ones (**43**) (Scheme 17).[37] It should be noted that the reactions of 2-chloro-3-oxo esters (**13**) with hydrazines go with dehalogenation.

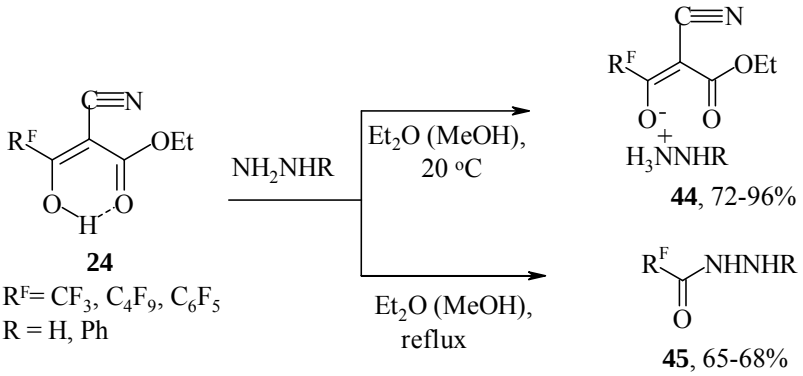


13 **42**, 48-83% **43**, 85-90% **1**

Scheme 17

For fluorine-containing 2-cyano-3-oxo esters (**24**) in the reactions with hydrazines depending on the conditions two processes are competing: the formation of salts (**44**) under mild conditions and acid

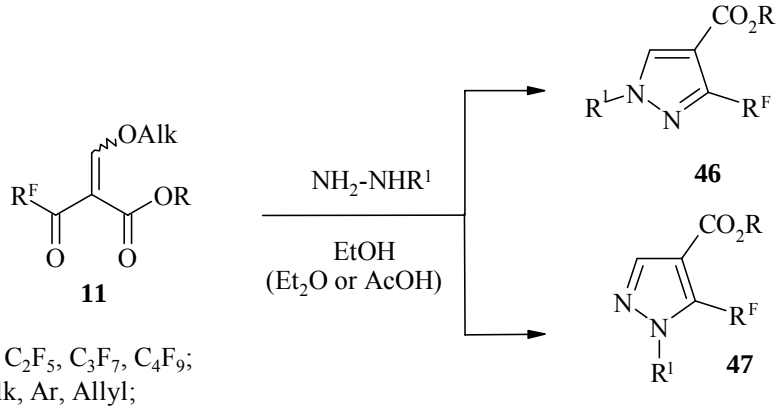
cleavage to produce polyfluorocarbonic acids hydrazides (**45**) under more severe reaction conditions (Scheme 18).[32] Such cardinal change in the reactivity of esters (**24**) is the result of their acidity increase due to the presence of the electron-withdrawing cyano group.



Scheme 18

The introduction of such functional groups as acyl, ethoxymethylidene, arylidene substituents in *meso*-position of 3-oxo esters (**1**) results in the change of the direction of pyrazole cycle formation. Heterocyclization occurs with the participation of these groups and fluoroacyl fragment and without the participation of alkoxycarbonyl substituent.

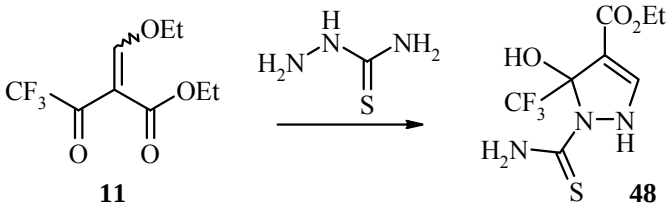
Information about the reactions of 2-alkoxymethylidene-3-oxo esters (**11**) with alkyl, aryl hydrazines is conflicted. So, the formation of 3-R^F-4-alkoxycarbonylpyrazoles (**46**) as a result of hydrazine primary amino group condensation at fluoroacyl substituent and followed by substitution of alkoxy group in methylidene fragment by the diamine secondary amino group is described in Japanese patents[38] (Scheme 19). However, Bec and co-worker[39] reported that these reactions afford regio-isomeric 5-R^F-4-ethoxycarbonylpyrazoles (**47**) due to the initial condensation of the primary amino group at ethoxymethylidene fragment and followed by cyclization at fluoroacyl residue.



R^F= CF_3, C_2F_5, C_3F_7, C_4F_9;
R = H, Alk, Ar, Allyl;
Alk= Me, Et, Pr, Bu;
Ar= C_6H_4-X-4; X= H, Cl, CF_3, OMe

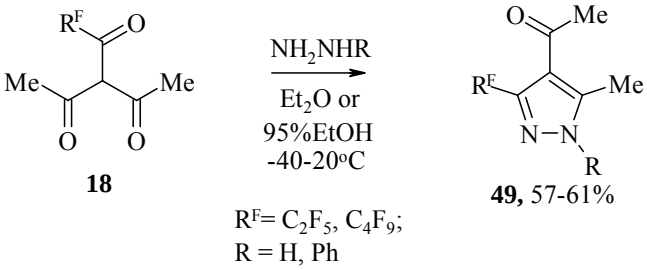
Scheme 19

The interaction of ethyl 2-ethoxymethylidene-3-oxo-4,4,4-trifluorobutanoate (**11**) with thiosemicarbazide yields 4-ethoxycarbonyl-5-hydroxy-5-fluoroalkyl-1-thiocarbomoylpyrazoline (**48**) (Scheme 20).[40]



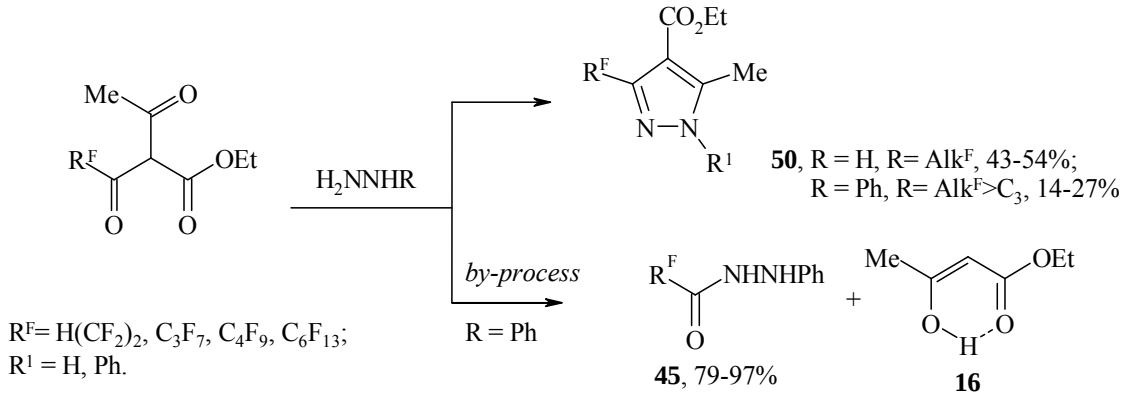
Scheme 20

The reactions of fluoroalkylated β,β'-tricarbonyl compounds (**18–20**) with hydrazine and phenylhydrazine proceed ambiguously depending on the type of compounds (**18–20**), the fluoroalkyl substituent and the solvent used.[41] So, β,β'-triketones condense with hydrazines regioselectively at fluoroalkyl-containing β-dicarbonyl fragment to yield 4-acetyl-3-fluoroalkyl-5-methylpyrazoles (**49**) (Scheme 21).



