PERFLUORINATED ACYL(AROYL)PYRUVATES AS BUILDING BLOCKS FOR THE SYNTHESIS OF HETEROCYCLES

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Abstract - Data on the synthesis and chemical transformations of 3-polyfluoroacyl- and 3-pentafluorobenzoylpyruvates and their derivatives are reviewed. Reactions giving fluorinated heterocycles and syntheses based on these transformations are discussed.

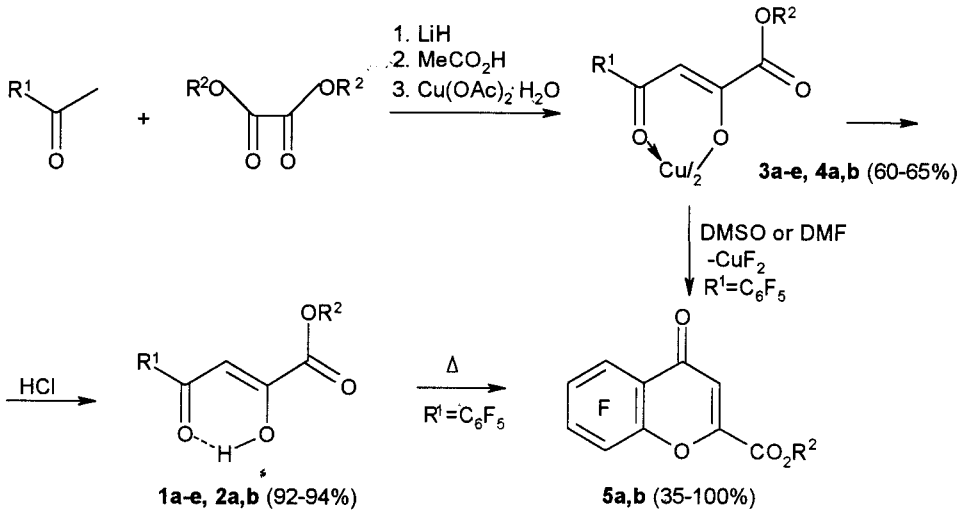
I. Introduction

In the past decades fluorine-containing α-keto esters, α-diketones, β-keto esters and β-diketones have been widely used as precursors for the synthesis of fluoroheterocycles.[1-3] Significant achievements have in particular been made in the creation of fluoroquinolones as a new generation of synthetic antibacterial agents (fluoroquinolones).[4-6] In all these antibiotics the structural fragment of fluorobenzoylacetic acid is present. In this context, the development of novel fluorinated dicarbonyl compound chemistry is of considerable interest. In our view, one of the most promising strategies in this area deals with the synthesis and reactions of polyfluoroacyl(aroyl)pyruvic acids and their derivatives containing both α- and β-dicarbonyl fragments. In this review the transformations of these versatile building blocks and synthetic strategies towards fluoroheterocycles will be presented based on recent literature data.

II. Synthesis and structures of polyfluorinated acyl(aroyl)pyruvates

Non-fluorinated acyl(aroyl)pyruvates were obtained as early as at the end of the last century.[7,8] Esters of 3-polyfluoroacyl- (**1a-e**)[9] and 3-pentafluorobenzoylpyruvates (**2a,b**)[10,11] were prepared by Claisen condensation of fluoroalkyl- and pentafluorophenyl ketones, respectively, with dialkyl oxalate in the presence of lithium hydride. Pyruvates (**1a-e, 2a,b**) were isolated *via* their copper chelates (**3a-e, 4a,b**) (Scheme 1).

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73th birthday.

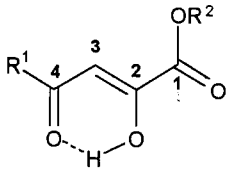


R^1= CF_3, R^2= Me (**1a,3a**); R^1= CF_3, R^2= Et (**1b,3b**); R^1= Me, R^2= Me (**1c,3c**);
R^1= C_4F_9, R^2= Et (**1d,3d**); R^1= HCF_2, R^2= Et(**1e,3e**);
R^1= C_6F_5, R^2= Et (**2a,4a,5a**), Me (**2b,4b,5b**).

Scheme 1

Copper chelates of polyfluoroacylpyruvates (**3a-e**) are stable compounds,[9] while the chelates of pentafluorobenzoylpyruvates (**4a,b**) undergo cyclization to 2-alkoxycarbonyl-5,6,7,8-tetrafluorochromones (**5a,b**) upon heating in DMSO or DMF.[10] Heating esters (**2a,b**) over 25°C also results in the formation of chromones (**5a,b**) (Scheme 1).[10,11] The cyclization proceeds through intramolecular substitution of the *ortho*-fluorine atom in the pentafluorophenyl substituent.

Table 1. Charges and Fukui indices at electrophilic centers of acyl(aroyl)pyruvates



1, 2

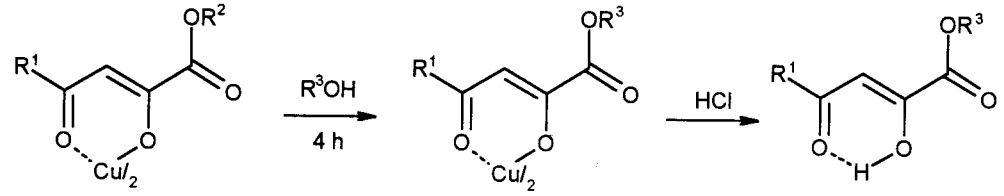
R^1	R^2	Charges				Fukui indices		
		H	C(1)	C(2)	C(4)	C(1)	C(2)	C(4)
Me	Me	+0.2586	+0.3609	+0.2076	+0.2996	0.1880	0.5250	0.3613
HCF_2	Me	+0.2561	+0.3624	+0.2123	+0.2429	0.1459	0.5170	0.4306
CF_3	Me	+0.2549	+0.3628	+0.2128	+0.2216	0.1289	0.5134	0.4540
C_4F_9	Me	+0.2558	+0.3630	+0.2128	+0.2502	0.1240	0.5661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

To discuss the reactivity of fluoroacyl(aroyl)pyruvates (**1, 2**) Fukui indices[12] (electron density at the frontier orbitals) at each atom of the highest occupied and lowest unoccupied molecular orbital (HOMO, LUMO) and charge distributions have been calculated *via* the CNDO/2 approach for acylpyruvates (**1**)[13]

and by using the MNDO-89 method[12] for pentafluorobenzoylpyruvate (**2**) (Table 1). It has been shown that the highest positive charge is at the C1 carbon atom, and the electron deficit at the C2 atom of the LUMO is the highest (with the exception of the pentafluorobenzoylpyruvate). The latter has similar values of Fukui indices at the C2 and C4 carbon atoms. Thus, if a process is the kinetically controlled, the C1 carbon atom will be the preferred site of attack of a nucleophilic in accordance with charge control, and the C2 carbon atom will be the place of attack in accordance with orbital control. In the case of pentafluorobenzoylpyruvate, an orbital controlled process is approximately equiprobable for the C2 and C4 reaction centers.

III. Transesterification of polyfluoroacyl(aroyl)pyruvates

When using fluoroacyl(aroyl)pyruvates as precursors for the synthesis of different heterocyclic systems their ability to undergo transesterification reactions should be taken into account. We have found, for example, that transesterification of copper (II) fluoroacylpyruvates (**3a,c,d**) with borneol proceeds readily without any catalyst (Scheme 2).[14]



3a,c,d **3f-h** (91-95%) **1f-h** (85-92%)

R^1= CF_3, R^2= Me (**3a**), R^3= Born (**3f,1f**);
R^1= Me, R^2= Me (**3c**), R^3= Born (**3g,1g**);
R^1= C_4F_9, R^2= Et (**3d**), R^3= Born (**3h,1h**).

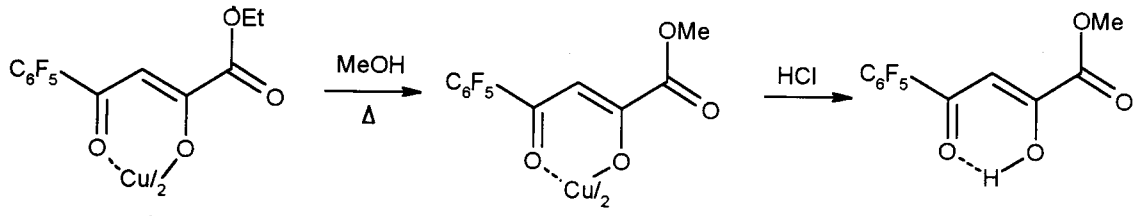
Born = 

Scheme 2

Interestingly, the interaction of the free pyruvates with borneol does not give any isolable products and results in strong resinification of the reaction mass. Acylpyruvates (**1f-g**) can then be readily obtained by hydrolysis of their copper chelates (**3f-g**) (Scheme 2).[14]

Copper (II) ethyl pentafluorobenzoylpyruvate (**4a**) also undergoes ready transesterification with methanol to form the corresponding methyl pyruvate chelate (**4b**) (Scheme 3).[15]

This reaction is common for the copper chelates of most β-keto esters, i.e. the chelates of acetyl- and trifluoroacetylacetonates.[14] However, these substrates require longer periods for transesterification than the chelates of acylpyruvates (**3a,c,d**), which is probably due to the participation of the ester groups of the keto esters in the intramolecular conjugation.

