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Fluorine-containing 2,4-dioxo acids in the synthesis of heterocyclic compounds †

V I Saloutin, Ya V Burgart, O N Chupakhin

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Abstract. The review surveys the data on the synthesis, tautomerism, electronic structures and chemical transformations of 4-polyfluoroalkyl- and 4-pentafluorophenyl-2,4-dioxo acids and their derivatives. The reactions yielding fluorinated heterocyclic compounds and their further conversions are considered. The bibliography includes 86 references.

I. Introduction

Fluorine-containing α-oxo esters,[15] α-diketones,[1] β-oxo esters[4–6] and β-diketones[7–9] are used in studies of tautomerism, carbonotropy, stereoisomerism and reactivity of dicarbonyl compounds (DCC). Fluorinated DCC often serve as building blocks for the preparation of various heterocyclic compounds.[1,6,7,10] Particularly impressive progress has been achieved in the design of drugs of the fluoroquinolone series with unique antibacterial activity, which are analogues of nalidixic acid.[11–16] These antibiotics contain a fluorobenzoylacetic acid structural fragment; for a number of these compounds, fluorinated β-DCC serve as starting compounds.[11–16]

The use of fluorinated DCC is not confined to their application as biologically active compounds. Certain fluorine-containing DCC and their derivatives can be used as catalysts of various reactions, surfactants, shift reagents, analytical reagents, including those used for the determination and separation of a number of metals by gas chromatography, extractive agents for various metals, dyes and oil and composite additives.[1,6,7,17] Therefore, further progress in the chemistry and practical application of fluorinated dicarbonyl compounds seems to be very promising.

Polyfluorinated 2,4-dioxo acids and their derivatives containing simultaneously α- and β-dicarbonyl fragments are convenient starting compounds for the preparation of fluorinated heterocycles. Therefore, the development of procedures for the synthesis of these compounds and investigation of their reactivity are topical problems. Although the chemistry of nonfluorinated 2,4-dioxo acids has been well studied (see, for example, Refs 18 – 21), this class of fluorine-containing compounds was not known until our first publications.[22–25]

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II. Synthesis and structures of esters of polyfluorinated 2,4-dioxo acids

Nonfluorinated 2,4-dioxo acids and their esters had been first prepared at the end of the 19th century. Esters of 4-polyfluoroalkyl- (**1a – d**)[22] and 4-pentafluorophenyl-2,4-dioxo acids (**1e**,**f**)[23–25] were first synthesised by the Claisen condensation starting from fluoroalkyl- and pentafluorophenyl ketones, respectively, and dialkyl oxalates. Lithium hydride was used as a condensing reagent. The target compounds were isolated *via* copper chelates **2a – f** (Scheme 1).

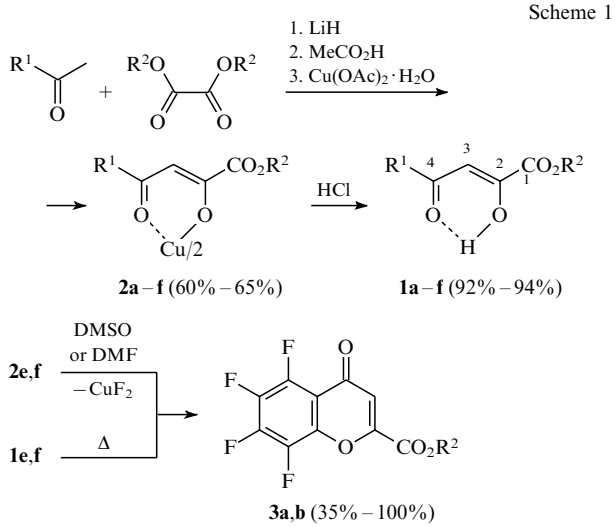
Copper chelates of esters **2a – d** are quite stable compounds.[22] However, chelates of pentafluorobenzoylpyruvates **2e**,**f** undergo cyclisation in DMSO or DMF to 2-alkoxycarbonyl-5,6,7,8-tetrafluorochromones **3a**,**b**.[23–25] Chromones **3a**,**b** are also formed upon heating of pentafluorobenzoylpyruvates **1e**,**f** above 25 °C.[23–25] Cyclisation occurs through intramolecular replacement of the *ortho*-fluorine atom of the pentafluorophenyl group.

In the design of syntheses on the basis of polyfluoroacyl(pentafluorobenzoyl)pyruvates, it is necessary to have an idea of keto – enol tautomerism, charge distribution on atoms and frontier-orbital electron density in these compounds.

As for enolisation, the tautomerism of nonfluorinated analogues of dioxo esters **1** has been reported in a series of publications. Thus ^{1}H NMR spectral studies demonstrated[28] that aroylpyruvates exist mainly as enols. It was also concluded[28] that the intramolecular hydrogen bond in the β-dicarbonyl fragment of the molecule is strengthened as the electron-accepting ability of substituents increases. On the basis of the ^{1}H and ^{13}C NMR spectral data, it was concluded that there was no tautomerism between two possible enol forms.[28,29] The proton is delocalised between two potential wells due to tunnelling. This agrees with the results of quantum-chemical SCF MO LCAO calculations by the CNDO/2 method.[30] In going from one substituent to another, ^{13}C chemical shifts are changed due to

† Dedicated to the memory of our teacher Academician I Ya Postovskii on the occasion of his 100th birthday.

Scheme 1



1, **2**: $R^1 = CF_3$, R^2 = Me (**a**); $R^1 = CF_3$, R^2 = Et (**b**); $R^1 = C_4F_9$, R^2 = Et (**c**); $R^1 = HCF_2$, R^2 = Et (**d**); $R^1 = C_6F_5$: R^2 = Et (**e**), Me (**f**);
3: R^2 = Et (**a**), Me (**b**).

the electron density redistribution in the dicarbonyl fragment.[31] It was attempted to determine the position of the proton in a series of β-DCC (including the acetylpyruvate molecule) by comparing the ^{13}C chemical shifts for β-DCC and their BF_2 chelates.[32, 33] Presumably,[32, 33] insignificant changes in the chemical shifts on going from β-DCC to their BF_2 chelates indicate that the structures are nearly quasi-symmetrical and that the proton is delocalised between the two oxygen atoms to approximately the same extent.

It was established by X-ray diffraction analysis that ethyl acetopyruvate is enolised at the C(2) atom.[34] A comparative analysis of the ^{13}C NMR spectra of ethyl acetylpyruvate and ethyl trifluoroacetylpyruvate (**1b**) demonstrated that compound **1b** is also enolised at the C(2) atom.[35] It was found that polyfluoroacyl(pentafluorobenzoyl)pyruvates **1** are completely enolised.[22, 23]

It is remarkable that, unlike fluoroacyl(aroyl)pyruvates under consideration, fluorinated β-diketones and β-oxo esters are only partially enolised.[6, 7] The degree of enolisation reaches 100% only in fluorine-rich β-DCC. In this case, enolisation occurs at the carbonyl group bound to the fluorinated substituent.[6, 7]

With the aim of discussing the reactivity of fluoroacyl(aroyl)pyruvates **1**, quantum-chemical SCF MO LCAO calculations of charges and Fukui indices were performed for (fluoro)acylpyruvates[35] by the CNDO/2 method and for pentafluorobenzoylpyruvic acid and methyl pentafluorobenzoylpyruvate‡ by the AM-1 method[37] using the MNDO-89 program.[36] The calculations demonstrated that the largest positive charge in fluoroacyl(aroyl)pyruvates is localised on the C(1) atom. The Fukui indices for the lowest unoccupied molecular orbitals (LUMO) in fluoroacylpyruvates and methyl pentafluorobenzoylpyruvate have the maximum values for the C(2) and C(4) atoms, respectively. In pentafluorobenzoylpyruvic acid, the values of the Fukui indices for LUMO of the C(2) and C(4) atoms have close values. Therefore, under kinetically controlled conditions the attack of a nucleophilic reagent occurs preferentially on the C(1) atom according to the charge control. According to the orbital control, the reactions of fluoroacylpyruvates should occur at the C(2) atom, while the reactions of methyl pentafluorobenzoylpyruvate should occur at the C(4) atom. In the case of pentafluorobenzoylpyruvic acid, the orbital-controlled process is approximately equally probable for the C(2) and C(4) reaction centres (Table 1).

‡ V I Saloutin, Ya V Burgart, O N Chupakhin, unpublished data.

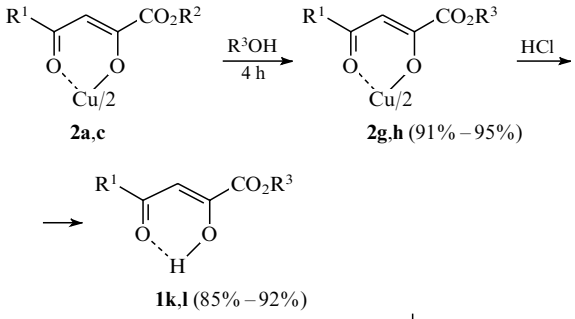
Table 1. Charges and Fukui indices for the electrophilic centres in acyl(aroyl)pyruvates.

