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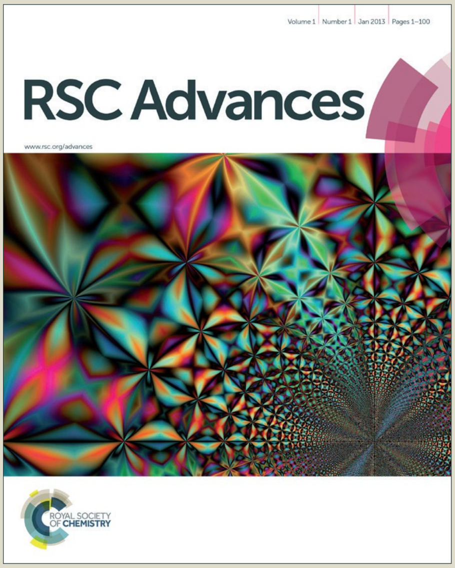

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Unsaturated polyfluoroalkyl ketones in the synthesis of nitorgen-bearing heterocycles

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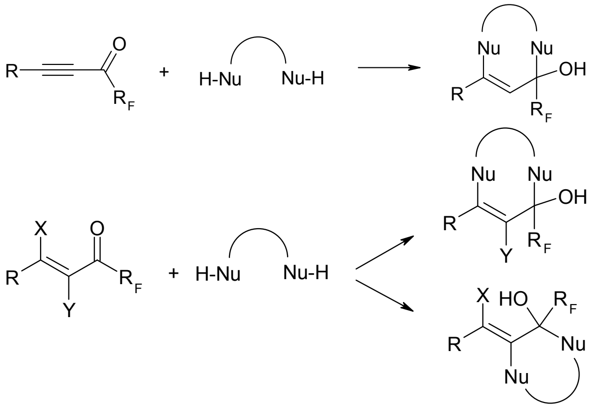
The review focuses on the recent achievements and new developments in the synthesis of polyfluorinated aza-heterocycles based on fluorine-bearing enones and ynones published in the last decade.

1. Introduction

The interest in development of versatile and effective approaches to the fluorine-containing organic compounds is due to the search for new materials possessing unique characteristics. It is well known that incorporation of fluorine atom(s) and/or fluorinated functional group(s) into molecule of organic compound often furnishes derivatives bearing remarkable chemical, physical and biological properties. Therefore it is not surprising that this modification is often used in materials science and agricultural, biological and pharmaceutical chemistry.[1,2] According to reported data, fluorine is incorporated into 10-15% of drugs synthesized during last half a century, and their number increased in the beginning of 21st century.[3–12] The molecules of more than 200 currently used drugs contain at least one fluorine atom.[13] In the past decades polyfluoroalkylated heterocyclic compounds are paid a great attention due to their use as agrochemicals and medicine. Among them, nitrogen-bearing heterocycles are of particular interest: they are recognized as privileged pharmacophores.[14–16] The currently used methods of their synthesis can be divided into two groups. The first approach presupposes the incorporation of polyfluoroalkyl moiety into existing heterocyclic core; the second one is based on the use of fluorine-containing synthones. The known methods of direct fluorination do not always allow the introduction of fluorine atom at the required position of molecule. Moreover, the hazard and toxicity of fluorinating reagents as well as the use of expensive equipment and tedious procedures significantly narrow the area of its application.[17] The use of fluorine-containing building blocks is more convenient approach to target compounds.[18,19] One-pot synthesis methodology intensively developing in the past decades provides the reducing of the number of reaction steps and amount of costs and waste products.[20,21] The reaction of unsaturated polyfluoroalkylketones with bidentate nucleophiles is considered nowadays as an effective approach to fluorinated heterocyclic compounds (Scheme 1).[2,22–24] Nucleophilic attack can be directed to carbonyl carbon as well as C_β of triple or double bond (in the latter case ring assembly initiated by aza-Michael reaction (aza-MIRC reactions) is implied).[25] The size and type of forming heterocycle are defined by both nature of reagents and reaction conditions. Various synthetic strategies have been proposed to assembly nitrogen heterocycles but the development of new efficient approaches to these derivatives is an ongoing challenge of the modern organic synthesis.

This review focuses on recent advances in the synthesis of fluorine-bearing aza-heterocycles from α,β-unsaturated polyfluoroalkylketones (mainly, CF_3-ynones and functionalized CF_3-enones) and bidentate nucleophiles, covering the data reported over the last seven years after the publication of Druzhinin *et al.*[22] The classification of this review is based on the type of assembled heterocycle.



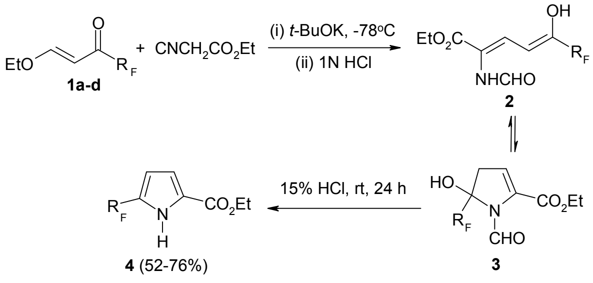
Scheme 1

2. Synthesis of five-membered heterocycles.

2.1. Pyrroles.

In spite of the fact that a number of approaches to CF_3-pyrroles was developed, the elaboration of novel methods of their preparation was attracting the attention in the past decade. Nowaday, the trifluoromethyl(β-alkoxyvinyl)ketones are considered as valuable building blocks for construction of wide type of heterocyclic systems. It is not surprising because these substrates are typical push-pull olefins having a highly polarized double carbon-carbon bond. That is why they are very active Michael-acceptors in reactions with nucleophiles.

Recently, fluorinated β-alkoxyenones **1** have been used as initial substrates in the original method of pyrrole core assembly (Scheme 2).[26]



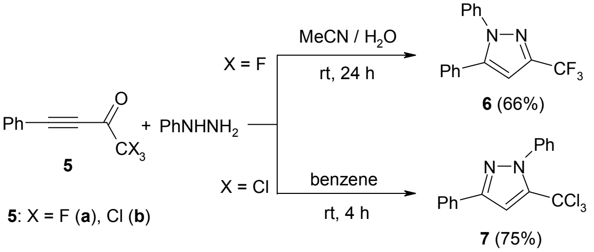
R_F = CF_3 (**a**), CHF_2 (**b**), C_2F_5 (**c**), C_3F_7 (**d**)

Scheme 2

As should be expected, the 1,2-addition of ethylisocyanate to enones **1** is found to be a minor process while the main reaction starts with nucleophilic attack on C_β-atom leading to product **2**. The latter exists in solution as a mixture of tautomers including cyclic form **3**, which is direct precursor to corresponding pyrrole **4**. Under mild conditions the derivatives **3** easily eliminate the molecule of formic acid and transform into polyfluoroalkylated pyrroles **4** which are isolated in good yields.

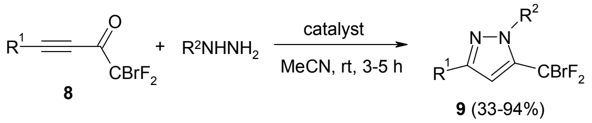
2.2. Pyrazoles.

