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Fluorine-containing β-Ketoesters

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Data on the methods of synthesis, the keto-enol tautomerism, chemical properties, and applications of fluorine-containing β-ketoesters are surveyed. The characteristic features of these compounds due to the presence of fluorine atoms are specified. The bibliography includes 157 references.

CONTENTS

I. Introduction	1185
II. Methods of synthesis	1185
III. Structure and acidity	1187
IV. Chemical properties	1188
V. Applications	1197

I. INTRODUCTION

β-Ketoesters without fluorine (β-KE) have found applications in organic synthesis and industry. They are known as biologically active preparations and as extractants for many metals and they serve as the starting materials for the synthesis of a large number of compounds (metal chelates, ketones, and N- and S-containing heterocycles), which are also used in the national economy and in medicine. Effective and selective catalysts of polymerisation and polycondensation, pesticidal, antibacterial, antimalarial, and antiradiation preparations, and substances generating laser radiation have been found among β-KE derivatives. At the same time β-KE are of undoubted theoretical interest for the study of reactivity in relation to nucleophiles and electrophiles, tautomerism, and geometrical isomerism.

The introduction of fluorine atoms into β-KE alters their physicochemical properties, reactivity, biological activity, and other properties of practical and theoretical importance.

In many instances the presence of fluorine atoms in β-KE and their derivatives is responsible for the increase of their biological and catalytic activity and their resistance to corrosive media or leads to the appearance of new aspects of their applications. However, there have been no reviews of the literature data in this field of the chemistry of organofluorine compounds. Reviews have been published recently on fluorine-containing α-diketones and α-ketoesters [1] and β-diketones.[2] Some information about fluorine-containing β-KE (β-FKE) is available in monographs.[3-5]

The aim of the present review is to survey the literature data on the synthesis, properties, and applications of β-FKE and to compare them with those of their hydrocarbon analogues, which makes it possible to discover the features due to the presence of fluorine atoms in β-KE. The review covers the literature up to 1983 inclusive.

II. METHODS OF SYNTHESIS

The first fluorine-containing β-KE, namely trifluoroacetoacetic ester (TFAAE) was obtained by Swarts[6] by the Claisen condensation in 1926.[6] In 1929 difluoroacetoacetic ester was obtained by the same method.[7]

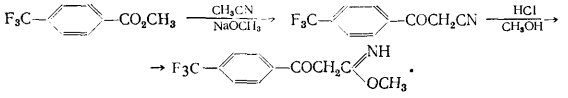
It has been shown[8] that the condensation of the methyl esters of difluoro- or trifluoroacetic acid with ethyl acetate in ether using equimolar proportions of the reactants in the presence of sodioethylene leads to the corresponding β-FKE in moderate yields (35 and 54% respectively). A method for the purification of β-FKE via copper chelates is described in the same communication. A β-KE with the heptafluoropropyl group has been obtained analogously:[9]

$$R_FCO_2C_2H_5 + CH_3CO_2C_2H_5 \xrightarrow[\text{ether}]{C_2H_5ONa} R_FCOCH_2CO_2C_2H_5;$$
$$R_F = HCF_2\ (35\%),\ CF_3\ (54\%)\ [8];\ C_3F_7\ (90\%)\ [9].$$

Acetoacetic ester (AAE) is formed by this method from ethyl acetate in 75% yield.[10] The condensation of ethyl monofluoroacetate with formic acid ester makes it possible to obtain the α-fluoro-substituted β-aldoester:[11]

$$CH_2FCO_2C_2H_5 \xrightarrow[C_2H_5ONa]{HCO_2C_2H_5} HCOCHFCO_2C_2H_5.$$

The self-condensation of monofluoroacetic ester in the presence of sodium alkoxides affords α,γ-difluoroacetoacetic ester in 23% yield.[12,13] Treatment of monofluoroacetic ester under these conditions with acetyl chloride leads to α-fluoroacetoacetic ester in 10% yield.[14] The ester of trifluoromethylbenzoic acid reacts with acetonitrile to form a β-ketonitrile whose alcoholysis makes it possible to obtain a β-ketoiminoester:[15]



The use of sodium alkoxides as condensing agents for the synthesis of β-FKE is not always effective. Thus the self-condensation of difluoroacetic ester and its reaction with trifluoroacetic ester do not lead to β-FKE on treatment with sodium alkoxides in ether,[8] although the use of sodium hydride makes it possible to obtain β-FKE containing one or two fluorine atoms in the α-position in 20–86% yields.[16,17] β-FKE with the pentafluoroethyl residue has also been synthesised by this method:[14,18]

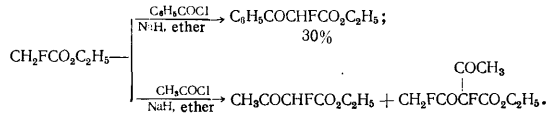
$$C_2F_5CO_2C_2H_5 + XCH_2CO_2C_2H_5 \xrightarrow[\text{ether}]{NaH} C_2F_5COCHXCO_2C_2H_5;$$
$$X = H\ (87\%),\ F\ (70\%)\ [14].$$

t-Butyl 4,4,4-trifluoro-3-oxobutanoate and ethyl 4,4,4-trifluoro-2-methyl-3-oxobutanoate have been obtained in the same way in 56 and 50% yields.[18] 2,2,2-Trifluoroethyl formylphenylacetate is formed under analogous conditions from trifluoroethyl phenylacetate and trifluoroethyl formate:[19]

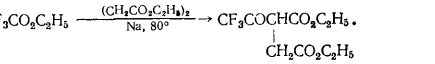
$$C_6H_5CH_2CO_2CH_2CF_3 \xrightarrow[NaH]{HCO_2CH_2CF_3} \underset{\displaystyle C_6H_5\ 46\%}{HCOCHCO_2CH_2CF_3}.$$

Monofluoroacetic ester reacts with t-butyl methyl ketone in the presence of sodium hydride in ether to form α,γ-difluoroacetoacetic ester.[20] Acetyl chloride and benzoyl chloride

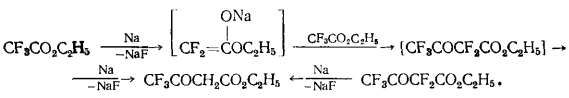
condense with monofluoroacetic ester on treatment with sodium hydride.[14] Both the α-fluoro-derivative of AAE and a diketoester, which is a product of the acylation of the α,γ-difluoro-derivative, are formed in the first case:



When metallic sodium is used as the condensing agent, TFAAE is formed in 77% yield;[21] trifluoroacetic ester and diethyl succinate give rise to an α-ethoxycarbonyl-substituted β-FKE in the presence of sodium:[22]

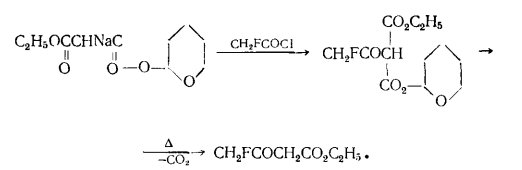


It is of interest that treatment of trifluoroacetic ester with sodium in liquid nitrogen does not produce pentafluoroacetic ester but gives rise to TFAAE and sodium fluoride.[23] The abstraction of fluorine atoms has been confirmed in the preparation of TFAAE on treating pentafluoroacetoacetic ester with sodium in ether:[23]

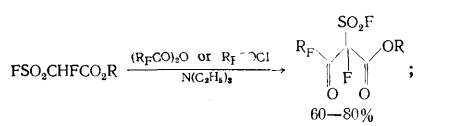


Hydrogen is probably abstracted from the solvent by the intermediate carbonium ion.

Triphenylmethylsodium was used in the condensation of trifluoroacetic ester with isobutyric ester.[17] γ-Fluoroacetoacetic ester has been obtained by acylating the sodium derivative of ethyl tetrahydropyranyl malonate with thermal decomposition of the product:[24]

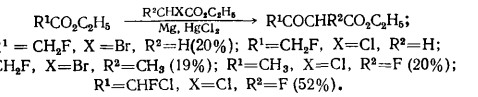


A convenient method of synthesis of the β-FKE with the fluorosulphonyl group in the α-position has been developed recently. It consists in the acylation of esters of fluorosulphonylfluoroacetic acid by the anhydrides or chlorides of carboxylic fluoroacids in the presence of triethylamine:[25]

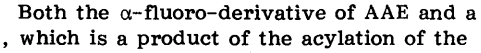


R = CH_3, iso-C_3H_7; R_F=CF_3, CF_2CF_2H, C_3F_7, C_4F_9, C_6F_{13}.

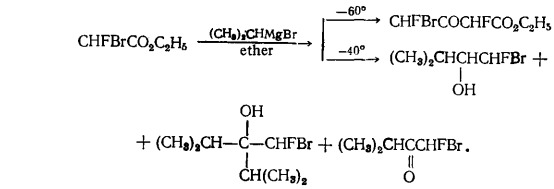
The synthesis of monofluoro- and difluoro-derivatives of β-KE by the condensation of halogen-containing esters in the presence of magnesium and mercury chloride in ether (in yields of 19–52%) has been described:[14]



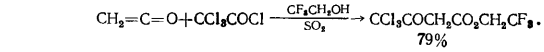
Sterically hindered esters of bromine-containing carboxylic acids can also be involved in this reaction in the presence of zinc in benzene:[26]



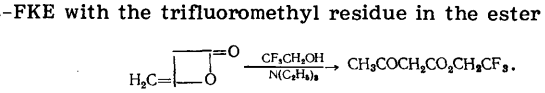
On treatment with isopropylmagnesium bromide, ethyl bromofluoroacetate gives rise to substituted β-KE at −60 °C in ether, whereas at −40 °C a mixture of alcohols and a ketone is formed:[27]



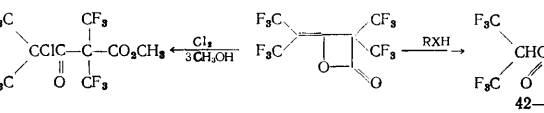
The interaction of keten and its derivatives with acid chlorides and alcohols yields β-KE which are difficult to obtain by other methods. Keten reacts with trifluoroethanol and trichloroacetyl chloride to form in a high yield β-FKE containing the trichloro- and trifluoro-methyl groups:[28]



The keten dimer reacts with trifluoroethanol to produce a β-FKE with the trifluoromethyl residue in the ester group:[29]

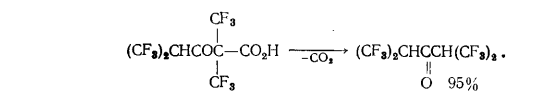


The cyclic dimer of perfluorodimethylketen forms a whole series of trifluoromethyl-substituted β-KE and their derivatives in reactions with HO-, HS-, and N-nucleophiles.[30,31] When the perfluorodimethylketen dimer is chlorinated in the presence of methanol, coupled addition takes place with formation of a γ-chloro-substituted β-FKE. In the absence of methanol, the reaction does not take place:[31]

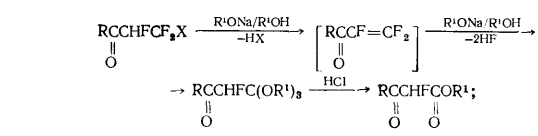


X = O, S, or NH; R = H, alkyl, or phenyl.