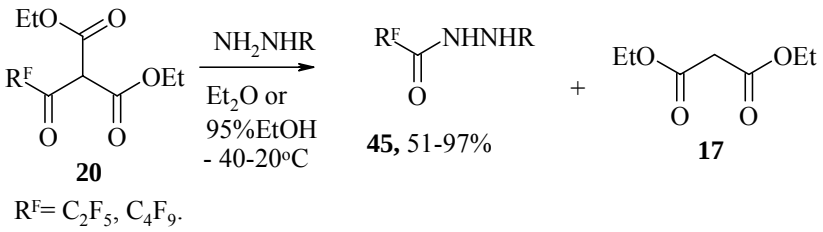
Scheme 21

α-Polyfluoroacylsubstituted acetoacetates (**19**) react with hydrazine at β-diketone moiety to afford 4-ethoxycarbonyl-3-fluoralkyl-5-methylpyrazoles (**50**) (R = H) (Scheme 22).[42] Unlike these reactions esters (**19**) interact with phenylhydrazine in ether to cleavage to phenylhydrazides (**45**) (R = Ph) and acetoacetate (**16**). However, the use of 95%-ethanol as a solvent permits to obtain 4-ethoxycarbonyl-3-fluoroalkyl-5-methylpyrazoles (**50**), but the formation of pyrazoles (**50**) (R= Ph) proceeds in the case of β,β'-dioxo esters (**19**) containing "long" fluoroalkyl substituents (C≥4) only. Acid decomposition in the case of esters (**19**) having more "short" fluoroalkyl substituents occurs also.



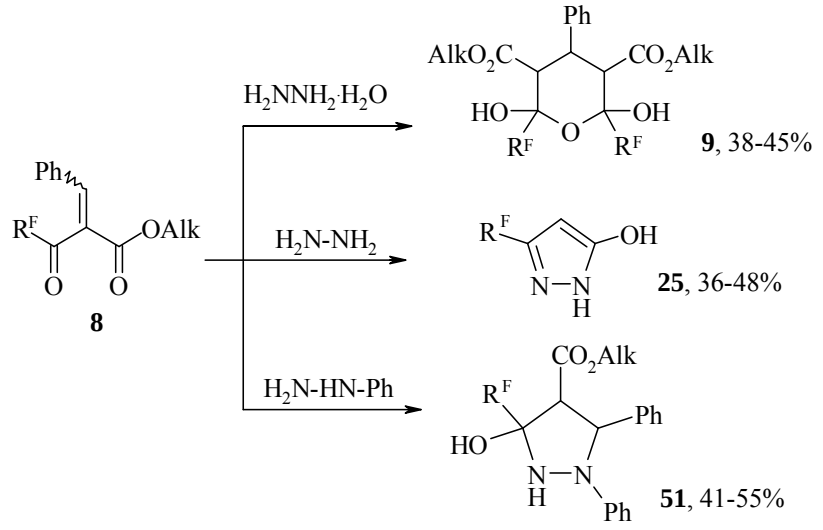
Scheme 22

The interaction of α-polyfluoroacylated malonates (**20**) leads to their acid decomposition to give hydrazides (**45**) and diethyl malonate (**17**) only (Scheme 23).[42]



Scheme 23

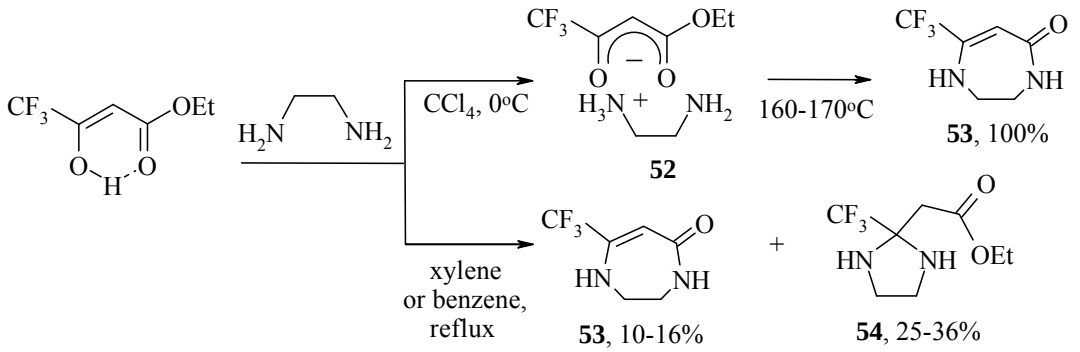
The transformations of 2-arylidene-3-oxo esters (**8**) are complicated by a tendency to decomposition. So, the esters (**8**) in the reaction with hydrazine hydrate easily convert into tetrahydropyranes (**25**) due to the partial decomposition (Scheme 24).[43] Under the treatment with anhydrous hydrazine the decomposition is the basic process, as pyrazoles (**25**) typical for the reactions of 3-oxo esters (**1**) were isolated in this case. Preparations of 4-alkoxycarbonyl-3-fluoroalkyl-3-hydroxy-1-phenylpyrazolidines (**51**) are possible in the reactions of esters (**8**) with phenylhydrazine as a result of the diamine addition to polyfluoroacylvinyl fragment.[43]



Scheme 24

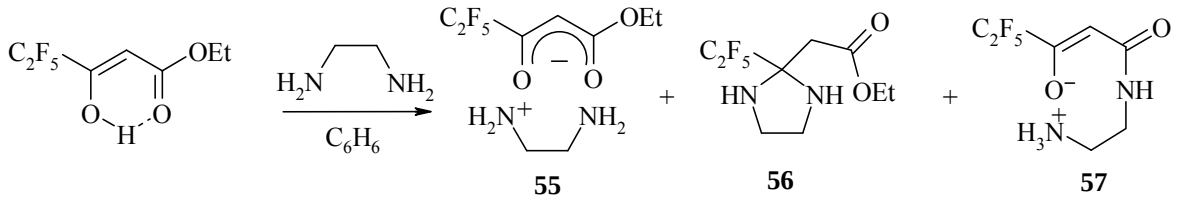
2. Reactions with ethylenediamine

Fluoroalkyl-containing 3-oxo esters (**1**) interact with ethylenediamine to give various products. It is likely that the initial process in these reactions is the formation of salts, which can be isolated. The further reaction direction is determined by the structure of fluoroalkyl substituent and the reaction conditions.[4] When the salt (**52**) having trifluromethyl substituent is heated at 160-170 °C, it is converted to 4-trifluoromethyl-1,2,3,4-tetrahydro-1,4-diazepin-2-one (**53**) as a result of cyclocondensation at β-dicarbonyl fragment. The reaction of trifluoacetoacetate with ethylenediamine in refluxing benzene or xylene affords the mixture of 1,4-diazepin-2-one (**53**) and 2-trifluoromethyl-2-carbethoxymethylimidazolidine (**54**) (Scheme 25).[4] When imidazolidine (**54**) is formed the diamine is added to β-carbonyl group of trifluoroacetoacetate.



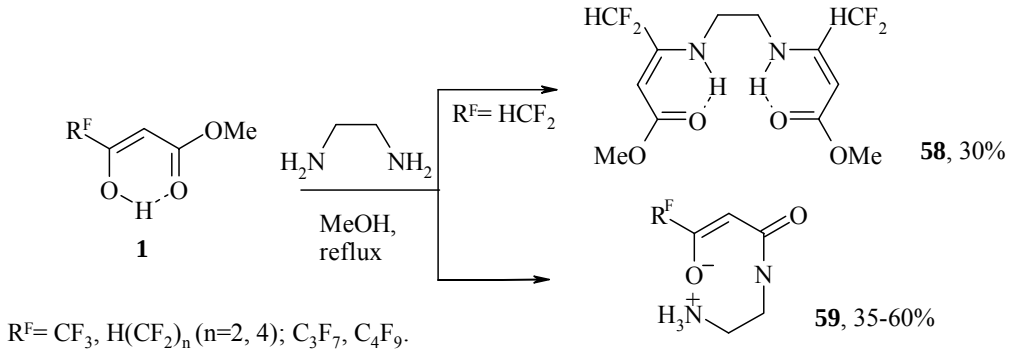
Scheme 25

Refluxing ethyl 4,4,5,5,5-pentafluoro-3-oxopropionate with ethylenediamine in benzene results in the mixture of salt (**55**), imidazolidine (**56**) and internal salt of β-oxo acid 2-aminoethylamide (**57**) (Scheme 26).[4]



Scheme 26

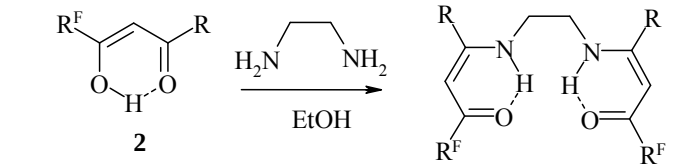
The use of methanol as a solvent in the reactions of 3-oxo esters (**1**) with ethylenediamine leads to simplification of the reaction composition.[34] The reaction direction is determined by esters (**1**) acidity. 3-Oxo ester (**1**) having difluoromethyl substituent condenses with the diamine at fluoroacyl group to afford 3,3'-(*N,N*'-diaminoethylene)-*bis*-1,1-difluoro-2-butenoate (**58**) while esters (**1**) containing trifluoromethyl or more "long" fluorinated residue react at methoxycarbonyl fragment to yield β-oxo acid 2-aminoethylamide (**59**) (Scheme 27).