Trifluoromethylpyrazoles are generally obtained by cyclocondensation of 1,3-diketones with hydrazines. However, despite the high yields of target heterocycles this method for synthesis of CF_3-containing pyrazoles has a substantial drawback: reactions of monosubstituted hydrazines with unsymmetrical ketones often lead to inseparable mixture of regioisomers.[27] The use of synthetic equivalents of 1,3-diketones – acetylenic or β-functionally substituted fluorine-containing ketones – is more attractive. Indeed, for the first time CF_3-pyrazoles were easily obtained from trifluoromethylated ynone **5a** and hydrazine.[28] Monosubstituted hydrazines *a priori* can give the mixture of isomeric pyrazoles. The reaction direction depends on its conditions and the structure of initial compounds. For instance, the reaction of phenylhydrazine with CF_3-ynone **5** in aqueous acetonitrile at room temperature results in formation of 3-CF_3-pyrazole **6** exclusively.[29] The replacement of CF_3-moiety by CCl_3-group in initial ketone affords its 5-substituted analogue **7** in good yield (Scheme 3). [30]



Scheme 3

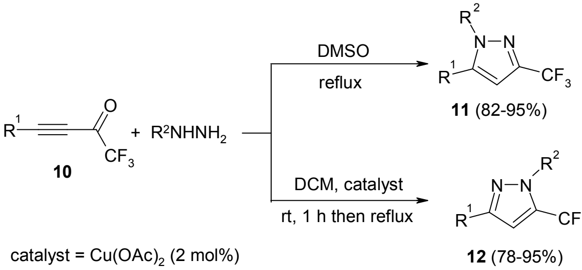
Selective synthesis of 5-substituted pyrazoles **9** is based on reaction of polyfluoroalkyl(alkynyl)ketones **8** with substituted hydrazines catalyzed by Lewis acids (Scheme 4).[31]



catalyst = Ph_3PAuCl, $AgSbF_6$
R^1 = Bu, Bn, Ph, $MeOCH_2$, $MeO(CH_2)_2$
R^2 = H, Bu, Ph, 4-$O_2NC_6H_4$, 2-Tolyl, 4-Tolyl, CH_2CH_2OH

Scheme 4

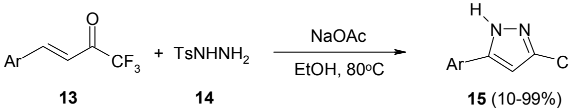
Very recently, a remarkable achievement in regio-switchable synthesis of trifluoromethylated pyrazoles has been reported.[32] It was shown that CF_3-ynones **10** react with monosubstituted aryl- and alkylhydrazines to give preferentially either 3- or 5-trifluoromethylpyrazoles **11** and **12** depending on reaction conditions (Scheme 5). When the reaction was carried out in highly polar aprotic solvent such as DMF and (especially) DMSO in the absence of any catalyst, the formation of pyrazoles **11** was observed. In contrast, the isomeric pyrazoles **12** were obtained with high selectivity in the presence of catalyst and in low polarity aprotic solvent (such as CH_2Cl_2). According to proposed mechanism, the assembly of 5-CF_3-pyrazoles **12** is initiated by aza-Michael addition of hydrazine derivative to ynone **10** followed by cyclization and dehydration to yield target heterocycle. In contrast, in the presence of Lewis acid ($Cu(OAc)_2$) the reaction starts with the generation of acetylenic hydrazone which transforms into pyrazole **11**.



R^1 = Ph, *n*-Bu, $SiMe_3$, Tol
R^2 = 2,4-$Cl_2C_6H_3$, 2-$O_2NC_6H_4$, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 4-$HOOCC_6H_4$, 4-$H_2NO_2SC_6H_4$, 2-benzothiazolyl, 2-pyridinyl, *t*-Bu

Scheme 5

Trifluoromethylenones can also be used as starting materials for the preparation of CF_3-pyrazoles. Thus, a simple procedure of the regioselective synthesis 3-trifluoromethylpyrazole **15** from enones **13** and tosylhydrazine **14** has been described.[33] The reaction proceeds through usual cyclization followed by 1,5-H shift transformation leading to pyrazoles **15** in moderate to high yield (Scheme 6).

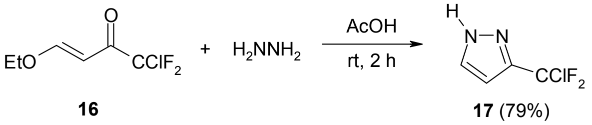


Ar = Ph, 4-MeC_6H_4, 4-*i*-PrC_6H_4, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, 4-BrC_6H_4, 2-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 2-FC_6H_4, 4-$CF_3C_6H_4$, 4-HOC_6H_4, $C_6H_5CH{=}CH$, 2-furyl

Scheme 6

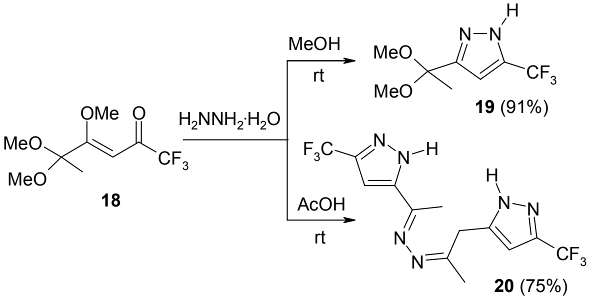
Of late years, enormous number of articles devoted to synthesis of pyrazoles from functionally substituted CF_3-enones (mainly β-alkoxy- and β-aminoenones) has been published. The main efforts of synthetic chemists are concentrated on expansion of area of reagents involved as well as development of "green" methods of selective assembly of pyrazole ring.

Polyfluoroalkylated β-alkoxy-[34–36] and β-aminovinylketones[37] as well as chromones[38] react with hydrazine hydrate to give required heterocycles. Thus, pyrazole **17** was obtained in high yield after holding of equimolar mixture of β-ethoxyenone **16** with hydrazine in acetic acid at room temperature (Scheme 7).[36]



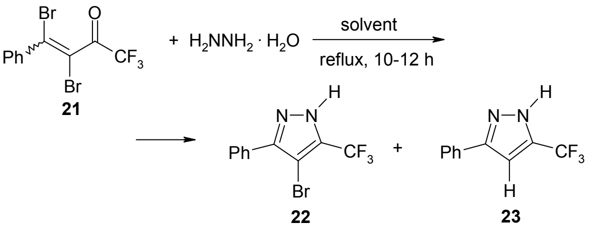
Scheme 7

Depending on reaction conditions, (methoxyalkenyl)enone **18** reacts with hydrazine hydrate to form either mono- or bis-pyrazoles **19** and **20** (Scheme 8).[34]



Scheme 8

Recently, Nenajdenko *et al.* described the synthesis of bromine-bearing CF_3-pyrazole **22** from α,β-dibromoenone **21** and hydrazine hydrate.[39] However, its analogue **23** containing no bromine was also formed. The authors hypothesized that the latter heterocycle is the result of halophilic attack of hydrazine to α-bromine atom of initial ketone. The reaction proceeds at reflux for 10-12 h leading to the mixture of brominated and non-brominated pyrazoles which were not separated (Scheme 9). Despite the good yields in some solvents, this method will be hardly used for the synthesis of such type of functionalized pyrazoles.



Solvent = MeOH, EtOH, PrOH, BuOH, TFE, THF, PhMe, $CHCl_3$

Scheme 9

The most intriguing problem in pyrazole synthesis from β-functionally substituted (polyfluoroalkyl)enones and monosubstituted hydrazines is the selectivity of addition reaction initiating pyrazole core assembly. Analysis of reported data indicates that cyclocondensation of these enones with alkyl- and arylhydrazines is much more selective process than the same procedure for non-fluorinated derivatives.

Generally, the major product (in some cases the sole product) in this reaction is 5-trifluoromethyl-*1H*-pyrazole. The formation of isomeric 3-trifluoromethyl-*1H*-pyrazoles is much more rare process. In spite of the abundance of material, it is quite difficult to predict accurately the structure of the major product. Authors[40] supposed that the reaction direction depends more on reactivity of substrate and less on the nature of substituents in hydrazine. However, this supposition is not always confirmed practically. Often, the relatively trivial changes in the structure of initial reagents and reaction conditions (method of activation, temperature, solvent, the presence of additional base) can lead to different types of products.