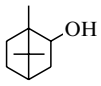
Compound	R^1	R^2	Charges (Fukui indices)			
			H	C(1)	C(2)	C(4)
1g	Me	Me	+0.2586	+0.3609 (0.1880)	+0.2076 (0.5250)	+0.2996 (0.3613)
1h	HCF_2	Me	+0.2561	+0.3624 (0.1459)	+0.2123 (0.5170)	+0.2429 (0.4306)
1a	CF_3	Me	+0.2549	+0.3628 (0.1289)	+0.2128 (0.5134)	+0.2216 (0.4540)
1i	C_4F_9	Me	+0.2558	+0.3630 (0.1240)	+0.2128 (0.5661)	+0.2502 (0.4624)
1f	C_6F_5	Me	+0.2651	+0.3302 (0.0271)	+0.1456 (0.1630)	+0.3252 (0.1740)
1j	C_6F_5	H	+0.2665	+0.3378 (0.0365)	+0.1439 (0.1862)	+0.3245 (0.1858)

III. Transesterification reactions

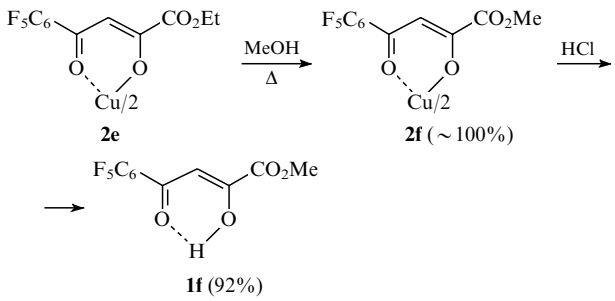
Esters are prone to transesterification. This property substantially enhances the synthetic potential of fluoroacyl(aroyl)pyruvates when using them as the starting compounds for constructing various heterocyclic systems.

Copper chelates of ethyl(methyl) acylpyruvates **2a**,**c** can be readily transesterified with a higher alcohol (borneol) even in the absence of catalysts.[38]



$R^1 = CF_3$, R^3 = Born (**2g**, **1k**), where Born = 
$R^1 = C_4F_9$, R^3 = Born (**2h**, **1l**).

Boiling the copper chelate of ethyl pentafluorobenzoylpyruvate **2e** in methanol also results in transesterification to form the chelate of methyl pentafluorobenzoylpyruvate **2f**.[39] Thereafter methyl pentafluorobenzoylpyruvate (**1f**) can be readily prepared from the copper chelate **2f**.

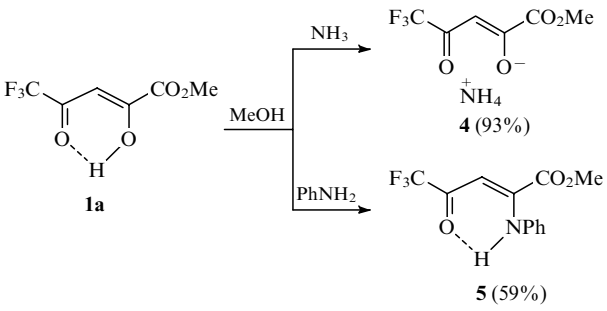


It should be noted that this reaction is common to copper chelates of β-oxo esters because the chelates of esters of both aceto- and trifluoroacetoacetic acids enter into this reaction.[38] However, the time required to achieve high degrees of conversion of the latter compounds is an order of magnitude larger than in the

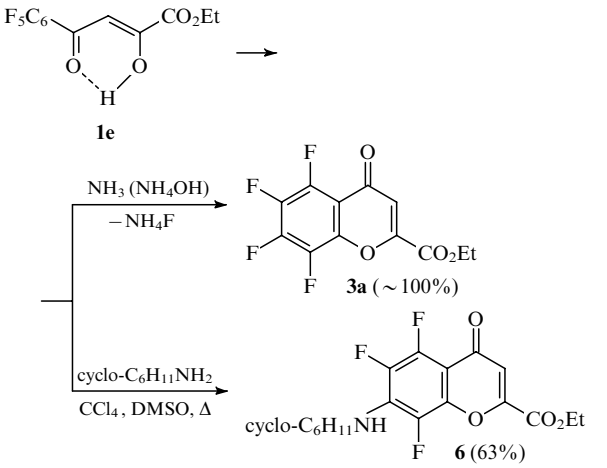
case of copper chelates of acylpyruvates **2a**,**c**. Apparently, this is associated with the involvement of the ester group of β-oxo ester in intrachelate conjugation. Free ligands can also undergo transesterification; however, the selectivity of the reaction decreases sharply and substantial resinification of the reaction mixture occurs. Apparently, copper(II) ions favour the reaction by orienting an alcohol molecule through coordination and suppress side processes.

IV. Reactions with amines

The reaction of methyl acetopyruvate with ammonia affords an enamine at the carbonyl C(2) atom.[40] The reaction of methyl trifluoroacetopyruvate (**1a**) with ammonia yields [methyl (trifluoroacetopyruvato)]ammonium (**4**), which remains unchanged on boiling in toluene.[41,42] However, compound **1a** reacts with a softer base (aniline) at the C(2) centre to form an enamine, *viz*., methyl 2-anilino-5,5,5-trifluoro-4-oxopent-2-enoate (**5**),[41,42] according to orbital control over the reaction.



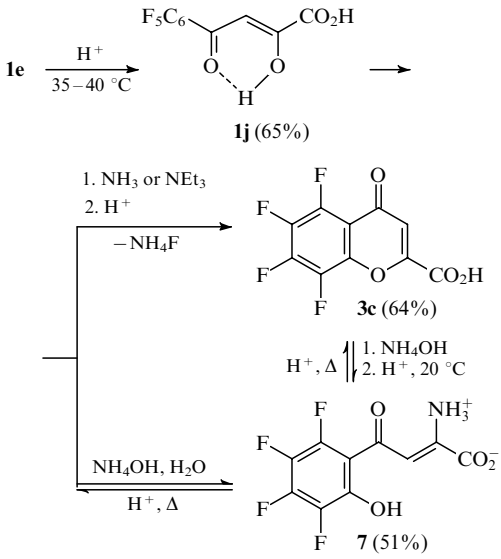
Treatment of pentafluorobenzoylpyruvate **1a** with gaseous or aqueous ammonia affords chromone **3a**. Apparently, the corresponding ammonium salt is initially formed, which is followed by intramolecular substitution of the aromatic *ortho*-fluorine atom.[42,43]



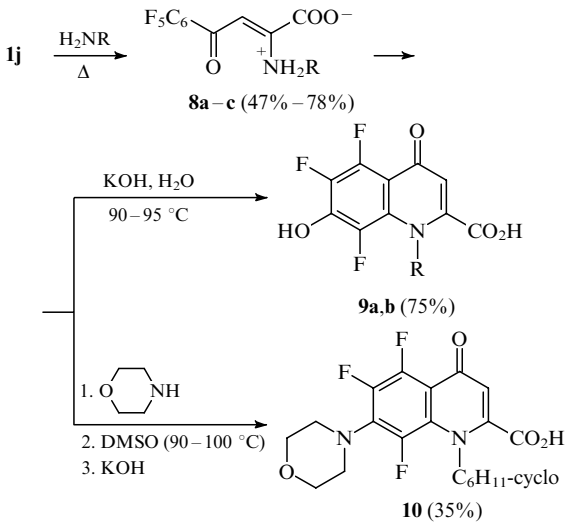
The reaction of pentafluorobenzoylpyruvate **1e** with cyclohexylamine proceeds analogously. However, in this case cyclisation is accompanied by the orbital-controlled replacement of the fluorine atom at position **7** of chromone to form 7-cyclohexylamino-2-ethoxycarbonyl-5,6,8-trifluorochromone (**6**).[42,43]

Thus, in the reactions of compound **1e** with ammonia or cyclohexylamine, intramolecular cyclisation dominates over addition of the nucleophile at the C(2) centre regardless of the solvent.

Pentafluorobenzoylpyruvic acid (**1j**) prepared by hydrolysis of ester **1e** reacts with anhydrous ammonia in dioxane or with tertiary amines (triethylamine) to form 2-carboxy-5,6,7,8-tetrafluorochromone (**3c**).[41,42] The reaction of acid **1j** with ammonium hydroxide affords 2-amino-3-(3,4,5,6-tetrafluoro-2-hydroxybenzoyl)acrylic acid (**7**), which exists as a zwitterion.[41,42] When heated in an acidic medium, the amino acid **7** is hydrolysed to the acid **1j** or undergoes cyclisation to form the chromone **3c**. When treated with aqueous ammonia followed by acidification, the latter, in turn, gives the amino acid **7**.[41,42] Consequently, in these cases intramolecular cyclisation also prevails.



The reactions of the acid **1j** with primary amines (aniline, isopropylamine or cyclohexylamine) yield addition–elimination products at the C(2) centre, *viz*., 2-alkylamino(anilino)-2-pentafluorobenzoylacrylic acids **8a**–**c**, which indicates that this reaction is an orbital-controlled process. In an alkaline medium, compounds **8a**,**b** undergo cyclisation and nucleophilic replacement of the fluorine atom at the C(7) atom by the hydroxy group, which is typical of these fluorine-containing systems, to form 5,6,8-trifluoro-7-hydroxy-1-R-4-quinolone-2-carboxylic acids **9a**,**b**.[41,42] The fact that it was the fluorine atom at position 7 of quinolone that has been replaced was established by X-ray diffraction analysis of a complex of compound **9a** with DMSO.[44,45] Cyclisation of compound **8a** in the presence of morpholine affords 1-cyclohexyl-5,6,8-trifluoro-7-morpholino-4-quinolone-2-carboxylic acid (**10**).[41,42]



R = cyclo-C_6H_{11} (**8a**, **9a**), Pr^i (**8b**, **9b**), Ph (**8c**).