The interaction of the perfluorodimethylketen dimer with water affords a β-ketoacid which is unstable at room temperature:[31]

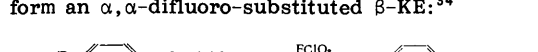


The method of synthesis of α-fluoro-substituted β-FKE involving the treatment of unsaturated fluoroketones with sodium alkoxides and subsequent acid hydrolysis of the products of the vinyl substitution of fluorine and addition to the double bond is apparently promising:[32,33]



R = alkyl or aryl; R^1 = CH_3, C_2H_5; X=F, Cl.

A number of methods of synthesis of β-FKE are based on the introduction of halogen atoms into the β-KE molecule. *p*-Fluorobenzoylacetic ester reacts with perchloryl fluoride to form an α,α-difluoro-substituted β-KE:[34]



A similar reaction takes place in alcohol in the presence of sodium ethoxide.[35,36] A fluorine atom can be introduced into the isopropyl group of the β-KE when isobutyric acid ester reacts with triphenylmethylsodium and perchloryl fluoride:[37]

$$(CH_3)_2CHCO_2CH_3 \xrightarrow[(C_6H_5)_3CNa]{FClO_3} (CH_3)_2CFCOCCO_2CH_3 \quad (30\%)$$

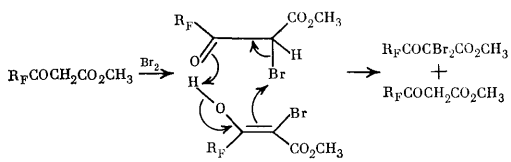
The chlorination of β-FKE or their copper chelates gives rise to α-chloro-derivatives:[38-40]

$$R_FCOCH_2CO_2R \xrightarrow[20^\circ]{Cl_2} R_FCOCHClCO_2R \xleftarrow[CHCl_3]{Cl_2} [R_FCOCHCO_2R]_2Cu;$$
$$R_F = CF_3,\ H(CF_2)_n,\ n = 1, 2, 4;\ C_3F_7,\ C_4F_9;\ R = CH_3,\ C_2H_5.$$

α-Chloro-derivatives of aromatic β-FKE with fluorine-containing substituents in the aromatic ring have been synthesised also by treatment with sulphuryl chloride in chloroform (in yields of 80–90%).[41] Treatment of TFAAE with bromine in a chloroform–pyridine mixture leads to a dibromo-substituted β-KE:[40,42]

$$CF_3COCH_2CO_2C_2H_5 \xrightarrow[CHCl_3,\text{pyridine}]{Br_2} CF_3COCBr_2CO_2C_2H_5.$$

However, when an attempt was made to synthesise α-monobromo-derivatives of β-FKE by treating them with bromine, as described for α-bromotrifluoroacetoacetic ester,[39,43] it was found that they are relatively unstable.[43] At room temperature or on vacuum distillation their disproportionation to α,α-dibromo-derivatives and the initial β-FKE is observed, apparently owing to the halogenophilic attack by the enol form of the α-bromo-derivative of the β-FKE on the bromine atom of the keto-form:



$R_F = CF_3,\ H(CF_2)_n,\ C_4F_9;\ n = 1, 2, 4.$

A second halogen atom can be introduced into the α-position in the β-KE by brominating the α-fluoro-derivative:[44]

$$CF_3COCHFCO_2C_2H_5 \xrightarrow[CCl_4,\ 70^\circ]{Br_2} CF_3COCFBrCO_2C_2H_5.$$

A β-FKE containing an aromatic polyfluoro-group can be synthesised by acylating malonic ester with the chloride of pentafluorobenzoic acid with subsequent hydrolysis and decarboxylation of the acylation product or by the condensation of pentafluorobenzoic ester with ethyl acetate in the presence of diisopropylaminomagnesium bromide:[45-47]

$$C_6F_5COCl \xrightarrow[MgBr(OC_2H_5)_2]{CH_2(CO_2C_2H_5)_2} C_6F_5COCH(CO_2C_2H_5)_2 \xrightarrow[H_2O]{H_2SO_4}$$
$$C_6F_5CO_2C_2H_5 \xrightarrow[(iso\text{-}C_3H_7)_2NMgBr]{CH_4CO_2C_2H_5} C_6F_5COCH_2CO_2C_2H_5.$$

The same compound was formed on oxidation of the β-hydroxyester, obtained by the Reformatskii reaction, with chromium trioxide or potassium permanganate:[47]

$$C_6F_5C(O)H \xrightarrow[Zn]{BrCH_2CO_2C_2H_5} C_6F_5CHCH_2CO_2C_2H_5 \xrightarrow{CrO_3}$$
$$\rightarrow C_6F_5COCH_2CO_2C_2H_5 + C_6F_5COCH_3 + C_6F_5CO_2H.$$
$$17\%$$

The first two methods of synthesis of pentafluorobenzoylacetic ester (PFBAE) are preferable because they lead to higher yields.

Thus one may conclude that the most universal and most convenient, as regards yields, purity of the reaction products, and the availability of the initial reagents, method of synthesis of a wide range of aliphatic β-FKE is the Claisen condensation. As for β-diketones,[2] the most convenient and most widely used method of purification of β-FKE involves the formation of copper chelates.

III. STRUCTURE AND ACIDITY

A whole series of monographs and reviews have been devoted to problems of the structure of β-dicarbonyl compounds,[48-50] but they are concerned mainly with β-KE without fluorine. Data obtained from studies of β-FKE by electronic absorption spectroscopy are virtually lacking in the literature and the available experimental absorption maxima and extinction coefficients are quoted mainly as characteristics of the given substances. The results obtained by Filler and Naqvi[51] permit the conclusion that the replacement of all three hydrogen atoms of the methyl group in AAE by fluorine atoms entails a hypsochromic shift of the absorption maximum (λ_{max} = 244 and 234 nm respectively in 2,2,4-trimethylpentane). For copper chelates of β-KE, such a shift has not been observed; on passing from AAE chelates of TFAAE chelates, there is almost no change in the position of the absorption band maxima in the ultraviolet spectra (278 and 276 nm in chloroform).[51]

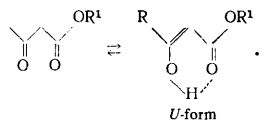
Table 1. Infrared spectra of β-KE [ν(cm^{-1}) in CCl_4].

Compound	Keto-form		Enolic form			Refs.
	>C=O	–C(=O)OR	>C(OR)–C(=O)H	>C=C<	–OH	
$CH_3COCH_2CO_2C_2H_5$	1715	1740	1645	1625	—	[28]
$CH_2ClCOCH_2CO_2C_2H_5$	1726	1745	1656	1632	—	[28]
$CCl_3COCH_2CO_2C_2H_5$	1767	1741	1662	1626	—	[28]
$CCl_3COCH_2CO_2CH_2CF_3$	1755	1777	1683	1627	—	[28]
$CH_2FCOCH_2CO_2C_2H_5$	1730	1745	1660	1635	—	[51]
$CHF_2COCH_2CO_2C_2H_5$	1765	1745	1670	—	3125,3565	[51]
$CF_3COCH_2CO_2C_2H_5$	1775	1740	1670	1640	—	[51]
Ditto	1775	1750	1680	—	3400,3965	[28]
$(CF_3)_2CHCOCO_2CH_3$*	1783	1755	—	—	—	[30]
$C_3F_5COCH_2CO_2C_2H_5$	1748	—	1656	—	—	[47]

*Without solvent.

Application of infrared (IR) spectroscopy to the study of the structures of halogen-containing β-KE revealed the presence of the keto- and enol forms. Table 1 shows that the reducton of halogen atoms (Cl and F) increases the absorption frequencies of the keto-groups in both the keto- and enol forms. This tendency has also been observed for the absorption by the C=C bond in the enolic forms of β-KE. In most studies it has been noted that acetoacid esters form

enols with the *U*-conformation (a *cis,cis*-enol with an intramolecular hydrogen bond):[48,50]



U-form

Table 2. The enolisation β-KE (pure liquids, ^{1}H NMR).