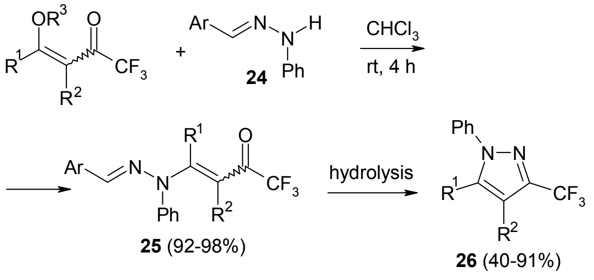
The examples combined in Table 1 show that pyrazoles are mostly obtained with refluxing of initial reagents in alcohols. However, the process under these conditions is quite long and not always effective. Recently, the successful efforts of synthesis of pyrazoles were applied in ionic liquids,[40–42] combined with microwave irradiation [41–46] or in supercritical CO_2 used as organic solvent substitute.[47]

The application of microwave irradiation provides not only decreasing of the reaction time (from several hours to several minutes compared to conventional heating) but yield increase of target heterocycles as well (including nitrophenyl-substituted hydrazines) (Table 1, entries 8, 11, 13). The type of heterocycle also depends on the irradiation rate: dihydropyrazoles are formed at 200W whereas at 300W the formation of pyrazoles was only observed (Table 1, entry 18).

The formation of pyrazoles successfully occurs in ionic liquids. Among them 1-butyl-3-methylimidazolium tetrafluoroborate [BMIM][BF_4] showed the highest catalytic activity (Table 1, entries 2, 7, 8). Synergic effect of ionic liquid and microwave irradiation provided shorter reaction time (up to 6 min) without decreasing yield of target heterocycles (Table 1, entry 7).

Pyrazoles were recently prepared under solvent free conditions.[43,47] This approach attractive from both economical and ecological point of view turned out to be very effective. For instance, mono-substituted β-methoxy-CF_3-enone and its analogues, bearing alkyl (Me) or aryl (Ph) substituents, react with phenylhydrazine, heated in supercritical carbon dioxide, to form 5-trifluoromethyl-*1H*-pyrazoles (Table 1, entry 3). The apparent merits of developed procedure are high ecological compatibility and facility of product isolation.

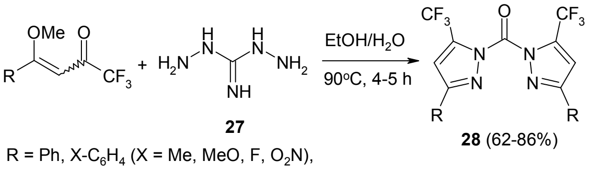
Original two-step method of selective assembly of 3-fluoromethylated pyrazoles **26** was proposed by Zanatta and coworkers (Scheme 10).[48] Using hydrazones **24**, prepared from phenylhydrazine and benzaldehyde and its derivatives, the authors obtained β-aminoenones **25**, which undergo intramolecular cyclization into target pyrazoles **26** under acidic conditions. The selective formation of 3-CF_3-pyrazoles makes this method more attractive compared to classic cyclocondensation reaction.



R^1 = H, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 2-furyl
R^2 = H, Me; R^3 = Me, Et

Scheme 10

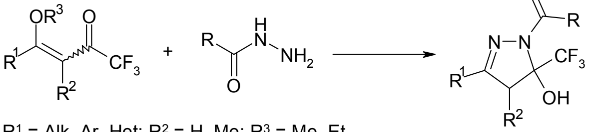
A priori, 1,3-diaminoguanidine **27** can react with β-methoxyalkenyl(trifluoromethyl)ketones as N-C-N or N-N binucleophile giving either pyrimidines or pyrazoles correspondingly. However, the latter case only is implemented practically: bis-pyrazoles **28** are smoothly prepared after 4-5 hours of refluxing in alcohol (Scheme 11).[59]



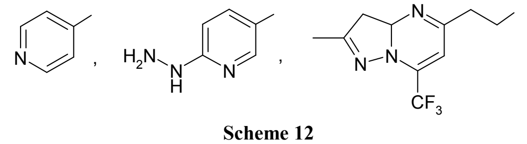
R = Ph, X-C_6H_4 (X = Me, MeO, F, O_2N),
2-naphthyl, 2-thienyl, 2-furyl

Scheme 11

Substituted hydrazides were also used as nucleophiles in the synthesis of pyrazoles. Compared to hydrazines, their reaction with β-alkoxyalkenyl(polyhaloalkyl)ketones occurs more selectively giving exclusively dihydropyrazoles **29** (Scheme 12). In almost all cases the required heterocycles were isolated in moderate to high yields after long refluxing of initial reagents in alcohol.[60–69] As it was observed for hydrazines, the use of ionic liquids[70] and microwave activation in the presence[71] or absence[72,73] of solvent shortened reaction time as well. The selectivity of reactions with hydrazides under these conditions was not affected at all.

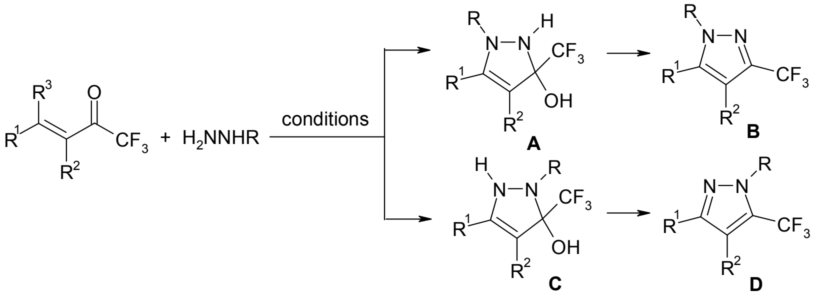


R^1 = Alk, Ar, Het; R^2 = H, Me; R^3 = Me, Et
R = MeO, H_2N, H_2NNH, $H_2NNHC(O)$, $H_2NNHC(O)CH_2CH_2$,
CH_2CN, $PhOCH_2$, $PhSCH_2$, $PhNHCH_2$, 2-NaphthylO, 2-HOC_6H_4,



Scheme 12

Table 1.

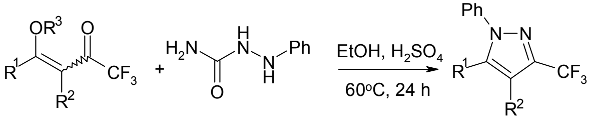


entry	enone			R	conditions	Product, yield (%)	Ref.
	R^1	R^2	R^3				
1	H, Ph, 4-XC_6H_4 (X = Me, MeO, F), 2-furyl	H, Me	MeO, EtO	Ph	MeCN, rfx, 24 h	**B** + **D** (78-95) [a]	48
2	H, Me, Ph	H	MeO, EtO	*t*-Bu	[BMIM][BF_4], Py, 78ºC, 15 h *or* EtOH, Py, 78ºC, 15 h	**B** + **D** (70-93) [b]	40
3	H, Me, Ph	H	MeO	Ph	sc-CO_2, 60-120 bar, 65-80ºC, 45 min	**D** (45-89)	47
4	H, Me, Ph	H	MeO, EtO	Ph, $(CH_2)_2OH$	Solvent free, MW, 1-12 min	**B** + **C** + **D** (70-95) [c]	43
5	Cl, Br	H	Cl, Br	Et, Bn	EtOH, Et_3N, rfx, 3 h	**B** (49-74)	49
6	MeS	H	MeS	Ph	EtOH, rfx, 2 h	**B** + **D** (≤20) [d]	50
7	H, Me, Bu, *i*-Bu, Ph, 4-XC_6H_4 (X = Me, F, Cl, Br, I), 2-furyl	H	MeO, EtO	Ph	[BMIM][BF_4], 25-150ºC, 1-3 h *or* [BMIM][BF_4], MW, 6 min	**D** (56-96) [e]	42
8	Me, Et, Pr, *i*-Pr, Ph, 4-FC_6H_4, 4-BrC_6H_4	H	MeO	C_6F_5	Solvent free, MW, 6 min *or* [BMIM][BF_4], 80ºC, 1 h	**C** (75-94) **C** (43-82)	41
9	Me	CO_2Bu^t	MeNH	Me, Et, $(CH_2)_2OH$	MeOH, -20ºC → rt	**B** + **D** (63-95) [f]	51
10	H	CO_2Et	EtO	4-NCC_6H_4	EtOH, rt, 16 h	**D** (77)	52
11	H	CO_2Et	EtO	4-$O_2NC_6H_4$	EtOH, rfx, 16 h *or* MW, 2 min	**D** (82)	44
12	H	CO_2Et	EtO	thiazolyl	EtOH, rfx, 30-40 min	**D** (62-88)	53
13	H, CF_3	H, CO_2Et	EtO	4-$O_2NC_6H_4$ 4-BrC_6H_4	MeOH, EtOH, PrOH, DMF, MW, 1,5-15 min	**D** (81-98)	45
14	$(MeO)_2CHCH_2$	H	MeO	C_6F_5, 2-furyl	EtOH, rfx, 4-20 h	**C** (90-97)	54
15	$(MeO)_2CHCH_2$	H	MeO	Me, *t*-Bu, Ph	MeOH, rfx, 20 h	**D** (89-98)	55
16	$MeO_2C(CH_2)_2$	H	MeO	Ph	MeOH, rfx, 8 h	**D** (94)	56
17	$Me_2S(O)N=$	H	EtO	Ph	EtOH, rfx, 16 h	**D** (78)	57
18	H, Me, Et, Pr, *i*-Pr, Bu, *i*-Bu, Ph	H	MeO, EtO	Ph	Toluene, MW, 200W, 3 min Toluene, MW, 300W, 10 min	**C** (80-91) **D** (83-90)	46
19	H	$(CH_2)_nO$, n = 1,2		C_6F_5, Ph	EtOH, rfx, 20 h	**C** (60-72) **D** (89-93)	58