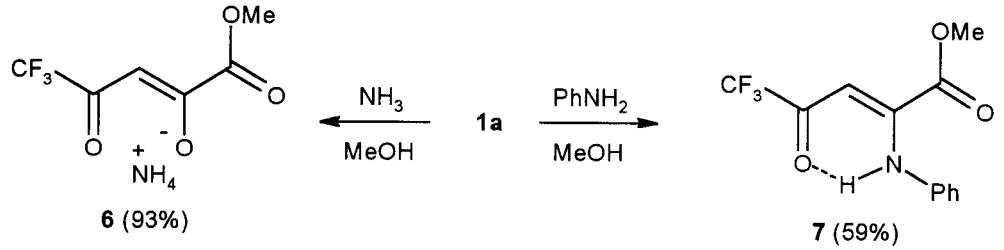


4a **4b**, ~100% **2b**, 92%

Scheme 3

IV. Reactions with amines

The reaction of methyl acetopyruvate with ammonia is known to afford the corresponding enamine at the C2 carbon atom.[16] In contrast, methyl trifluoroacetopyruvate (**1a**) reacts with ammonia to give ammonium methyl trifluoroacetopyruvate (**6**) which is stable to refluxing toluene.[17] However, a similar reaction with aniline does result in the formation of an enamine – methyl 2-anilino-5,5,5-trifluoro-4-oxopent-2-enoate (**7**) (Scheme 4).[17]

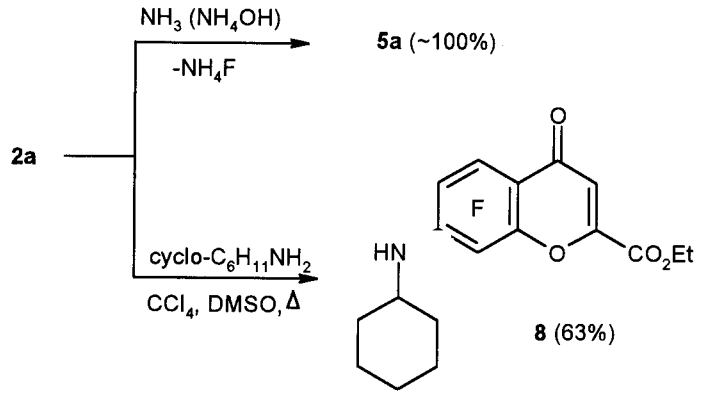


Scheme 4

The treatment of pentafluorobenzoylpyruvate (**2a**) with gaseous or aqueous ammonia provides chromone (**5a**).[17,18] This heterocycle may result from the formation of the corresponding ammonium salt followed by intramolecular displacement of the aromatic *ortho*-fluorine atom (Scheme 5).

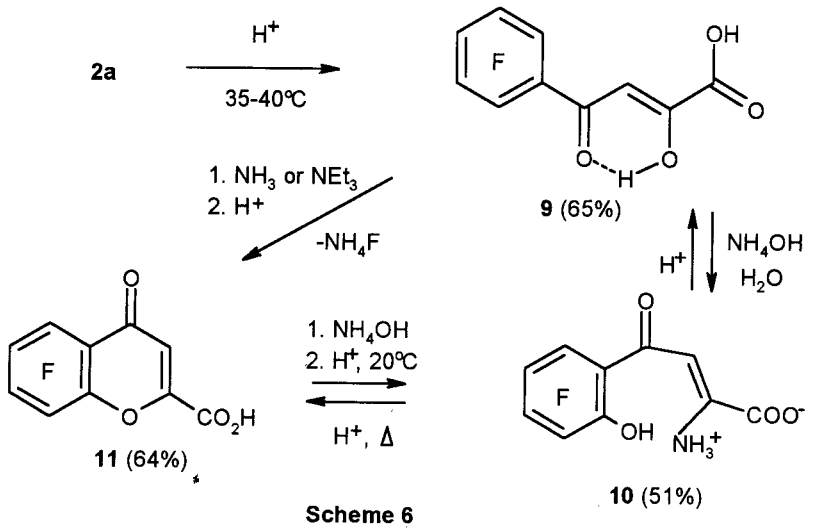
By analogy, pentafluorobenzoylpyruvate (**2a**) reacts with cyclohexylamine to give a chromone product, but in this case the cyclization is accompanied by substitution of the fluorine atom at the C7 position of the chromone by cyclohexylamine yielding 7-cyclohexylamino-2-ethoxycarbonyl-5,6,8-trifluorochromone (**8**) (Scheme 5).[17,18]

Thus, the cyclization and with the formation of a chromone structure but not the addition of the amine to the C2 carbon atom predominates in the reactions of pyruvate (**2a**) with ammonia and cyclohexylamine.



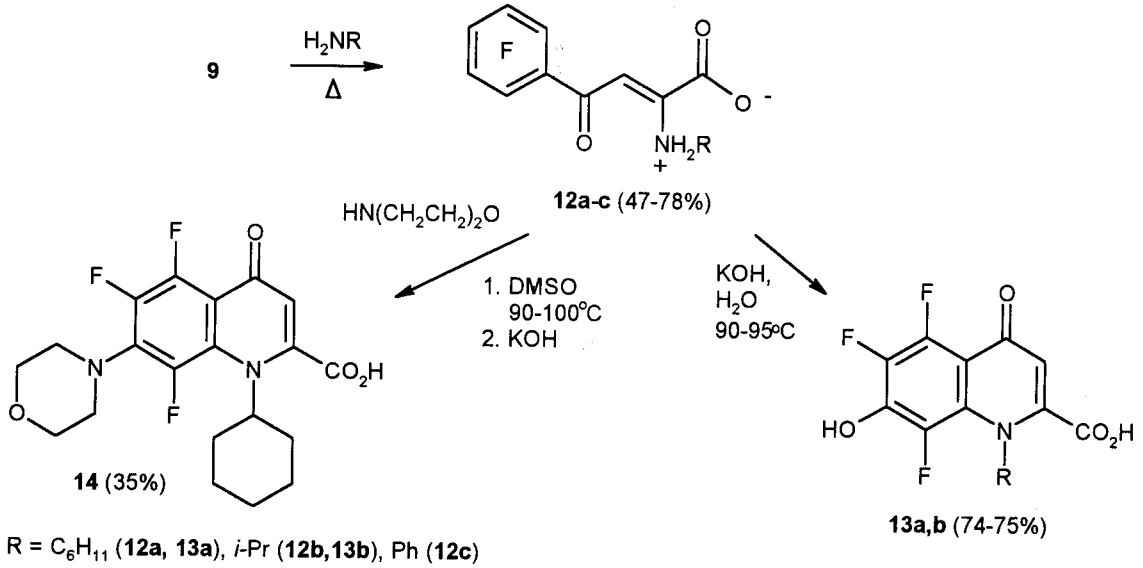
Scheme 5

The reaction of pentafluorobenzoylpyruvic acid (**9**), produced by hydrolysis of its esters (**2a**) with ammonium hydroxide, results in the formation of 2-amino-3-(3,4,5,6-tetrafluoro-2-hydroxybenzoyl)acrylic acid (**10**) in the form of a zwitterion (Scheme 6). When heating in an acid medium zwitterion (**10**) is hydrolyzed to acid (**9**) which cyclizes into 2-carboxy-5,6,7,8-tetrafluorochromone (**11**). The treatment of the latter substance with ammonium hydroxide followed by acidification also forms amino acid (**10**). The interaction of acid (**9**) with anhydrous ammonia or triethylamine in dioxane affords the same chromone (**11**).[17]



Scheme 6

In contrast, acid (**9**) reacts with primary amines (isopropyl-, cyclohexylamines or aniline) at the C2 carbon atom to furnish 2-alkylamino(anilino)-3-pentafluorobenzoylacrylic acids (**12a-c**) (Scheme 7), which testifies to the orbital control in these reactions. Under alkaline conditions acids (**12a,b**) can be transformed into 1-substituted 7-hydroxy-5,6,8-trifluoro-4-quinolone-2-carboxylic acids (**13a,b**).[17] Cyclization of the cyclohexyl analog (**12a**) in the presence of morpholine results in the formation of 1-cyclohexyl-5,6,8-trifluoro-7-morpholino-4-quinolone-2-carboxylic acid (**14**).[17]



Scheme 7

The regiospecific substitution of the fluorine atom by the hydroxy group at the C7 position of the quinolone ring was confirmed by X-Ray analysis of the DMSO-**13a** complex.[19]

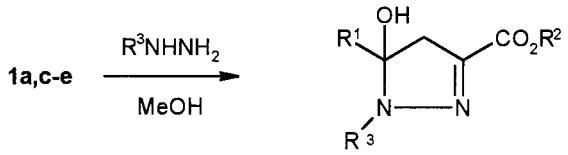
V. Interaction with dinucleophiles

Interaction of acyl(aroyl)pyruvates with bifunctional nucleophiles is of significant interest for the synthesis of various heterocycles. Non-fluorinated acyl(aroyl)pyruvates are known to react with dinucleophiles both at the β-dicarbonyl and α–keto ester fragments depending on the nature of dinucleophile.