Compound	K_e^* (Ref.55)	Content of enol, %	References
$CH_3COCH_2CO_2C_2H_5$	0.087	6—8	[52—54]
Ditto	—	7.7***	[56]
$CH_2BrCOCH_2CO_2C_2H_5$	—	6	[52]
$CH_2FCOCH_2CO_2C_2H_5$	0.22	7.2	[53]
Ditto	—	18.2***	[56]
$CHF_2COCH_2CO_2C_2H_5$	1.13	53	[53]
$CF_3COCH_2CO_2C_2H_5$	5.7	89	[52,53]
Ditto	—	49***	[56]
$CF_3COCH(CH_3)CO_2C_2H_5$	0.9	—	—
$CF_3COCH(C_6H_5)CO_2C_2H_5$	1.4	—	—
$CF_3COCH(OCH_3)CO_2C_2H_5$	3.0	—	—
$CF_3COCH(C_3H_7)CO_2C_2H_5$	0.22	—	—
$CF_3COCH(C_3H_7\text{-iso})CO_2C_2H_5$	0.003	—	—
$CH_3COCHBrCO_2C_2H_5$	—	5	[50]
$CH_3COCHClCO_2C_2H_5$	—	15	[50]
$CH_2ClCOCHClCO_2C_2H_5$	0.158	—	—
$CH_3COCHFCO_2C_2H_5$	0.158	15	[50]
Ditto	—	0.99***	[56]
$CCl_3COCH_2CO_2CH_2CF_3$	—	21.2	[28]
$HCOCH(C_6H_5)CO_2CH_2CF_3$	—	54	[19]
$C_6F_5COCH_2CO_2C_2H_5$	1.17	54	[47]
$C_6H_5COCH_2CO_2C_2H_5$	0.28**	20	[47]

*K_e = [enol]/[ketone].
**Filler et al.[47]
***Data obtained by the method involving titration with bromine.[56]

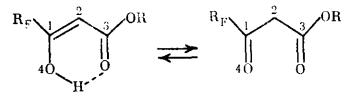
The methods for the investigation of the keto–enol equilibria involving β-KE which are most convenient and yield most information are IR and NMR spectroscopy.[19,47,50,52–55] Data for the enolisation of β-KE, obtained by titration with bromine,[56] agree satisfactorily with the results obtained by other methods (Table 2) only for β-KE without halogens. In the case of fluorine-containing β-KE they are clearly erroneous, in all probability owing to the uncertainty as to the course followed in the bromination process.[40] Table 2 shows that the introduction of halogen atoms into the α- and γ-positions in β-KE entails a sharp increase of the enol content in the equilibrium mixture, which may be attributed to a greater increase in the CH acidity than the OH acidity. The β-KE are enolised only at the carbonyl oxygen atom.[50] The lower degree of enolisation of β-KE compared with β-diketones[2,50] is in all probability associated with the greater electron density on the carbon atom of the carbonyl group owing to the presence of alkoxy-groups. The contribution of the influence of γ-substituents in the enolic forms of β-KE to the intramolecular hydrogen bond is not additive, in contrast to β-diketones.[57]

The charges on the atoms and the bond energies in the keto- and enol forms of a series of α- and γ-fluoro-substituted β-KE have been calculated[55] by Del Re's method. Correlations between the keto-enol equilibrum constants ($\lg K_e$) and the parameters of the reaction centres have been investigated. A linear relation has been observed ($r = 0.995$, $\alpha = 0.95$) between $\lg K_e$ and the charges on the β-carbon atoms in the keto and enol forms of β-KE and on the hydrogen atom of the enolic hydroxyl and also the O–H bond energy of the enol.[55]

The acidity of β-FKE has been investigated by Kurts et al.,[58] who established that the introduction of fluorine atoms into the γ-position in β-KE increases their activity, in conformity with the inductive effect of the substituents [AAE: $pK_a = 12.6$; γ-F-AAE: $pK_a = 11.2$; TFAAE: $pK_a = 7.4$ (in dimethylformamide)]; consequently the stability of the enolate ion increases under these conditions. One can also note that, on passing from β-KE to the corresponding β-diketones (replacement of OC_2H_5 by CH_3), the acidity increases [acetylacetone: $pK_a = 11.7$; trifluoroacetylacetone: $pK_a = 5.1$ (in dimethylformamide)], which also agrees with the inductive effect of the substituents.

IV. CHEMICAL PROPERTIES

Fluorine-containing β-ketoesters have four reaction centres: C(1), C(2), C(3), and O(4):



This is the reason for their varied reactivity in relation to nucleophiles and electrophiles. The introduction of fluorine atoms increases the reactivity in relation to nucleophiles and in many cases alters the reaction mechanisms compared with their hydrocarbon analogues. The presence of the ester group leads to the appearance of chemical properties uncharacteristic of fluorine-containing β-ketones.

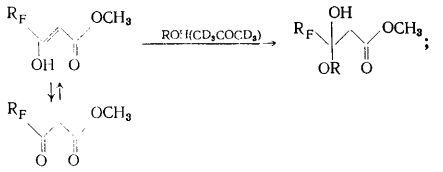
1. Interaction with Nucleophiles

HO, HS, HN, and other nucleophiles react with β-FKE, forming addition and addition-elimination products from which one can infer the characteristic features of substances of this class. In the study of reactions of the given type, the question of the direction of the primary processes, namely either via the C(1) carbon atom in the keto- or enol form or via the C(3) atom (the ester group), is significant. However, one cannot rule out the process involving the formation of a salt of the enol form. Thus the reactions of β-FKE with nucleophiles must be regarded as competing interactions with the C(1), C(2), and C(3) reaction centres. Naturally one must also take into account the influence of the medium.

(a) Reactions with Hydroxylated Nucleophiles

In the absence of a solvent, TFAAE combines with water and alcohol, forming hydrates and hemiketals, which are in equilibrium with keto- and enol forms.[59] Since the enolisation constant K_e, determined by ^{19}F NMR, increases after the addition of water to TFAAE, the authors of the above study concluded that the addition is to the keto-form and that the reaction is faster than the attainment of the keto–enol equilibrium. However, in another study by the ^{1}H and ^{19}F NMR methods, of the interaction of β-FKE with water and alcohols in deuterioacetone, it was shown that they add to the

enol form of β-FKE and that K_e diminishes with time:[60]

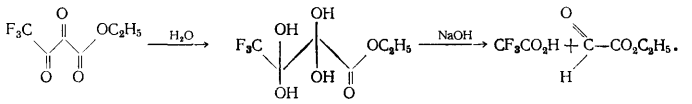


R_F=H(CF_2)$_n$, (n = 1, 2, 4), CF_3, C_3F_7, C_4F_9, R=H, CH_3, C_2H_5.

The discrepancy between the results obtained cannot be accounted for by the influence of the solvent (CD_3COCD_3), since in the case of asymmetric fluorine-containing β-diketones, hydroxylated nucleophiles also added to the enol form, the content of the keto-form hardly changing under these conditions, while the solvent (CD_3COCD_3) does not influence the reaction mechanism.[61] The results of the study of Camps et al.[59] cannot be interpreted in detail because of the inadequacy of the experimental data presented. Furthermore, the use of the analysis of the [enol]/[ketone] ratio is not quite correct, since there are no data concerning the influence of alcohols on the keto–enol equilibria of β-FKE.

An increase in the length of the fluoroalkyl group (from difluoromethyl to nonafluorobutyl) in β-FKE and also the increase of the bulk of the alkyl substituents in the hydroxylated nucleophile lead to a decrease of the fraction of the adduct, which is in all probability associated with steric hindrance.[60] It is of interest that butyl 2,2,4,4,4-pentafluoroacetoacetate reacts with butanol to form a stable adduct, which can be isolated pure, this being due to the appreciable decrease of the electron density at the C(1) centre compared with TFAAE as a result of the replacement of the methylene group by the difluoromethylene group.[16] It is clearly seen from the data of Burdett and Rogers[52] and Fomin et al.[60] that the introduction of the trifluoromethyl group in AAE instead of the methyl group entails an increase in the reactivity and stability of the products of the addition of hydroxylated nucleophiles compared with AAE, for which the formation of large amounts of adducts is not a characteristic feature. On heating PFBAE with aqueous alcohol, the ester undergoes keto cleavage to pentafluoroacetophenone, which has not been observed for benzoylacetic ester (BAE).[62]

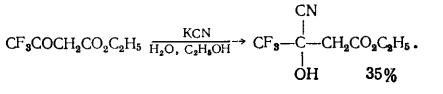
Trifluoro-α-oxoacetoacetic ester reacts with water to form a dihydrate, while in its reaction with aqueous alkali it undergoes acid cleavage:[63,64]



Thus the interaction of β-FKE containing fluoroalkyl groups in the β-position with hydroxylated nucleophiles, including the hydroxide anion, is directed to the C(1) centre. The ketone cleavage of PFBAE in a water–alcohol mixture is apparently associated with its low thermal stability.

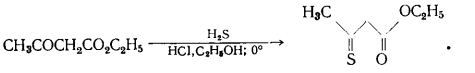
(b) Interaction with C-Nucleophiles

TFAAE reacts with potassium cyanide[65,66] to form a cyanohydrin analogously to the behaviour of carbonyl compounds without fluorine atoms:[10]

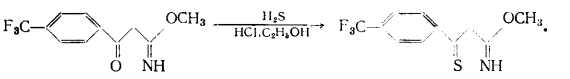


(c) Interaction with HS-Nucleophiles

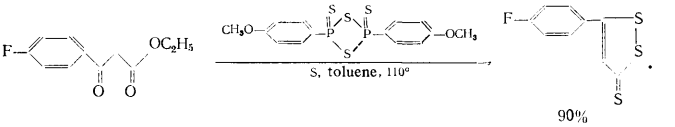
AAE reacts with hydrogen sulphide to form thioacetoacetic esters:[67]



A similar reaction of TFAAE has not so far been described. Only thio-derivatives of aromatic β-KE with the trifluoromethyl substituent in the benzene ring have been obtained:[15]



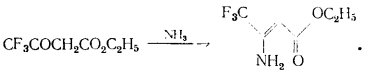
On interaction with *p*-fluorobenzoylacetic ester, the "*p*-methoxyphenylthionophosphine sulphide dimer", which is an effective thionating agent, gives rise to only a cyclic disulphide, as for AAE:[68]



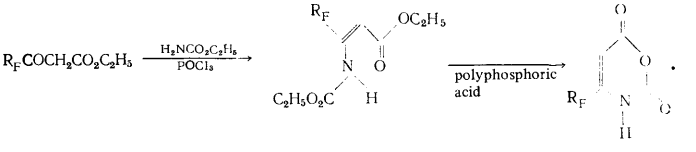
Thioesters cannot be isolated in this instance. The mechanism of the interaction of this reagent with β-KE is still obscure. This branch of the chemistry of β-FKE has remained virtually uninvestigated, while in the case of fluorine-containing β-diketones it has been adequately developed.[2]

(d) Interaction with Amines

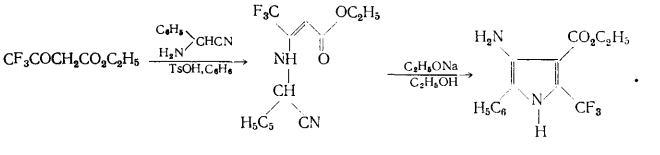
The interaction of AAE with ammonia leads to ethyl β-aminocrotonate in 90% yield.[69] TFAAE also reacts with ammonia to form β-aminotrifluorocrotonic ester:[6,70,71]