R^F= CF_3, $H(CF_2)_n$ (n=2, 4); C_3F_7, C_4F_9.

Scheme 27

Fluoroalkylated 1,3-diketones (**2**) react with ethylenediamine to give *N,N'*-ethylene-*bis*(aminovinylketones) (**60**) (Scheme 28).[5] When compounds (**60**) are formed, two molecules of 1,3-diketones (**2**) condense at fluoroacyl group with one molecule of diamine.

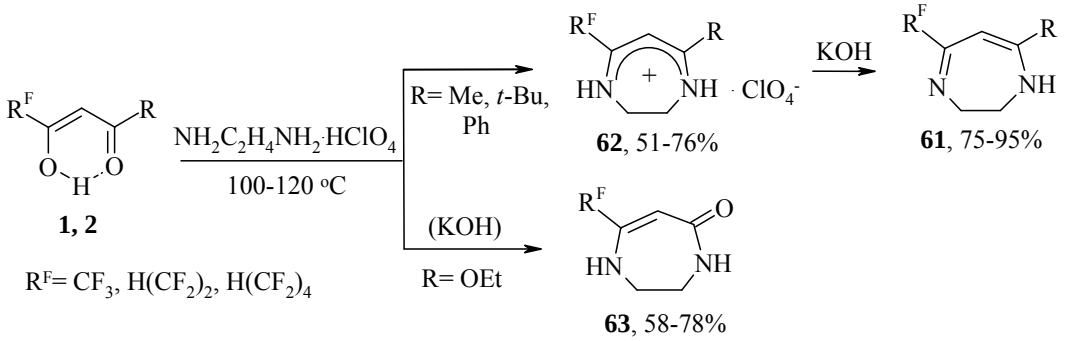


R^F= CF_3, $H(CF_2)_2$, $H(CF_2)_4$;
R= Me, Ph

60, 33-60%

Scheme 28

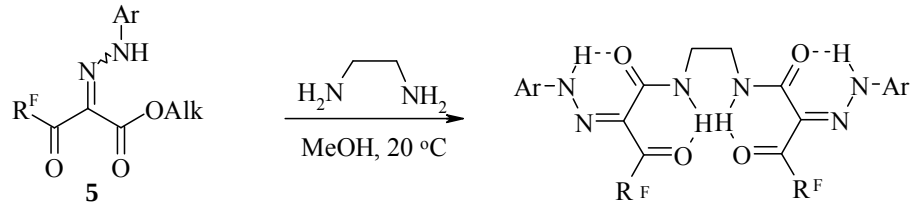
The convenient method for the preparation of 7-alkyl(aryl)-5-fluoroalkyl-1*H*-2,3-dihydro-1,4-diazepines (**61**) is the melting 1,3-diketones (**2**) with ethylenediamine hydroperchlorate at that intermediate salts (**62**) can be isolated (Scheme 29).[44] By analogy 7-fluoroalkyl-1*H*-1,2,3,4-tetrahydro-1,4-diazepin-5-ones (**63**) may be obtained from 3-oxo esters (**1**). However, the intermediate salts are not educed in this case.[44]



R^F= CF_3, $H(CF_2)_2$, $H(CF_2)_4$

Scheme 29

The interaction of 2-arylhydrazono-3-oxo esters (**5**) with ethylenediamine occurs at alkoxycarbonyl group to furnish open-chain *N,N′*-ethylenediamides of 2-arylhydrazono-3-oxo-3-alkylpropionic acids (**64**)[45] (Scheme 30).

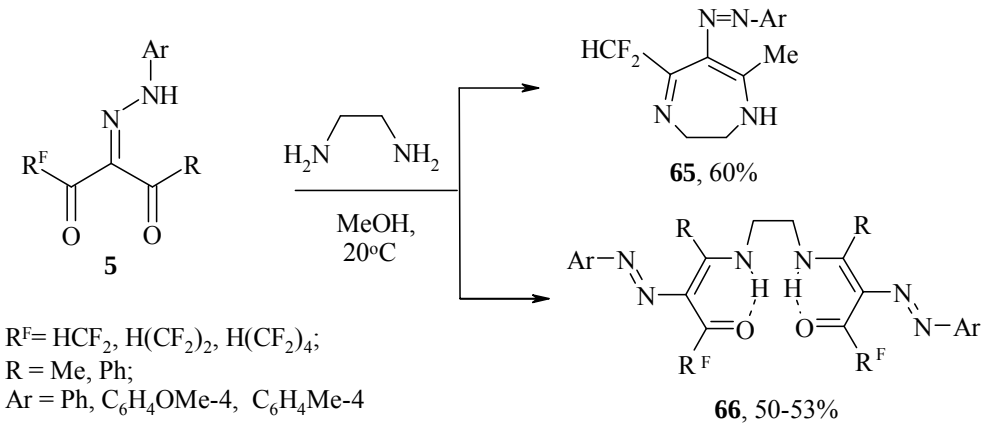


64, 38-56%

R^F = $H(CF_2)_2$, C_4F_9;
Alk = Me, Et;
Ar = Ph, C_6H_4Me-4, C_6H_4OMe-4

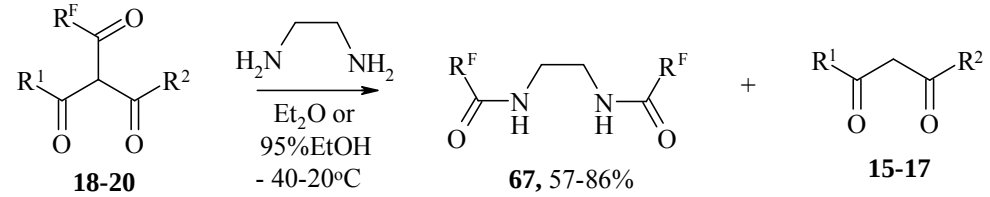
Scheme 30

Fluoroalkyl-containing 2-arylhydrazones of 1,2,3-triketones (**6**) react ambiguously with ethylenediamine depending on of the fluorinated substituent.[46] Arylhydrazone (**6**) with difluoromethyl group cyclizes in methanol at the room temperature into 6-arylazo-5-difluoromethyl-7-methyl-1,2-dihydro-1,4-diazepines (**65**). Under similar conditions arylhydrazones (**6**) containing "longer" fluoroalkyl substituent afford acyclic *N,N′*-ethylene-*bis*(2-arylazo-1,3-aminovinylketones) (**66**) (Scheme 31).



Scheme 31

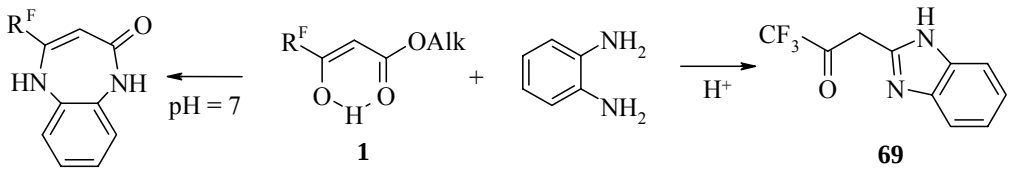
Fluoroalkylated β,β'-tricarbonyl compounds (**18–20**) in the reactions with ethylenediamine under mild conditions (anhydrous diethyl ether or 95%-ethanol at -40 – 20 °C) undergo acid cleavage to afford *N,N'-bis*-(polyfluoroacyl)ethylenediamides (**67**) and non-fluorinated 1,3-dicarbonyl compounds (**15-17**) (Scheme 32).[41] Obviously, the initial dinucleophile attack proceeds at polyfluoroacyl group.