1. Reactions with hydrazines and hydroxylamine.

Condensations of non-fluorinated acyl(aroyl)pyruvates with hydrazines result in the formation of 3-alkoxycarbonyl-5-methyl(phenyl)pyrazoles.[7,8,20] Ethyl acylpyruvate condenses with hydroxylamine to afford 3-ethoxycarbonyl-5-methylisoxazole or 5-ethoxycarbonyl-3-methylisoxazole, or the mixture of both isoxazoles depending on the reaction conditions.[7,21] Ethyl benzoylpyruvate condenses with hydroxylamine to afford 3-ethoxycarbonyl-5-phenylisoxazole, the reaction proceeding *via* the formation of an α–oxime intermediate.[8,22]

Ethyl(methyl) polyfluoroacylpyruvates (**1a,c-e**) react with hydrazine and phenylhydrazine at the β-dicarbonyl fragment like their non-fluorinated analogues,[7,20] fluorinated β-keto esters,[2] and β-diketones.[3] However, the interaction of pyruvates (**1a,c-e**) with hydrazines results in the formation of stable 3-alkoxycarbonyl-5-fluoroalkyl-5-hydroxypyrazolines (**15a-e**) (Scheme 8).[13] The position of the hydroxy group in **15b** was established by ^{13}C NMR spectroscopy.

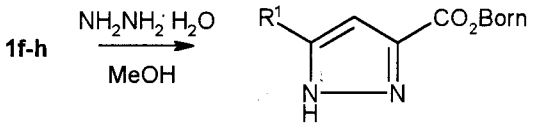


15a-e (67-73%)

R^1= CF_3, R^2= Me, R^3= H (**15a**), Ph (**15b**); R^1= Me, R^2= Me, R^3= H (**15c**);
R^1= C_4F_9, R^2= Et, R^3= H (**15d**); R^1= HCF_2, R^2= Et, R^3= H (**15e**).

Scheme 8

Unlike methyl(ethyl) fluoroacylpyruvates (**1a,c-e**), the reaction of the corresponding bornyl esters of polyfluoroacylpyruvic acids (**1f-h**) with hydrazine hydrate furnishes 3-bornyloxycarbonyl-5-fluoroalkylpyrazoles (**16a-c**) (Scheme 9) [14]

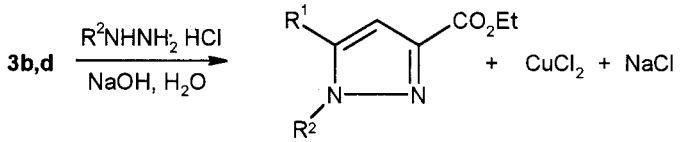


16a-c (61-68%)

R^1= CF_3 (**16a**); Me (**16b**); C_4F_9 (**16c**)

Scheme 9

In contrast to uncomplexed acylpyruvates the copper chelates of acylpyruvates (**3b,d**) condense with hydrazine and phenylhydrazine hydrochlorides to produce substituted pyrazoles (**16d-f**) (Scheme 10).[23]



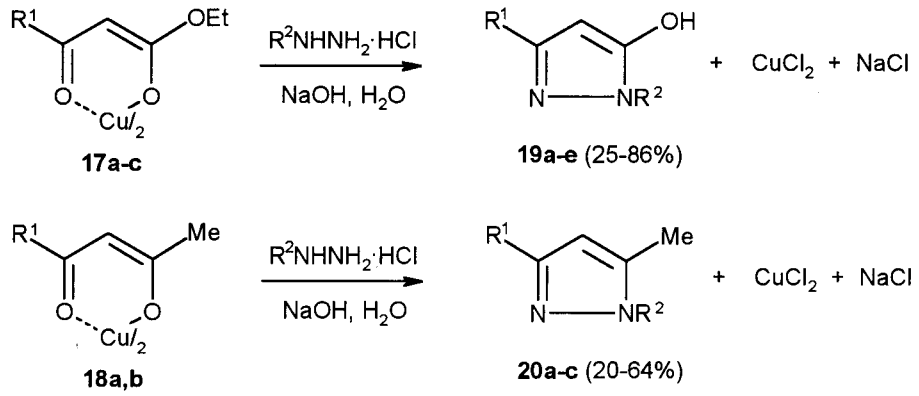
16d-f (70 - 75%)

R^1= C_4F_9, R^2= H (**3d,16d**); R^1= CF_3, R^2= H (**3b,16e**), Ph (**16f**)

Scheme 10

For comparison purposes we have studied the interaction of copper β–keto esterates (**17a-c**) and β-diketonates (**18a,b**) with hydrazine hydrochloride.[24] The reactions result in the formation of the

corresponding pyrazoles (**19a-e, 20a-c**) in low yield which may be increased through the presence of base (Scheme 11). The position of the phenyl substituent in **19c** was established by an X-Ray analysis.

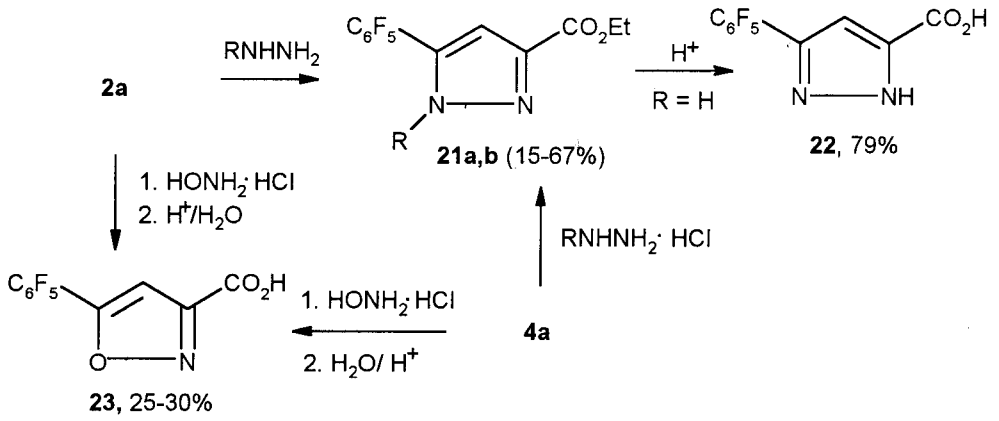


R^1= HCF_2 (**17a**), R^2= H (**19a**); R^1= CF_3 (**17b**), R^2= H (**19b**), Ph (**19c**);
R^1= C_4F_9 (**17c**), R^2= H (**19d**), Ph (**19e**); R^1= CF_3 (**18a**), R^2= H (**20a**), Ph (**20b**);
R^1= C_6F_{13} (**18b**), R^2= H (**20c**).

Scheme 11

Pentafluorobenzoylpyruvate (**2a**) and its copper chelate (**4a**) react with hydrazine to form 3-ethoxycarbonyl-5-pentafluorophenylpyrazole (**21a**) which may be hydrolyzed in acidic medium to 3-pentafluorophenylpyrazole-5-carboxylic acid (**22**) (Scheme 12).[23]

Interaction of pentafluorobenzoylpyruvate (**2a**) with phenylhydrazine and chelate (**4a**) with phenylhydrazine hydrochloride results in the corresponding pyrazole (**21b**) (Scheme 12). Similar reactions of compounds (**2a**) and (**4a**) with hydroxylamine hydrochloride give 5-pentafluorophenylisoxazole-3-carboxylic acid (**23**).[25]



R = H (**21a**), Ph (**21b**)

Scheme 12

The formation of substituted pyrazoles and isoxazoles in condensations with hydrazines and hydroxylamine is characteristic for both fluorinated-[26] and non-fluorinated aroylpyruvic acids.[27]

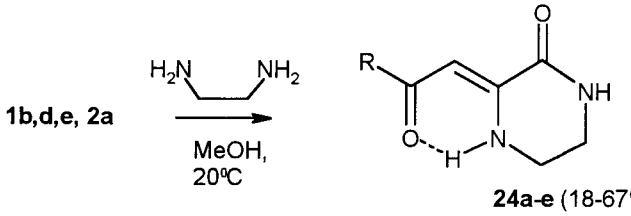
2. **Reactions with aliphatic and aromatic 1,2-dinucleophiles.**

Non-fluorinated acyl(aroyl)pyruvates react with 1,2-dinucleophiles at the α–keto ester fragment to form piperazinone derivatives (in the case of ethylenediamine),[28] substituted quinoxalones (with *o*-phenylenediamine),[29,30] or benzoxazinone derivatives (with *o*-aminophenol).[30,31]

We have found that condensation of polyfluoroacylpyruvates (**1b,d,e**) with ethylenediamine results in the formation of 3-(2-oxofluoroalkylidene)piperazin-2-ones (**24a-c**) in MeOH at room temperature (Scheme 13). Similar treatment of **1b-e** with *o*-phenylenediamine results in the formation of 3-(2-oxofluoroalkylidene)-1,2,3,4-tetrahydroquinoxalin-2-ones (**25a-d**).[13] The same products were derived from chelates (**3b-c**).[23]

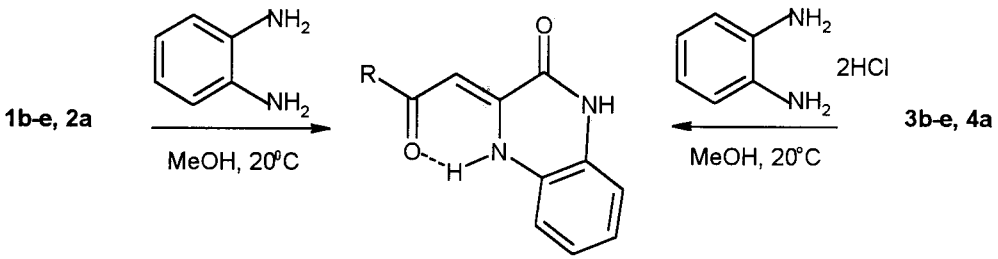
Under mild conditions pentafluorobenzoylpyruvate (**2a**) reacts with ethylenediamine to give piperazinone (**24d**). When heating **2a** with ethylenediamine, a piperazinone (**24e**) with a 2-hydroxytetrafluorophenyl substituent was obtained (Scheme 13).[25] The mechanism of this latter process is discussed below.

