Conference paper

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Polyfluoroalkylated 2-ethoxymethylene-3-oxo esters: synthesis and chemical properties overview

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Abstract: The review focuses on the synthesis and chemical properties of polyfluoroalkylated 2-ethoxymethylene-3-oxo esters. The scope and peculiarities of their use as organic reagents in reactions with various N-, C-, O-, mono- and dinucleophiles are discussed in detail. The high reactivity of such derivatives is employed in the construction of enaminoketone, arene and heterocycle frameworks. Particular attention is paid to applications of these building blocks as chemicals for fine organic synthesis, bioactive compounds and metal complexes synthesis.

Keywords: 2-ethoxymethylene-3-oxo esters; condensation; fluorinated building blocks; heterocycles; Mendeleev XX; open-chain ligands; tautomerization; transition metal complexes.

Introduction

The introduction of fluorine-containing substituents into organic structures can significantly modify their physical, chemical and biological properties [1]. Therefore, nowadays approximately 20 % of recently developed pharmaceuticals including the blockbuster drugs Prozac (Fluoxetine), Lipitor (Atorvastatin), Celebrex (Celecoxib), Levofloxacin, and up to 30 % of agrochemicals contain fluorine [1–4]. Fluorine substituents become extremely popular motif in drug design enhancing their bioavailability, lipophilicity, solubility as well as hydrolytic and metabolic stabilities [5, 6]. Fluorine is also an important tool in the development of advanced materials, including nano-sized ones with exceptional magnetic, luminescent, optical and catalytic properties [7–9]. The substitution of hydrogen on fluorine atoms in molecules leads to the higher thermal and oxidative stability, low polarity, weak intermolecular interactions, a high volatility and a small surface tension compared to non-fluorinated analogues [10, 11].

The importance of fluorinated groups (such as CF_3, C_2F_5, HCF_2, CF_3S, etc.) in the structures of organic compounds in pharmaceuticals, agrochemicals and materials has prompted the development of methods of fluorinated moiety incorporation into molecular frameworks as well as the elaboration of fluorinated

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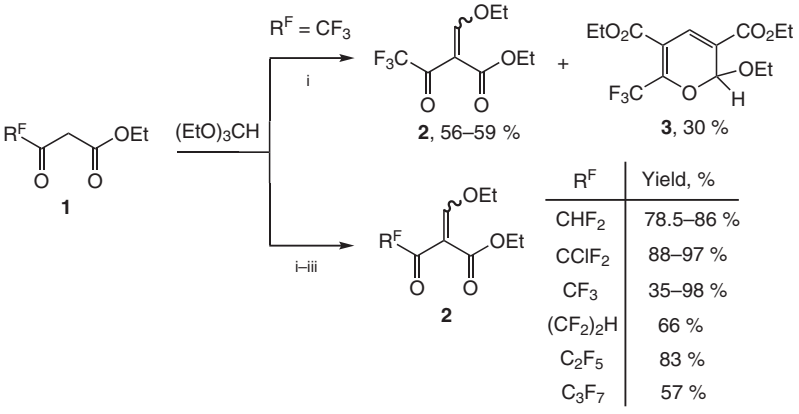
reagents. For instance, the direct construction of C–CF_3 bond with fluorinated precursors is one of the ultimate goals in this field. Despite the significant advantages of such approach, the commonly used fluorinated agents are very expensive and the regioselectivity of the C–H fluoroalkylation process remains a challenging task [12, 13]. From this point of view, the consistent construction of different fluorinated organic structures from simple and highly available multifunctional compounds bearing fluoroalkylated group (so called "building blocks") is one of the hot topic of modern organic synthesis. In this context, fluorinated 1,3-dicarbonyl compounds and their derivatives are attractive starting materials. Being highly reactive these compounds are used in the preparation of a wide range of five- or six-membered heterocycles and aliphatic derivatives.

α-Functionalization of fluorinated 3-oxopropionates is one of the promising approaches to extend their application scope. The chemistry of such derivatives are partially mentioned in a number of reviews concerning fluorinated building blocks with 1,3-dielectrophilic nature [4, 14, 15]. This review presents a comprehensive survey of 2-ethoxymethylene derivatives of fluorinated 3-oxo esters and summarizes the data on their preparation, chemical properties and synthetic applicability.

Synthesis of polyfluoroalkylated 2-ethoxymethylene-3-oxo esters

General approach to polyfluoroalkylated 2-ethoxymethylene-3-oxo esters **2** is based on the condensation of commercially available fluorinated 3-oxoesters **1** with triethyl orthoformate (Scheme 1) [16–31]. Fluorinated β-ketoesters **1** are highly reactive CH-acids which form 2-ethoxymethylene derivatives **2** in satisfactory isolated yields without the usage of catalysts. This two-component reaction can be realized by the heating 3-oxo esters **1** with four-fold excess of triethyl orthoformate under simultaneous removal of liberated ethanol by distillation [16]. Recently it was found that under condensation of ethyl 4,4,4-trifluoroacetoacetate **1** with $CH(OEt)_3$ the formation of diethyl 2-ethoxy-6-CF_3-2*H*-pyran-3,5-dicarboxylate **3** as a by-product takes place thereby reducing the yield of target 2-ethoxymethylene derivative 2 [17]. In work [18] the high conversion of ethyl 4-chloro-4,4-difluoro-3-oxobutanoate **1** with quantative yield (97 %) of its 2-ethoxymethylene derivative **2** ($R^F = CClF_2$) was achieved by using catalytic amount of triethylamine. However, the most described in literature and widely used method is three-component condensation of esters **1** with triethyl orthoformate in the presence of acetic anhydride resulting in target compounds with up to quantative yields [19–31]. It should be noted that there is no data on the preparation of fluorinated 2-ethoxyalkylidene-3-oxo esters. In contrast to $CH(OEt)_3$, no product formation from the reaction of fluorinated acetoacetates with $MeC(OEt)_3$ was observed [32].



R^F	Yield, %
CHF_2	78.5–86 %
$CClF_2$	88–97 %
CF_3	35–98 %
$(CF_2)_2H$	66 %
C_2F_5	83 %
C_3F_7	57 %

Reagents and conditions: (i) Δ, 1 h; (ii) NEt_3, 110 °C; (iii) Ac_2O, 120–140 °C, 1.5 –12 h.