V. Reactions with dinucleophiles

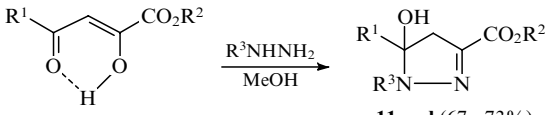
Various heterocyclic systems can be constructed by reactions of 2,4-dioxo esters with bifunctional nucleophiles. The reactions of acyl(aroyl)pyruvates can involve both the α-dicarbonyl and β-dicarbonyl fragments depending on the nature of the nucleophile.

1. Reactions with hydrazines and hydroxylamine

The reactions of acetyl(aroyl)pyruvates with hydrazines give 3-alkoxycarbonyl-5-methyl(aryl)pyrazoles.[26,27,46–48] The reactions of ethyl acetylpyruvates with hydroxylamine yield 3-ethoxycarbonyl-5-methylisoxazole, isomeric 5-ethoxycarbonyl-3-methylisoxazole or a mixture of isoxazoles depending on conditions.[26,49] Ethyl benzoylpyruvate reacts with hydroxylamine to afford 3-ethoxycarbonyl-5-phenylisoxazole, the reaction proceeds *via* intermediate α-oxime.[27,50]

Ethyl(methyl) fluoroacylpyruvates **1a**,**c**,**d** react with hydrazine hydrate and phenylhydrazine at the β-dicarbonyl fragment like hydrocarbon analogues and fluorine-containing β-oxo esters[6] and β-diketones.[7] However, unlike the latter compounds, the reactions with **1a**,**c**,**d** give stable 3-alkoxycarbonyl-5-fluoroalkyl-5-hydroxy-Δ^2-pyrazolines **11a**–**d** (Scheme 2). The position of the hydroxy group in the pyrazoline ring was established by ^{13}C NMR spectral study of compound **11b**.[35]

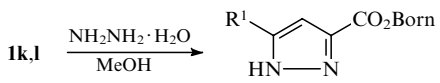
Scheme 2



1a,**c**,**d** **11a**–**d** (67–73%)

11: $R^1 = CF_3$, R^2 = Me: R^3 = H (**a**), Ph (**b**);
$R^1 = C_4F_9$, R^2 = Et, R^3 = H (**c**); $R^1 = HCF_2$, R^2 = Et, R^3 = H (**d**).

Unlike methyl(ethyl) fluoroacylpyruvates **1a**,**c**,**d**, the reactions of bornyl esters **1k**,**l** with hydrazine hydrate give 3-bornyloxycarbonyl-5-fluoroalkylpyrazoles **12a**,**b**.[38]

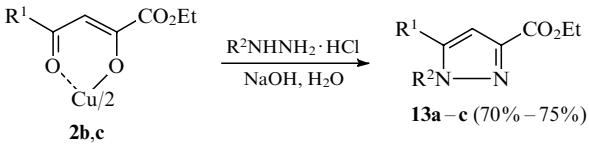


12a,**b** (61%–68%)

12: $R^1 = CF_3$ (**a**), C_4F_9 (**b**).

The reactions of chelates **2b**,**c** with hydrazine and phenylhydrazine hydrochlorides in water or methanol afford pyrazoles **13a**–**c** rather than hydroxypyrazolines (Scheme 3).[51]

Scheme 3



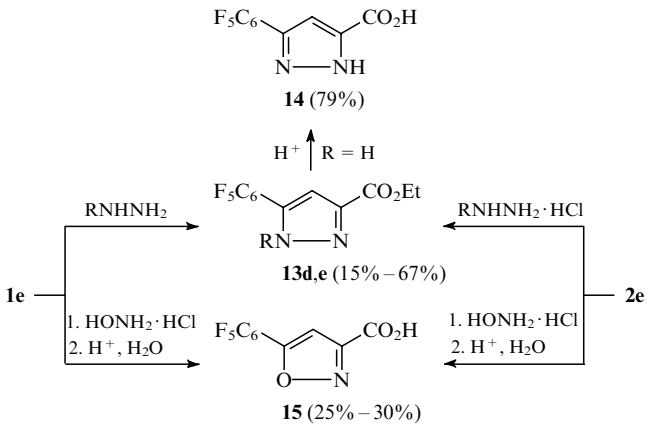
2b,**c** **13a**–**c** (70%–75%)

$R^1 = C_4F_9$, R^2 = H (**2c**, **13a**); $R^1 = CF_3$, R^2 = H (**2b**, **13b**), Ph (**13c**).

The reactions of copper chelates of trifluoroacetylacetone and ethyl trifluoroacetylacetate with hydrazine hydrochloride in DMF, which were studied for comparison, yielded 3-methyl-5-trifluoromethylpyrazole and 5-hydroxy-3-trifluoromethylpyrazole, respectively.[52]

Pentafluorobenzoylpyruvate **1e** and its copper chelate **2e** react with hydrazine hydrate to give 3-ethoxycarbonyl-5-pentafluorophenylpyrazole **13d**, which can be readily hydrolysed in an acidic medium to 3(5)-pentafluorophenylpyrazole-5(3)-carboxylic acid (**14**).[51]

Pentafluorobenzoylpyruvate **1e** reacts with phenylhydrazine and copper chelate **2e** reacts with phenylhydrazine hydrochloride to form pyrazole **13e**.[53] The reactions of hydroxylamine hydrochloride with compounds **1e** and **2e** afford 5-pentafluorophenylisoxazole-3-carboxylic acid (**15**).[53]



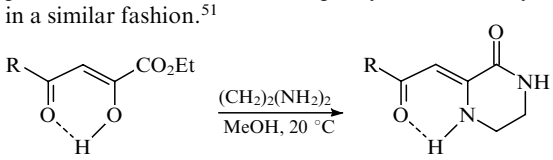
13: R = H (**d**), Ph (**e**).

The formation of pyrazole and isoxazole derivatives in the reactions with hydrazines and hydroxylamine is typical also of both pentafluorobenzoylacetic ester[54] and derivatives of non-fluorinated aroylpyruvic acids.[55]

2. Reactions of 2,4-dioxo esters with aliphatic and aromatic 1,2-dinucleophiles

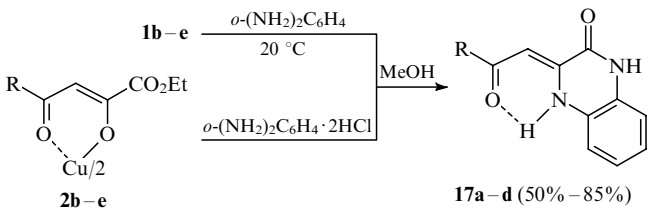
Acyl(aroyl)pyruvates react with 1,2-dinucleophiles at the α-oxo ester fragment. The reactions with ethylenediamine, *o*-phenylenediamine or *o*-aminophenol as dinucleophiles give piperazinone derivatives,[56] substituted quinoxalinones[57–63] or benzoxazinones, respectively.[63–65]

The reactions of polyfluoroacylpyruvates **1b**–**d** with ethylenediamine and *o*-phenylenediamine give 3-(2-oxofluoroalkylidene)piperazin-2-ones **16a**–**c** and 3-(2-oxofluoroalkylidene)-1,2,3,4-tetrahydroquinoxalin-2-ones **17a**–**c**, respectively.[35] Copper chelates **2b**–**d** react with *o*-phenylenediamine hydrochloride in a similar fashion.[51]



1b–**e** **16a**–**d** (18%–67%)

16: R = CF_3 (**a**), C_4F_9 (**b**), HCF_2 (**c**), C_6F_5 (**d**).



2b–**e** **17a**–**d** (50%–85%)

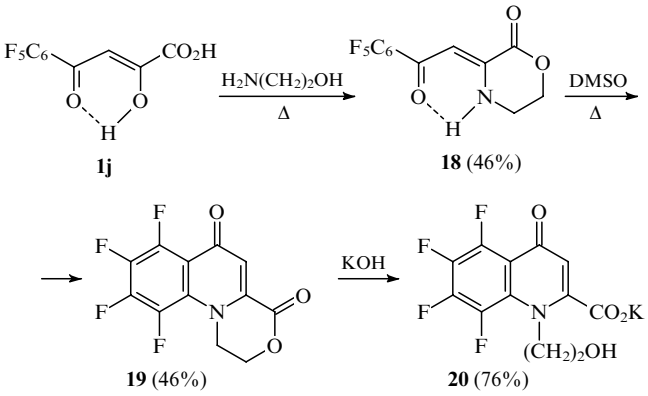
17: R = CF_3 (**a**), C_4F_9 (**b**), HCF_2 (**c**), C_6F_5 (**d**).

1e $\xrightarrow{\Delta}$ **16e**

R = *o*-HOC_6F_4 (**16e**).