Scheme 32

3. Reactions with *o*-phenylenediamine

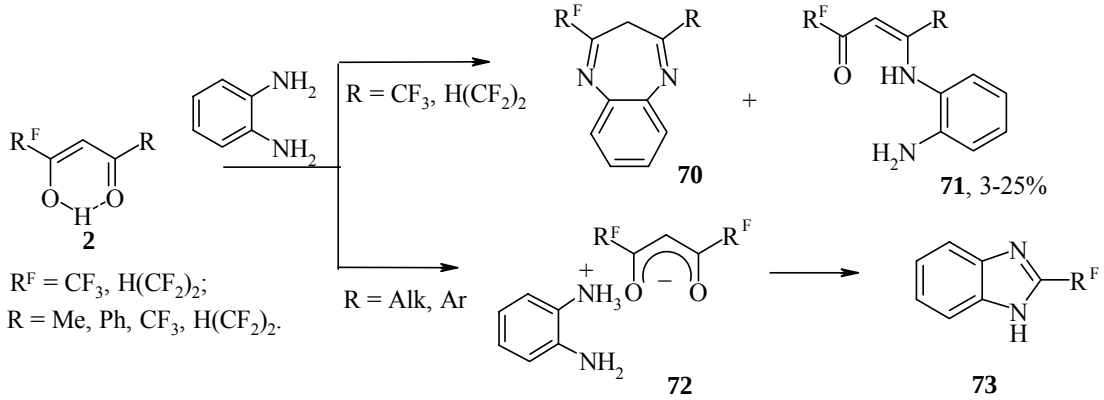
Fluoroalkylated 3-oxo esters (**1**) react with *o*-phenylenediamine at β-dicarbonyl moiety to give 4-fluoroalkyl-*1H*-1,5-benzodiazepin-2-ones (**68**) under the neutral conditions (Scheme 33), but in the case of fluoroacetoacetate ester the formation of 2-(3,3,3-trifluoro-2-oxopropyl)benzimidazole is described under acid medium.[4,34]



Scheme 33

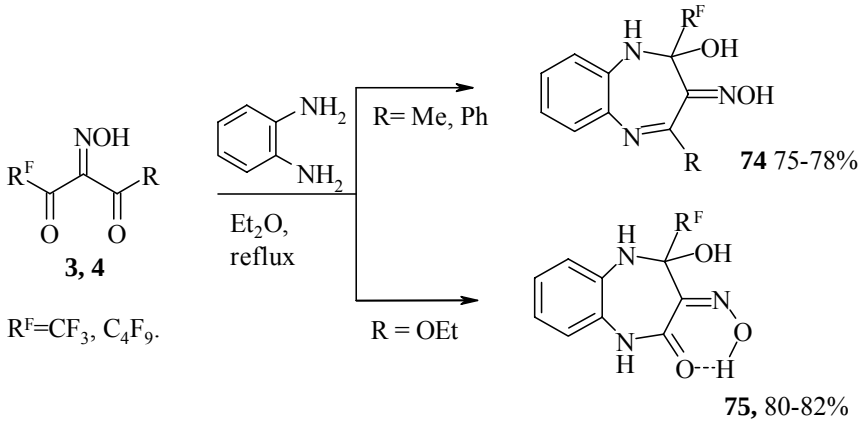
The basic products in the reactions of fluoroalkyl-containing 1,3-diketones (**2**) with *o*-phenylenediamine are 4-fluoroalkyl-2-alkyl(aryl)-1,5-benzodiazepines (**70**) (Scheme 34), but the small content of non-cyclic

α-aminovinylketones (**71**) is formed depending on the fluorinated substituents. Under usual condensation conditions β-diketones having two fluoroalkyl substituents produce with *o*-phenylenediamine the salts (**72**) that are converted into 2-fluoroalkylbenzimidazoles (**73**) in refluxing ethanol in the presence of acetic acid.[4,47]



Scheme 34

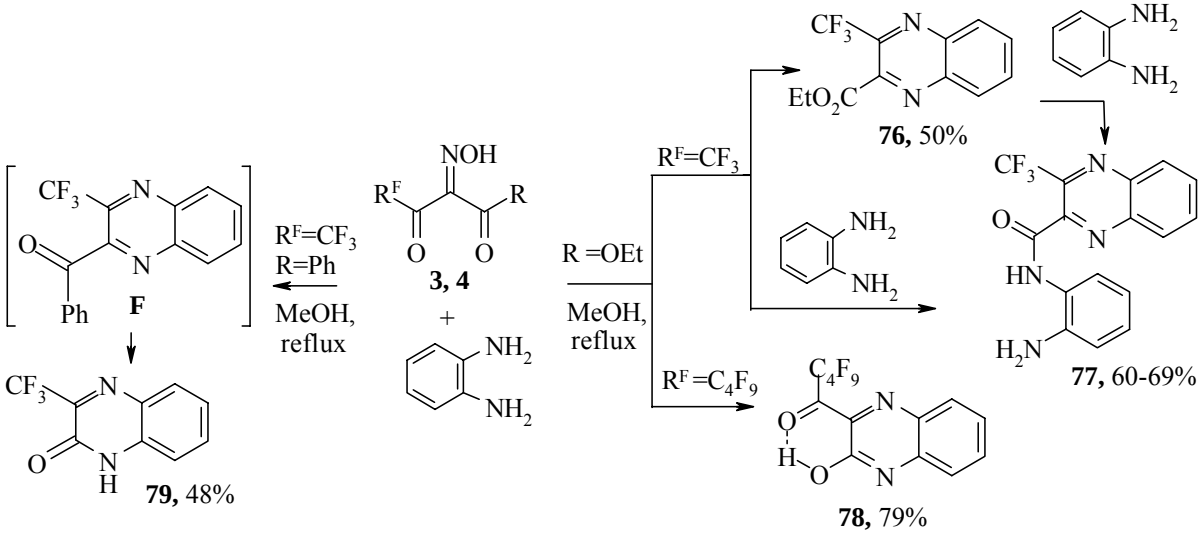
2-Hydroxyiminocontaining 3-oxo esters (**3**) and 1,3-diketones (**4**) under mild conditions (refluxing ethyl ether) react with *o*-phenylenediamine at 1,3-dicarbonyl fragment to afford the substituted tetrahydro-1,5-benzodiazepin-2-ones (**74**) and dihydro-1,5-benzodiazepines (**75**) also (Scheme 35).[48]