Scheme 1: Polyfluoroalkylated 2-ethoxymethylene-3-oxo esters preparation.

Chemical properties of polyfluoroalkylated 2-ethoxymethylene-3-oxo esters

The molecule of polyfluoroalkylated 2-ethoxymethylene-3-oxo ester has three carbon electrophilic centers, i.e. two non-equivalent carbonyl groups and the methylene carbon atom. Due to the presence of β-alkoxyenone scaffold both reactions of addition-elimination with different mono-nucleophilic reagents at the activated C=C bond and 1,3-(hetero)cyclization with dinucleophiles are possible for these objects.

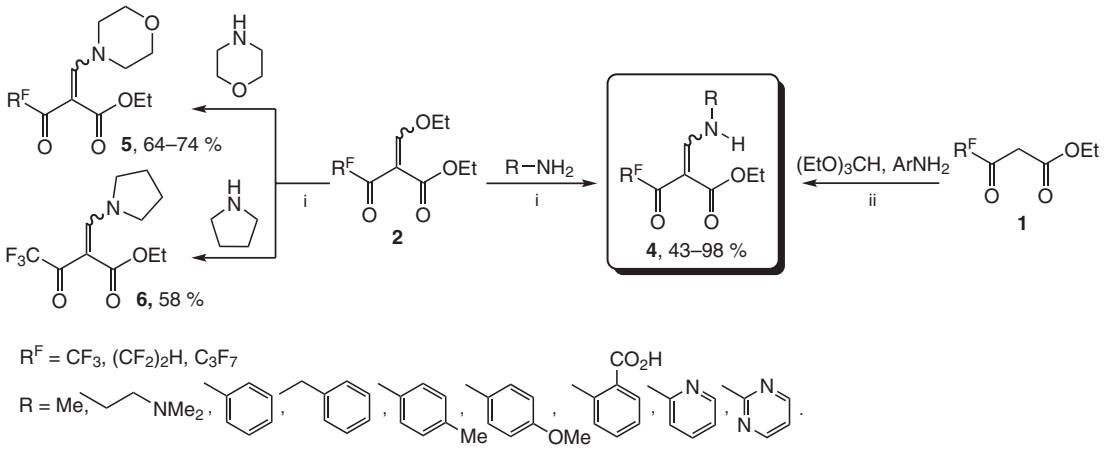
Synthesis of 2-aminomethylene-3-fluoroalkyl-3-oxo esters

As a result of condensation of polyfluoroalkylated 2-ethoxymethylene-3-oxo esters **2** with aliphatic, aromatic and heterocyclic primary and secondary amines the series of 2-aminomethylene derivatives **4–6** were obtained (Scheme 2) [16, 33–35]. Reactions occur under mild conditions in good yields with regiospecific substitution of ethoxy group at the methylene carbon atom by the action of N-nucleophiles. 2-(Arylamino) methylidene-3-oxo-esters **3** can also be synthesized by three-component reaction from corresponding fluorinated acetoacetates **1**, $CH(OEt)_3$ and aromatic amines [16].

(Het)aryl diamines react with 2-ethoxymethylene precursors **2** to give, depending on the reactant ratio, both mono- and bis-condensation products **7–12** (Scheme 3) [36–39]. However, in case of 4,5-diaminopyrimidine the reaction proceeds only with the participation of more nucleophilic amino group of the heterocycle to give mono-substituted derivatives **12**. Aliphatic diamines form solely bis-condensation products **9** even under using equimolar ratios of reactants as a result of their higher reactivity compared with (het)aryl ones.

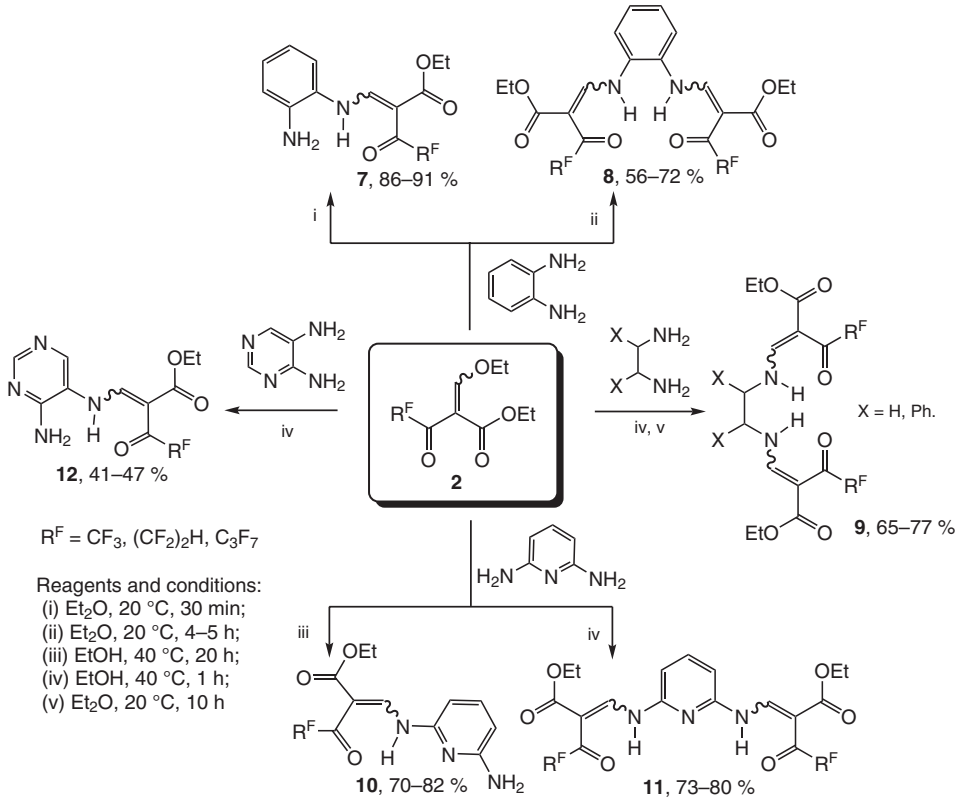
NH_2-functionalized R^F-2-aminomethylene derivatives of β-ketoesters **7** can be further modified: (i) condensation with another molecule of ester **2** yields non-symmetrical bis-esters **13** possessing two different fluoroalkyl substituents; (ii) reactions with mono- and dialdehydes results in a series of Schiff bases **14–16** (Scheme 4) [36, 40–42].