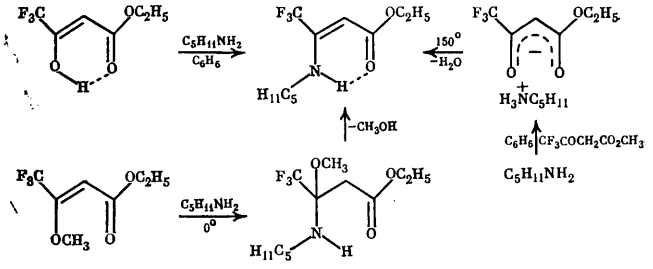
Fluoro- and trifluoro-acetoacetic esters react with urethane in the presence of phosphoryl chloride, forming esters of *N*-substituted-aminocrotonic acids, which cyclise to oxazinediones on treatment with polyphosphoric acid;[72] AAE condenses immediately to oxazinedione,[22] which can apparently be accounted for by the fact that in the case of fluorine-containing compounds the reactivity of the enamine formed is reduced in relation to electrophiles owing to the presence of electron-accepting groups (CH_2F, CF_3):



The interaction of TFAAE with α-aminophenylacetonitrile in the presence of toluene-*p*-sulphonic acid in benzene gives rise to a derivative of aminotrifluorocrotonic acid, from which a substituted pyrrole is formed on treatment with sodium ethoxide in ethanol:[73]

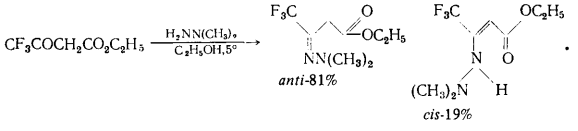


Analogous products have been obtained from AAE and *p*-fluorobenzoylacetic ester.[73] It has been shown that, depending on the order of the addition of the reactants, the interaction of TFAAE with pentylamine leads either to 4,4,4-trifluoro-3-(1-pentylamino)but-2-enoate or to the pentylammonium salt of TFAAE, which is converted into an enamine with elimination of water at 150 °C.[18] Presumably the enolic form of the β-ketoester reacts with the amine, since trifluoro-β-methoxycrotonic ester reacts with pentylamine to form initially a relatively unstable adduct which splits off methanol and is converted into 4,4,4-trifluoro-3-(1-pentylamino)but-2-enoate:[18]



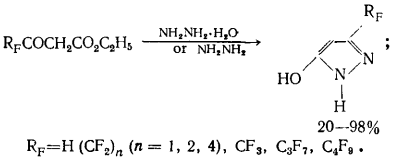
(e) Interaction with Hydrazines

TFAAE reacts with asymmetric *NN*-dimethylhydrazine to give a 62% yield of a hydrazone, which exists, according to ^{1}H NMR data, in the form of an equilibrium mixture of the *anti*-hydrazone form (81%) and the *cis*-enehydrazine form (19%):[74]



Under analogous conditions, the corresponding AAE hydrazone exists as a mixture of the hydrazone form (15% of the *syn*-isomer and 10% of the *anti*-isomer) with the enehydrazine form (72% of the *cis*-isomer and 3% of the *trans*-isomer).[74]

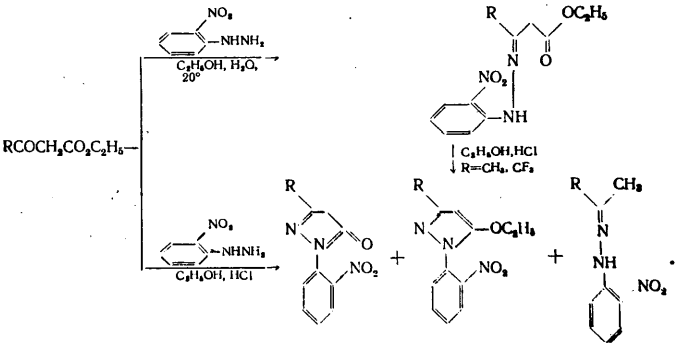
TFAAE andother β-FKE react with hydrazine hydrate or hydrazine to form 5(3)-fluoroalkyl-3(5)-hydroxypyrazoles:[75-77]



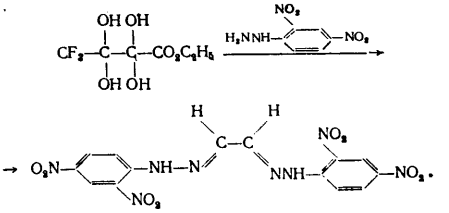
R_F=H $(CF_2)_n$ (n = 1, 2, 4), CF_3, C_3F_7, C_4F_9.

β-KE monosubstituted by fluorine in the α-position also give rise to hydroxypyrazoles.[78]

β-FKE react with phenylhydrazine and methanol at 20 °C to form *N*-phenylhydrazones, which cyclise to 5-fluoroalkyl-3-hydroxy-*N*-phenylpyrazoles on refluxing in methanol.[77] The formation of hydrazone has been noted in the reaction of γ-fluoroacetoacetic ester with 2,4-dinitrophenylhydrazine [24] and of TFAAE with 2-nitrophenylhydrazine.[79] However, as a rule oxo- or hydroxy-pyrazoles are formed in the reactions of β-FKE with hydrazines.[75-77,80,81] A more detailed study of this process in relation to the reaction of AAE or TFAAE with 2-nitrophenylhydrazine showed that the results depend to a large extent on the experimental conditions.[79] Thus the products in aqueous alcohol at 20 °C are arylhydrazones, which, on treatment with alcoholic hydrogen chloride, afford a mixture of pyrazolone, ethoxypyrazole, and the hydrazone of the corresponding methyl ketone, formed apparently on ketone cleavage of the β-KE, whereas in alcohol containing hydrogen chloride the above mixture of products is formed immediately:[79]



On treatment with 2,4-dinitrophenylhydrazine, the dihydrate of trifluoro-2-oxoacetoacetic ester decomposes with formation of glyoxal bis-2,4-dinitrophenylhydrazone:[64]

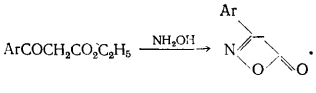


In the reactions of β-FKE with pentafluorophenyl groups in the β-position with hydrazine[62] and phenyl- and pentafluorophenylhydrazines,[82] the corresponding pyrazolones are formed. On the other hand, BAE reacts with pentafluorophenylhydrazine to form the pentafluorophenylhydrazone;[82] cyclisation to a pyrazolone is not observed in this case, apparently as a consequence of the insufficient nucleophilicity of the nitrogen in the HN groups of the hydrazone. At the same time, the pentafluorophenylhydrazone of PFBAE cyclises spontaneously to the pyrazolone, which is in all probability due to the electrophilic properties of the carbon atom in the ethoxycarbonyl group enhanced under the influence of the pentafluorophenyl residue.

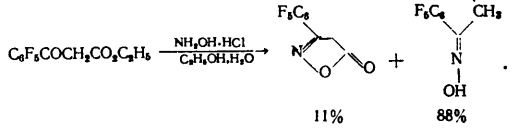
According to IR spectroscopic data, pyrazolones containing one or two pentafluorophenyl substituents consist in the solid state of a mixture of the hydroxy-form with a small amount of the keto-form, while 1,3-diphenyl-5-pyrazolone exists under these conditions as the keto-form.[82] In alcoholic solutions these pyrazolones exist in the enolic-form, while in carbon tetrachloride or in methylene chloride they are present predominantly in the keto-form.[82] It follows from the above that, in the interaction of hydrazines with β-FKE, the primary attack by the hydrazine is directed to the C(1) carbon atom, which is indicated by the formation of hydrazones in certain cases, the interaction involving the C(3) reaction centre and cyclisation to pyrazolones only under more severe conditions.[77,79]

(f) Interaction with Hydroxylamine

The *para*- and *meta*-trifluoromethyl derivatives of PAE react with hydroxylamine to form isoxazolones:[83-85]



Pentafluorobenzoylacetic ester reacts with hydroxylamine to form a salt and not an isoxazolone, which can be explained by its high acidity.[82] However, when PFBAE is heated with hydroxylamine hydrochloride in aqueous alcohol, 3-pentafluorophenyl-5-isoxazolone is obtained together with pentafluoroacetophenone oxime:[62]

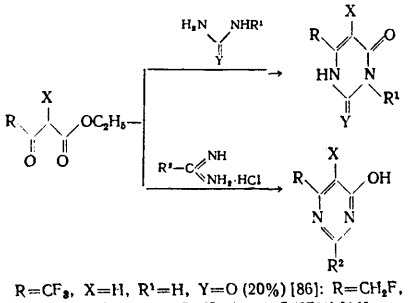


11% 88%

The formation of the oxime agrees well with the fact that, on heating in aqueous alcohol, PFBAE undergoes ketone cleavage to pentafluoroacetophenone, whose reaction with hydroxylamine affords the oxime.[62]

(g) Interaction with Ureas, Guanidine, Semicarbazides, and Amidines

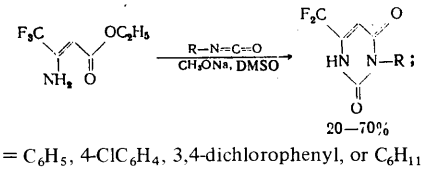
The interaction of β-FKE with ureas[14,86–88] in basic[86] or acid[14] media, with thiourea in the presence of sodium methoxide,[14] with guanidine carbonate,[14] and with carboxylic acid amidines[14–89] leads to uracils, thiouracils, isocytosines, and hydroxypyrimidines substituted in the 2-position respectively:



R=CF_3, X=H, R¹=H, Y=O (20%) [86]: R=CH_2F, X=H, R¹=H, Y=O (73%) or S (67%) [14]; R=CH_3, X=F, R¹=Ar, Y=O [87, 88];

R=CH_3, CH_2F, CF_3 or C_2F_5, X=H or F, R¹=H, Y=NH·H_2CO_3 [14]; R=CH_3, CH_2F, CF_3 or C_2F_5, X = H or F, R^2 = CH_3 or iso-C_3H_7 [14, 89].

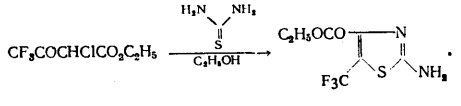
Fluorine-containing uracils are formed also from β-aminocrotonic esters and isocyanates:[71, 90]



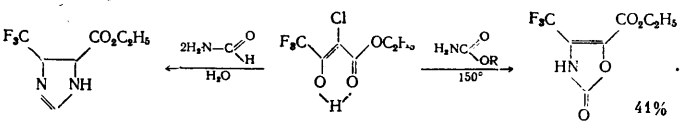
20–70%

R = C_6H_5, 4-ClC_6H_4, 3,4-dichlorophenyl, or C_6H_{11}.