Scheme 35

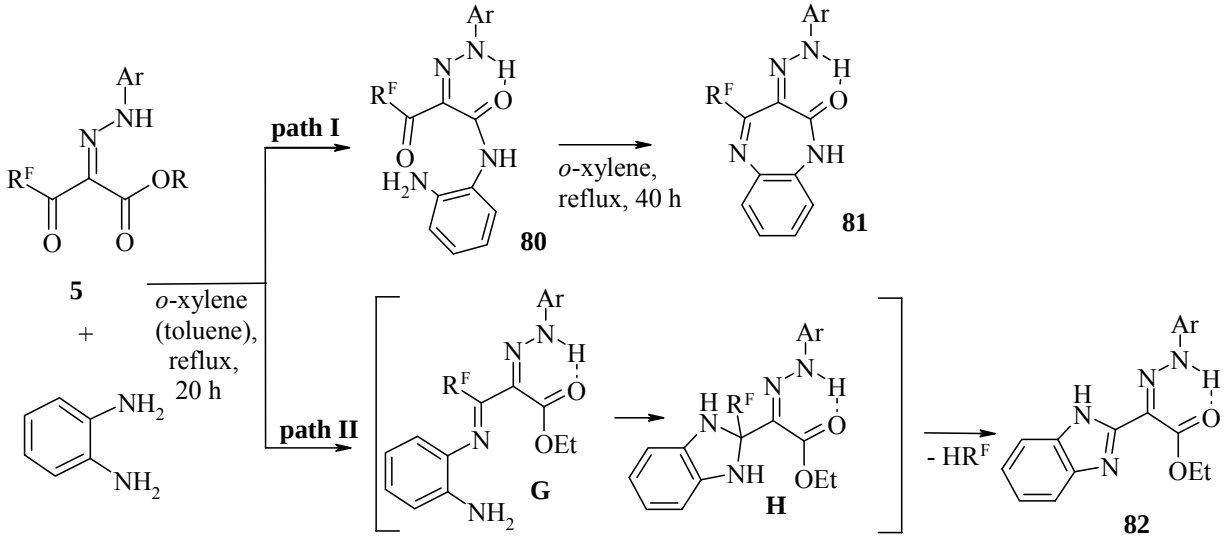
However, introducing 2-hydroxyimino group in 1,3-dicarbonyl compounds changes customary reaction course in a number of cases. So, interaction of 2-hydroxyimino-3-oxo esters (**3**) and 1,3-diketones (**4**) with *o*-phenylenediamine in methanol, benzene or toluene results in the substituted quinoxalines (**76-79**) (Scheme 36).[48] The formation of quinoxalines in these reactions is possible due to the diamine cyclocondensation at hydroxyimino fragment and one of carbonyl groups of the starting compounds (**3, 4**). These reactions are the region-directed since the nucleophilic attack is realized at the least steric laboured carbonyl carbon atom. Ethyl trifluoroacetoacetate cyclocondenses with the diamine on fluoroacyl group to give 2-ethoxycarbonyl-3-trifluoromethylquinoxaline (**76**) while ester (**3**) having the nonafluorobutyl residue cyclises at the ethoxycarbonyl moiety to produce nonafluoro-1-(3-hydroxyquinoxalin-2-yl)pentan-1-one (**78**). When *o*-diamine excess is used, 3-trifluoromethylquinoxalin-2-yl-carbonic acid

o-anilide (**77**) is prepared in the reaction of ester (**1**) (R^F = CF_3). *o*-Anilide (**77**) can be obtained from quinoxaline (**76**) as a result of ethoxycarbonyl group aminolyse. Although the product isolated from the reaction of 1,3-diketone (**4**) has quinoxaline structure (**79**) it is formed apparently by unstable intermediate (**F**) cleavage.



Scheme 36

2-Arylhydrazono-3-oxo esters (**5**) do not react with *o*-phenylenediamine under mild conditions, but in refluxing *o*-xylene (toluene) they interact with this *o*-diamine at ethoxycarbonyl fragment to give 2-arylhydrazono-3-oxo acids *o*-aminoanilides (**80**) as the basic products (Scheme 37).[49] Amides (**80**) upon prolonged heating in o-xylene undergo intramolecular cyclization to afford 3-arylhydrazono-4-fluoroalkyl-1,2-dihydro-*1H*-1,5-benzodiazepin-2-ones (**81**).



R^F = C_6F_{13}, C_4F_9, $H(CF_2)_2$, HCF_2, CF_3;
R = Et, Me;
Ar = C_6H_4Me-4, C_6H_4OMe-4, Ph

Scheme 37

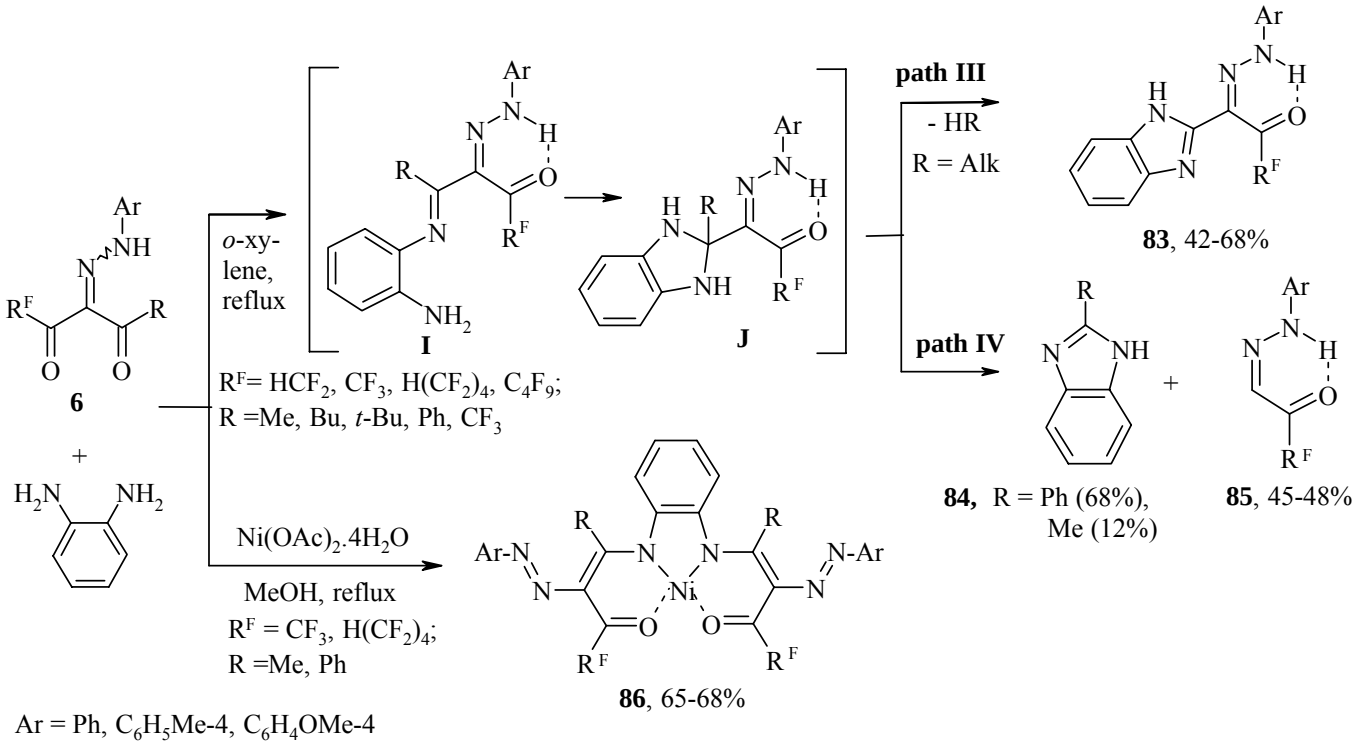
Unlike esters (**5**), having the "long" polyfluorinated substituent, 2-arylhydrazono-3-oxo esters (**5**) with

"short" difluoromethyl fragment react with *o*-phenylenediamine in refluxing *o*-xylene both *via* path **I** to yield *o*-aminoanilides (**80**) and *via* path **II** at difluoroacetyl group to give 2-(benzimidazol-2-yl)-2-arylhydrazo ester (**82**) (Scheme 37).[49,50] The formation of this product results from the cyclization of intermediate 3-arylaminocrotonate (**G**) to C=N bond at difluoromethyl group. The formed 2-disubstituted benzimidazoline (**H**) easily undergoes an aromatization through the elimination of a difluoromethane molecule to afford ethyl 2-(benzimidazol-2-yl)-2-(4-methylphenyl)hydrazono-ethanoate (**82**). Trifluoromethyl substituted ester (**5**) react with *o*-phenylenediamine to yield the mixture of products, from which only 2-(benzimidazol-2-yl)-2-arylhydrazo ester (**82**) in small amount was prepared. This fact confirms the variety of the reaction paths of esters with "short" (fluoro)alkyl fragment and *o*-phenylenediamine.