It is worth noting that the general property of all described 2-aminomethylene-3-fluoroalkyl-3-oxo esters is their ability to isomerize under dissolution. Thus, in solid form they exist as E-isomers, and in solutions – as a mixture of Z- and E-forms. The spectral characteristics to assign Z- and E-isomers were identified [16]. These substrates represent an example of push-pool tautomeric system in which the rotation barrier around the double C=C bond is significantly reduced because of delocalization thereby providing the appearance of Z-isomers in solution.

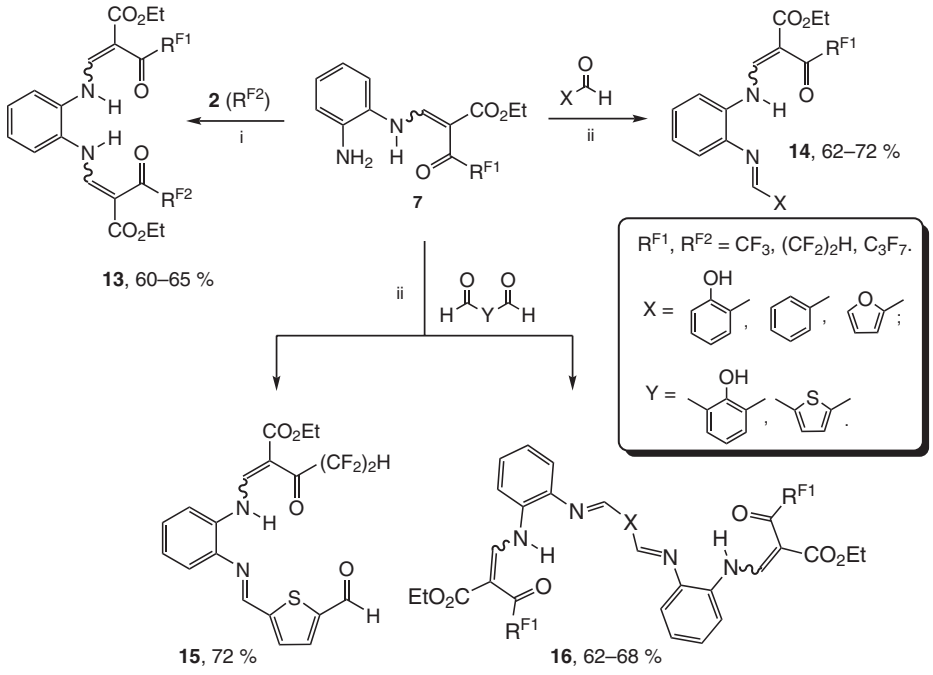


Reagents and conditions: (i) Et_2O, 20–25 °C, 15–40 min; (ii) EtOH, Δ, 12 h.

Scheme 2: Reactions with amines.



Scheme 3: Reactions with (het)aryl and aliphatic diamines.



Scheme 4: NH_2-functionalization of R^F-2-aminomethylene derivatives **7**.

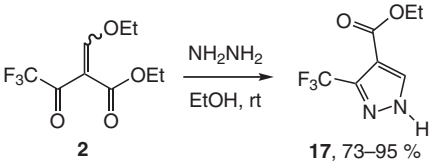
Synthesis of heterocyclic compounds

Five-membered heterocycles

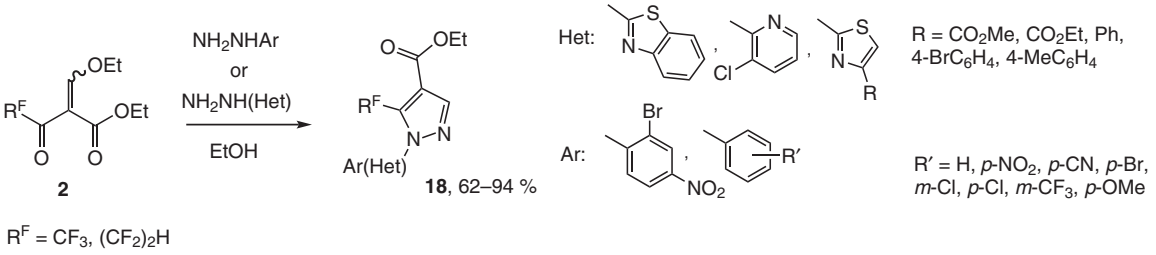
The condensation of ethyl 2-ethoxymethylene-4,4,4-trifluoro-3-oxobutanoate with hydrazine yields CF_3-pyrazole **17** as a result of binucleophile heterocyclization with β-ethoxyenone fragment (Scheme 5) [21, 27, 43].

The synthetic approach to 5-(polyfluoroalkyl)pyrazole derivatives **18** was established based on the reactions of different (het)aryl hydrazines with 2-ethoxymethylene 3-(polyfluoroalkyl)-3-oxo propionates **2** (Scheme 6) [44–51]. The regioisomeric structure of pyrazoles can be unambiguously identified based on X-ray and ^{1}H, ^{19}F, ^{13}C NMR data. The NMR characteristics for determination of 3- or 5-(trifluoromethyl)pyrazoles are summarized on Fig. 1 [21, 46, 52]. However, the lack of spectral data (based only on ^{1}H NMR spectra) led to incorrect identification of substituted pyrazoles structures synthesized by the condensation of CF_3- and CF_2H-substituted 2-ethoxymethylene 3-oxo esters **2** with 3-chloro-2-hydrazinyl pyridine [53, 54]. In work [55] the authors provided the description of ^{13}C NMR spectra of heterocycles without multiplicity and spin-spin coupling constants of carbon signals. Based on these data the choice of 5-(trifluoromethyl)pyrazoles is not obvious.