[a] Ratio **B** : **D** varies from 100:0 to 88:12.
[b] Ratio **B** : **D** varies from 15:85 to 57:43; when NaOH was used instead of pyridine, pyrazole **D** was obtained only.
[c] Ratio **B** : **D** varies from 20:80 to 80:20.
[d] Ratio **B** : **D** is 35:65.
[e] In some cases a mixture of isomeric pyrazoles **B** and **D** (ratio varies from 1:1 to 1:10) was obtained.
[f] Ratio **B** : **D** varies from 50:50 to 80:20.

Interestingly, reactions of hydrazides with alkoxyenones and 1,3-dicarbonyl compounds proceeds in different ways. Thus, when CF_3-enones were treated with hydrazide of cyanoacetic acid the dihydropyrazoles were obtained whereas 1,3-diketones furnished the pyridine derivatives.[74]

3-CF_3-Pyrazoles **30** were obtained in high yield from the reaction of β-alkoxyalkenyl(trifluoromethyl)ketones with phenylsemicarbazide (Scheme 13).[75] The key steps of the mechanism of this transformation are: aza-Michael reaction with participation of more nucleophilic nitrogen atom attached to phenyl group, water elimination, intramolecular cyclization, and subsequent aromatization of five-membered ring. Reaction proceeds in alcohol in the presence of catalytic amounts of sulfuric acid. The method proposed stands out for the conducting facility of multi-step reaction and exclusive formation of 3-CF_3-pyrazoles (the ratio of isomeric pyrazoles in most cases is 100:0).

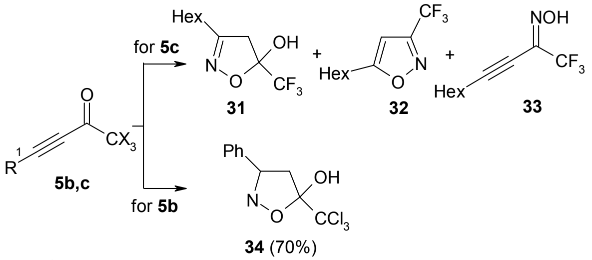


R^1 = H, Me, Ph, 2-furyl; $R^1R^2 = (CH_2)_4$; R^3 = Me, Et **30** (50-85%)

Scheme 13

2.3. Isoxazoles.

Generally, isoxazoles are obtained by cyclocondensation of β-dicarbonyl derivatives, ynones, and β-alkoxyvinylketones with hydroxylamine. The former is generated *in situ* from its salts (as a rule, hydrochloride) by organic (pyridine, alkali metals alcoholates) or mineral (alkali metals hydroxides and carbonates) bases.[76] The main problem in the synthesis of these heterocycles is control of regioselectivity. The analysis of reported data showed that selectivity of isoxazole formation depends on the structure of initial reagents, stability of forming cycle, and reaction conditions. Thus, Linderman in his pioneer work, devoted to the synthesis of trifluoromethylated five-membered N-heterocyclic compounds, mentioned the formation of complex mixture of isoxazole **31**, dihydroisoxazole **32**, and oxime **33** in reaction of CF_3-ynone **5** with hydroxylamine (Scheme 14).[28] In analogous reaction the CCl_3-ynone was selectively transformed into 5-trichloromethyl-4,5-dihydroisoxazole **34** in 70% yield.[30]



5b: R^1 = Ph, X = Cl;
5c: R^1 = Hex, X = F

Conditions: $H_2NOH \cdot HCl$, MeOH

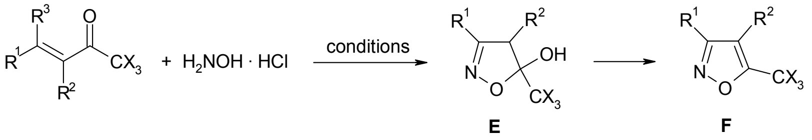
Scheme 14

In the past decade new efficient synthetic routes to polyhaloalkyl-substituted isoxazoles were developed. Almost all of them are based on the reaction of push-pull alkoxyenones with hydroxylamine. The apparent advantage of using β-alkoxyalkenyl(polyhaloalkyl)ketones is almost complete independence of selectivity from any changes in reagent structure and reaction conditions. The presence of strong electron withdrawing group and, therefore, substantial difference in electrophilicity of β-olefinic carbon atom and C=O moiety of substrate as well as a difference in nucleophilicity of two heteroatom centers of hydroxylamine provide an excellent selectivity of nucleophilic addtition. At that, more nucleophilic nitrogen atom of hydroxylamine is added to C_β atom of enone (aza-Michael reaction) whereas oxygen attacks the carbon of carbonyl group.

5-Hydroxy-4,5-dihydroisoxazoles are generally unstable and after elimination of water transform into isoxazoles. The stability of dihydroisoxazoles having strong electron withdrawing substituent at position 5 is so high that they can be easily isolated in a pure state by column chromatography. However, when 5-hydroxy-5-polyhaloalkyl-4,5-dihydroisoxazoles were treated with a strong dehydrating reagent (usually H_2SO_4), the corresponding isoxazoles were obtained. Some examples of the isoxazoles synthesis are combined in Table 2.

Besides β-alkoxyvinylketones, their morpholine-substituted analogue can be used in reaction with hydroxylamine (Table 2, entry 5). But in this case, however, the yield of required heterocycle is lower.[77]

Table 2.

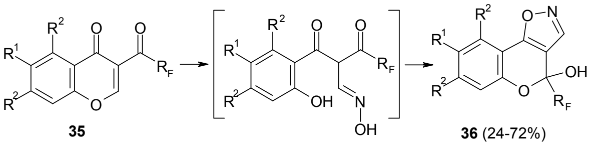


entry	enone				conditions	product, (yield, %)	Ref.
	R^1	R^2	R^3	X			
1	$(CH_2)_2CO_2Me$	H	MeO	F, Cl	MeOH, Py, rfx, 8 h	**E** (90-95%)	56
2	$(CH_2)_2CO_2Me$	H	MeO	F, Cl	H_2O, rfx, 12 h	**F** (68-75 %) [a]	56
3	$CH_2CH(OMe)_2$	H	MeO	F	Py, 45ºC, 24 h	**E** (73%)	55
4	$Me_2S(O)$=N	H	EtO	F	MeOH, Py, 65ºC, 16 h	**E** (71%)	57
5	$(EtO)_2P(O)CH_2$	H	$O(CH_2CH_2)_2N$	F	MeOHaq, $NaHCO_3$, rt, 3 h	**E** (27%)	77
6	Ar	H	MeO	F, Cl	(*i*) MeOH, Py, MW, 6 min (*ii*) H_2SO_4 conc., MW, 10 min	**F** (78-90%)	79
7	$(CH_2)_n$; n = 5, 6, 10		MeO	F	H_2O, Py, 45ºC, 24 h	**E** (61-85%)	82
8	Ar	H	MeO	F	MeOH, HCl, 70ºC, 48 h	**F** (67-80 %)	78
9	MeS	H	MeS	F	MeOH, KOH, rfx, 4 h	**E** (54%)	50

[a] Transformation of CCl_3 group into COOH occurs for CCl_3 derivative.