The condensation of pentafluorobenzoylpyruvate (**2a**) or its copper chelate (**4a**) with *o*-phenylenediamine furnishes quinoxalone (**25e**) (Scheme 13).[23,25]



24a-e (18-67%)

R = CF_3 (**24a**), C_4F_9 (**24b**), CHF_2 (**24c**), C_6F_5 (**24d**), *o*-HOC_6F_4 (**24e**)

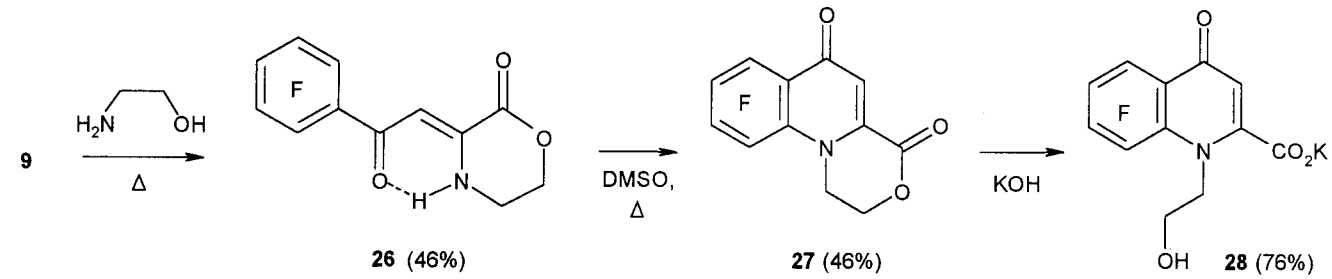


25a-e (50-85%)

R = CF_3 (**25a**), Me (**25b**), C_4F_9 (**25c**), CHF_2 (**25d**), C_6F_5 (**25e**)

Scheme 13

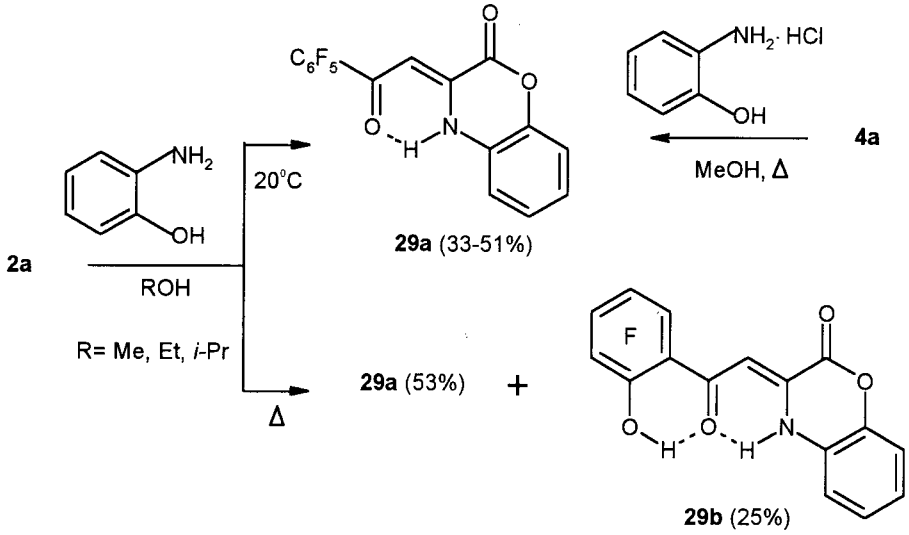
Interaction of pentafluorobenzoylpyruvic acid (**9**) with ethanolamine in dioxane results in the formation of 3-pentafluorobenzoylmethylidenemorpholin-2-one (**26**), which cyclizes to 7,8,9,10-tetrafluoro-4-oxo-1,2,4,5-tetrahydro[1,4]oxazino[4,3-*a*]-4-quinolone (**27**) upon heating in DMSO.[17] Alkaline hydrolysis of oxazinone (**27**) leads to the potassium salt of 5,6,7,8-tetrafluoro-1-(2-hydroxylethyl)-4-quinolinone-2-carboxylic acid (**28**) (Scheme 14).[17] This is one of the few known methods of fluorinated quinolone-2-carboxylic acids synthesis.



26 (46%) **27** (46%) **28** (76%)

Scheme 14

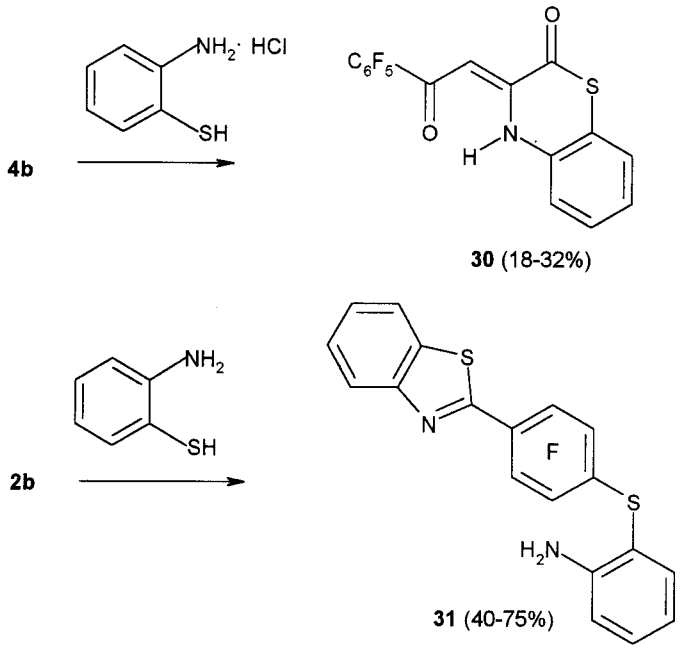
Pentafluorobenzoylpyruvate (**2a**) and its chelate (**4a**) react with *o*-aminophenol (or its hydrochloride) under mild conditions to form 3-pentafluorobenzoylmethylidene-2*H*-1,4-benzoxazin-2-one (**29a**). Under more drastic conditions a benzoxazinone (**29b**) with a 2-hydroxytetrafluorophenyl substituent may be obtained similar to the that produced in the reaction with ethylenediamine (Scheme 15).[25,32]



Scheme 15

We believe that the heterocycles (**24e**) and (**29b**) with a 2-hydroxytetrafluorophenyl substituent arise from the interaction of the diamine with 2-ethoxycarbonylchromone (**5a**) or 2-carboxychromone (**11**) formed as intermediates in this reaction. This was confirmed by independent synthesis of these compounds directly from 2-ethoxycarbonyl- (**5a**) and 2-carboxychromones (**11**).[25,32]

The chelate of pentafluorobenzoylpyruvate (**4b**) reacts with *o*-aminothiophenol hydrochloride at the α-keto ester fragment to give 3-pentafluorobenzoylmethylidene-2*H*-1,4-benzothiazin-4-one (**30**).[15] In contrast to chelate (**4b**), ester (**2b**) undergoes acid cleavage and nucleophilic displacement of the aromatic fluorine atom under mild conditions to form 2-(4-(2-aminophenylthio-2,3,5,6-tetrafluoro)phenyl)benzothiazole (**31**) in the reaction with *o*-aminothiophenol (Scheme 16).[15]



Scheme 16

In general, polyfluoroacylpyruvates (**1**) react with hydrazines at the β-dicarbonyl and with ethylenediamine or *o*-phenylenediamine at the α-dicarbonyl fragments. The attack of the amino group of an NH-dinucleophile at the C2 electrophilic center is likely to be the first step in these reactions and is determined by orbital control. The attack of the second amino group may proceed either at the C1 or C4 center. In the case of hydrazines, the nucleophilic attack occurs at the C4 center to give five-membered heterocycles (Schemes 8-10). In the case of ethylenediamine and *o*-phenylenediamine condensation takes place at the C1 center to form six-membered heterocycles (Scheme 13) and is likely due to thermodynamic factors.

The cyclization pathway with the formation of 2-ethoxycarbonylchromone (**5a**) predominates in the reactions of diamines with pentafluorobenzoylpyruvate (**2a**). The latter reacts with hydrazines and hydroxylamine at the β-dicarbonyl fragment (Scheme 12) and with ethylenediamine, *o*-phenylenediamine, and *o*-aminophenol at the α-dicarbonyl fragment (Schemes 13,15,16).