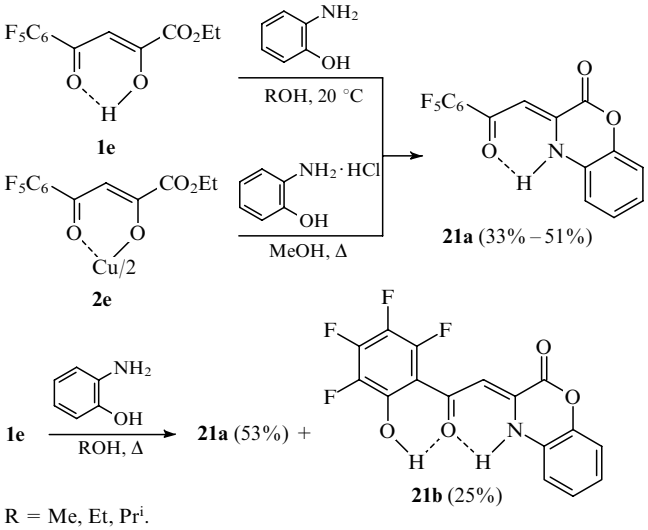
Under mild conditions, pentafluorobenzoylpyruvate **1e** reacts with ethylenediamine to form piperazinone **16d**. However, heating of the reaction mixture affords piperazinone **16e** containing the tetrafluoro-2-hydroxyphenyl substituent.[53] The mechanism of formation of the latter is discussed below. The reactions of compound **1e** and its copper chelate **2e** with *o*-phenylenediamine or its hydrochloride yield quinoxolone **17d**.[51,53]

The reaction of pentafluorobenzoylpyruvic acid (**1j**) with ethanolamine yields 3-pentafluorobenzoylmethylidenemorpholin-2-one (**18**).[41,42] When refluxed in DMSO, the morpholinone **18** undergoes cyclisation to form 7,8,9,10-tetrafluoro-4-oxo-1,2,4,6-tetrahydro[1,4]oxazino[4,3-*a*]-4-quinolone (**19**). Treatment of compound **19** with an aqueous KOH solution affords potassium 5,6,7,8-tetrafluoro-1-(2-hydroxyethyl)-4-quinolone-2-carboxylate (**20**).[41,42] This procedure is one of a few methods for the synthesis of fluorine-containing 2-carboxyquinolones.



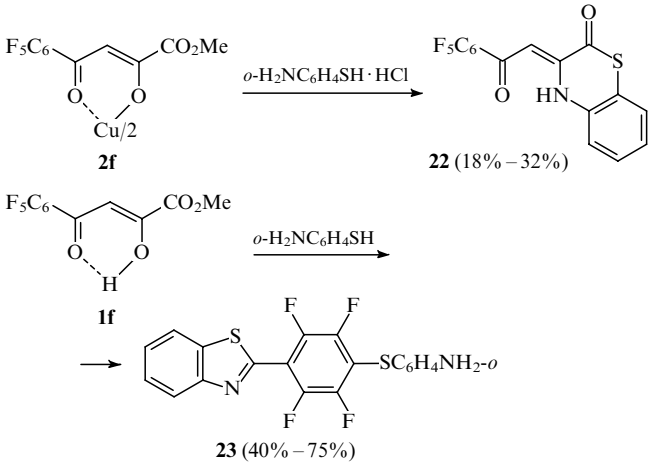
1j **18** (46%) **19** (46%) **20** (76%)

Pentafluorobenzoylpyruvate **1e** and its chelate **2e** react with *o*-aminophenol and its hydrochloride under mild conditions to form 3-pentafluorobenzoylmethylidene-2*H*-1,4-benzooxazin-2-one (**21a**). Under more severe conditions, this reaction, like the reaction of compound **1e** with ethylenediamine,[53] yields 3-(3,4,5,6-tetrafluoro-2-hydroxybenzoylmethylidene)-2*H*-benzooxazin-2-one (**21b**) containing the tetrafluoro-2-hydroxyphenyl substituent as a minor product in addition to compound **21a**.[53,66] Apparently, the product **21b** is formed either from 2-ethoxycarbonyl- (**3a**) or from 2-carboxy-5,6,7,8-tetrafluorochromone (**3c**), which are generated under the reaction conditions. This suggestion was confirmed by the synthesis of compound **21b** directly from the chromones **3a** or **3c**.[53,66]



R = Me, Et, Pr^i.

The reactions of pentafluorobenzoylpyruvate **1f** and its copper chelate **2f** with *o*-aminobenzenethiol were studied. It was demonstrated that the chelate **2f** reacted with 2-aminobenzenethiol hydrochloride at the α-oxo-ester fragment to form 3-pentafluorobenzoylmethylidene-2*H*-1,4-benzothiazin-2-one (**22**). In the reaction with *o*-aminobenzenethiol under mild conditions, the ester **1f**, unlike the chelate **2f**, undergoes acid scission accompanied by nucleophilic replacement of the fluorine atom in the pentafluorobenzoyl fragment of the molecule by the 2-aminophenylthio group to form 2-[4-(2-aminophenylthio)-2,3,5,6-tetrafluorophenyl]ben-zothiazole (**23**).[39]



Thus, polyfluoroacylpyruvates react with hydrazines at the β-dicarbonyl fragment, while their reactions with ethylenediamine and *o*-phenylenediamine proceed at the α-oxo-ester fragment. Apparently, the first stage of the reactions with HN-dinucleophiles, as in the case of aniline, involves the attack of one amino group on the electrophilic C(2) centre according to the orbital control over the reaction. Subsequent attack of the second amino group can occur on two centres, *viz*., either on the electrophilic C(1) centre or on the C(4) atom. Apparently, the nucleophilic attack on the C(4) centre to form five-membered rings in the case of hydrazines and on the C(1) centre to form six-membered rings in the case of ethylenediamine and *o*-phenylenediamine is governed by thermodynamic factors.

In the reactions of pentafluorobenzoylpyruvate **1e** with amines, intramolecular cyclisation to 2-ethoxycarbonylchromone **3a** is the dominant reaction route. Reactions at the β-dicarbonyl fragment are typical of the reactions of pentafluorobenzoylpyruvates with hydrazines and hydroxylamine, while reactions at the α-oxo-ester fragment are characteristic of the reactions with ethylenediamine, *o*-phenylenediamine and *o*-aminophenol. It is believed that the main regularities manifested in these reactions are similar to those observed in the case of polyfluoroacylpyruvates.

The use of copper chelates of β-di- and tricarbonyl compounds instead of free ligands in the reactions with nucleophiles does not necessarily lead to the formation of identical products. Thus the reactions of copper acylpyruvates **2b**,**c** with hydrazines afford pyrazoles **13a**–**c** rather than hydroxypyrazolines **11** (see Schemes 2 and 3). Apparently, this is due to the template role of the copper cation. In some instances, for example, in the reactions of β-DCC chelates with hydrazine hydrochlorides as well as in the reactions of copper acylpyruvates with hydroxylamine hydrochlorides and *o*-phenylenediamine hydrochlorides, identical products were obtained in comparable yields.

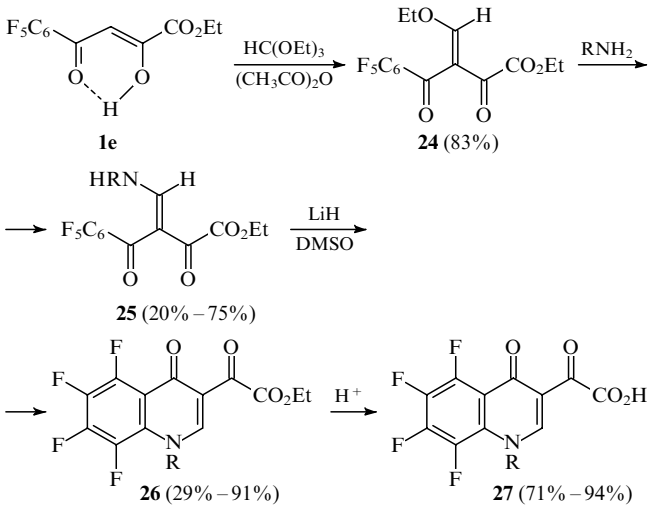
In addition, the use of the copper chelate of pentafluorobenzoylpyruvate **2f** allows one to obtain substituted benzothiazinone **22** by the reaction with *o*-aminobenzenethiol, while pentafluorobenzoylpyruvate **1f** as such undergoes acid scission under the reaction conditions.

VI. Preparation and reactions of 3-substituted polyfluorinated 2,4-dioxo acids

Preparation of fluorine-containing 3-substituted chromones and quinolones by cyclisation of aroylpyruvates requires that an alkoxymethylene group be introduced at the C(3) atom of the initial pyruvates.

Ethyl pentafluorobenzoylpyruvate (**1e**), like other β-DCC,[11,12,23,24,67] readily reacts with ethyl orthoformate to form ethyl 3-ethoxymethylidene-2,4-dioxo-4-pentafluorophenylbutyrate (**24**). The reactions of compound **24** with amines followed by cyclisation of the resulting ethyl 3-

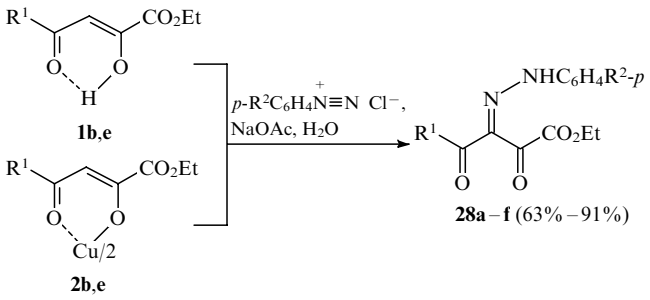
alkylaminomethylidene-2,4-dioxo-4-pentafluorophenylbutyrates (**25**) afford 3-ethoxalyl-1-R-5,6,7,8-tetrafluoro-4-quinolones (**26**). 2-(1-R-5,6,7,8-Tetrafluoro-4-oxo-1,4-dihydroquinolin-3-yl)glyoxylic acids (**27**) were prepared by hydrolysis of the esters **26**.[68]



R = H, Me, Et, cyclo-C_3H_5, C_6H_{13}, C_2H_4OH, *o*-MeC_6H_4.