If there is a chlorine atom, which is more mobile than the fluorine atom, in the α-position in β-FKE, then the reaction follows another pathway: the ethyl ester of 2-amino-4-trifluoromethylthiazolecarboxylic acid is formed on interaction with thiourea:[41,91]



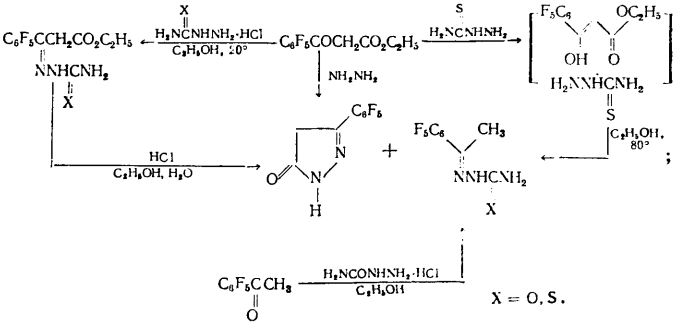
The mobility of the chlorine atom in the α-position in β-FKE is also manifested in the interaction of the chloro-substituted TFAAE with formamide or urethane:[92,93]



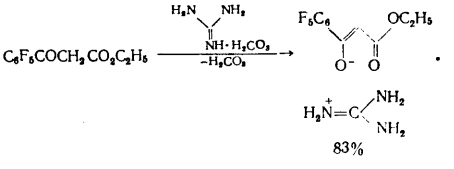
41%

The interaction of PFBAE with semicarbazide hydrochloride or thiosemicarbazide hydrochloride at 20–25 °C involves the C(1) reaction centre.[62] On heating, the PFBAE derivative undergoes the ketone cleavage and the semicarbazone residue decomposes to the hydrazone residue, so that a derivative of pentafluoroacetophenone is obtained together with pentafluorophenylpyrazolone.[62] The reaction with thiosemicarbazide gives rise not to the thiosemicarbazone but to an unstable salt, which is converted on heating into the same products as thiosemicarbazide hydrochloride.[62]

The presence of 3-pentafluorophenyl-5-pyrazolone in the products of the reaction of PFBAE with semicarbazide can be accounted for by the partial decomposition of the latter to hydrazine.[62,95] Its structure has been demonstrated by specific synthesis from a β-FKE and hydrazine:[62]



The formation of a salt with thiosemicarbazide is extremely probable, since the guanidinium salt of the enolic form of PFBAE has been isolated in the reaction with guanidine carbonate:[82]



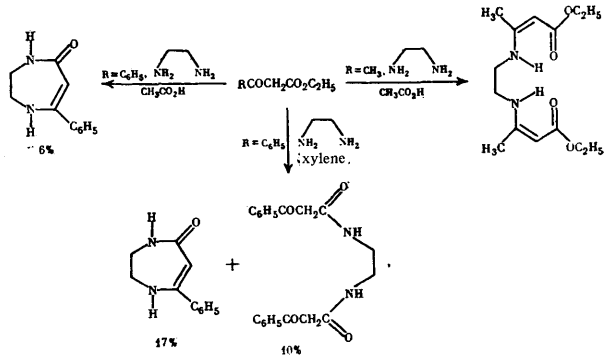
83%

In this case BAE gives rise to 4-phenylisocytosine.[94] This can be explained by the increased acidity and degree of enolisation of PFBAE compared with BAE.[47]

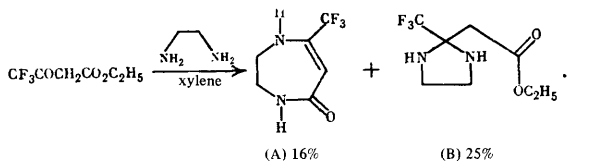
(h) Reactions with Bifunctional Nucleophiles

The interaction of AAE with ethylenediamine (EDA) in acetic acid does not give rise to an azepinone, but produces *NN'*-ethylenebis-3-amino-but-2-enoate.[96] However BAE does form 7-phenyl-1,2,3,4-tetrahydro-1,4-diazepin-5-one under

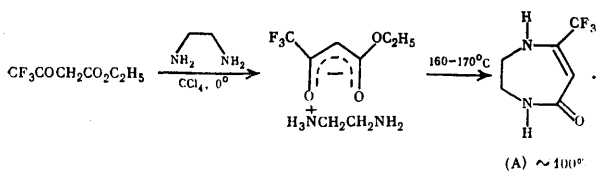
these conditions, while in xylene *NN'*-ethylenebisbenzoylacetamide is obtained in addition;[96]



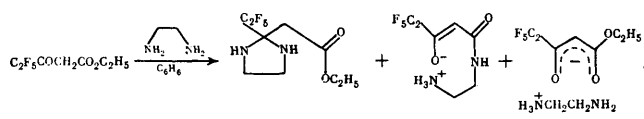
In contrast to this, the reaction of TFAAE with EDA in xylene affords a mixture of 7-trifluoromethyl-1,2,3,4-tetrahydro-1,4-diazepin-5-one (A) and 2-ethoxycarbonylmethyl-2-trifluoromethylimidazolidine (B):[97]



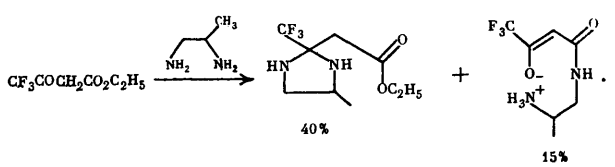
When TFAAE was added to EDA in boiling benzene, 36% of compound (B) and 10% of compound (A) were obtained while in ethanol only the product (B) was formed in 19% yield. On the other hand, after the addition of EDA in TFAAE, compound (B) was obtained in 81% yield, while the diazepine (A) was not isolated.[18] The addition of EDA to a solution of TFAAE in carbon tetrachloride results in the formation of the ethylenediammonium salt of TFAAF, which is converted quantitatively into the diazepinone (A) on heating:[18]



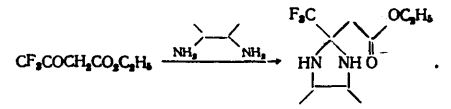
The addition of EDA to a boiling benzene solution of ethyl 4,4,5,5,5-pentafluoro-3-oxopentanoate produces 2-ethoxycarbonylmethyl-2-perfluoroethylimidazolidine, *N*-(2-aminoethyl)-3-hydroxy-4,4,5,5,5-pentafluoropent-2-enamide, and the ethylenediammonium salt of the β-FKE:[18]



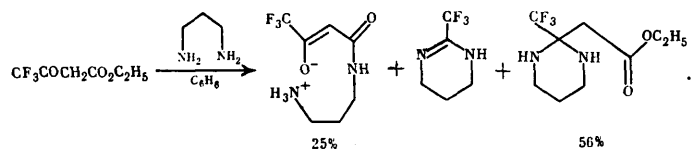
The addition of TFAAE to 1,2-diaminopropane in benzene results in a mixture of the *d*- and *l*-isomers of a substituted imidazolidine together with *N*-(2-aminepropyl)-3-hydroxy-4,4,4-trifluorobut-2-enamide, which gives rise to 2-methyl-7-trifluoromethyl-1,2,3,4-tetrahydro-1,4-diazepin-5-one on heating:[18]



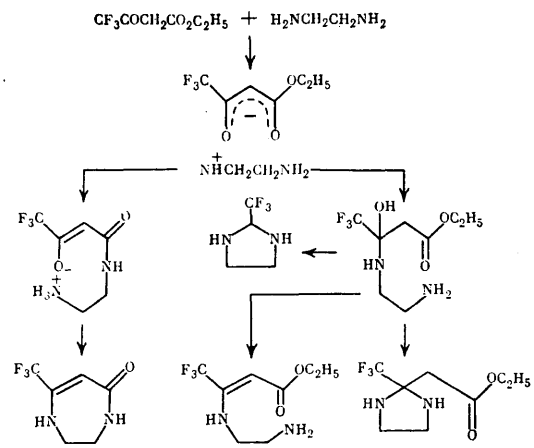
The reaction of TFAAE with 2,3-diaminobutane produces a mixture of the *d*-, *l*-, and *meso*-isomers of a substituted imidazolidine:[18]



The reaction of 1,3-diaminopropane with TFAAE leads to *N*-(3-aminopropyl)-3-hydroxy-4,4,4-trifluorobut-2-enamide, 2-trifluoromethyl-3,4,5,6-tetrahydropyrimidine, and 2-ethoxycarbonylmethyl-2-trifluoromethylhexahydropyrimidine:[18]



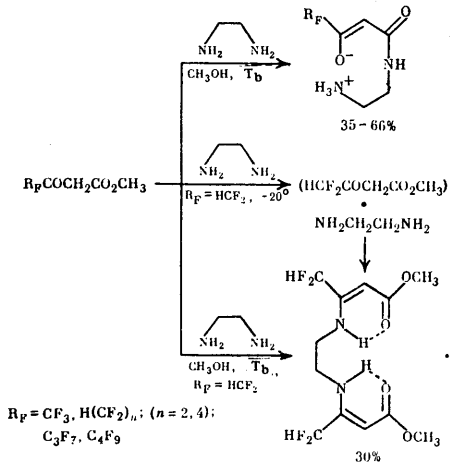
From the above data, the following mechanism of the reaction of TFAAE with EDA in aprotic solvents has been proposed:



As can be seen from the above scheme, the authors[18] suggest the presence of two competing pathways in the reaction of the TFAAE salt with EDA: the formation of an adduct via the C(1) centre with subsequent dehydration and the substitution of the ethoxy-group in the ester group of TFAAE [attack on the C(3) centre].