Thus, the presence of bulky polyfluoroalkyl group in 2-arylhydrazono-3-oxo esters (**5**) promotes *regio*-directive proceeding of reactions with *o*-phenylenediamine at ester group, while esters (**5**), containing difluoro-, trifluoroacetyl substituent, react with *o*-diamine both at ester fragment and at fluoroacetyl group.[49,50]

1,2,3-Triketone 2-arylhydrazones (**6**) do not react with *o*-phenylenediamine under conditions of formation of 1,5-benzodiazepines (**70**) from unsubstituted 1,3-diketones (**2**). Under more severe conditions (on boiling in *o*-xylene, toluene or ethanol in the presence of acid), 2-substituted benzimidazoles (**83**) and (**84**) are the main products of these reactions (Scheme 38).[49,51] In this case, the nature of the substituent at the 2-position of the benzimidazole ring depends on the structures of starting 1,2,3-triketone 2-arylhydrazones (**6**). Thus, compounds (**6**) with alkyl (methyl, butyl, and *tert*-butyl) substituents mainly form 1-(benzimidazol-2-yl)-1,2-dioxoalkane arylhydrazones (**83**)**,** whereas phenyl-substituted 1,2,3-triketone 2-arylhydrazones (**6**) give only 2-phenylbenzimidazole (**84**). Hexafluoroacetylacetone 2-arylhydrazone (**6**) react with *o*-phenylenediamine to yield both 1-(benzimidazol-2-yl)-1,2-dioxo-3,3,3-trifluoropropane 4-arylhydrazone (**83**) and 2-trifluoromethylbenzimidazole (**84**).

It is likely that the initial step in the formation mechanism of the reaction leading to benzimidazoles (**83**) and (**84**) is the same. Obviously, an amino group of *o*-phenylenediamine attacks the alkyl or aryl substituted carbonyl group of 1,2,3-triketone 2-arylhydrazone (**6**) to form intermediate diimine (**I**) (Scheme 38). Next, the free amino group of the intermediate (**I**) adds to the C=N bond at the R-substituent to form 2-substituted benzimidazoline (**J**), and not to the carbonyl group containing the R^F-substituent to give alternatively a 1,5-benzodiazepine. The change of the direction of addition depends on steric hindrance produced by the bulky arylhydrazone group. Intermediate benzimidazoline (**J**) has two possibilities for aromatization: path **III** by elimination of a saturated hydrocarbon molecule (RH) or path **IV** by elimination of a fluorinated 2-arylhydro substituted ketone (**85**). In this case, it is likely that the direction of aromatization depends on thermodynamic factors.[49]



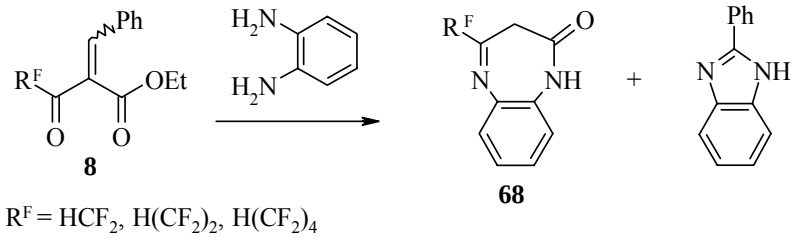
Scheme 38

1,2,3-Triketone 2-arylhydrazones (**6**) containing alkyl substituents primarily react *via* path **III**; in this case, 1-(benzimidazol-2-yl)-1,2-dioxoalkane arylhydrazones (**83**) are formed, whereas phenyl-containing analogues react *via* path **IV** to result in 2-phenylbenzimidazole (**84**). However, these reactions in the case of the alkyl substituted compounds (**6**) occur *via* path **III** also to produce 2-methylbenzimidazole (**84**) and arylhydrazone (**85**) in small amounts together the main benzimidazoles (**83**).[49,51]

The formation of 2-methyl(phenyl)benzimidazoles (**84**) *via* path **III** is typical of the reactions of 1,3-diketones (**2**) with *o*-phenylenediamine whereas the cleavage of 1,2,3-triketone 2-arylhydrazones (**6**) in the reaction with the *o*-diamine is unexpected because only "acid" cleavage was previously known for the reactions of 1,3-diketones, including 2-mono- and 2,2-disubstituted compounds, with alkaline and basic reagents.

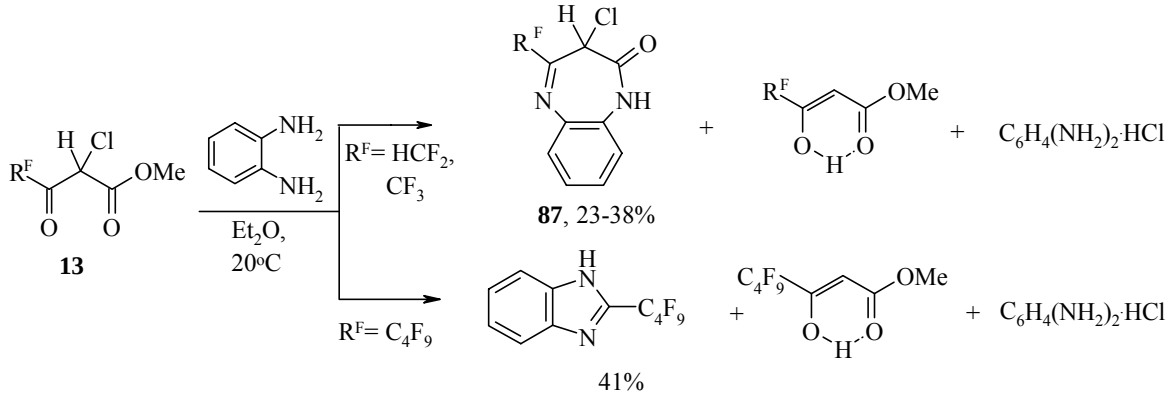
When the reactions of 1,2,3-triketone 2-arylhydrazones (**6**) with *o*-phenylenediamine are carried out under template synthesis conditions in the presence of nickel(II) ions, *N,N'*-phenylene-*bis*(aminovinylketones) nickel chelates (**86**) are obtained (Scheme 38).[49]

In the reactions with *o*-phenylenediamine, 2-benzylidene-3-oxo esters (**8**) undergo *retro*-decomposition similarly to their transformation with anhydrous hydrazine. So esters (**8**) react with diamine independently of the reaction conditions (refluxing in dry benzene, anhydrous diethyl ether or ethanol) to yield benzodiazepine-2-ones (**68**) and 2-phenylbenzimidazole (Scheme 39) as a result of interaction of esters (**1**) and benzaldehyde with *o*-phenylenediamine in the end.[43]



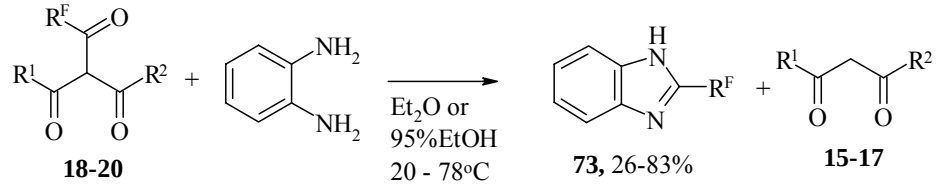
Scheme 39

2-Chloro-3-oxo esters (**13**) having "short" fluoroalkyl substituents cyclocondense with *o*-phenylenediamine to give 2-chloro-4-fluoroalkyl-1,2-dihydro-1,5-benzodiazepin-2-ones (**87**) while nonafluorobutyl-substituted ester (**13**) undergoes "acid" cleavage to form 2-nonafluorobutylbenzimidazole.[37] In all cases together with the basic reactions, dehalogenation of the starting esters (**13**) occurs (Scheme 40).