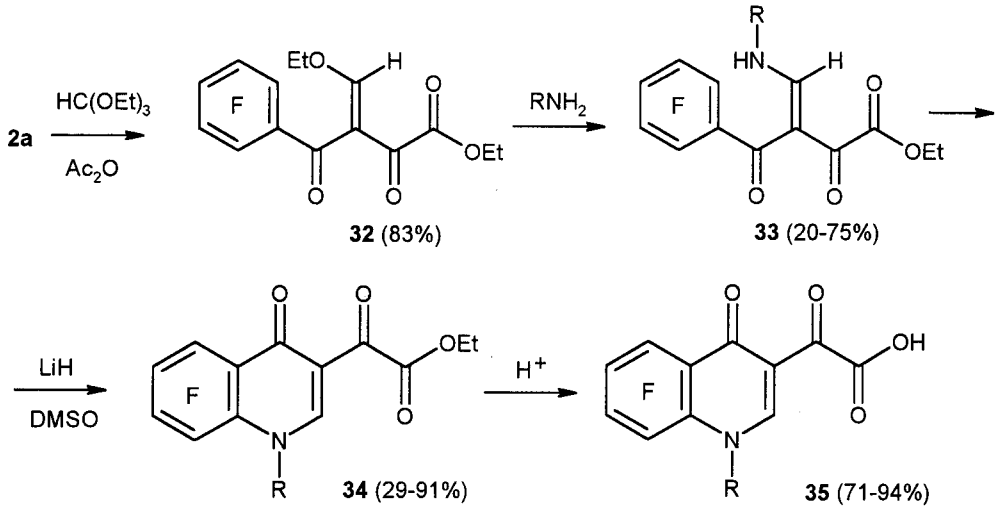
It should be noted that using the corresponding copper chelates of di- and tricarbonyl compounds instead of the free ligands does not always result in the formation of the same products. For example, interaction of copper acylpyruvates (**3**) with hydrazines produces pyrazoles (**16**) rather than hydroxysubstituted pyrazoles (**15**) (Schemes 8,10), which is likely to be due to the template effect of the copper cation.

In addition, employing the copper chelate of pentafluorobenzoylpyruvate (**4**) in the reaction with *o*-thioaminophenol makes it possible to obtain benzothiazine (**31**), while under identical conditions the free ligand (**2**) undergoes acid cleavage (Scheme 16).

VI. Synthesis and reactions of 3-substituted pentafluorobenzoyl(trifluoroacetyl)pyruvates

The ability of pentafluorobenzoylpyruvate to react at the C3 center is important for the synthesis of fluorine-containing chromone, quinolone and cinnolone derivatives.

We have found that pentafluorobenzoylpyruvate (**2a**) (like other β-dicarbonyl compounds)[4,5,10,33] reacts with ethyl orthoformiate to furnish ethyl 3-ethoxymethylene-2,4-dioxo-4-pentafluorophenylbutyrate (**32**).



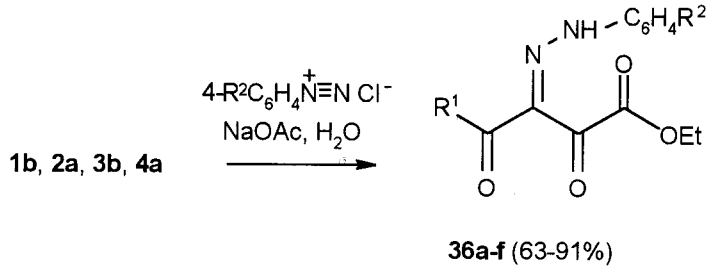
R= H, Me, Et, cyclo-Pr, C_6H_{13}, C_2H_4OH, *o*-MeC_6H_4

Scheme 17

The interaction of the latter with amines results in 1-substituted 3-ethoxalyl-5,6,7,8-tetrafluoro-4-quinolones (**34**) *via* the intermediate formation of ethyl 3-alkylaminomethylidene-2,4-dioxo-4-pentafluorophenylbutyrates (**33**). Compounds (**34**) were hydrolyzed to 1-substituted 2-(5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinolin-3-yl)glyoxylic acids (**35**) (Scheme 17).[34] Esters (**34**) and their acids (**35**) are useful building blocks for the following transformations.

1,3-Dicarbonyl compounds are known to react with aryldiazonium salts to form the corresponding 2-arylhydrazone-1,2,3-tricarbonyl compounds.[35] Data on the coupling of fluorine-containing 1,3-dicarbonyl compounds are available only for the transformations of a few fluorinated 1,3-diketones,[36,37] trifluoroacetoacetic[36] and pentafluorobenzoylacetic[38] esters. Recently, we have described the synthesis of fluorinated 2-arylhydrazono-1,3-dicarbonyl compounds and studied their reactions with N,O-dinucleopiles.[39,40] Data on the synthesis of arylhydrazones from fluorinated acyl(aroyl)pyruvic esters are not available, although their non-fluorinated analogues have been known.[41]

For the first time 3-arylhydrazones (**36a-f**) of 5,5,5-trifluoro-2,3,4-trioxopentanoate and 4-pentafluorophenyl-2,3,4-trioxobutyrate were synthesized by coupling of fluoroacyl(aroyl)pyruvates (**1b,2a**) or their chelates (**3b,4a**) with aryldiazonium chlorides (Scheme 18).[40]



36a-f (63-91%)

R^1= CF_3, R^2= H (**36a**); Me (**36b**), OMe (**36c**);
R^1= C_6F_5, R^2= H (**36d**); Me (**36e**), OMe (**36f**).

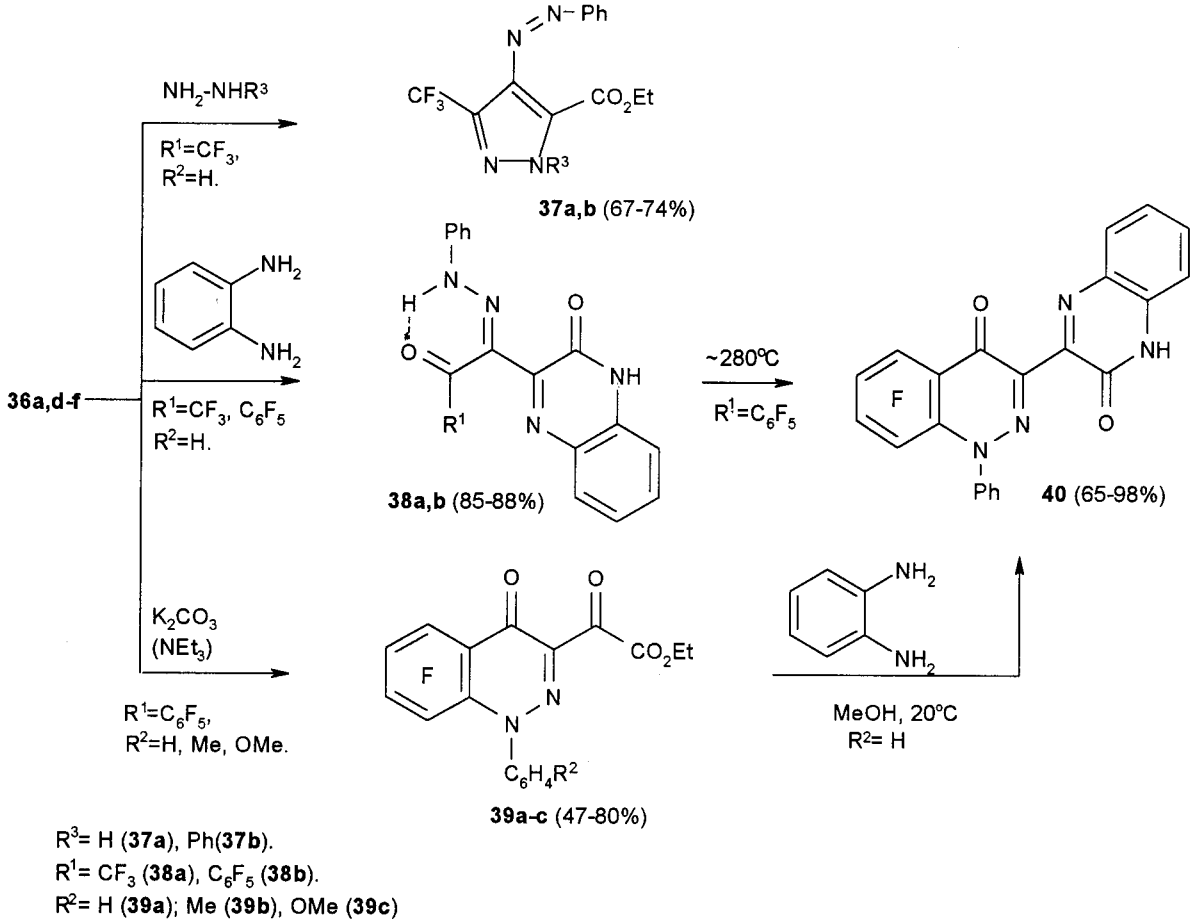
Scheme 18

The arylhydrazones (**36**) were used as precursors for the synthesis of the following heterocycles. Hydrazone (**36a**) reacts with hydrazine hydrate and phenylhydrazine to yield 1-substituted 5-ethoxycarbonyl-4-phenylazo-3-trifluoromethylpyrazoles (**37a,b**), unlike the pentafluorophenyl substituted analogue (**36d**). A similar reaction of this latter analog gives a mixture of products that is difficult to separate. Arylhydrazones (**36a,d**) upon treatment with *o*-phenylenediamine in refluxing ether form 3-(2-substituted-1,2-dioxo-1-phenylhydrazone)-1,2-dihydroquinoxalin-2-ones (**38a,b**) (Scheme 19).[40]