Generally, 5-hydroxy-4,5-dihydroisoxazoles are successfully prepared from both CF_3- and CCl_3-enones (Table 2, entry 1). But under dehydratation conditions the CCl_3-moiety often undergoes transformation onto carboxylic function (Table 2, entry 2). The new method of the isoxazoles synthesis under microwave irradiation not only reduces the reaction time and amount of waste products (in comparison with classical method[78]) but saves CCl_3-group as well.[79]

In contrast with non-fluorinated analogues, 3-(polyfluoroacyl)chromones **35** easily react with hydroxylamine hydrochloride in methanol by 1,4-addition scheme, leading to annelated isoxazoles **36** (Scheme 15).[80]

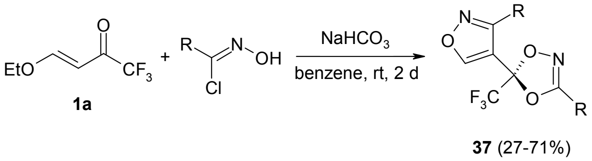


$R_F = CF_3, CHF_2, (CF_2)_2H$

conditions: $H_2NOH \cdot HCl$, KOH, MeOH, rt

Scheme 15

Finally, nitriloxides participate in 1,3-dipolar cycloaddition to β-ethoxyvinyl(trifluoromethyl)ketone to give bicyclic compounds **37** containing both isoxazole and dioxazole moieties (Scheme 16).[81] Considering tendency of nitriloxide to dimerization, the authors generated the latter *in situ* from hydroxamyl chloride by basic reagents. The best results were obtained when reaction proceeded in benzene at room temperature in presence of $NHCO_3$.



R = Ph, $4\text{-}BrC_6H_4$, $4\text{-}O_2NC_6H_4$, $4\text{-}FC_6H_4$, $4\text{-}MeC_6H_4$,
$3\text{-}O_2NC_6H_4$, $2\text{-}FC_6H_4$, $2\text{-}ClC_6H_4$, PhCH=CH

Scheme 16

3. Synthesis of six-membered heterocycles.

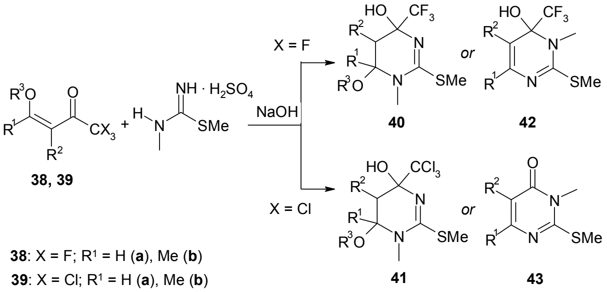
3.1. Pyrimidines.

Being a structural fragments of nucleic acids and drugs, pyrimidines attract particular attention of synthetic chemists. There are many methods of assembly of pyrimidine core, but the development of new and modification of already existing approaches remain the actual goal of modern organic chemistry. The emergence of new pharmaceutical drugs possessing broad spectrum of activities stimulates the search for novel reagents for the synthesis of pyrimidine derivatives.

One of the common approaches to these heterocycles involves the cyclocondensation reaction of 1,3-dicarbonyl compounds and their equivalents with binucleophiles bearing N-C-N moiety. Since the beginning of nineties of 20th century β-alkoxyvinyl(perfluoroalkyl)ketones have been intensively used in reaction with amidines, urea and its derivatives (such as thiourea and guanidines).

The reaction with urea in common solvents proceeds, as a rule, under harsh conditions in presence of catalytic amounts of Lewis or Bronsted acids leading to target heterocycles in mild yields (mainly, 50-60%) after boiling for a long time (20–480 h) (Table 3, entries 2-6). In ionic liquids the reaction time is shorter (3-6 h) and yield is better (up to quantitative).[83] Push-pull aminoenones react with thiourea to give pyrimidines in low yield (Table 3, entry 7).

The reactions of β-alkoxyvinyl(polyhaloalkyl)ketones with methylthiopseudourea or 1,2-dimethylisothiourea result in formation of di- or tetrahydropyrimidines depending on reaction conditions and structure of initial enone.[84,85] For instance, the treatment of trifluoro- **38a** or trichloromethylketone **39a** with 1,2-dimethylisothiourea generated from its salt by 1M NaOH at room temperature furnishes the tetrahydropyrimidines **40a** and **41a** correspondingly (Scheme 17).[84] When reaction mixture of enone **39a** with the same nucleophile is heated, the elimination of CCl_3 group occurs to form pyrimidinone **43a** in almost quantitative yield. In contrast with ketones **38a** and **39a**, their methyl-substituted analogues **38b** and **39b** under the same conditions give dihydropyrimidines **42b** and **43b** correspondingly. Authors explained this result by steric interactions of methyl substituents of enone and nucleophile.

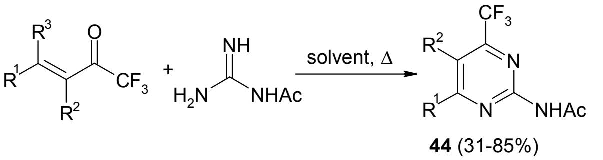


38: X = F; R¹ = H (**a**), Me (**b**)
39: X = Cl; R¹ = H (**a**), Me (**b**)

Scheme 17

Non-substituted guanidine generated *in situ* from its salt by aqueous alkali solvent reacts with 4-(2-hetaryl)-4-methoxy-1,1,1-trifluoromethyl-3-buten-2-one giving pyrimidines in mild yield (Table 3, entry 8).

To study the chemoselectivity of cycloaddition the authors of articles[55,57,86–89] used N-substituted guanidines as unsymmetrical binucleophiles bearing N-C-N moiety in reaction in reaction with β-alkoxyalkenyl(trifluoromethyl)ketones. Thus, CF_3-pyrimidines **44** were obtained when N-acetylguanidine was treated with β-alkoxyenones in boiling acetonitrile or isopropanol (Scheme 18).[55, 57, 86]

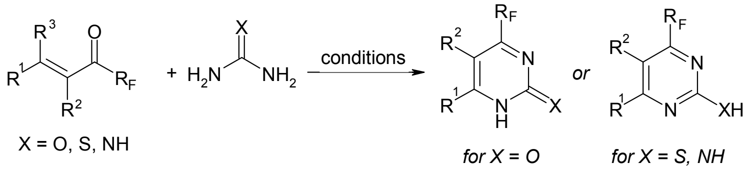


R^1 = Me, Ph, XC_6H_4 (X = 4-Me, 4-OMe, 4-F, 4-Cl, 4-Br, $4\text{-}O_2N$),
2-furyl, 2-thienyl, 1-naphtyl, $CH_2CH(OMe)_2$, $N{=}S(O)Me_2$;
R^2 = H, Me; $R^1R^2 = (CH_2)_4, (CH_2)_5$;
R^3 = OMe, OEt