The active methylene group in compounds containing a β-dicarbonyl fragment is the reaction site for azocoupling with aryldiazonium salts to form the corresponding arylhydrazones.[69] Until recently, the data on the participation of fluorine-containing β-DCC in azocoupling have been limited to only a few examples of the reactions of fluorinated β-diketones,[70,71] trifluoroacetoacetates [70] and pentafluorobenzoylacetates.[72] Recently, the synthesis of fluorinated 2-arylhydrazono-1,3-dicarbonyl compounds was reported and their reactivity with respect to N,O-dinucleohilies was studied.[73] Data on the possibility of the synthesis of arylhydrazones using fluorine-containing acyl(aroyl)pyruvates are lacking in the literature although nonfluorinated analogues of acyl(aroyl)pyruvate arylhydrazones were reported.[74]

3-Arylhydrazones of 5,5,5-trifluoro-2,3,4-trioxopentanoates and 4-pentafluorophenyl-2,3,4-trioxobutyrates **28a – f** were first prepared by the reactions of trifluoroacetyl(pentafluoroben-zoyl)-pyruvates **1b**,**e** and their copper chelates **2b**,**e** with aryldiazonium chlorides in an aqueous medium.[75]



28: $R^1 = CF_3$: R^2 = H (**a**), Me (**b**), OMe (**c**); $R^1 = C_6F_5$: R^2 = H (**d**), Me (**e**), OMe (**f**).

Arylhydrazones **28a**,**d** were subjected to heterocyclisation with hydrazines and *o*-phenylenediamine. Compound **28a** reacts with hydrazine hydrate and phenylhydrazine to give 1-R^3-5-ethoxycarbonyl-4-phenylazo-3-trifluoromethyl-Δ^2-pyrazol-ines **29a**,**b**, unlike pentafluorobenzoyl-substituted arylhydrazone **28d**, which reacts with hydrazine hydrate to form a mixture of products which are difficult to separate. 3-(2-R-Ethyl-2-oxo-1-phenylhydrazono)-1,2-dihydroquinoxalin-2-ones **30a**,**b** were synthesised from arylhydrazones **28a**,**d** and *o*-phenylenediamine by boiling in diethyl ether (Scheme 4).[75]

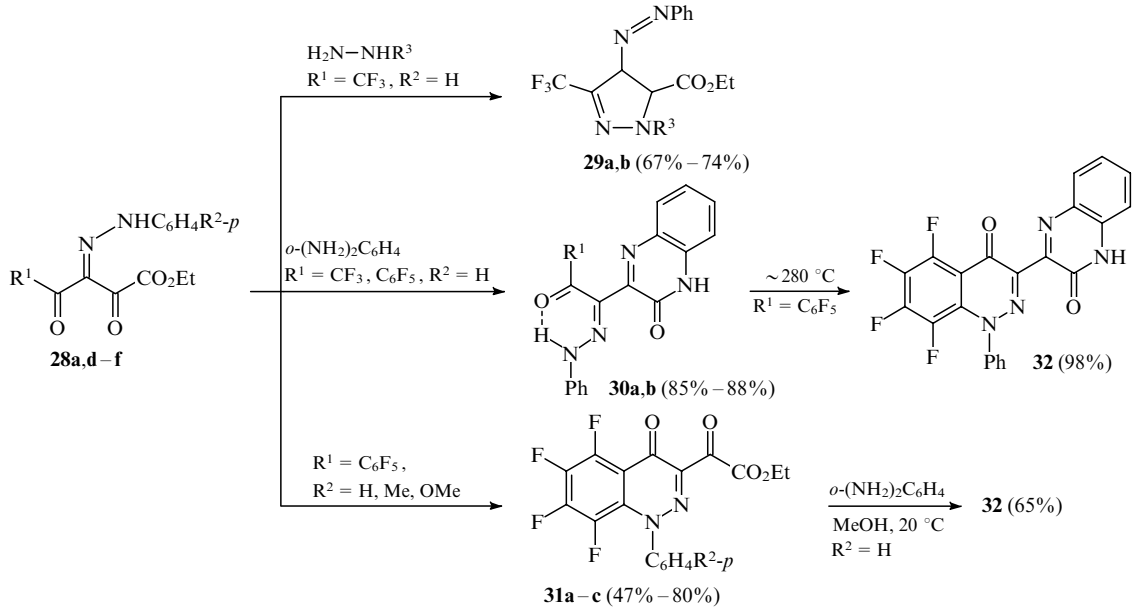
Thus, arylhydrazones of fluoroacyl(aroyl)pyruvates, like their nonsubstituted analogues, react with hydrazines and *o*-phenylenediamine at the β-dicarbonyl and α-oxo-ester fragments, respectively.

The presence of a pentafluorobenzoyl substituent in arylhydrazones **28d – f** makes it possible to use them for constructing heterocyclic compounds of the cinnolone series. Thus when heated in DMSO in the presence of K_2CO_3 or refluxed in chloroform with a twofold excess of triethylamine, arylhydrazones **28d – f** give 3-ethoxalyl-5,6,7,8-tetrafluoro-1-(4-R^2-phenyl)-1,4-dihydrocinnolin-4-ones **31a – c**.[75]

Cyclisation of quinoxalinone **30b** upon heating affords 5,6,7,8-tetrafluoro-3-(2-oxo-1,2-dihydroquinoxalin-3-yl)-1-phenyl-1,4-dihydrocinnolin-4-one (**32**). Compound **32** is also formed in the reaction of cinnolinone **31a** with *o*-phenylenediamine.

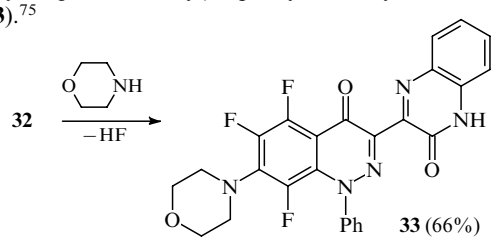
Nucleophilic replacement of the fluorine atom at position 7 in the reactions with various alkylamines is typical of fluorine-containing cinnolinones, fluorochromones and quinolones.[12] For example, the reaction of cinnolinone **32** with an excess of

Scheme 4



29: R^3 = H (**a**), Ph (**b**); **30**: $R^1 = CF_3$ (**a**), C_6F_5 (**b**); **31**: R^2 = H (**a**), Me (**b**), OMe (**c**).

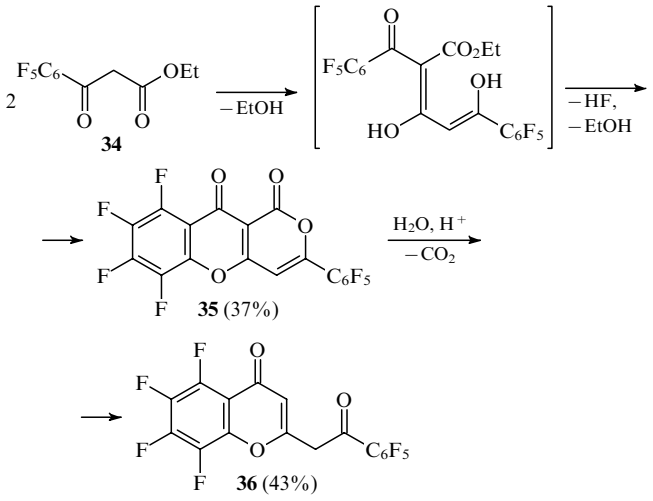
morpholine in DMSO yields a product of replacement of the fluorine atom, *viz*., 5,6,8-trifluoro-7-morpholino-3-(2-oxo-1,2-dihydroquinoxalin-3-yl)-1-phenyl-1,4-dihydrocinnolin-4-one (**33**).[75]



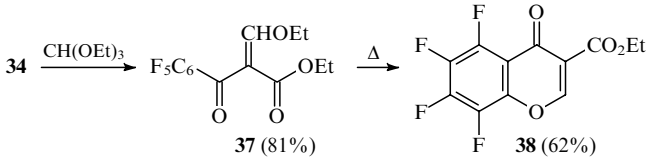
From the aforesaid it may be concluded that modification of fluoroacyl(aroyl)pyruvates by introducing alkoxymethylidene and arylhydrazone fragments at position 3 qualitatively changes and substantially extends synthetic possibilities of the compounds under consideration.

VII. Reactions of 2-ethoxycarbonyl(carboxy)-5,6,7,8-tetrafluorochromone

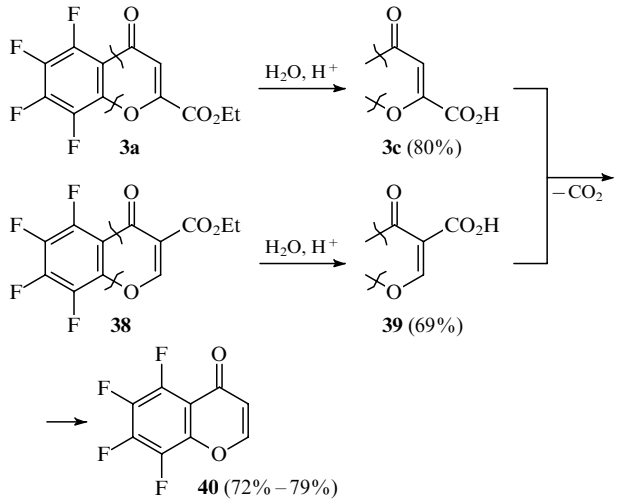
A characteristic feature of pentafluorobenzoylpyruvate **1e** and its chelate **2e** (see Scheme 1) is their conversion into 2-ethoxycarbonylchromone **3a** due to their ability to undergo intramolecular cyclisation to form a six-membered ring.[23,24] Under analogous conditions, ethyl pentafluorobenzoylacetate (**34**) undergoes self-condensation. The latter reaction is accompanied by the Dieckmann condensation and intramolecular cyclisation of an intermediate product to yield 1-oxo-3-pentafluorophenyl-1*H*-pyrano[4,3-*b*]-6,7,8,9-tetrafluorochromone (**35**).[76] 2-Pentafluorobenzoylmethyl-5,6,7,8-tetrafluorochromone (**36**) was prepared by acid hydrolysis of compound **35**. It should be mentioned that self-condensation is typical of both fluorinated [77] and nonfluorinated β-oxo esters.[78] However, in the case of pentafluorobenzoylpyruvate **1e**, intramolecular cyclisation dominates.