In case of methyl hydrazine the reaction with ethyl 4-chloro-2-(ethoxymethylene)-4,4-difluoro-3-oxobutanoate **2** resulted in the mixture of regioisomeric products **19** and **20** with predominant formation of 3-(fluoroalkyl)pyrazole **19** (Scheme 7) [18]. But only difluoromethylated pyrazole **21** was isolated in high yield from the condensation of HCF_2-containing β-ethoxyenone with methyl hydrazine [56].



Scheme 5: Interaction with hydrazine.



Scheme 6: The synthesis of 5-(fluoroalkyl)pyrazole derivatives.

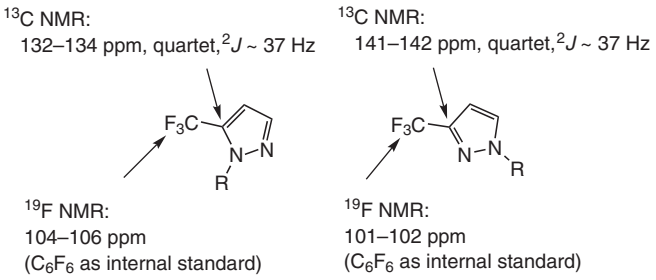
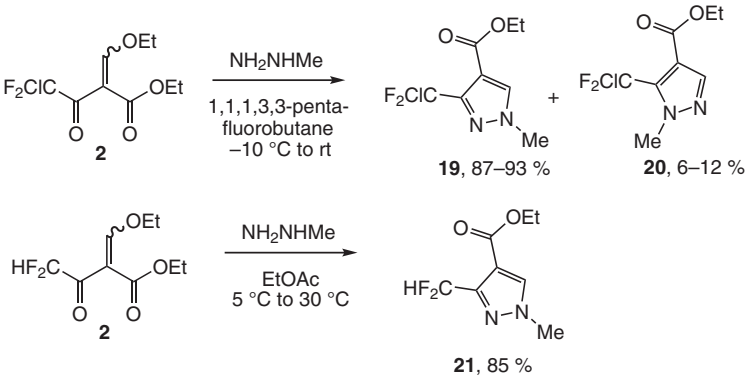


Fig. 1: NMR characteristics of regioisomeric (trifluoromethyl)pyrazoles.

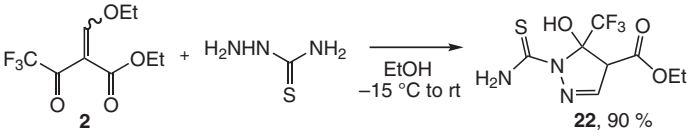


Scheme 7: Reaction with methyl hydrazine.

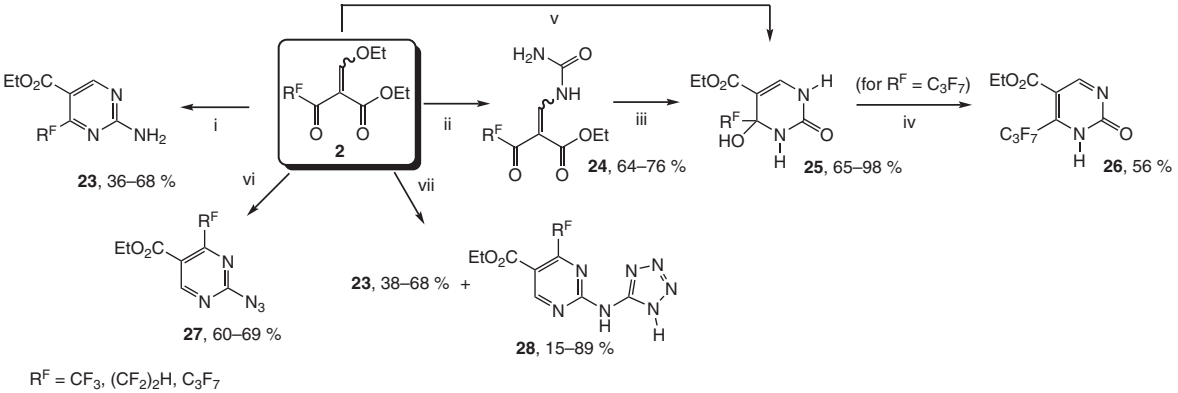
Sanfilippo et al. described the preparation of fluorinated pyrazole derivative *via* the interaction of thiosemicarbazide with ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate **2** [29]. Later the result of this condensation was revised by Donohue and co-authors [57]. Based on ^{19}F, ^{13}C NMR data the formation of corresponding pyrazoline **22** as a sole product was proved (Scheme 8). The stability of such hydrated heterocycles can be attributed to the formation of strong intramolecular hydrogen bonds between heteroatoms of N-substituent and the hydroxyl group adjacent to CF_3 [52].

Six-membered heterocycles

The pyrimidine synthesis based on the condensation of 2-ethoxymethylene derivatives **2** with urea or guanidine was described (Scheme 9) [20, 58, 59]. The interaction of urea with β-ethoxyenone was shown to proceed *via* the subsequent formation of open-chain derivatives **24** with the further intramolecular cyclization to give



Scheme 8: Reaction with thiosemicarbazide.



R^F = CF_3, $(CF_2)_2H$, C_3F_7

Reagents and conditions: (i) guanidine carbonate, 1,4-dioxane, AcONa, Δ, 16–18 h; (ii) urea, DMF, 22 °C, 3 days; (iii) EtOH, Δ, 30 min; (iv) AcOH, Δ, 14 days; (v) urea, DMF, 80 °C, 6–8 days, (vi) 5-aminotetrazole, CF_3CH_2OH, Δ, 32–38 h; (vii) 5-aminotetrazole, AcONa, 1,4-dioxane, Δ, 16–18 h.

Scheme 9: Synthesis of fluoroalkylated pyrimidines.