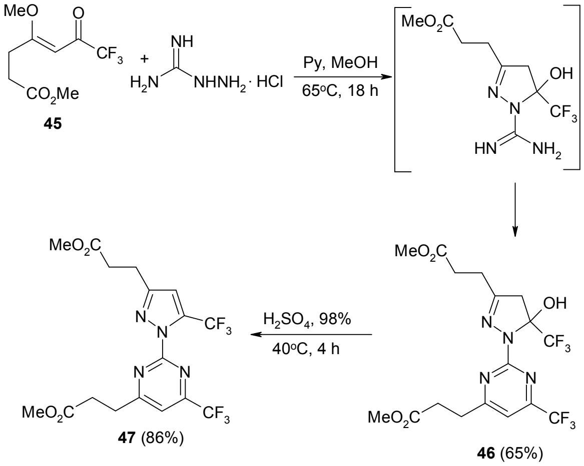
Scheme 18

Interestingly, aminoguanidine reacts with β-methoxyalkenyl(trifluoromethyl)ketone **45** to give bicyclic compound **46** containing both five- and six-membered rings (Scheme 19).[56] When heated in the presence of sulfuric acid the intermediate **46** dehydrated smoothly to give pyrazolylpyrimidine **47** in high yield. The unique role of trifluoromethyl group in assembly of derivative **47** is confirmed by the fact that efforts to obtain its CCl_3-analogue under the same conditions failed.[56] It should be noted that, in contrast to monoaminoguanidine, 1,3-diaminoguanidine reacts with β-methoxyalkenyl(trifluoromethyl)ketones exclusively as hydrazine leading to formation of bis-pyrazole derivatives (see chapter **2.2**): pyrimidine core has not been formed in this case.[59]

Table 3.



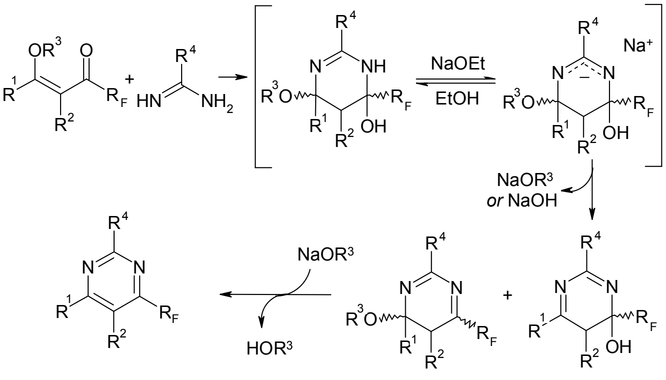
entry	enone				urea	conditions	yield, %	Ref.
	R^1	R^2	R^3	R_F	X			
1	Ph, 4-YC_6H_4 (Y = MeO, Me, F, Cl, Br, I), 2-thienyl, 2-naphthyl	H, Me	MeO	CF_3	O	[BMIM][BF4], HCl, 100ºC, 3-6 h	70-97	83
2	H	CO_2Et	EtO	C_3F_7	O	DMF, 80ºC, 6-8 d; AcOH, rfx, 14 d	56	90
3	H, Me	H, Me	MeO, EtO	CF_3	O	MeOH, HCl, rfx, 20 h	61-90	91
4	2-furyl, 2-thienyl	H	MeO	CF_3	O	*i*-PrOH, $BF_3 \cdot Et_2O$, 45-50ºC, 20 h	48-52	92
5	$(CH_2)_2CO_2Me$	H	MeO	CF_3	O	MeOH, rfx, 20 h	57-71	93
6	$(CH_2)_n$; n = 5, 6, 10		MeO	CF_3	O	*i*-PrOH, $BF_3 \cdot Et_2O$, rfx, 20 h	50-58	82
7	$(EtO)_2P(O)CH_2$	H	morpholine	CF_3	S	MeOH, H2O, HCl, rt, 144 h	21-23	77
8	2-furyl, 2-thienyl	H	MeO	CF_3	NH	MeOH, NaOH, 50ºC, 1 h	50-67	92



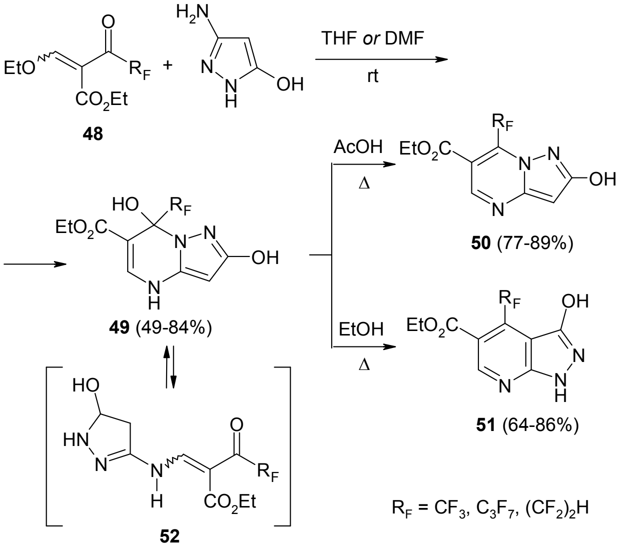
Scheme 19

Besides urea derivatives, amidines can also be used as binucleophiles in preparation of pyrimidines.[36,50,94–96] In the study of the reaction of arylamidines with 4-ethoxyvinyl(difluoro)ketone, the crucial role of solvent in successful assembly of pyrimidine core was shown (Scheme 20).[94] As expected, the first step – aza-Michael addition – is promoted by protic solvents: the reaction proceeds smoothly in ethanol at temperature 5^{o}C after generating of amidine from its salt. The intermediate formed is quite stable: it remains almost unchanged during several hours at 35^{o}C. The next step – aromatization – is a limiting stage for the whole cascade of transformations. In alcohols this transformation proceeds slowly causing required heterocycles to be formed in mild yields. On the contrary, polar aprotic solvents (DMSO, DMF, DMAc) have an accelerating effect on this reaction shifting the equilibrium between base and amidine anion towards latter which results in rate increase of elimination of alkoxy-group and aromatization of cycle.

Scientific teams from Russia and Brazil have obtained series of pyrimidine derivatives by reaction of polyfluoroalkylated β-alkoxyenones with aminosubstituted pyrazoles,[97-101] triazoles,[100,102–104] imidazoles[101] and benzimidazoles.[105, 106] It was shown that results are strongly dependent on reaction conditions. Thus, Goryaeva *et al* reported that aminopyrazoles as N,N-binucleophiles easily react with carbonyl compound **48** to form pyrimidinecarboxylates **49** with a good yield (Scheme 21).[98] After long boiling in glacial acetic acid these derivatives undergo transformation into pyrazolopyrimidines **50**. On the contrary, their isomers, pyrazolopyridines **51**, were unexpectedly isolated when crude products were recrystallized from alcohol. According to the authors's assumption, this transformation proceeds *via* acyclic intermediate **52** which undergoes an intramolecular Michael addition. This type of recyclization proceeds peculiarly in the case of perfluoroalkylated pyrazolopyrimidines and is not observed for non-fluorinated analogues.

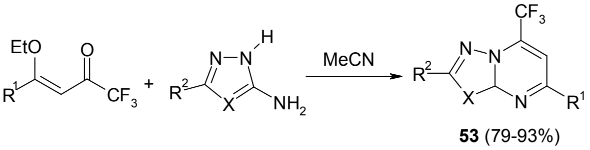


Scheme 20



Scheme 21

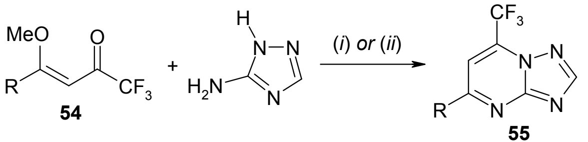
Aminopyrazoles and aminotriazoles react under mild conditions with CF$_3$-enones to afford exclusively corresponding azolopyrimidines **53** (Scheme 22).[100] The authors managed to register the key intermediate – pyrazolopyrimidinol – and monitor its gradual transformation into final reaction product.