It should also be noted that ethyl 2-ethoxymethylidenepentafluorobenzoylacetate (**37**), like the ester **1e**, undergoes cyclisation to form 3-ethoxycarbonyl-5,6,7,8-tetrafluorochromone (**38**).[23,24]



Chromones **3a** and **38** are readily hydrolysed to the corresponding acids **3c** and **39**, which undergo decarboxylation upon heating to form 5,6,7,8-tetrafluorochromone (**40**).[23,24]



The reactivity of fluorochromones was discussed [79] with recourse to quantum-chemical AM-1 [37] calculations of the charges and Fukui indices for tetrafluoro-2-methoxycarbonylchromone, 2-carboxytetrafluorochromone and its anion and their nonfluorinated analogues using the MNDO-90 method [36] (Table 2).

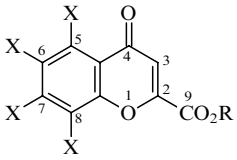
The calculated data make it possible to reveal the following regularities. The introduction of fluorine atoms into the aromatic ring of chromone has virtually no effect on the charge distribution in the pyrone ring. The maximum positive charges in the pyrone and fluorine-containing aromatic rings are localised on the C(9) and C(5) atoms, respectively.[79]

In the pyrone rings, the maximum values of the Fukui indices for LUMO correspond to the C(2) atom in the fluorine-substituted ester and acid and to the C(4) atom in the anion. In the fluorine-containing aromatic rings of the ester, acid and anion, the maximum values of the Fukui index correspond to the C(7) atom.[79]

Thus, according to the charge control, the kinetically controlled reactions of chromones with nucleophilic reagents should occur predominantly at the C(9) atom of the ester fragment, carboxyl group and the anion of the acid. According to orbital control, the reactions of the ester and acid should occur at the C(2) atom of the pyrone ring, while the reactions of the anion should occur at the C(4) atom. The orbital-controlled nucleophilic replacement of the fluorine atom should occur predominantly at the C(7) atom.[79]

2-Ethoxycarbonyl- **3a** and 2-carboxychromones **3c** possess different reactivity with respect to ammonia and primary amines.[43] Thus 2-ethoxycarbonylchromone **3a** does not react with ammonia or aniline. Methylamine reacts with the ester group and the C(7) atom of the fluorinated ring of compound **3a** to form *N*-methyl-5,6,8-trifluoro-7-methylaminochromone-2-carboxamide (**41**) (Scheme 5). This behaviour is untypical of the known nonfluorinated chromones. Under these conditions, the latter add a nucleophile at the C(7) atom with the opening of the heterocycle.[78] Under the action of cyclohexylamine, only the fluorine atom at the C(7) atom of chromone **3a** is replaced to form chromone **6** (see Scheme 5).[79] It should be noted that the replacement at the C(7) atom is an orbital-controlled reaction, while the formation of methylamide at the C(9) atom is a charge-controlled process.

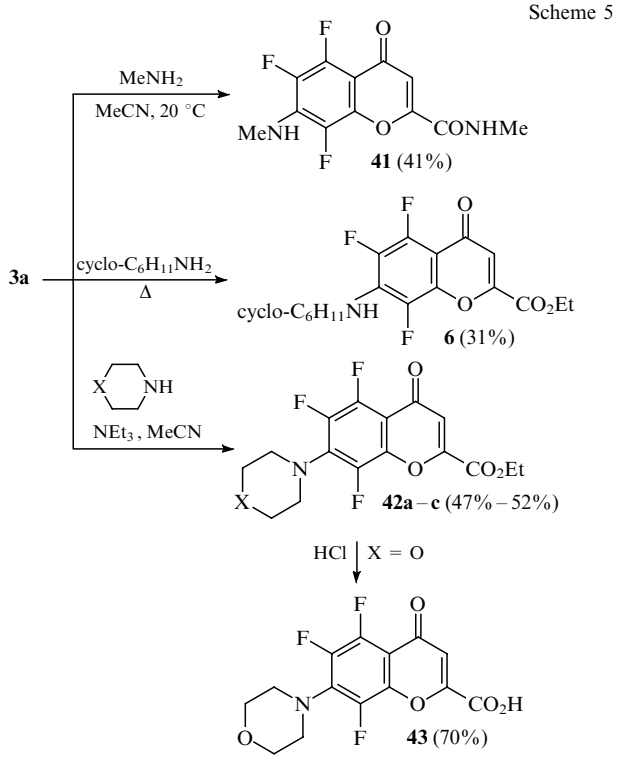
Table 2. Charges and Fukui indices for the electrophilic centres in substituted chromones.



R	X	Charges							Fukui indices						
		C(2)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(2)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)
Me	F	+0.0564	+0.3041	+0.1618	+0.0060	+0.1015	+0.0429	+0.3454	0.197	0.186	0.312	0.00158	0.365	0.207	0.0406
H	F	+0.0543	+0.3033	+0.1620	+0.0072	+0.1019	+0.0440	+0.3531	0.224	0.192	0.300	0.00026	0.333	0.197	0.0521
See.[a]	F	+0.0754	+0.3184	+0.1539	+0.0306	+0.0748	+0.0297	+0.3916	0.0246	0.0676	0.338	0.0165	0.564	0.370	–
Me	H	+0.0567	+0.3039	−0.0451	−0.1630	−0.0748	−0.1536	+0.3439	0.476	0.237	0.124	0.00650	0.0959	0.0743	0.153
H	H	+0.0547	+0.3036	−0.0449	−0.1622	−0.0742	−0.1531	+0.3514	0.480	0.226	0.114	0.00710	0.0837	0.0672	0.171
See.[a]	H	+0.0836	+0.3162	−0.0553	−0.1973	−0.0977	−0.1669	+0.3861	0.0567	0.153	0.333	0.0154	0.542	0.285	–

[a] Anion of 2-carboxychromone.

Scheme 5

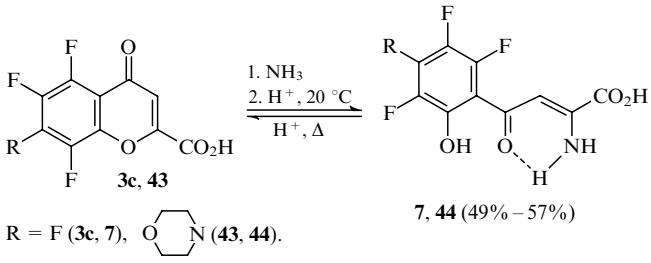


42: X = O (**a**), NMe (**b**), CH_2 (**c**).

The reactions of chromone **3a** with secondary amines (morpholine, *N*-methylpiperazine or piperidine) proceed analogously without the opening of the heterocycle (which is typical of the reactions of nonfluorinated chromones with secondary amines) to form the corresponding 2-ethoxycarbonyl-7-R-5,6,8-trifluorochromones **42a**–**c**. Boiling of chromone **42a** with HCl gives 5,6,8-trifluoro-7-morpholinochromone-2-carboxylic acid (**43**) (see Scheme 5).[43]

Thus, the reactions of 2-ethoxycarbonylchromone **3a** with primary and secondary amines are orbital-controlled and yield products of replacement at the C(7) atom.

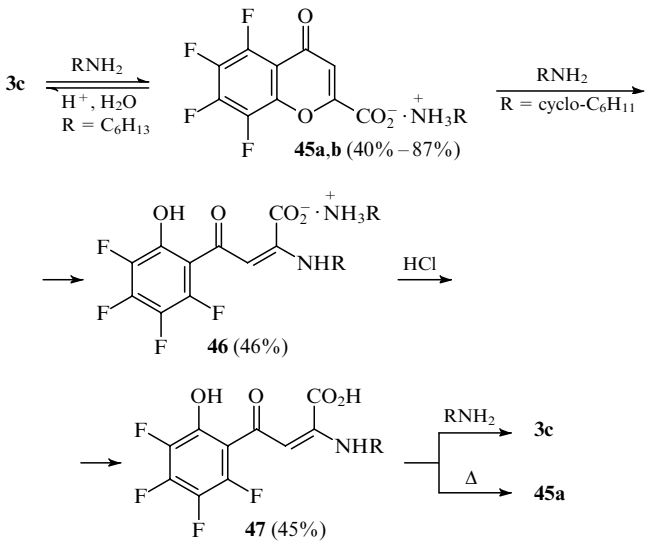
In contrast to 2-ethoxycarbonylchromone **3a**, the reactions of 2-carboxychromones **3c** and **43** with ammonia are accompanied by the opening of the pyrone ring, which is typical of the known chromones.[78] These reactions afford 2-amino-3-(4-R-3,5,6-trifluoro-2-hydroxybenzoyl)acrylic acids **7** and **44**, which can undergo recyclisation to form the initial compounds **3c** and **43** upon boiling in an acidic medium.[43]



R = F (**3c**, **7**), (**43**, **44**).