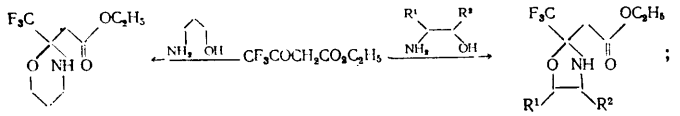
The replacement of an aprotic solvent by a proton-donating solvent (methanol) entails an appreciable simplification of the composition of the products of the reaction of β-FKE with EDA.[77] Thus, when difluoroacetoacetic ester is refluxed with EDA in methanol, 3,3'-(*NN'*-diaminoethylene)bis-1,1-difluorobut-2-enoate is formed,[77] which is also characteristic of AAE,[96] while at −20 °C it is possible to isolate a 2:1 salt of difluoroacetoacetic ester with EDA, which is converted on heating into the same dicarboxylic acid ester.[77] The replacement of the difluoromethyl group by the trifluoromethyl group or the lengthening of the fluoroalkyl residue results in the formation of an inner salt of the aminoethyleneamide of the β-ketoacid as the sole reaction

product:[77]

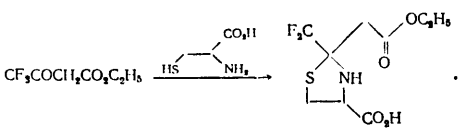


Apparently the primary process in the interaction of EDA with β-FKE in a proton-donating solvent[77] is, as in an aprotic solvent,[18] the formation of a salt of the β-FKE. However, the subsequent reaction pathway is apparently determined by the acidity of the β-FKE and, in the case where $R_F = HCF_2$, the reaction involving the C(1) centre (a carbonyl group) takes place, whereas under conditions where R_F has been lengthened the reaction involves the C(3) centre (the ester group).

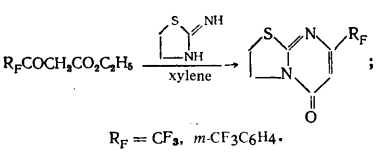
TFAAE reacts with aminoalcohols to form 2-ethoxycarbonylmethyl-2-trifluoromethylperhydroxooxazine or the corresponding oxazolidine:[18]



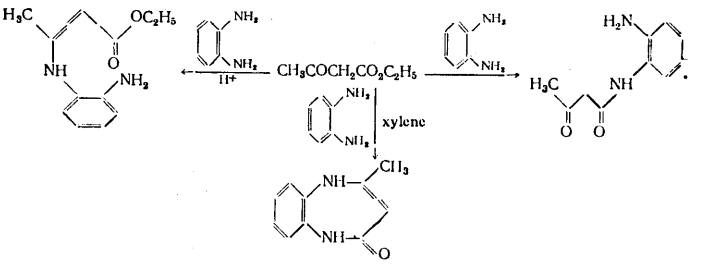
Cysteine reacts with TFAAE to form 4-carboxy-2-ethoxycarbonylmethyl-2-trifluoromethylthiazolidine:[18]



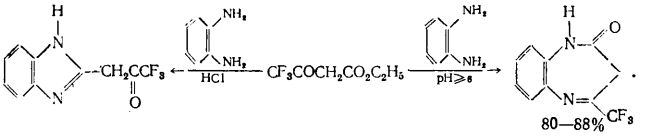
These reactions also show that the attack by the HO-, HN-, and HS-nucleophiles is directed to the C(1) centre, although in the case of the HN-nucleophiles this can be preceded by the formation of a salt with the β-FKE. 2-Iminothiazolidine reacts with β-FKE to form thiazolinopyrimidine derivatives:[98]



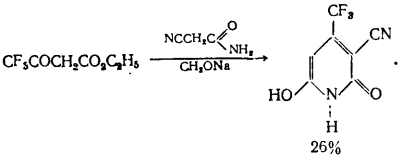
The reaction of AAE with *o*-phenylenediamine (OPDA) results in the formation of various products depending on the basicity of the medium and the character of the solvent.[99–111] In an acid medium the product of the condensation involving a keto-group is formed, in xylene containing pyridine the *o*-aminoanilide is obtained, while in a neutral medium the product is a substituted benzodiazepinone:[100]



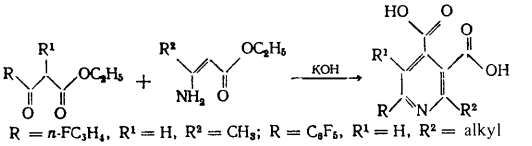
However, there exist data showing that these processes are more complex.[99,101] For example, in methanol 2-methylbenzimidazole was isolated together with a derivative of β-aminocrotonic ester.[101] The interaction of TFAAE and other β-FKE with OPDA in a neutral or weakly alkaline medium entails the formation of 4-(fluoroalkyl)-1*H*-1,5-benzodiazepin-2(3*H*)-ones,[77] while in an acid medium the product is 3-(2-benzimidazolyl)-1,1,1-trifluoro-2-propanone:[102]



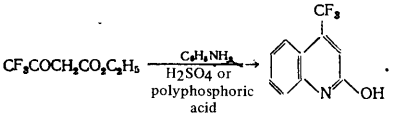
Methyl-*o*-phenylenediamine reacts with TFAAE to produce a mixture of two isomers.[103] β-FKE react with bifunctional nucleophiles containing an active methylene group together with the amino-, hydroxy-, or thio-groups, which leads to different heterocyclic systems.[104–118] Thus the reaction of TFAAE with cyanoacetamide gives rise to a substituted pyridone;[104]



Under the influence of alkali, β-FKE react with β-aminocrotonic esters to form derivatives of dibasic acids of the pyridine series,[105] which is also characteristic of AAE:[106]

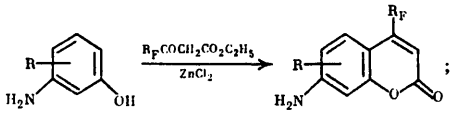


Like AAE,[10] TFAAE reacts with aniline and its derivatives in the presence of sulphuric or polyphosphoric acid to form hydroxyquinolines and their derivatives.[107–113] The yields of the reaction products are then as a rule higher in the case of polyphosphoric acids:[108–110]



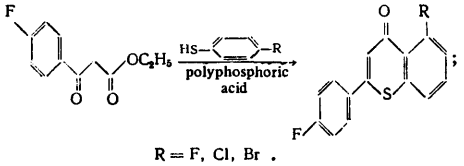
Like the fluorine-free β-KE,[10] β-FKE react with aromatic dihydric phenols and aminophenols via the hydroxy-group and the *ortho*-position in the ring, forming coumarins in

20–80% yields:[114–117]



$R_F = CF_3, C_3F_7, C_5F_{11}, C_7F_{15}$; R = OH, NH_2, $C_6H_5CH_2$— .

Thiophenols react with β-FKE via the S–H and –CH= groups:[118]



R = F, Cl, Br .

The considerable synthetic possibilities of the reactions of β-FKE with nucleophiles, which makes it possible to obtain various classes of fluorine-containing organic compounds, are evident from the foregoing data for these reactions; their characteristic features, which distinguish them from their hydrocarbon analogues, must also be emphasised.

2. Interaction with Electrophiles

The reactions with electrophiles, namely acids,[8,16,22,34,39,44,47,119] carbonyl compounds,[126–129] and alkylating and acylating agents[51,119,143,144] (see Section II about the halogenation of β-FKE) are characteristic of β-FKE, as in the case of their hydrocarbon analogues.

(a) Reactions with Acids

Fluorine-containing β-ketoesters having a fluoroalkyl substituent in the β-position and not more than one fluorine atom in the α-position undergo the ketone cleavage by sulphuric[8,16,44] or hydrobromic[39] acid with formation of fluoroalkylmethyl, fluoroalkylhalogenomethyl, or fluoroalkyldihalogenomethyl ketones in high yields (50–90%):

$$R_FCOCXYCO_2C_2H_5 \xrightarrow[-CO_2,\ -C_2H_5OH]{H^+} R_FCOCHXY;$$
R_F = fluoroalkyl; X = H, F, Cl, Br; Y = H, Br .

In the presence of two fluorine atoms in the α-position in β-FKE acid hydrolysis of the ester group, leading to β-keto acids, is observed under similar conditions and not the ketone cleavage:[16]

$$CF_2XCOCF_2CO_2C_2H_5 \xrightarrow[-C_2H_5OH]{H_2SO_4} CF_2XCOCF_2CO_2H;$$
X = H (53%), F (56%).

Ketone cleavage takes place only under more severe conditions, giving rise to 1,1,3,3-tetrafluoroacetone (62%) in the first case and 1,1,1,3,3-pentafluoroacetone (35%) in the second case.[16] Treatment of a β-KE having the $CH_2CO_2C_2H_5$ substituent in the α-position with sulphuric acid makes it possible to obtain a γ-ketoacid:[22]

$$CF_2COCHCO_2C_2H_5 \xrightarrow[-CO_2,\ -C_2H_5OH]{H_2SO_4} CF_2COCH_2CH_2CO_2H .$$
61%

Treatment of β-FKE mono- and di-substituted in the α-position with a mixture of bromine and sulphuric acid makes it possible to obtain di- and tri-halogeno-substituted methyl ketones respectively:[44]

$$CF_2COCFXCO_2C_2H_5 \xrightarrow[-CO_2,\ -C_2H_5OH]{Br_2,\ H_2SO_4} CF_2COCFXBr;$$
X = H (95%), Br (84%).

In contrast to fluoroalkyl-containing β-FKE, on treatment with concentrated sulphuric acid PFBAE hydrolyses at 20 °C to pentafluorobenzoylacetic acid, while on treatment with 20% sulphuric acid or a mixture of sulphuric and acetic acids it is cleaved to pentafluoroacetophenone:[47,82]

$$C_6F_5COCH_2CO_2H \xleftarrow{H_2SO_4\ (conc.)} C_6F_5COCH_2CO_2C_2H_5 \xrightarrow[\text{or } H_2SO_4\text{–}CH_3CO_2H]{20\%\ H_2SO_4} C_6F_5COCH_3.$$
48%

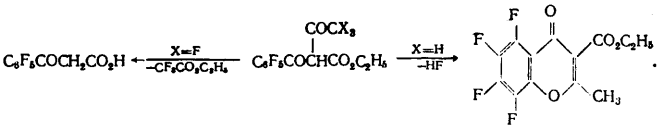
α-Ethoxycarbonylpentafluorobenzoylacetic ester reacts with 10% sulphuric acid to form PFBAE:[47]

$$C_6F_5COCHCO_2C_2H_5 \xrightarrow{10\%\ H_2SO_4} C_6F_5COCH_2CO_2C_2H_5.$$
48%

The ketone cleavage of β-FKE with benzoyl, pentafluorobenzoyl and pentafluorophenylacetyl substituents in the α-position is a convenient method of synthesising β-diketones with one or two pentafluorophenyl groups:[119]

$$C_6F_5COCHCO_2C_2H_5 \xrightarrow[-CO_2,\ -C_2H_5OH]{H_2SO_4(conc.)} C_6F_5COCH_2COR;$$
R = C_6H_5, C_6F_5 (78%), $CH_2C_6F_5$ (77%).