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

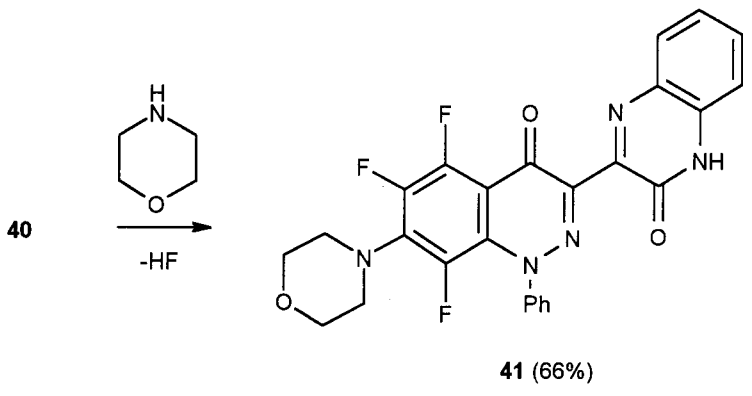
The arylhydrazones derived from benzoylacetic esters with *ortho*-fluorine atoms are known to undergo cyclization through nucleophilic displacement of an *ortho*-fluorine atom to give a cinnolone structure. We have found that arylhydrazones of pentafluorobenzoylpyruvic ester (**36d-f**) form 3-ethoxalyl-5,6,7,8-tetrafluoro-1-aryl-1,4-dihydrocinnolin-4-ones (**39a-c**) (Scheme 19) upon heating in DMSO at 100°C in presence of K_2CO_3 and dibenzo-18-crown-6, or refluxing in $CHCl_3$ with an excess of triethylamine.[40]

Compound (**38b**) also undergoes intramolecular cyclization to yield 5,6,7,8-tetrafluoro-3-(2-oxo-1,2-dihydroquinoxalin-3-yl)-1-phenyl-1,4-dihydrocinnolin-4-one (**40**). The same compound was isolated from the reaction of cinnolinone (**39a**) with *o*-phenylenediamine (Scheme 19).



Scheme 19

The nucleophilic substitution of the fluorine atom at the C7 carbon atom by different alkylamines is typical both for fluorine-containing cinnolinones, fluorochromones, and fluoroquinolones.[5] The reaction of cinnolinone (**40**) with an excess of morpholine in DMSO leads to the 7-substituted product – 5,6,8-trifluoro-7-morpholino-3-(2-oxo-1,2-dihydroquinoxalin-3-yl)-1-phenyl-1,4-dihydrocinnolin-4-one (**41**) (Scheme 20).[40]

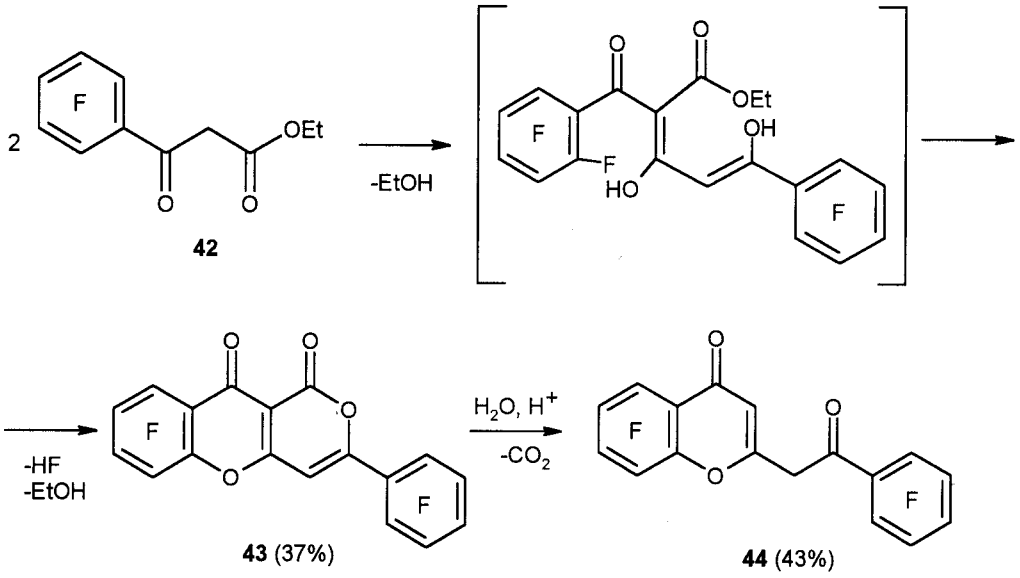


Scheme 20

In general, 3-alkoxymethylidene- and 3-arylhydrazone derivatives of fluoroacyl(aroyl)pyruvates may serve as building blocks for a variety of novel fluoroheterocycles.

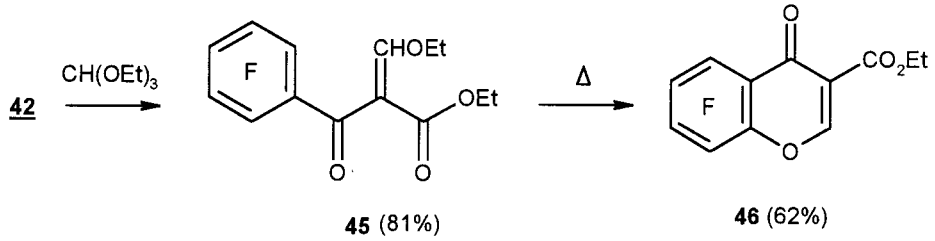
VII. **Reactions of 2-ethoxycarbonyl(carboxy)-5,6,7,8-tetrafluorochromones**

The formation of 2-ethoxycarbonylchromone (**5a**) from pentafluorobenzoylpyruvate (**2a**) or its copper chelate (**4a**) is a specific feature of these compounds, that takes place *via* cyclization to a six-membered ring (Scheme 1).[10] Under identical reaction conditions ethyl pentafluorobenzoylacetate (**42**) undergoes self-condensation to furnish 1-oxo-3-pentafluorophenyl-1*H*-pyrano[4,3-*b*]6,7,8,9-tetrafluorochromone (**43**) (Scheme 21).[42] The latter was hydrolyzed to 2-pentafluorobenzoylmethyl-5,6,7,8-tetrafluorochromone (**44**). It is known that such self-condensations are typical for both fluorinated[43] and non-fluorinated[44] β-keto esters. Nevertheless, for pentafluorobenzoylpyruvate (**2a**) the cyclization pathway is preferred.



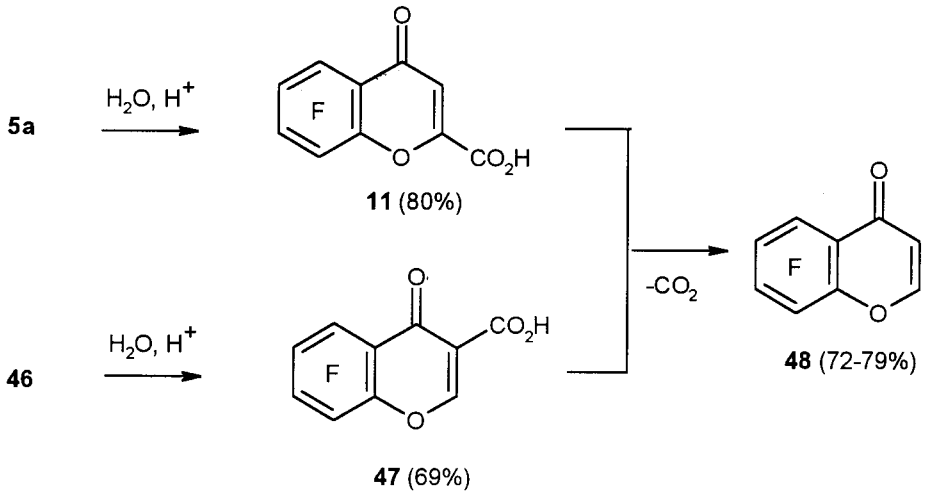
Scheme 21

Cyclization of ethyl 2-ethoxymethylidenepentafluorobenzoylacetate (**45**) affords 3-ethoxycarbonyl-5,6,7,8-tetrafluorochromone (**44**) in analogy to ester (**2a**) (Scheme 22).[10]



Scheme 22

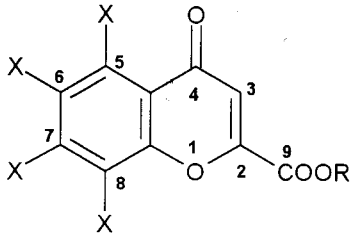
Esters (**5a**) and (**46**) were readily hydrolyzed under acidic conditions to give the isomeric carboxylic acids (**11**) and (**47**), respectively. Sublimation of either of the two acids (**11**) and (**47**) produces 5,6,7,8-tetrafluorochromone (**48**) (Scheme 23).[10]



Scheme 23

To discuss the reactivity of fluorochromones the Fukui indices and the charge distribution were calculated using the AM1 method[13] for 2-methoxycarbonyl-5,6,7,8-tetrafluorochromone, 2-carboxy-5,6,7,8-tetrafluorochromone, its anion, and the non-fluorinated analog (Table 2).[45]

Table 2. Charges and Fukui indices at electrophilic centers of the substituted chromones.