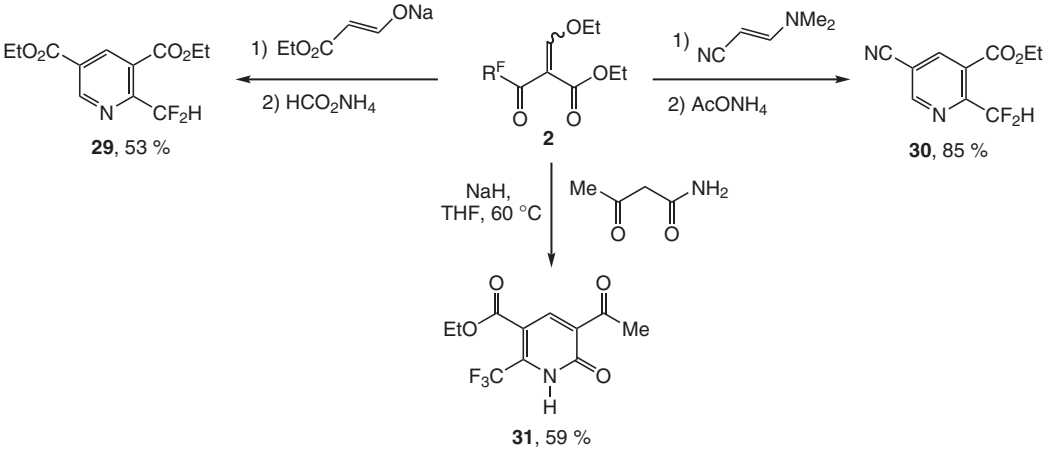
pyrimidine framework [58]. In contrast to earlier described synthesis [20] the trifluoromethyl analog was isolated as a stable tetrahydropyrimidine **25** and only heptafluoropropyl-substituted derivative underwent the dehydration to give **26** [58]. The unexpected one-pot preparation of fluorinated 2-azidopyrimidines **27** was observed from the condensation of fluoroalkylated 2-ethoxymethylene 3-oxo esters **2** with 5-aminotetrazole under reflux in 2,2,2-trifluoroethanol (Scheme 9) [59, 60]. Carrying out the same reaction in 1,4-dioxane in the presence of sodium acetate led to a mixture of pyrimidine derivatives **23** and **28** as a result of azide group transformations.

The addition-elimination reaction of ethyl 2-ethoxymethylene difluoroacetoacetate **2** with enamine and enolate followed by the heterocyclization in the presence of ammonium salts resulted in pyridine derivatives **29**, **30** in moderate to good yields (Scheme 10) [28, 61]. One-pot synthesis of trifluoromethylated pyridine-2(1H)-one derivative **31** was achieved by the condensation of appropriate fluorinated β-ethoxyenone with acetoacetamide under the action of NaH [62].

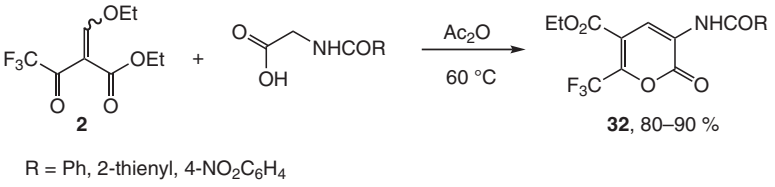
From trifluoromethyl-substituted 2-ethoxymethylene β-oxo ester **2**, the 2*H*-pyran-2-ones **32** were obtained in high yields under the action of N-acylglycines in the presence of acetic anhydride (Scheme 11) [63].

Condensed heterocycles

Fluorinated ethoxycarbonyl-substituted ethoxyenones **2** react with aminoazoles to give dihydroazolo[1,5-*a*]pyrimidines **33**, **35**, **37** (Scheme 12) [64, 65]. Dihydrotriazolo[1,5-*a*]pyrimidines **33** and dihydropyrazolo[1,5-*a*]pyrimidines **35** can be further dehydrated in acetic acid under reflux to yield compounds **34** and **36**, respectively. It should be noted that the common feature of all synthesized polyfluoroalkylated dihydroazolo[1,5-*a*]pyrimidines **33**, **35** and **37** is their ability to exist as a mixture of two isomers under dissolution. Thus, the formation of open-chain isomers **33′**, **35′**, **37′** was observed as a result of the opening of pyrimidine ring at C7–N8 bond.

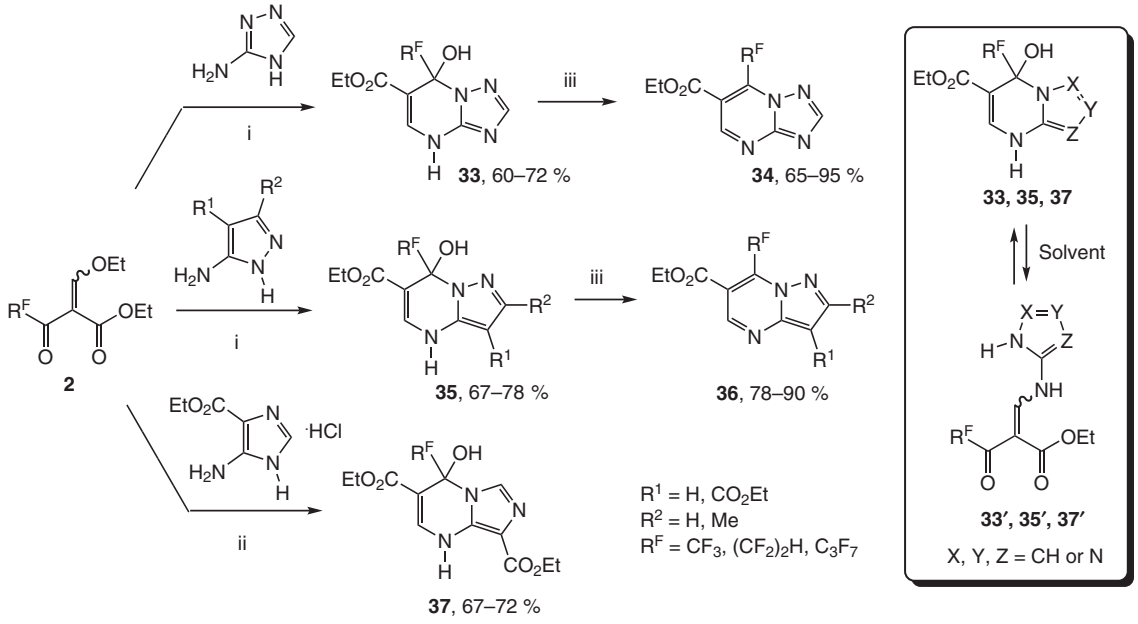


Scheme 10: Synthesis of fluoroalkylated pyridines.