However, when the acetyl group is present in the α-position, a substituted flavone is formed, while in the presence of the trifluoroacyl substituent pentafluorobenzoylacetic acid is obtained.[119] The formation of the flavone can be explained by the cyclisation of the initial β-FKE owing to the intramolecular substitution of the *ortho*-fluorine atom in the pentafluorobenzene ring and the formation of pentafluorobenzoylacetic acid can be accounted for by the fact that in this case the α-ethoxycarbonyl-β-diketone undergoes acid and not keton cleavage:



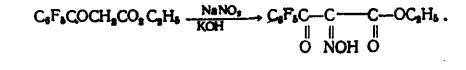
α,α-Difluoro-substituted *p*-fluorobenzoylacetic ester reacts with a mixture of hydrochloric acid and acetic acid to form the corresponding substituted benzophenone:[34]



Thus the majority of β-FKE are converted into ketones on interaction with acids. The first stage of this reaction is the acid hydrolysis of the ester group to the β-ketoacid, which is then decarboxylated to the ketone.

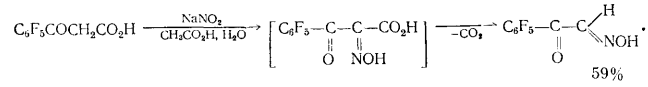
(b) Nitrosation and Diazotisation

These reactions are known only for β-FKE with the pentafluorophenyl group.[82,120] Treatment of PFBAE with sodium nitrite is accompanied by the formation of pentafluoroisonitrosobenzoylacetic ester:[82,120]



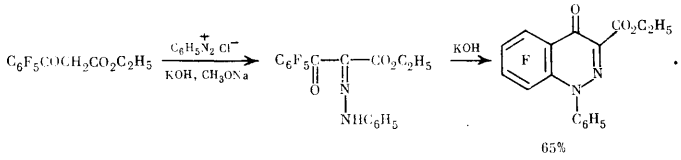
In contrast to this, pentafluorobenzoylacetic acid reacts with sodium nitrite in an acid medium to form the oxime of pentafluorophenylglyoxal, which is in all probability the

product of the decomposition of the intermediate pentafluoroisonitrosobenzoylacetic acid:[120]



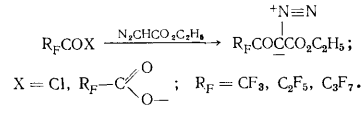
59%

The reaction of PFBAE with benzenediazonium chloride in an alkaline medium gives rise to a cinnolinone derivative:[82]

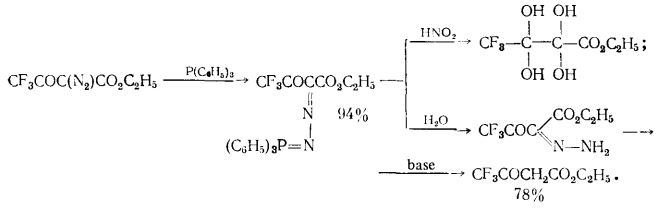


65%

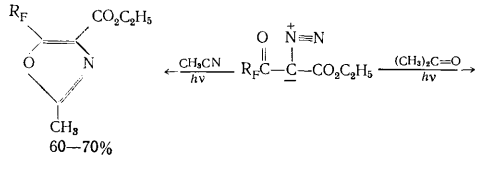
Here we should mention the α-diazo-derivatives of β-FKE, although they are not products of the reactions of β-FKE and are formed as a rule from diazoacetic ester and the chlorides or anhydrides of carboxylic fluoroacids:[64,121,122]



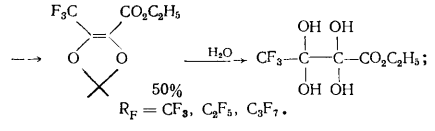
Numerous β-FKE can be obtained from these compounds.[43,64,121–125] α-Diazotrifluoroacetoacetic ester reacts with triphenylphosphine to form a product whose treatment with water gives rise to a compound with the structure of a hydrazone; the hydrolysis of the latter in a basic medium produces TFAAE.[121] However, when the product is treated with nitrous acid in tetrahydrofuran and not with water, it is possible to obtain the dihydrate of the ethyl ester of 4,4,4-trifluoro-2,3-dioxobutyric acid:[64]



As a result of the formation of trifluoroacetoxycarbonylcarbene on irradiation of α-diazotrifluoroacetoacetic ester and its homologue with ultraviolet light, it is possible to obtain from these substances heterocyclic compounds as a consequence of [2+3]-cycloaddition.[43,122–125] Thus the reaction with acetonitrile on irradiation affords oxazoles,[43,122,124,125] while the reaction with acetone produces a dioxolen.[123] The latter is hydrolysed by atmospheric moisture to the dihydrate of ethyl 4,4,4-trifluoro-2,3-dioxobutyrate:[123]



60—70%

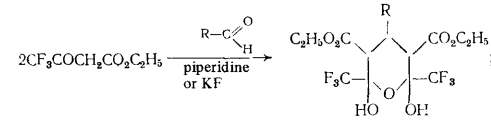


50%

$R_F = CF_3$, C_2F_5, C_3F_7.

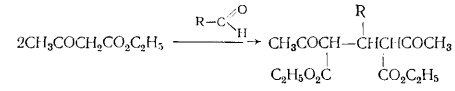
(c) Interaction with Aldehydes

TFAAE condenses with aldehydes, which involves the tetrahydropyran ring closure and the formation of 4-R-3,5-diethoxycarbonyl-2,6-dihydroxy-2,6-bis(trifluoroethyl)-tetrahydropyran:[126]

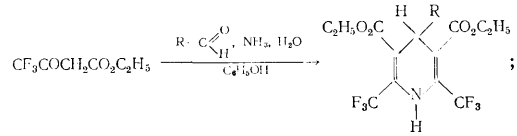


R = H (53%), CH_3 (55%), C_2H_5 (62%), C_6H_5 (19%), *p*-$CH_3C_6H_4$ (38%), *p*-FC_6H_4 (30%).

AAE reacts with aldehydes to form acyclic condensation products:[10]



In the Hantzsch reaction TFAAE apparently behaves in the same way as AAE,[10] forming 4-R-3,5-diethoxycarbonyl-2,6-bis(trifluoromethyl)-1,4-dihydropyridines:[127,128]



R = H, CH_3, C_2H_5, n-C_3H_7, C_6H_5, C_6H_4N, $O_2NC_6H_4$.

However, it has been stated that, in contrast to AAE, TFAAE involved in the Hantzsch synthesis gives rise to 2,6-dihydroxy-4-(*p*-nitrophenyl)-2,6-bis(trifluoromethyl)-piperidine-3,5-dicarboxylate, which does not split off water on treatment with sulphuric acid, acetic anhydride, titanium chloride, or dicyclohexylcarbodiimide.[129]

(d) Reactions of β-FKE Enolates

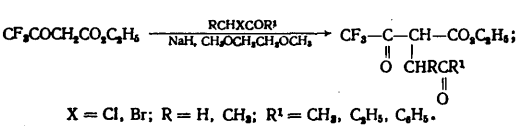
The β-KE enolate anions exhibit a dual reactivity, which depends significantly on the nature of the cation, the type of the ion pair, and the character of the solvent. These questions have been examined in detail in a review.[130] Here we shall deal only with data concerning β-FKE.

In order to account for the reactivity of the enolate anions derived from β-dicarbonyl compounds in alkylation reactions, a calculation based on the distribution of electron density in β-KE has been carried out by the LCAO-MO SCF method in the CNDO/2 approximation for the stable (*W*) and unstable (*U*) conformations of the enolate ions derived from malonic ester, AAE, TFAAE, and the chelate contact ion pair of the lithium enolate derived from AAE in the *U* conformation.[131] It has been shown that the highest negative charge is concentrated at the oxygen atom of the carbonyl group in all the enolate ions (in the *W* and *U* conformations). The introduction of the trifluoromethyl group (TFAAE) reduces the charge of the carbonyl oxygen and on the α-carbon atom of the enolate ion. A decrease of the basicity of the anion and of the alkylation rate constant corresponds to this effect.[132] It has also been established that the reactivity of the enolate ions and ion pairs derived from certain alkali metal enolates in alkylation reactions is controlled by the distribution of electron density in the highest occupied MO of the anion or its ion pair.[131] However, the negative charge on the carbonyl oxygen atom remains higher than on the α-carbon atom in all the structures; consequently the overall distribution of charges is

not the factor determining the result of the reaction, since the α-carbon atom is usually the preferred centre of attack. The distribution of electron density in the highest occupied MO of the anion or the ion pair derived from malonic and acetoacetic esters is consistent with the results of the alkylation, but the reactivity of the TFAAE anion is not controlled by the distribution of electron density in the highest occupied MO, since the alkylation reactions are in this case directed to the carbonyl oxygen atom. The presence of the trifluoromethyl group next to the carbonyl oxyen atom causes an additional increase of the negative electrostatic potential in the region of this atom compared with the region adjoining the α-carbon atom. The role of the electrostatic factor increases and the assumption that the alkylation reaction is controlled solely by electron density in the frontier MO becomes inadequate.[131]

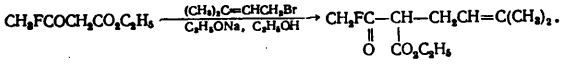
In the light of the above data, the experimental results obtained in the study of the kinetics and of the composition of the products of the alkylation of the sodium, potassium, and caesium enolates derived from AAE and its γ,γ-dimethyl and γ,γ,γ-trimethyl derivatives as well as TFAAE by ethyl tosylate in a highly aprotic solvent (hexamethylphosphoramide) become understandable.[132-134] The formation of only the *O*-isomer has been observed in the alkylation of the caesium enolate of TFAAE, while in the case of AAE and its fluorine-free derivatives, the products of both *O*- and *C*-alkylation are obtained. The effective rate constant for the ethylation of the caesium enolates decreases under these conditions in the sequence AAE > $(CH_3)_2CHCOCH_2CO_2C_2H_5$ > $(CH_3)_2CCOCH_2CO_2C_2H_5$ > TFAAE, while the acidity of β-KE diminishes in the opposite sequence. It has also been shown that, under the given conditions, the reacting species is only the enolate anion.[132,133]

The alkylation of TFAAE by α-chloro- or α-bromo-ketones in the presence of sodium hydride in dimethoxyethane gives rise to the *C*-alkylation products:[135-138]

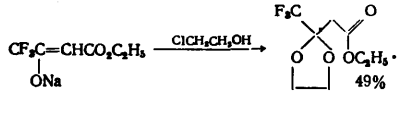


X = Cl, Br; R = H, CH_3; R^1 = CH_3, C_2H_5, C_6H_5.