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

Based on these calculations the following rules became evident:

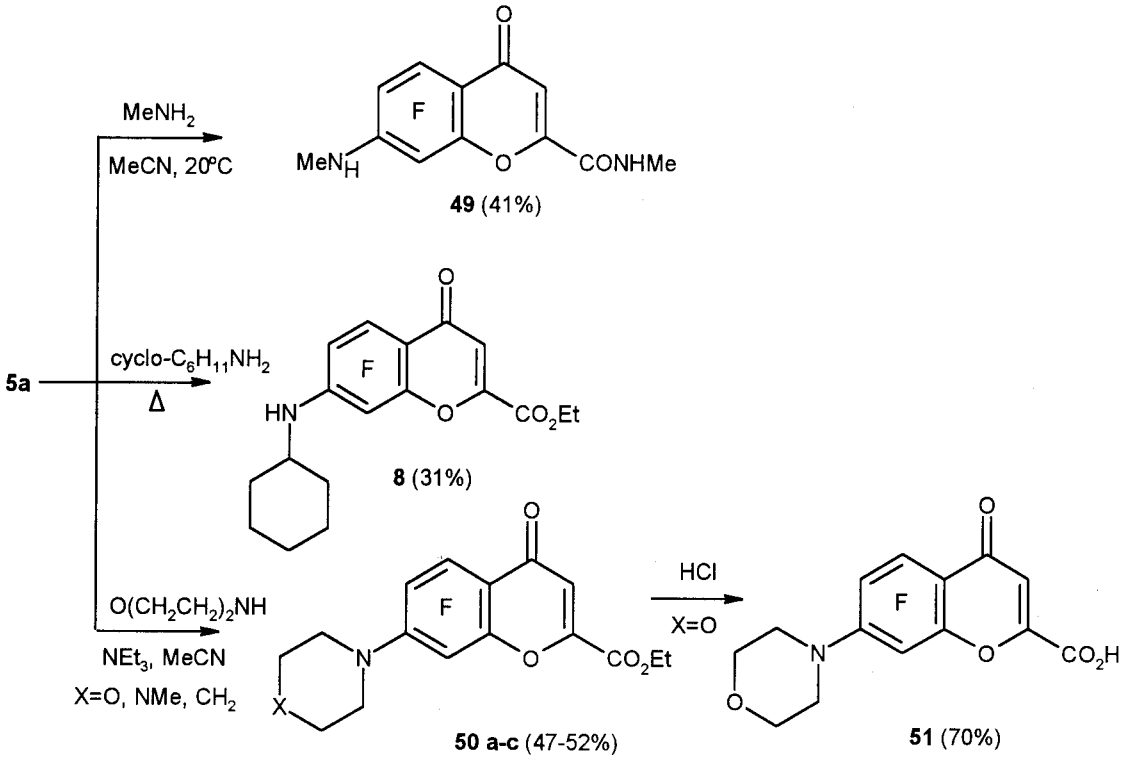
a) the fluorine atoms do not affect significantly the charge distribution in the pyrone ring;

b) the maximum positive charge in all these compounds is located at the C9 carbon atom;
c) the next highest positive charge is at the C4 carbon atom of the pyrone ring;
d) the maximum positive charge in fluoroaromatic cycle is located at the C5 position.

For the ester and acid of fluorochromone the highest electron deficit is at the C7 atom of the LUMO, the next in descending order is at the C4 carbon atom. For the anion the largest electron deficit is at the C4 atom. In the fluoroaromatic ring the largest electron deficit is at the C7 atom for all compounds in this series.

Therefore, if a reaction process is kinetically controlled, the C9 carbon atom will be the preferable site of the attack of a nucleophilic reagent in accordance with the charge control. On the other hand, the C2 carbon atom will be the site of attack for ester, acid and the C4 of the anion in accordance with the orbital control. The orbital controlled nucleophilic displacement of the fluorine atom will take place at the C7 atom, rather than at C5 and C8 carbon atoms.[45]

We have also observed the different reactivity of 2-ethoxycarbonyl- (**5a**) and 2-carboxychromones (**11**) towards ammonia and primary amines.[18] Thus, 2-ethoxycarbonylchromone (**5a**) does not react with ammonia or phenylamine. The treatment of the chromone (**5a**) with methylamine furnishes the *N*-methylamide of 5,6,8-trifluoro-7-methylaminochromone-2-carboxylic acid (**49**), which results from reaction at the ethoxycarbonyl group and nucleophilic displacement of the fluorine atom at the C7 position of the heterocycle (Scheme 24).[19] This is quite untypical for the known chromone structures. Under these conditions the latter undergoes opening of the heterocycle due to the addition of the nucleophile to the C2 center.



X= O (**50a**), NMe (**50b**), CH_2 (**50c**)

Scheme 24

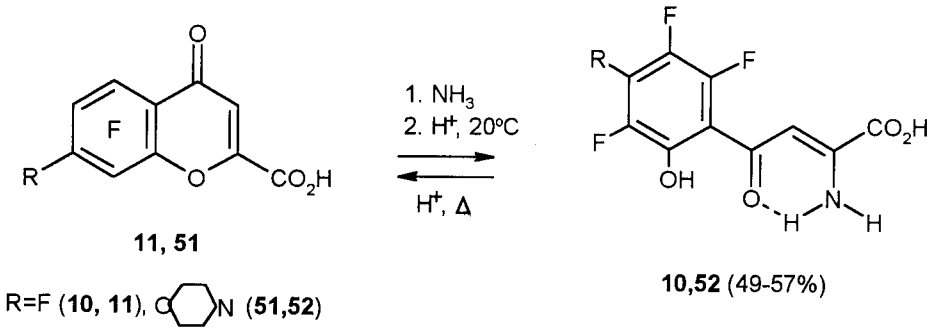
In the reaction of chromone (**5a**) with cyclohexylamine the displacement of the fluorine atom at the C7

position takes place only to form compound (**8**) in accordance w ı an orbital controlled process (Scheme 24).[45] However, the formation of methylamide (**49**) is determined by charge control.

Interaction of chromone (**5a**) with secondary amines (i.e. morpholine, *N*-methylpiperazine, piperidine) occurs in the same manner, not interfering with the heterocycle (typical for reactions of non-fluorinated chromones with secondary amines), but instead results in the formation of 7-substituted 2-ethoxycarbonyl-5,6,8-trifluorochromones (**50a-c**) (Scheme 24). Chromone (**50a**) gives 5,6,8-trifluoro-7-morpholinechromone-2-carboxylic acid (**51**) on refluxing with HCl.[18]

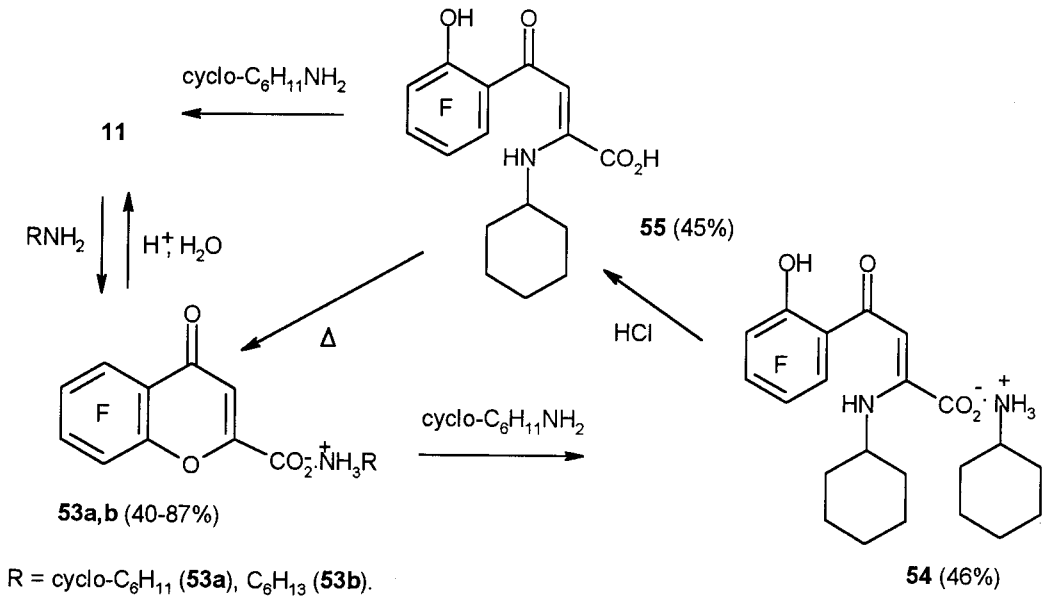
Thus, the reactions of chromone (**5a**) with primary and secondary amines are orbital controlled and furnish the coresponding 7-substituted products.