R = Ph, 2-thienyl, 4-$NO_2C_6H_4$

Scheme 11: Synthesis of trifluoroalkylated 2*H*-pyran-2-ones.

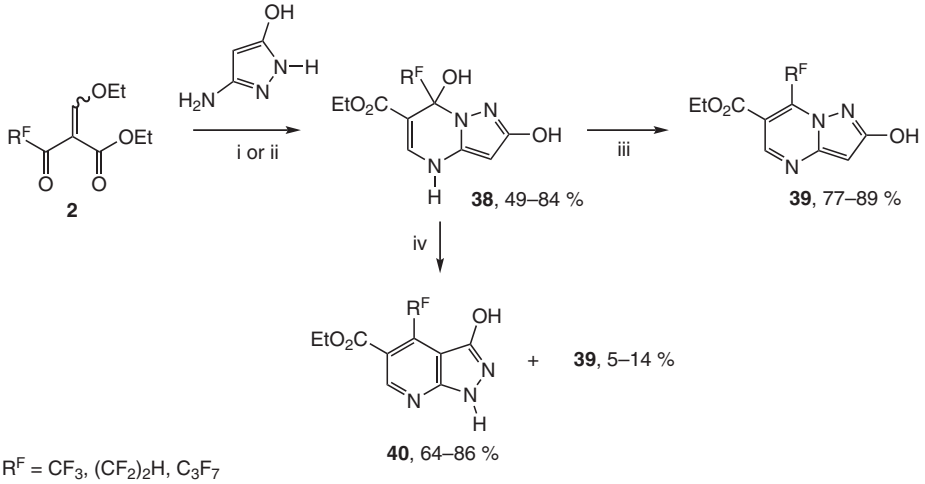


Reagents and conditions: (i) 1,4-dioxane, Δ, 16–18 h; (ii) AcONa, 1,4-dioxane, Δ, 12–14 h; (iii) AcOH, Δ, 60 h.

Scheme 12: Synthesis of fluoroalkylated azolo[1,5-*a*]pyrimidine derivatives.

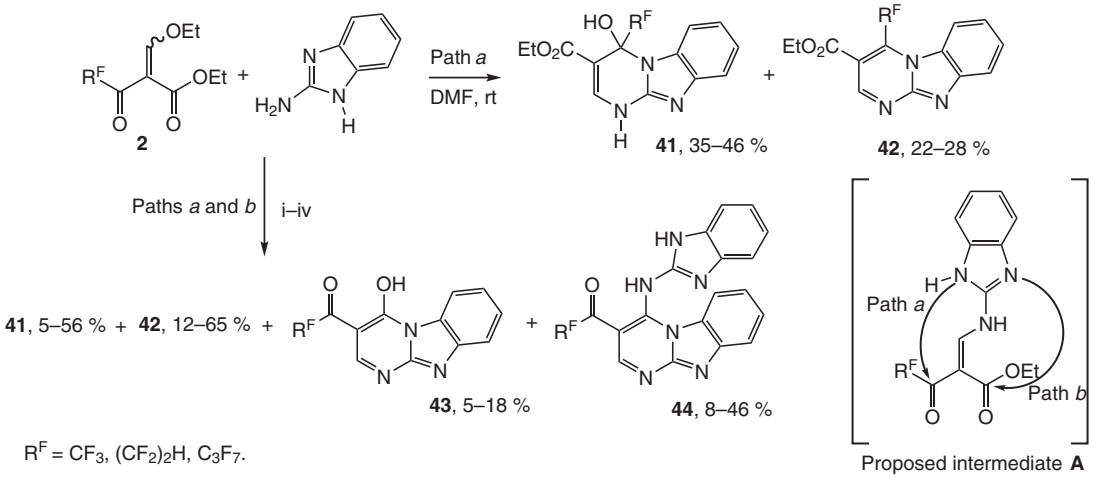
The reaction of fluorinated 2-ethoxymethylene ketoesters with 3-amino-5-hydroxypyrazole in THF or DMF resulted in fluoroalkylated dihydropyrazolo[1,5-*a*]pyrimidines **38** (Scheme 13) [66]. These compounds are easily transformed into heterocycles **39** under acid conditions. However, pyrazolo[3,4-*b*]pyridines **40** were unexpectedly isolated as a major products after the crystallization of **38** in ethanol. Authors of this work note that revealed recyclization is specific property of polyfluoroalkylated derivatives while such transformation for non-fluorinated analogues is not reported.

The result of fluorinated ethoxyenones **2** condensation with 2-aminobenzimidazole depends on the reaction conditions (Scheme 14) [67, 68]. Thus, the hydrated derivatives **41** and benzoannulated imidazolo[1,2-*a*]pyrimidines **42** were isolated by using DMF as a reaction media at ambient conditions. In case of other organic solvents the reaction proceeded less selectively with four fluorinated heterocyclic products **41–44**



Reagents and conditions: (i) THF, rt; (ii) DMF, rt; (iii) AcOH, Δ; (iv) EtOH, Δ.

Scheme 13: Synthesis of fluoroalkylated pyrazolo[1,5-*a*]pyrimidines and pyrazolo[3,4-*b*]pyridines.



Scheme 14: Reaction with 2-aminobenzimidazole.