The reactions of 2-carboxychromone **3c** with primary amines are governed by both the nature of the amine and the reaction conditions.[79] Thus boiling of chromone **3c** with an equimolar amount of amine (cyclohexylamine or hexylamine) in dioxane affords cyclohexylammonium (hexylammonium) 5,6,7,8,-tetrafluorochromone-2-carboxylate (**45a**,**b**). Salts **45a**,**b** are stable on prolonged boiling in toluene. In the presence of an excess of amine, the pyrone ring in compound **45a** is opened to form 2-cyclohexylamino-3-(3,4,5,6-tetrafluoro-2-hydroxybenzoyl)-acrylate (**46**). Acidification of the salt **46** affords 2-cyclohexylamino-3-(3,4,5,6-tetrafluoro-2-hydroxybenzoyl)acrylic acid (**47**). Treatment of the hexylammonium salt **45b** with hydrochloric acid affords the initial chromone **3c** (Scheme 6).[79]

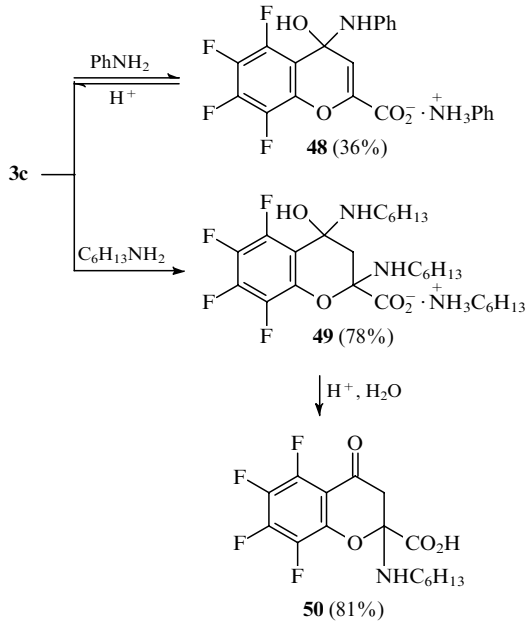
Scheme 6



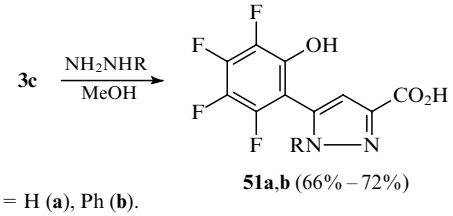
45: R = cyclo-C_6H_{11} (**a**), C_6H_{13} (**b**).

The reactions of chromone **3c** with hexylamine and aniline in a mixture of chloroform and water at 30 – 35 °C can proceed both as nucleophilic addition of the amine at the activated C = C bond and as the reaction at the carbonyl group of the chromone. Thus chromone **3c** reacts with aniline to form anilinium 4-anilino-5,6,7,8-tetrafluoro-4-hydroxychromene-2-carboxylate (**48**). The reaction of chromone **3c** with hexylamine affords hexylammonium 2,4-bis(hexylamino)-5,6,7,8-tetrafluoro-4-hydroxychromane-2-carboxylate (**49**), which is converted into 5,6,7,8-tetrafluoro-2-hexylamino-4-oxochromane-2-carboxylic acid (**50**) upon acidification (Scheme 7).[43]

Scheme 7



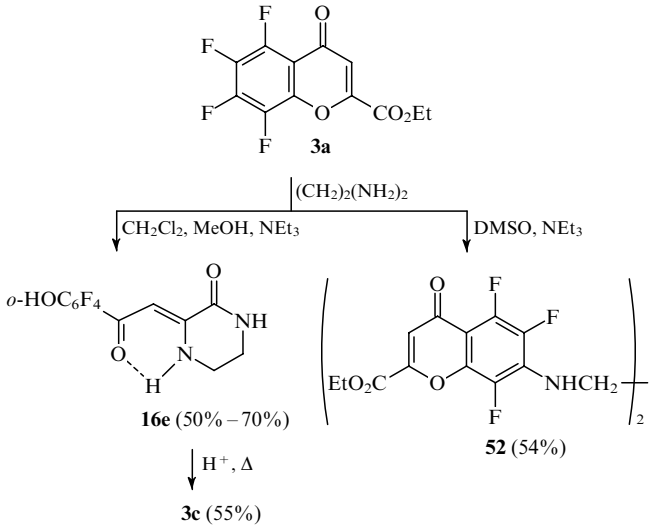
The reaction of 2-ethoxycarbonylchromone **3a** with hydrazine yields a mixture of products, which are difficult to identify. 2-Carboxychromone **3c**, like nonfluorinated analogues, reacts with hydrazine and phenylhydrazine more selectively to form the corresponding 1-R-5-(tetrafluoro-2-hydroxyphenyl)pyrazole-3-carboxylic acids **51a**,**b**.[79]



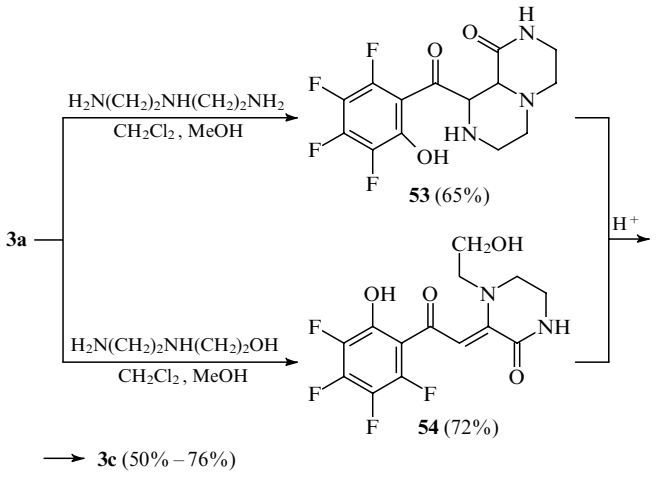
R = H (**a**), Ph (**b**).

The reaction of 2-ethoxycarbonylchromone **3a** with ethylenediamine yields either piperazin-2-one **16e** as a result of the reaction at the C(2) atom and the ester group or a product of nucleophilic aromatic replacement of the fluorine atom at position 7, *viz*., *N*,*N*′-ethylenebis(7-amino-2-ethoxycarbonyl-5,6,8-trifluorophenylchromone) (**52**), depending on the solvent (Scheme 8).[43] The formation of these compounds is attributable to an increase in the electron-withdrawing ability of the polyfluoroaryl ring (and consequently, the ability to undergo nucleophilic replacement of the fluorine atom) in going from protic solvents (alcohols) to a bipolar aprotic solvent (DMSO).[80] However, the reaction of chromone **3a** with ethylenediamine in acetonitrile also affords piperazin-2-one **16e**.[43] Apparently, acetonitrile, unlike DMSO, does not hinder the formation of an ionic pair of ethylenediamine with chromone at the electrophilic carbon atom of the ester group or at the C(2) atom.

Scheme 8



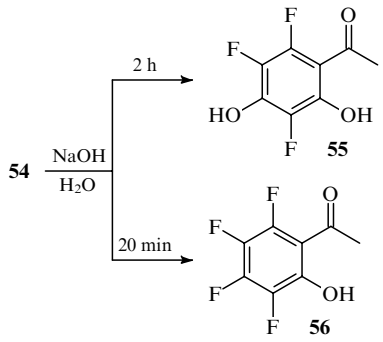
2-Ethoxycarbonylchromone **3a** reacts with diethylenetriamine with the involvement of all three nucleophilic centres to form a binuclear triazaheterocyclic derivative, *viz*., 9-(3,4,5,6-tetrafluoro-2-hydroxybenzoyl)perhydropyrazino[1,2-*a*]pyrazin-1-one (**53**).[81] An analogous bicyclic system is obtained by the reaction of 2-amino-4-iminoperfluoropent-2-ene (an aza analogue of heptafluoroacetylacetone) with diethylenetriamine.[82, 83]



The reaction of chromone **3a** with *N*-(2-hydroxyethyl)-ethylenediamine under analogous conditions is completed in the stage of formation of a mononuclear heterocyclic compound, *viz*., 3-(3,4,5,6-tetrafluoro-2-hydroxybenzoylmethylidene)-4-(2-hydroxyethyl)piperazin-2-one (**54**).[81]

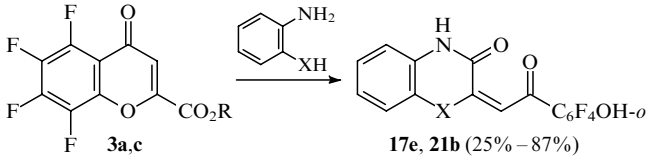
Attempts to perform further intramolecular heterocyclisation of compound **54** with the use of acid or base catalysis, which favours nucleophilic addition of the hydroxy group at the C = C bond, failed. Under conditions of acid catalysis in the presence of water, compound **54** is readily hydrolysed to form carboxychromone **3c**. When boiled in toluene with *p*-toluenesulfonic acid, the initial piperazinone **54** remains unchanged. Heating of compound **54** in an alkaline medium results in its decomposition to 3,5,6-trifluoro-2,4-dihydroxyacetophenone **55** or, in the case of the shorter reaction time, to tetrafluoro-2-hydroxyacetophenone **56**.[81]

Analogous hydrolytic cleavage to form dihydroxy(hydroxy)-polyfluoroacetophenones was also observed in the cases of piperazinone **16e** and aminoacrylic acid **7**.[84]



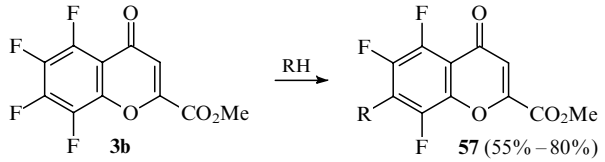
2-Ethoxycarbonylchromone **3a** and 2-carboxychromone **3c** react with *o*-phenylenediamine to form quinoxaline derivative **17e** (the yields were 70% and 30%, respectively) (Scheme 9).[79] The reactions of compounds **3a** and **3c** with *o*-aminophenol afford benzooxazinone **21b** containing the tetrafluorohydroxyphenyl fragment.[53, 66]

Scheme 9



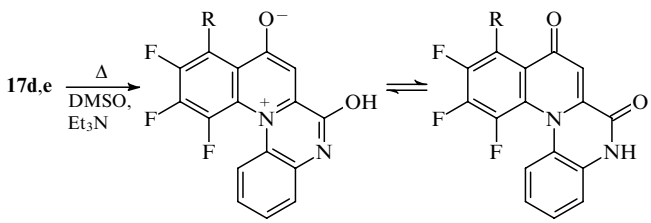
R = Et (**3a**), H (**3c**); X = NH (**17e**), O (**21b**).