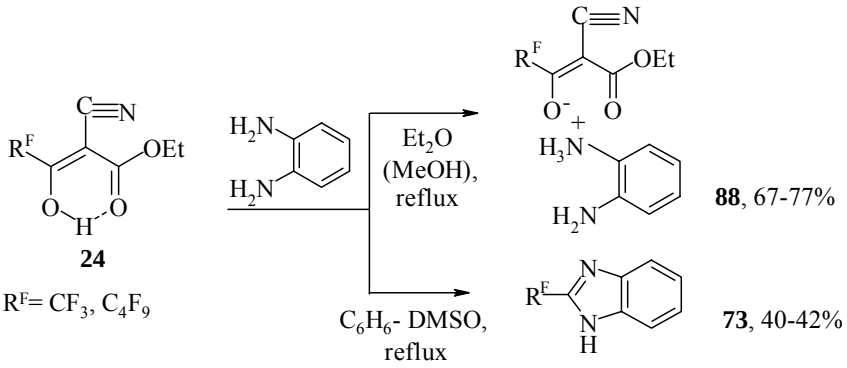
Scheme 40

Fluoroalkyl-containing β,β'-tricarbonyl compounds (**18-20**) react with *o*-phenylenediamine at the polyfluoroacyl group with the followed elimination of 2-polyfluoroalkylbenzimidazoles (**73**) and the corresponding β-dicarbonyl compounds (**15-17**) (Scheme 41).[41]



Scheme 41

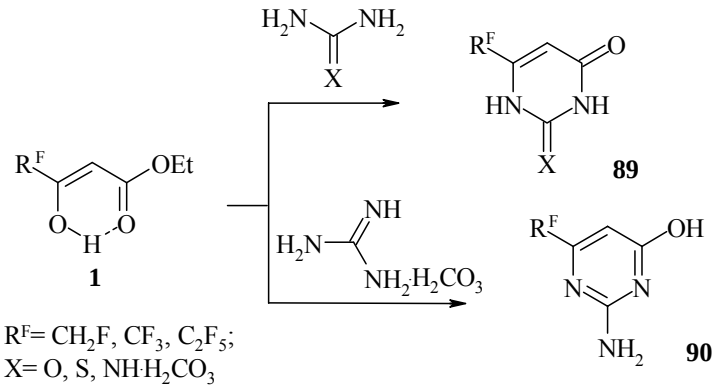
Attempts to obtain heterocycles from 2-cyano-3-oxo esters (**24**) and *o*-phenylenediamine failed. Under mild conditions the salts (**88**) formation is the main process while refluxing in the mixture of benzene and DMSO results in benzimidazoles (**73**) due to acid cleavage (Scheme 42).[32]



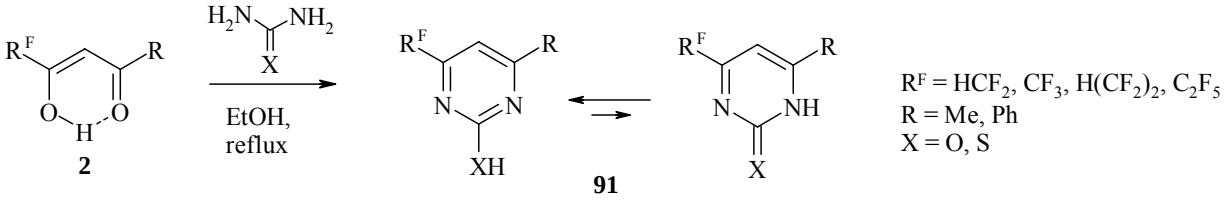
Scheme 42

4. The reactions with ureas and azolylamines

Cyclocondensation of both fluoroalkyl-containing 3-oxo esters (**1**) and 1,3-diketones (**2**) with urea, thiourea and guanidine is used for preparation of the substituted pyrimidines (**89-91**) (Scheme 43, 44).[4,5]

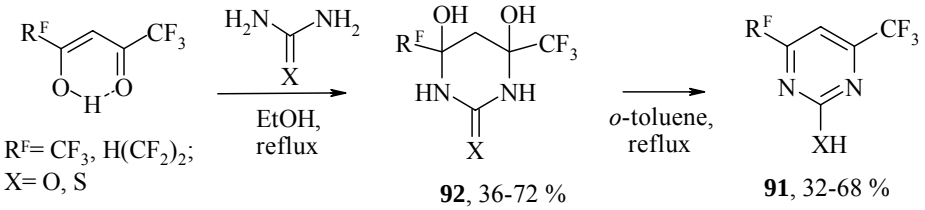


Scheme 43



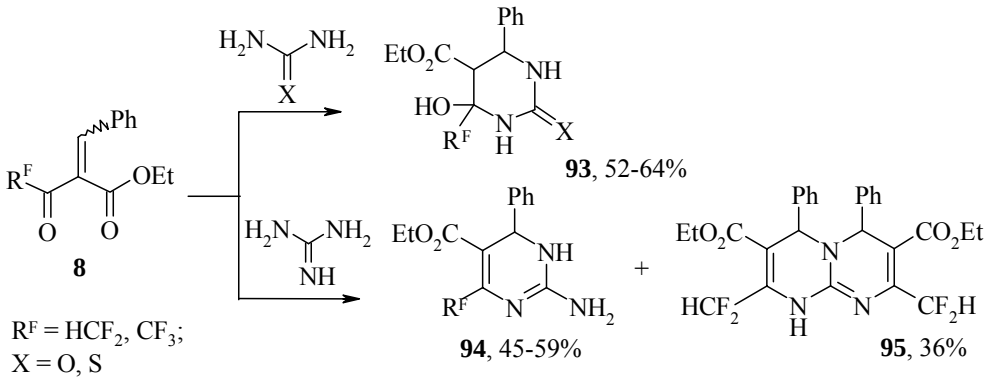
Scheme 44

In contrast to monofluoroalkylated 1,3-diketones (**2**), *bis*(fluoroalkyl)-containing 1,3-diketones react with urea or thiourea to give 4,5-*bis*(hydroxy)-4-trifluoromethyl-6-fluoroalkylhexahydropyrimidin-2-ones(thiones) (**92**)[52] (Scheme 45). Dehydration of hexahydropyrimidinones(thiones) (**92**) results in the formation of 2-hydroxy(mercapto)-4-trifluoromethyl-6-fluoroalkylpyrimidines (**91**).



Scheme 45

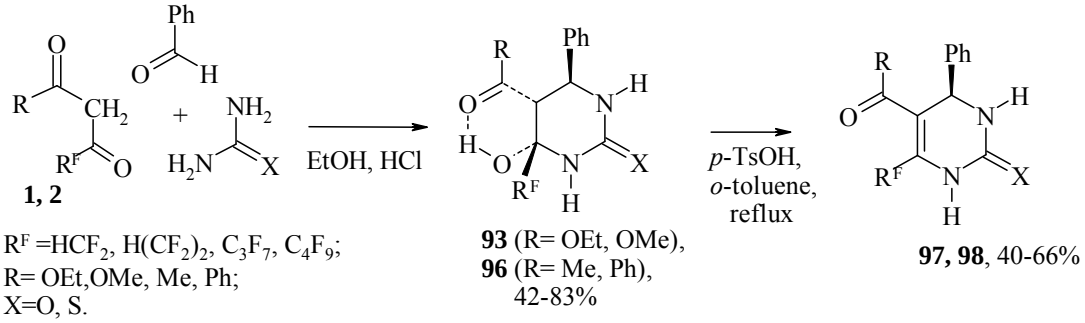
The 2-arylidene-3-oxo esters (**8**) were used also as precursors for the synthesis of the functionalized pyrimidine derivatives. So heating esters (**8**) with urea or thiourea in DMF in the presence of sodium acetate leads to the formation of ethyl 4-hydroxy-6-phenyl-4-fluoroalkyl-2-oxo(thioxo)hexahydro-pyrimidin-5-carboxylates (**93**).[43] In contrast to urea and thiourea, the more basic guanidine sulphate reacts with esters (**8**) in refluxing DMF in the presence of the base to give ethyl 2-amino-6-phenyl-4-fluoroalkyl-1,6-dihydropyrimidin-5-carboxylates (**94**)[43] (Scheme 46).