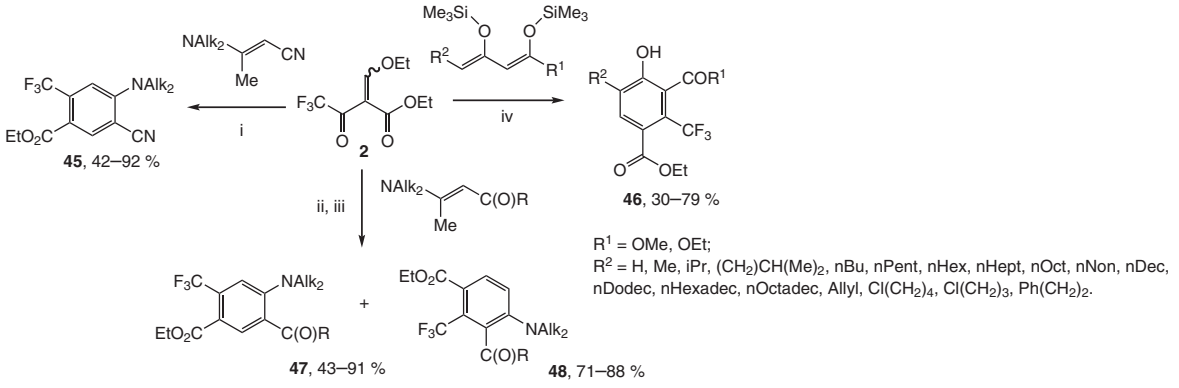
formation. The low regioselectivity of this process can be referred to the simultaneous realization of two possible intramolecular cyclizations of proposed intermediate **A** (paths *a* and *b*).

Synthesis of aromatic compounds

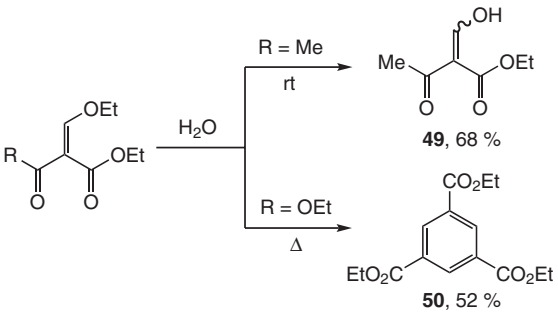
The reaction of functional enamines with fluorinated 2-ethoxymethylene 3-oxoesters **2** resulted in substituted arene **45, 47, 48** formation (Scheme 15) [69]. Another possibility to construct aromatic scaffold **46** includes the cyclization of CF_3-ethoxyenone **2** with 1,3-bis(silyloxy)-1,3-butadiene in the presence of TiCl [22].

Other reactions

It was shown that the reaction of 2-ethoxymethylene-3-oxobutanoate with water at room temperature yields 2-hydroxymethylene derivative **49** (Scheme 16) [70]. In case of diethyl 2-ethoxymethylene malonate the unexpected synthesis of triethyl 1,3,5-benzenetricarboxylate **50** was observed (Scheme 16) [71]. Unlike non-fluorinated analogues the interaction of fluoroalkylated 2-ethoxymethylene 1,3-dicarbonyl compounds **2** with



Scheme 15: The reactions with C-nucleophiles.



Scheme 16: Interaction with water.

water results in the formation of low-weight products mixture [71]. Probably, the decomposition of alkoxyenone structure under aqueous conditions can be caused by electron-withdrawing properties of trifluoromethyl group leading to enhanced electrophilicity of trifluoroacetyl moiety of 2-ethoxymethylene 3-oxoesters. On this account the detrifluoroacetylation process of 2-functionalized 1,3-dicarbonyl compounds, such as difluoro(fluoro)- or hydroxyimino- derivatives was also observed [72, 73].

Applications of fluoroalkylated 2-ethoxymethylene-3-oxo esters and its derivatives

2-Ethoxymethylene derivatives of fluorinated acetoacetates represent the widely used building blocks for a construction of heterocyclic frameworks which are particularly interesting in medical and agrochemical fields. The presence of ethoxycarbonyl moiety capable of the further modification is one of the advantages of these fluorinated ethoxyenones. A number of substituted heterocycles with amide or carboxylic acid functionalities based on 2-ethoxymethylene derivatives of fluorinated 3-oxo esters was described (Fig. 2) [20, 28, 45, 47, 74]. It should be mentioned that in some cases the carboxamide group at the 5-position of pyrimidine derivative plays a crucial role for biological activity [20].

For example, ethyl 3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylate **51** is a key building block in the synthesis of fungicides such as Sedaxane, Fluxapyroxad, Bixafen, etc. (Fig. 3) [18]. The scalable and cost-competitive synthetic approach to pyrazole **51** based on the catalytic hydrodechlorination of above mentioned compound **19** (Scheme 7) is reported.

On the other hand, the use of fluorinated β-aminoenketones in the synthesis of transition metal complexes is well documented [35, 36, 38–40, 42]. Fluorinated 2-alkylaminomethylene-1,3-ketoesters were

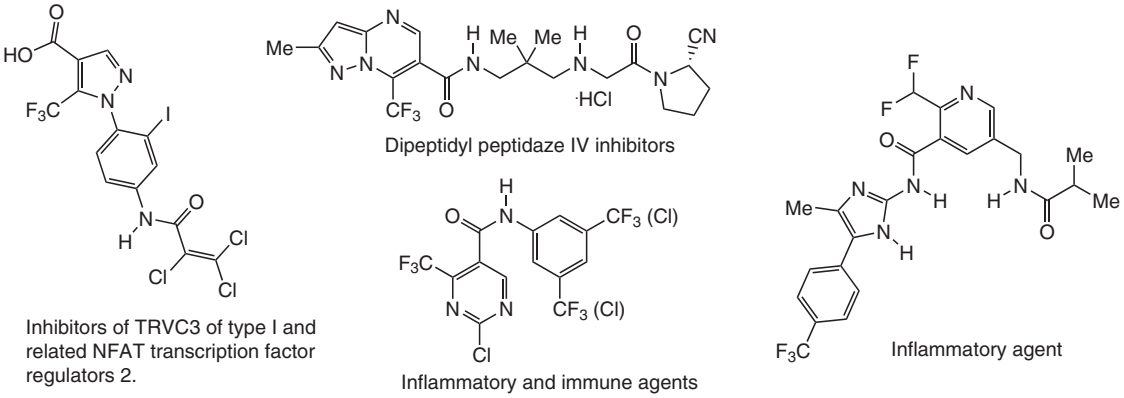


Fig. 2: Examples of biologically active compounds based on 2-ethoxymethylene derivatives of fluorinated acetoacetates.