The reaction of 2-methoxycarbonylchromone **3b** with *o*-aminothiophenol yields only a product of nucleophilic replacement of the fluorine atom, *viz*., 7-(2-aminophenylthio)-5,6,8-trifluoro-2-methoxycarbonylchromone (**57**).[39]



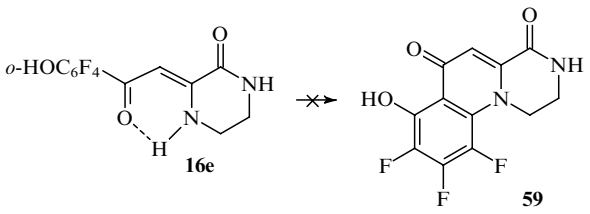
R = *o*-$H_2NC_6H_4S$.

When heated in DMSO in the presence of triethylamine, both quinoxalones containing the hydroxy group in the fluoroaromatic fragment (**17e**) and hydroxy-free quinoxalones (**17d**) undergo heterocyclisation to form 1,2,3-trifluoro-4-R-(5*H*)-5-oxoquinolino[1,2-*a*]-8*H*-quinoxalin-7-ones **58a**,**b** due apparently to the completely aromatic character of the possible zwitterion.[79]

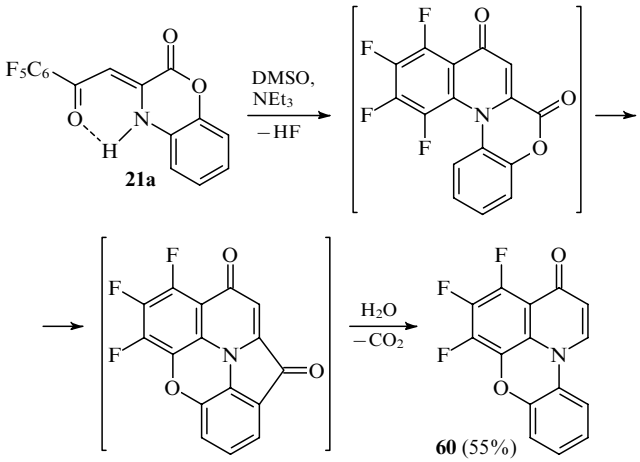


R = F (**17d**, **58a**), OH (**17e**, **58b**).

In this connection it should be noted that piperazinone **16e** whose nitrogen atoms should be more nucleophilic than those in quinoxalone does not give the corresponding heterocyclic system **59** either under analogous conditions or under more drastic conditions (K_2CO_3 or LiH). Apparently, this is associated with the fact that none of its possible tautomeric forms is completely aromatic.[79]



It is remarkable that the benzooxazinone derivative **21a** also undergoes intramolecular cyclisation upon heating in DMSO. This reaction, unlike the above-mentioned transformation of quinoxalones **17d**,**e** into quinolinoquinoxalones **58a**,**b**, affords 4,5,6-trifluoro-3*H*-pyrido[3,2,1-*k*,*l*]phenoxazin-3-one (**60**). Apparently, the formation of compound **60** proceeds *via* intermediates shown in the following scheme:[85]



Summarising the data on the reactions of 2-alkoxycarbonyl- (**3a**,**b**) and 2-carboxy-5,6,7,8-tetrafluorochromones (**3c**) with binucleophiles, it can be suggested that the mechanisms of the first stages of the reactions of chromones **3a**,**b** and **3c** are different, although the reactions can afford identical products (for example, in the reactions with *o*-phenylenediamine and *o*-aminophenol).

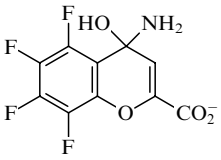
Apparently, the initial stage of the reactions of chromones **3a**,**b** with N-dinucleophiles involves the charge-controlled attack of one amino group of the reagent on the electrophilic C(9) centre. It counts in favour of this suggestion that the reaction of chromone **3a** with methylamine affords *N*-methylamide **41** (see Scheme 5). However, the reaction with an excess of methylamine involves also the orbital-controlled attack of the nucleophile on the C(7) centre. In this connection it should be noted that the orbital control may become predominant, *e.g*., in the reactions of chromone **3a** with primary and secondary amines in dioxane yielding 7-substituted products **42** and **6** (see Scheme 5) or in the reaction of chromone **3a** with ethylenediamine in DMSO to form product **52** (see Scheme 8). This regioselectivity is apparently determined by the effect of specific solvation of the initial reagents by the solvent, much as in the reactions of 5-aryl-2,3-dihydrofuran-2,3-diones with aromatic amines in dioxane.[86]

The second amino group of the N-dinucleophile (ethylenediamine, *o*-phenylenediamine or *o*-aminophenol) attacks the nearest C(2) atom of chromone **3a**. In this case, the pyran ring is opened to form new heterocyclic compounds, *viz*., piperazinones **16e**, quinoxalones **17e** or oxazines **21b**, respectively (see Schemes 8 and 9). Evidently, this process is governed by thermodynamic factors.

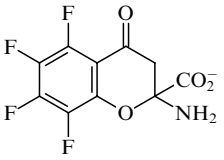
Unlike 2-alkoxycarbonylchromones **3a**,**b**, 2-carboxychromone **3c** reacts with an equimolar amount of primary amines to form stable salts **45** (see Scheme 6). The reactions of these salts with an excess of amine follow different routes. Thus heating in dioxane results in resinification of the reaction mixture. In an aqueous medium, the reversible interaction of the amino group of primary amine with the electrophilic C(4) and C(2) centres occurs. In the latter case [the reaction at the C(2) atom], either products of

addition at the double C(2)=C(3) bond (products **49** and **50**) can be formed (see Scheme 7) or derivatives of aminoacrylic acid, *viz*., compounds **46** and **47**, can be obtained due to the opening of the heterocycle of the chromone, as in the case of the reaction with cyclohexylamine (see Scheme 6). However, when heated in dioxane, the products of addition of cyclohexylamine undergo identical conversions to form apparently the more stable initial salts.

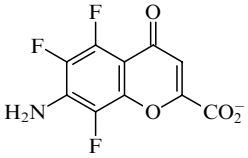
It is remarkable that under kinetically controlled conditions the reaction at the C(4) atom can occur as a charge-controlled process because the charge on this atom is the second largest, exceeded in value only by the C(9) atom. However, the reaction of amine at the C(2) atom of the carboxylate anion, as in the case of 2-ethoxycarbonylchromone, is not apparently kinetically controlled. Actually, calculations of model compounds demonstrated that the attack of a nucleophile on the C(2) atom of the fluorinated carboxylate anion affords a thermodynamically more stable reaction product than the attacks on the C(4) and C(7) nucleophilic centres. This is evident from the comparison of the enthalpies of formation of the following compounds (ΔH /kJ mol^{-1}):[79]



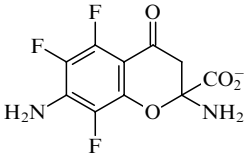
$\Delta H = -1313.94$



$\Delta H = -1388.47$



$\Delta H = -1128$



$\Delta H = -1217$

In our opinion, the formation of the corresponding carboxylate anion followed by the attack of a nucleophile (an excess of amine in the case of hydrazines and the second amino group in the case of *o*-phenylenediamine and *o*-aminophenol) on the C(2) atom is also typical of the reactions of 2-carboxychromone **3c** with hydrazines, *o*-phenylenediamine and *o*-aminophenol. The subsequent reaction path is determined by the thermodynamic stability of the final products, as in the case of nonfluorinated aroylpyruvic acids.

VIII. Conclusion

Analysis of the above-considered published data demonstrated that the reactions of fluorinated acyl(aroyl)pyruvates are analogous to the reactions of nonfluorinated α- and β-DCC. Thus fluoroacyl(aroyl)pyruvates react at the β-dicarbonyl fragment (for example, with hydrazines) and enter into the reactions at the active methylene group as β-DCC (for example, with orthoformate and aryldiazonium salts) and at the α-oxo-ester fragment as α-DCC (for example, with diamines).

However, the introduction of fluorine atoms into aroylpyruvate molecules can radically change their reactivity. Thus the heterocyclisation of fluoroaroylpyruvates, which is untypical of their nonfluorinated analogues, affords 2-ethoxycarbonyl(carboxy)-5,6,7,8-tetrafluorochromones. The latter, in turn, can react with HO-, HN- and HS-nucleophiles to form various fluorinated heterocyclic compounds.

In summary the above-considered data substantially extend the knowledge of synthetic potentialities of fluorinated 2,4-dioxo acids and their derivatives for constructing various classes of heterocyclic systems.

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