Scheme 46

In spite of dihydropyrimidines (**94**), 2,7-di(difluoromethyl)-4,5-diphenyl-3,6-diethoxycarbonyl-4,5-dihydro-*1H*-pyrimido[1,2-*a*]pyrimidine (**95**) was prepared by the reaction of esters (**1**) having difluoromethyl substituent (Scheme 46).[43]

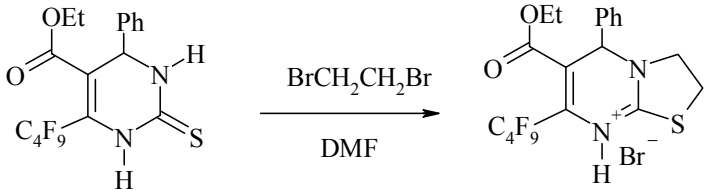
Ethyl 4-fluoroalkyl-4-hydroxy-2-oxo(thioxo)-6-phenylhexahydropyrimidine-5-carboxylates (**93**) can be derived by tree-component condensation of fluorinated 3-oxo esters (**1**) with benzaldehyde and (thio)urea (Scheme 46).[53-55] Besides, the use of fluoroalkylated 1,3-diketones (**2**) in the condensation can be applied for the synthesis of 5-acyl-(aroyl)-4-fluoroalkyl-4-hydroxy-6-phenylhexahydropyrimidin-2-ones(thiones) (**96**).[54,55] The formation of hexahydropyrimidines having *gem*-hydroxyamine moiety is the distinguishing feature of fluorinated compounds as compared to non-fluorinated analogs. It results from stabilizing effect of fluoroalkyl substituent which hinders the easy elimination of water molecule (Scheme 47).



Scheme 47

Hexahydropyrimidines (**93**) and (**96**) undergo dehydration in refluxing toluene in the presence of *p*-toluenesulfonic acid to form 1,2,3,4-tetrahydropyrimidines (**97**) and (**98**) (Scheme 47). Such tetrahydropyrimidines may be used as precursors for the synthesis of fused heterocyclic systems. For

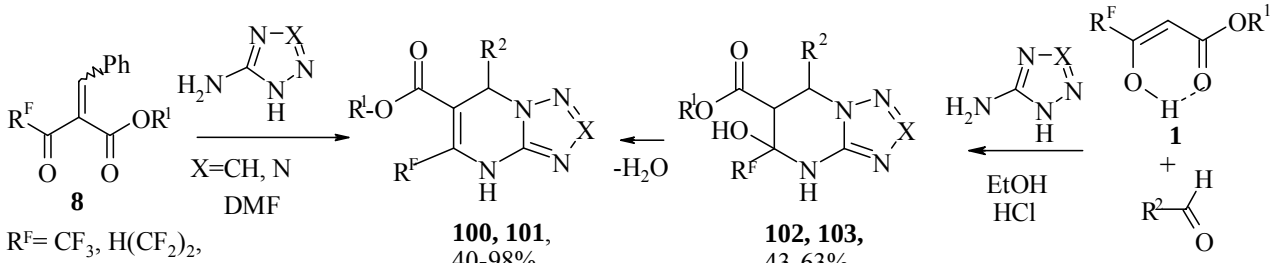
example, tetrahydropyrimidin-2-thione (**98**) on refluxing with dibromoethane in DMF affords the substituted thiazolopyrimidine (**99**) as hydrobromide salt (Scheme 48).[54]



98 **99**, 42%

Scheme 48

The cyclocondensation of esters (**8**) with azolylamines (3-amino-1,2,4-triazole or 5-aminotetrazole) on heating in DMF proceeds regioselectively at the fluoroacylvinyl moiety to produce alkyl 7-aryl-5-fluoroalkyl-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidin-6-carboxylates (**100**) and alkyl 7-aryl-5-fluoroalkyl-4,7-dihydroterazolo[1,5-*a*]pyrimidin-6-carboxylates (**101**) (Scheme 49).[56] Heterocycles (**100**, **101**) can be derived by three-component condensation of 3-oxo esters (**1**) with aldehydes and azolylamines. Although in the reactions of esters (**1**) with azolylamines the main products are dihydroazolopyrimidines (**100**, **101**), ethyl 5-hydroxy-5-fluoroalkyl-7-aryl-4,5,6,7-tetrahydro-tetrazolo[1,5-*a*]pyrimidin-6-carboxylates (**102**) were obtained in a number of cases. However when esters (**1**) condense with acetic aldehyde and azolylamines ethyl 5-hydroxy-5-fluoroalkyl-7-methyl-4,5,6,7-etrahydroazolo[1,5-*a*]pyrimidin-6-carboxylates (**102**, **103**) are the only products (Scheme 49).[56]



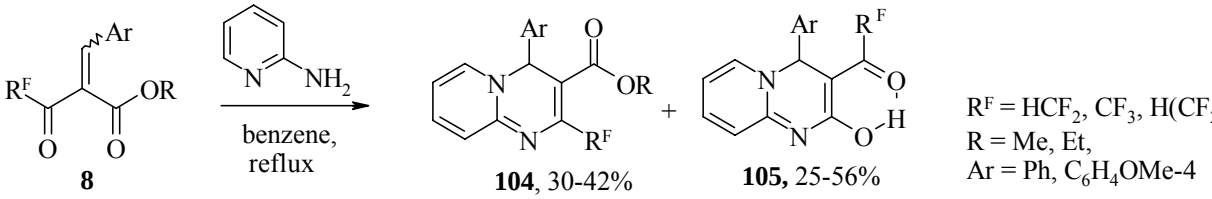
8
R^F= CF_3, $H(CF_2)_2$,
R^1= Me, Et;
R^2= Ph, Me, C_6H_4OMe-4

100, 101, 40-98%

102, 103, 43-63%

Scheme 49

Cyclizations of esters (**8**) with 2-aminopyridine proceed at both polyfluoroacylvinyl and alkoxycarbonylvinyl fragments to result in the formation of alkyl 4-aryl-2-fluoroalkyl-*4H*-pyrido[1,2-*a*]pyrimidin-3-carboxilates (**104**) and 4-aryl-2-hydroxy-3-fluoroacyl-*4H*-pyrido[1,2-*a*]-pyrimidines (**105**) (Scheme 50).[57]



8

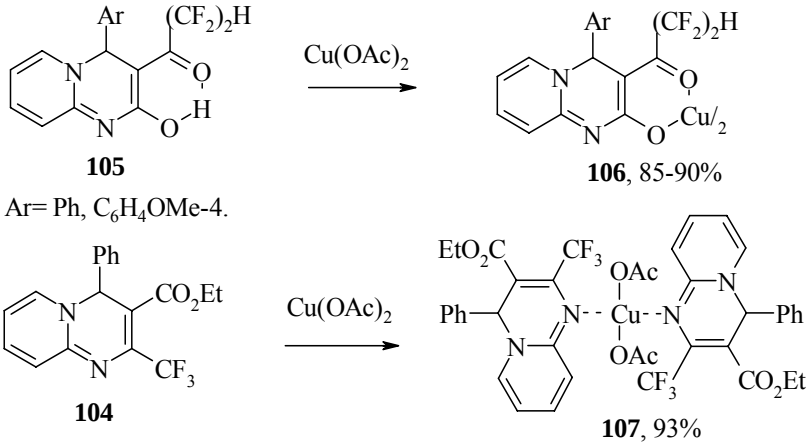
104, 30-42%

105, 25-56%

R^F = HCF_2, CF_3, $H(CF_2)_2$;
R = Me, Et,
Ar = Ph, C_6H_4OMe-4

Scheme 50

The obtained pyrido[1,2-*a*]pyrimidines (**104, 105**) possess the ability to complexation. So the treatment of heterocycles (**104, 105**) with cupric(II) acetate produces metalocomplex compounds (**106, 107**) (Scheme 51).[57]



Scheme 51

III. CONCLUSION

In the present review, we have shown that the promising approach to expand the use of fluorinated 1,3-dicarbonyl compounds in organic synthesis is the introduction of the additional functionalized group at the position 2 of their molecules. It leads not only to the increase in number of the reaction flows, but to the generation of new competitive reaction routes. This new perspective direction in the chemistry of fluorinated 1,3-dicarbonyl compounds is distinguished by the variety of chemical conversions and allows to produce a wide series of functionalized heterocycles of different classes based on the small number of starting "block-synthons".

In general, 2-functionalized fluoroalkyl-containing 1,3-dicarbonyl compounds are available and versatile building blocks for the synthesis of various heterocyclic systems. All above mentioned makes it possible to consider these compounds significant for the future research in the area of heterocyclic and medicinal chemistry.

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