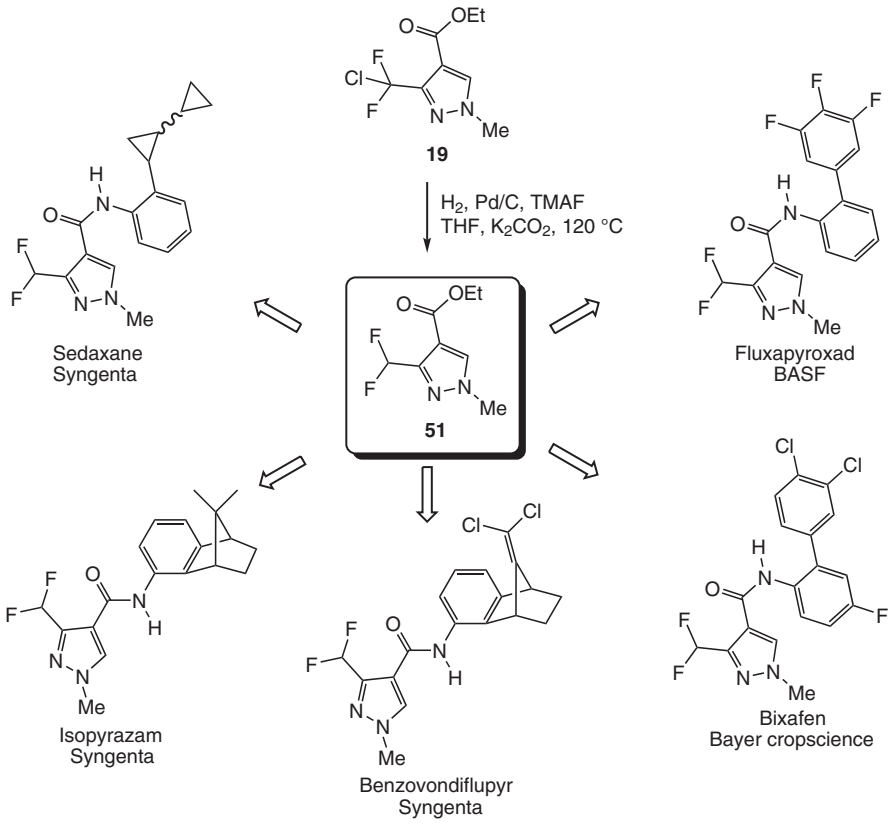
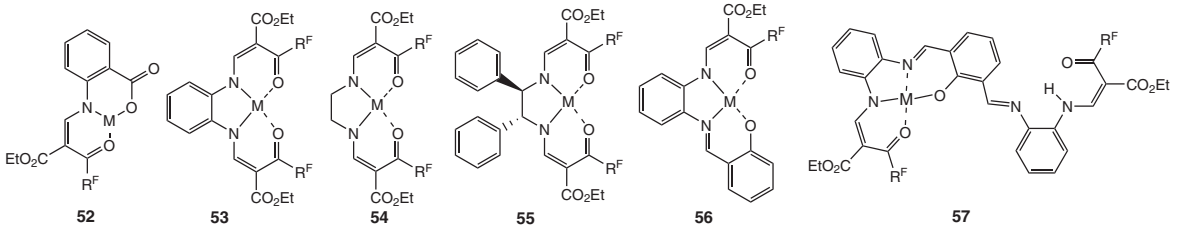


Fig. 3: Developed fluorinated fungicides.

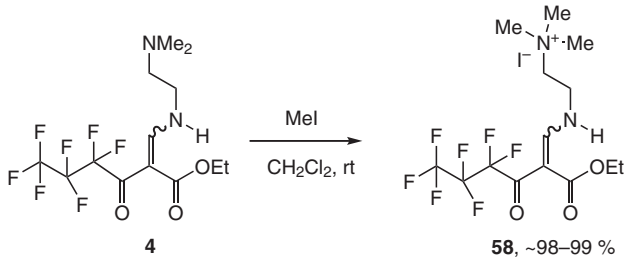
successfully applied in the series of novel metal-organic complexes **52–57** preparation (Fig. 4). The coordination of metal ion with oxygen atoms of fluoroacyl group rather than ethoxycarbonyl one is the general structural characteristic for all synthesized complexes determined based on X-ray analysis data. It was shown that copper complexes **56** are efficient catalysts of the radical addition of perfluoroalkyl iodides to some alkenes and alkynes to give partially fluorinated hydrocarbons in good yields [75].

Dimethylamino group in 2-aminomethylene derivative of C_3F_7-substituted 3-oxo ester **4** can be selectively alkylated with methyl iodide to give quaternary ammonium salts **58** in quantitative yields (Scheme 17). This water-soluble enaminoketones can act as surfactants during cadmium and zinc sulfides synthesis in an aqueous media with controlled particle size [33]. Also it was demonstrated that obtained quaternary ammonium salts can be efficient corrosion inhibitors of steel in highly acidic media [34].



R^F = CF_3, $(CF_2)_2H$, C_3F_7;
M = Ni (II), Cu (II), Co (II).

Fig. 4: Examples of transition metal complexes.



Scheme 17: Synthesis of water-soluble quaternary ammonium salts.

Conclusions

The reactivity studies of fluorinated 2-ethoxymethylene-3-oxo esters with mono- and bifunctional nucleophiles were covered in this review. Structurally different molecules such as aliphatic or heterocyclic derivatives can be synthesized from the same substrates by convenient methods. Varying the nature of N,N-binucleophile in the condensation reactions with fluorinated alkoxyenones, the five-, six-membered or condensed heterocyclic compounds can be obtained. In some cases the stability of hydrated forms of heterocycles is attributed to the presence of fluoroalkylated group. The one of the advantages of such fluorinated building blocks is the possibility to modify ethoxycarbonyl functional group on the later stages of synthesis to prepare more complex molecules. Employing of fluorinated 2-ethoxymethylene derivatives of 3-oxo esters in heterocyclizations provides hetaromatic compounds perspective for the further C–H functionalization. Thus, the class of represented compounds is very attractive for the further investigations and development in organic synthesis.

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