R^1 = Me, Ph, EtO; R^2 = H, Me, 4-ClC$_6$H$_4$; X = CH, CPh, CCN, CBr, N

Scheme 22

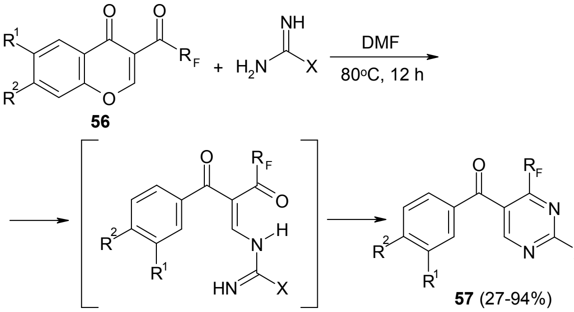
Recently ultrasound irradiation has been utilized to accelerate the assembly of triazolopyrimidines **55**. Thus, conventional heating of the mixture of methoxyenones **54** and 5-amino-1,2,4-triazole in acetic acid affords the target heterocycles in 6 hours whereas ultrasound irradiation reduces reaction time up to 5-15 minutes (Scheme 23).[99,102]



R = Ph, XC$_6$H$_4$ (X = 4-Me, 4-MeO, 4-F, 4-Br, 4-I),
2-thienyl, 4-biphenyl
(*i*) AcOH, reflux, 6 h; yield 84-97%;
(*ii*) US, AcOH, 99°C, 5-15 min; yield 60-87%

Scheme 23

Finally, polyfluoroacylchromones **56** and their heteroaryl-analogues also can also be used as starting materials in the synthesis of functionally substituted polyfluoroalkylpyrimidines **57** (Scheme 24).[107] Availability of initial reagents, experiment facility and good to high yields of target heterocycles indicate the appeal of this method. Interestingly, when the same chromones react with 1,3-C,N-binucleophiles (for example, ester, nitrile or amide of β-aminocrotonic acid), the novel polyfluoroalkylated nicotinic acid derivatives were obtained.[108]

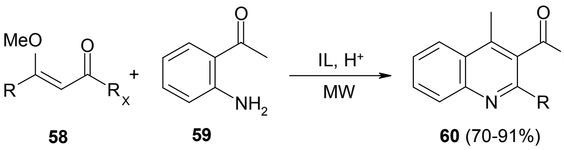


R^1 = H, Me, Cl; R^2 = H, MeO;
X = H, Me, Ph, 4-HOC$_6$H$_4$, 4-H$_2$NC$_6$H$_4$, NH$_2$, NMe$_2$, N(CH$_2$CH$_2$)$_2$O

Scheme 24

3.2. Quinolines.

One of the classical approaches to the quinolines is based on the condensation reaction of substituted anilines with carbonyl compounds bearing active α-methylene component (Friedländer annulations). But its use in the synthesis of polyfunctional quinoline derivatives containing electron withdrawing polyhaloalkyl group was limited because the starting materials required for this method are rather difficult to obtain. This problem was solved when 2-aminoacetophenone **59** and polyhaloalkyated β-alkoxyenones **58** were used as initial reagents (Scheme 25). It was found that the best results were obtained in ionic liquid (IL) under microwave irradiation.[109] In this case the target heterocycles were isolated in high yields (70-91%) in short time (10-20 minutes). Although equimolar amounts of ionic liquid and *p*-toluenesulfonic acid were used the quinolines **60** were isolated by chloroform extraction. After solvent evaporation no purification of reaction product was needed.



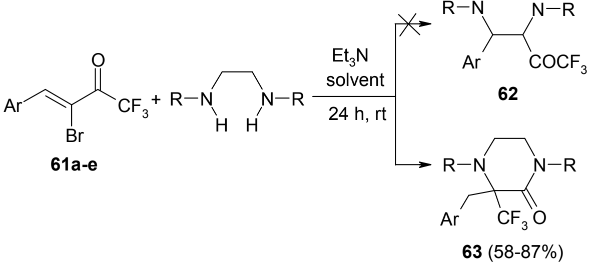
R = Me, Et, Pr, Bu, *i*-Bu, *i*-Pentyl
R$_X$ = CF$_3$, CF$_2$CF$_3$, CClF$_2$, CCl$_3$, CHCl$_2$

Scheme 25

The authors assume that reaction proceeds *via* formation of push-pull aminoenone which undergoes subsequent intramolecular cyclization and dehydration. At that the combination of ionic liquid and Brønsted acid have a catalytic effect on the final steps of all cascade of transformations.

3.3. Piperazines.

Piperazine ring is known to have a special rank in medicinal chemistry because it is structural fragment of many biologically active compounds. The authors of papers,[110,111] seeking for the shortest approach to trifluoroacetylated piperazines, have studied the reaction of CF_3-bromoenones **61** with 1,2-diamines (Scheme 26). Ethylenediamine derivatives were supposed to react with enones **61a-e** by classic aza-MIRC scheme including initial attack to *β*-olefinic carbon atom and subsequent nucleophilic substitution of halogen atom. However, the reaction of trifluoromethylated ketones **61a-e** with symmetrically substituted ethylenediamine derivatives did not give the expected trifluoroacetylpiperazines **62**. The authors, to their surprise, isolated isomeric piperazinones **63** bearing CF_3-moiety at quaternary carbon atom of the cycle. This reaction proceeds smoothly, without any catalyst at room temperature.

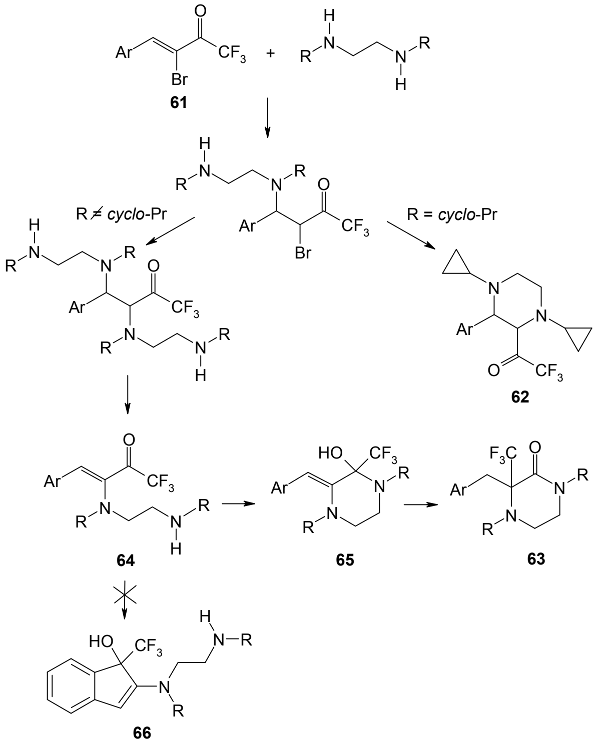


R = Et, *i*-Pr, Bn, Cy, Allyl, $MeOCH_2CH_2$

Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 2,5-$(MeO)_2C_6H_3$ (**c**), 3-MeC_6H_4 (**d**), 3-$MeOC_6H_4$ (**e**)

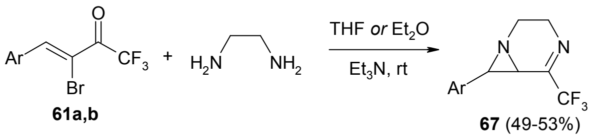
Scheme 26

The NMR minotoring (^1H, ^{19}F, ^{13}C) allowed the authors to register the formation of piperazinol **65** as key intermediate of all cascade of transformations and trace its transformation into final reaction product **63**. These data formed the basis of the hypothesis of possible mechanism of rearrangement. The first step is the formation of captodative aminoalkene **64** by the classic scheme *Ad-S$_N$-E*. The next step is intramolecular condensation with participation of the second amino group. The extra amino center of diamine directs the reaction towards piperazinol **65**. In its absence (in the case of secondary monoamines) the reaction results in formation of indenole **66**.[112,113] The whole cascade of transformation finishes with formal 1,2-shift of trifluoromethyl group. According to proposed hypothesis, the polar solvents should promote the reaction and that was observed experimentally. Thus, it is trifluoroethanol that provides the highest yields of piperazinones **63** due to good balance of its polarity and acidity. The authors developed an approach to a very rare and hard to access type of piperazine derivatives and the rearrangement itself is the first example of easy migration of trifluoromethyl group to adjacent carbon atom. Interestingly, among all N,N-binucleophiles there was one exception – dicyclopropyl derivative of ethylenediamine.[111] In this case, instead of piperazinone **63** the isomeric trifluoroacetylpiperazine **62** was obtained (Scheme 27). Theoretical analysis showed that the main reason of different behavior of diamines consists in different solvation of transition states of nucleophilic substitution reaction of halogen atom.