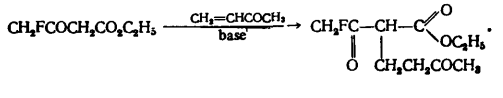
γ-Monofluoroacetoacetic ester is also alkylated at the carbon atom:[139]



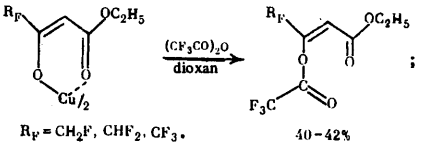
Interesting results have been obtained in the reaction of sodium enolate of TFAAE with ethylenechlorohydrin. This entails the formation of 2-ethoxycarbonylmethyl-2-trifluoromethyl-1,3-dioxolan,[140] while the sodium enolate of AAE reacts with ethylenechlorohydrin to form the *C*-alkylation product:[141]



In the Michael reaction with methyl vinyl ketone, γ-monofluoroacetoacetic and α,γ-difluoroacetoacetic esters give rise to the *C*-alkylation products:[142]

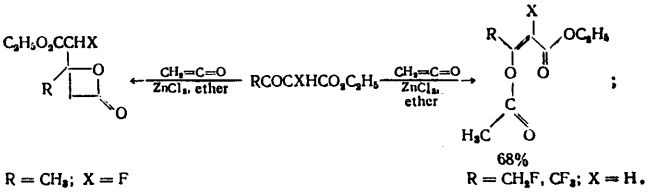


The copper chelates of β-FKE yield unstable *O*-acylation products on acylation with the anhydride of trifluoroacetic acid:[51]



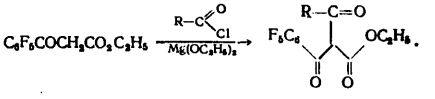
R_F = CH_2F, CHF_2, CF_3. 40-42%

It is of interest that γ-monofluoroacetoacetic ester and TFAAE react with keten to form *O*-acylation products, while α-monofluoroacetoacetic ester gives rise to the product of cycloaddition involving the keto-group under the same conditions, which the authors explain by the lower degree of enolisation of the α-fluoroester:[56]



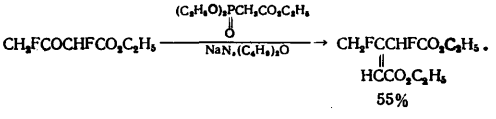
R = CH_3; X = F 68% R = CH_2F, CF_3; X = H.

The acylation of PFBAE by acid chlorides in the presence of magnesium ethoxide makes it possible to obtain *C*-acylation products, which is of interest for the synthesis of β-diketones with pentafluorophenyl groups:[119,143,144]



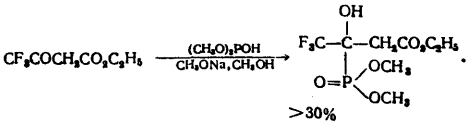
(a) Interaction with Phosphorus-containing Reagents

α,γ-Difluoroacetoacetic ester reacts with diethyl phosphonoacetate to form diethyl 4-fluoro-3-fluoromethylprop-1-ene-1,3-dicarboxylate:[17]



55%

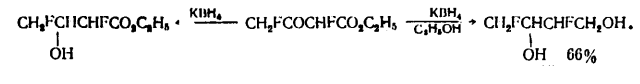
The reaction of TFAAE with dimethyl phosphite affords dimethyl 2-ethoxycarbonyl-1-hydroxy-1-trifluoromethylethylphosphonate:[56]



>30%

3. Oxidation-Reduction Reactions

The reduction of α,γ-difluoroacetoacetic ester with potassium tetrahydroborate involves only the carbonyl group or the ester and carbonyl groups depending on the reactant ratio:[13]



66%

Trifluoroacetoacetic ester reacts with sodium tetrahydroborate to give the product of the reaction of the carbonyl group while in the reaction with lithium tetrahydroaluminate both the carbonyl and ester groups are reduced:[145]

$$CF_3CHCH_2CO_2C_2H_5 \xleftarrow[\text{ether}]{NaBH_4} CF_3COCH_2CO_2C_2H_5 \xrightarrow[\text{ether}]{LiAlH_4} CF_3CHCH_2CH_2OH.$$
$$\quad OH \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad OH \quad 83\%$$

The reduction with hydrogen in the presence of Raney nickel, studied in relation to β-FKE with the heptafluoropropyl group, involves only the carbonyl group:[146–148]

$$C_3F_7COCH_2CO_2CO_3 \xrightarrow[Ni]{H_2} C_3F_7\overset{OH}{\overset{|}{C}}HCH_2CO_2CH_3.$$

The same reaction pathway obtains also in the biochemical reduction of β-FKE by bakers' yeast:[149]

$$R_FCOCH_2CO_2C_2H_5 \xrightarrow{\text{baker's yeast}} R_F\overset{OH}{\overset{|}{C}}HCH_2CO_2C_2H_5;$$

$R_F = CF_3$ (92%), C_7F_{15} (87%).

Pentafluorobenzoylacetic ester is oxidised by selenium dioxide to ethyl pentafluorobenzoylglyoxylate:[82]

$$C_6F_5COCH_2CO_2C_2H_5 \xrightarrow[\text{toluene}]{SeO_2} C_6F_5C{-}\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{C}}OC_2H_5.$$
(38%)

V. APPLICATIONS

In most cases β-FKE are used as the starting materials for the synthesis of compounds with various useful properties. One of the aspects of the application of β-FKE is based on their capacity for complex formation with metal ions.[136,143,150–157] The β-FKE substituted in the α-position have been patented as extractants for the lanthanide and transuranic elements.[136,143] The chelate complexes of TFAAE with manganese, copper, cobalt, iron, and nickel have been recommended as antioxidants for various liquids and greases.[154] The copper and manganese chelates of β-FKE are effective catalysts in the formation of urethanes from isocyanates and alcohols.[155–157] β-Ketoesters with the heptafluoropropyl group are used as the starting materials for the synthesis of latexes used to impregnate fabrics in order to implant to them water-, oil-, and dirt-repelling properties and to reduce their susceptibility to inflammation.[146–148] TFAAE is used to obtain dyes suitable for the dyeing of synthetic fibres.[80]

The wide range of applications of derivatives of β-FKE such as coumarins,[114,116] pyridonaphthyridines,[112] and pyrroloquinolines [111] is based on their ability to fluoresce and to generate laser radiation.

7-Amino-4-trifluoromethylcoumarin and its salts with aminoacids and peptides are used as fluorescent markers for aminoacids and peptides in biological research.[114] Derivatives of 1,8-naphthyridine, 1,2-dihydropyrido[2,3-*b*]-1,8-naphthyridine, and 2*H*-pyrano[2,3-*b*]-1,8-naphthyridine exhibit a stable fluorescence in the range 393–482 nm in ethanol.[112] 1,6,6,7,8-Pentamethyl-2-oxo-4-trifluoromethyl-6,7-dihydro-1*H*, 2*H*, 8*H*-pyrido[3,2-*f*] indole serves as a source of blue laser radiation.[111]

Many derivatives of β-FKE exhibit physiological and pesticidal activities. α-Alkenyl derivatives of monofluoroacetoacetic ester have a hypocholesterolaemic activity.[86]

R-4-R^1-5-trifluoromethylfurans show coccidiostatic and growth accelerating activities.[135,138] Trifluoromethyltolylisoxazoles exhibit vasodilating, anticonvulsant, and muscle relaxing activities.[85] 1-Substituted 5-pyrazolones are diuretics.[81] 5-Trifluoromethylimidazoles behave as inhibitors of histamine activity.[92]

The ethyl ester of 2-acetoamido-4-trifluoromethylthiazolecarboxylic acid exhibits an antiinflammatory activity.[91] 6-(3-R-5-phenylisothiazolyl-4-formamido)penicillanic acids containing the trifluoromethyl group possess an antibacterial activity.[15]

The trifluoromethyl substituent is also present in thiazolino-5-pyrimidinones, which have been patented as analgesics.[98] Nicotinic and picolinic acids obtained from β-FKE exhibit analgesic and antipyretic activities.[105] 3,5-Diethoxycarbonyl-4-R-2,6-bis(trifluoromethyl)-1,4-dihydropyridines show cytotoxic, bacteriostatic, and hypotensive activities.[127,128] Derivatives of 3-trifluoromethylquinoline—analogues of quinine and quinidine—possess an antimalarial activity.[108–110] 5-Trifluoromethyl-2-R-quinolines are antiradiation reagents.[107] Benzothiopyrans containing fluorine exhibit an antimalarial activity.[118]

Fluorine-containing uracils possess herbicidal properties[69–71] and do not damage maize, flax, safflower, alfalfa, strawberries and gladioli.[88] 6-Trifluoromethyluracil has been used to synthesise 2-amino-6-trifluoromethylpurine, which is used as the antagonist of metabolites.[86] 4-Hydroxy-6-trifluoromethylpyrimidine is the starting material for the synthesis of insecticides.[89]

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Thus the introduction of fluorine atoms into the molecules of β-ketoesters is responsible for the appearance of a number of their characteristic features and leads to the alteration of the physicochemical properties, reactivities, and applied properties of these compounds and their derivatives. The existing data concerning their practical application make it possible to use fluorine-containing β-ketoesters and their derivatives in the national economy. At the same time, one should note the almost complete absence of studies of the reaction mechanisms and of the optimisation of the processes described, which undoubtedly holds back the further development of this field of organic chemistry.

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