Scheme 27

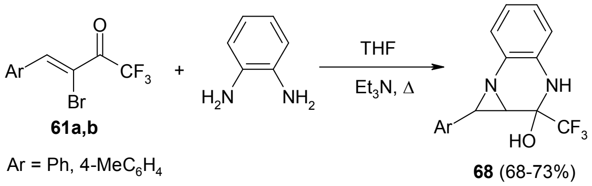
In contrast to symmetrically substituted ethylenediamines, their analogues containing two primary amino groups react with CF_3-bromoenones **61a,b** to give bicyclic derivatives **67** (Scheme 28).[114] The reaction proceeds under mild conditions leading to 1,4-diazabicyclo[4.1.0]hept-4-enes **67** in good yield. Their synthesis is highly stereoselective: only one diastereoisomer is formed in all cases.



Ar = Ph, 4-MeC_6H_4

Scheme 28

Less nucleophilic *ortho*-phenylenediamine (*o*-PDA) was also successfully involved in reaction with CF_3-bromoenones **61a,b** (Scheme 29). However, in this case the cascade of transformations stops at the stage of formation of hemiaminals **68** which were isolated in high yields.[115]



Ar = Ph, 4-MeC_6H_4

Scheme 29

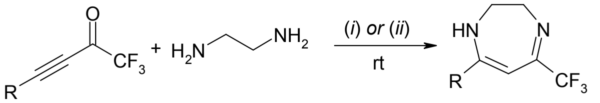
The synthesis of heterocycles **67** and **68** confirms that reaction of bromoenones **61** with diamines bearing two amino groups proceeds by classic scheme involving such key steps as Michael addition of diamine, intramolecular substitution of bromine leading to formation of aziridine ring, and finally, closure of piperazine ring as a result of attack of second nucleophilic center on carbon atom of carbonyl group.[116,117]

4. Synthesis of seven-membered heterocycles.

4.1. Diazepines.

Non-fluorinated diazepines are generally obtained by condensation reaction of 1,2-diamines with acetylenic ketones[118] or 1,3-diketones.[119,120] However, CF_3-diketones react in different way to give benzimidazoles, aminoenones, or macrocycles.[121,122] The high polarity of triple bond as well as different nature of two electrophilic *sp*- and *sp*^{2}-centers of polyfluoroalkylated acetylenic ketones favours selective synthesis of fluorine-containing diazepines which makes them more attractive substrates.

Indeed, ethylenediamine reacts with CF_3-ynones **5a,d** leading to diazepines **69** in mild yield (Scheme 30). The formation of exclusively enamine tautomer seems to be due to the emergence of longer conjugation chain.[123]



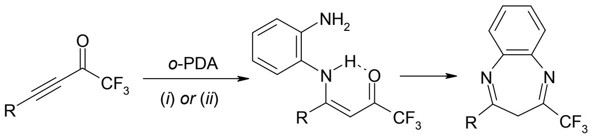
5a,d **69** (37-45%)

(*i*): EtOH; (*ii*): CF_3CH_2OH

5: R = Ph (**a**), 4-*t*-BuC_6H_4 (**d**)

Scheme 30

Similarly to ethylenediamine, *o*-phenylenediamine reacts with acetylenic CF_3-ketones **5a,c,d** to give benzodiazepines **70** in good yield (Scheme 31). The mild yield of hexyl-substituted diazepine (R = Hex) is explained by high content of push-pull aminoenone **71** in reaction mixture. According to NMR-spectroscopy, the latter is a key intermediate of all cascade of transformations.[123]



5a,c,d **71** **70** (34-72%)

(*i*): EtOH, rt; (*ii*): PhH, D

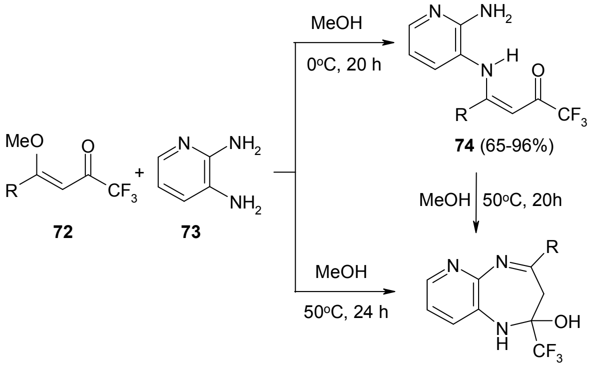
5: R = Ph (**a**), *n*-Hex (**c**), 4-ClC_6H_4 (**d**)

Scheme 31

The proposed method of the synthesis of trifluoromethyl-containing [1,4]-diazepines is more attractive in comparison with that one based on 1,3-diketones: the target heterocycles are formed under mild conditions in good yield and with high selectivity.

Push-pull aminoenones **74** are formed on the first step of reaction of trifluoromethylated β-alkoxyenones **72** with 2,3-diaminopyridine **73** (Scheme 32). When reaction proceeds at low temperature (MeOH, 0ºC), they can be isolated in high yield.[124] Subsequent long heating of reaction mixture in methanol leads to formation of diazepinols **75**. The target heterocycles **75** can be obtained in one step from initial alkoxyenones in yield 54-71%.

In contrast with CF_3-enones, their trichloromethylated analogues react under similar conditions with 2,3-diaminopyridine to form corresponding diazepinones in good yield.[125]

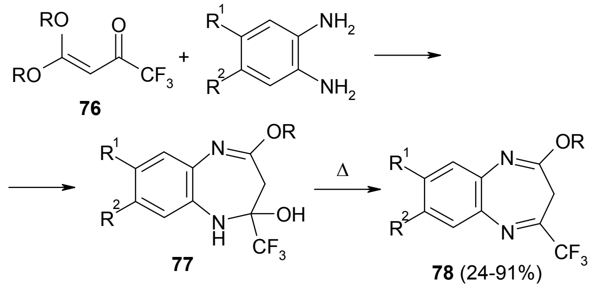


72 **73** **74** (65-96%) **75** (54-71%)

R = Me, Pr, *i*-Pr, *i*-Bu, *i*-Pentyl, *n*-Hex, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 1-Naphtyl, 2-Thienyl

Scheme 32

It was reported earlier that CF_3-enone **76** bearing two methoxy groups at β-position reacted with *ortho*-arylenediamines under microwave irradiation to give benzimidazoles instead of expected diazepines.[126] One decade later Okada *et al* repeated this reaction at room temperature [127,128] and obtained diazepinols **77** with traces of corresponding diazepines **78** (Scheme 33). The efforts to carry out acid-catalyzed dehydratation of diazepinols **77** failed: in all cases the reaction led to formation of complex multi-component mixtures. The solution of this problem was found when diazepinols **77** were distilled *in vacuo* at the temperature 110-150ºC.[127]



76 **77** **78** (24-91%)

R = Me, Et; R^1, R^2 = H, Me, Cl, C(O)Ph, NO_2

Scheme 33

5. Conclusions and Future Outlook

Despite a number of procedures for the preparation of fluorinated nitrogen-bearing heterocycles, the development of new synthetic approaches to these compounds is still challenging research topic to the world chemical community. The future progress in the synthesis of such type of heterocyclic compounds will require the development of new starting materials. A significant number of new synthetic protocols based on the reactions of unsaturated polyfluoroalkylated ketones were elaborated during the last decade. Their understanding and wide application provides easy access to target heterocycles which sometimes cannot be prepared by other methods. There is no doubt that further research will enjoy much attention and unsaturated carbonyl compounds will play a major role in this field.

Acknowledgment

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