In contrast to ester (**5a**), chromonecarboxylic acids (**11**) and (**51**) readily undergo cleavage of the heterocyclic ring when treated with an excess of ammonia to yield 2-amino-3-(4-substituted-3,5,6-trifluoro-2-hydroxybenzoyl)acrylic acids (**10**) (R = F) and (**52**) (R = morpholino). Refluxing compounds (**10**) and (**52**) in an acid medium results in the formation of the starting compounds (**11**) and (**51**) (Scheme 25).[18]



Scheme 25

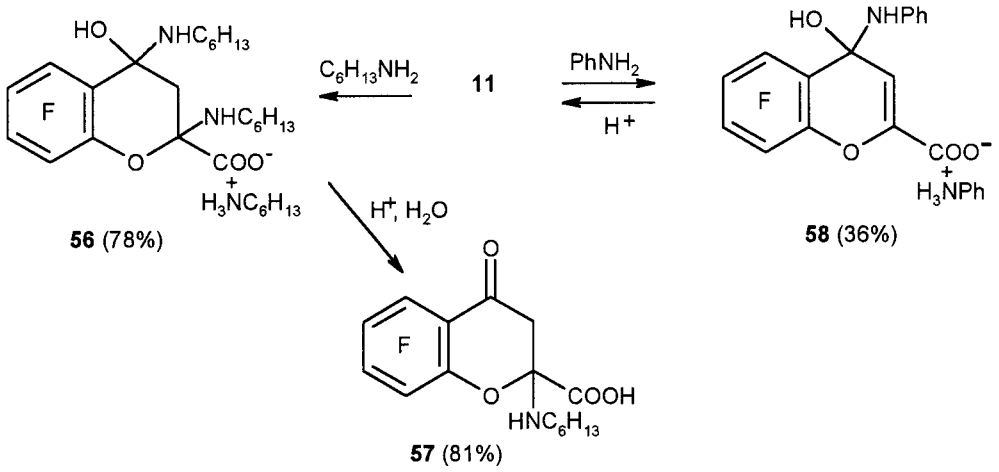
Reaction path of chromone (**11**) with primary amines depends on both the nature of the amine and the reaction conditions.[45] Refluxing chromone (**11**) in dioxane with equimolar amounts of amine (cyclohexylamine, hexylamine) furnishes (cyclo)hexylammonium 5,6,7,8-tetrafluorochromone-2-carboxylates (**53a,b**) (Scheme 26).



Scheme 26

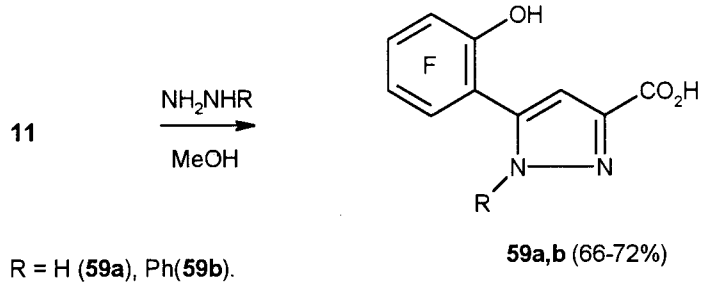
These salts (**53a,b**) are stable upon refluxing in toluene, and react differently ambiguously with an excess of the amine. Thus, compound (**53a**) undergoes opening of chromone heterocycle to form cyclohexylammonium 2-cyclohexylamino-3-(3,4,5,6-tetrafluoro-2-hydroxybenzoyl)acrylate (**54**). The treatment of this salt with HCl produces 2-cyclohexylamino-3-(3,4,5,6-tetrafluoro-2-hydroxybenzoyl)acrylic acid (**55**). The same treatment of hexylammonium salt (**53b**) gives the starting chromone (**11**).[45]

In the reaction of 2-carboxychromone (**11**) with hexylamine and aniline, both a nucleophilic addition at the activated C=C bond and an interaction at the carbonyl group of the chromone ring may occur, which makes it possible to characterize 2-carboxychromone as a typical carbonyl vinylog.[18] Thus, chromone (**11**) reacts with hexylamine to form hexylammonium 2,4-bis(hexylamino)-5,6,7,8-tetrafluoro-4-hydroxychromanyl-2-carboxylate (**56**) (Scheme 27). The treatment of the latter with HCl results in 2-carboxy-5,6,7,8-tetrafluoro-2-hexylaminochroman-4-one (**57**). Chromone (**11**) with aniline gives anilinium 4-anilino-5,6,7,8-tetrafluoro-4-hydroxychromanyl-2-carboxylate (**58**)[18].



Scheme 27

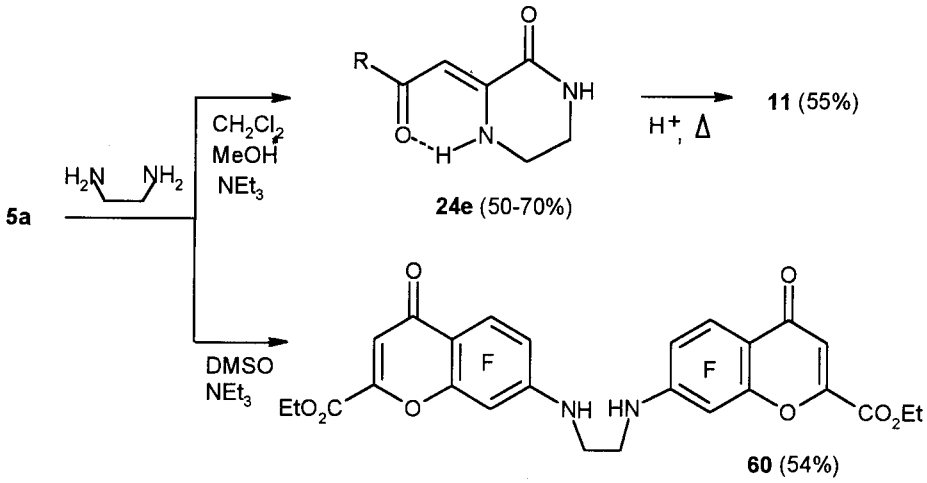
2-Ethoxycarbonylchromone (**5a**) reacts with hydrazine to give a mixture of products that is difficult to separate. In contrast, the corresponding 1-substituted 5-(tetrafluoro-2-hydroxyphenyl)pyrazole-3-carboxylic acids (**59a,b**) were derived from 2-carboxychromone (**11**) on refluxing in MeOH with hydrazine and phenylhydrazine (Scheme 28).[45]



Scheme 28

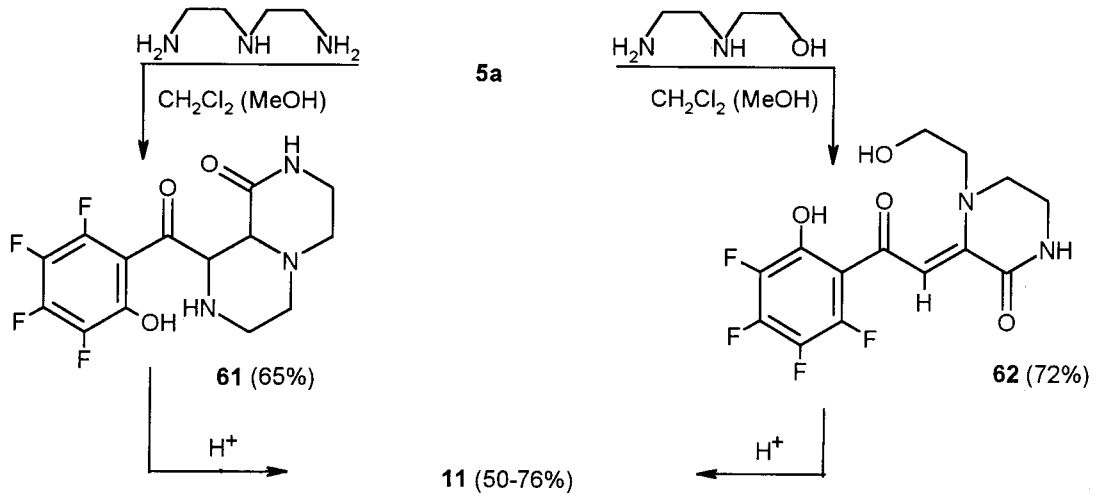
Depending on the solvent, the reaction of 2-ethoxycarbonylchromone (**5a**) with ethylenediamine gives either piperazinone (**24e**) *via* addition of the amine to the α-dicarbonyl fragment, or an aromatic displacement product at the C7 position – 7-*N,N'*-ethylenebis-(7-amino-2-ethoxycarbonyl-5,6,8-

trifluorophenylchromone) (**60**) (Scheme 29).[18] The electron-withdrawing character of the polyfluoroaryl ring (hence the ability of a nucleophilic substitution of a fluorine atom) greatly increases in switching from protoic solvents (i.e. alcohols) to aprotoic solvents (i.e. DMSO).[46] This explains the formation of compound (**24e**) in alcohols and product (**60**) in DMSO. However, piperazinone (**24e**) also may be obtained from chromone (**5a**) and ethylenediamine in acetonitrile.[18] Probably, acetonitrile (unlike DMSO) cannot prevent the formation of an ionic pair of ethylenediamine and the chromone, either at the electrophilic carbon atom of the ethoxycarbonyl group or at the C2 carbon atom.



Scheme 29

2-Ethoxycarbonylchromone (**5a**) reacts with diethylenetriamine at all three nucleophilic centers to form 9-(3,4,5,6-tetrafluoro-2-hydroxybenzoyl)perhydropyrazino[1,2-*a*]pyrazin-1-one (**61**) (Scheme 30),[47] similarly to the reaction of perfluoropentene or the heptafluoroacetylacetone aza-analogue with diethylenetriamine.[48]

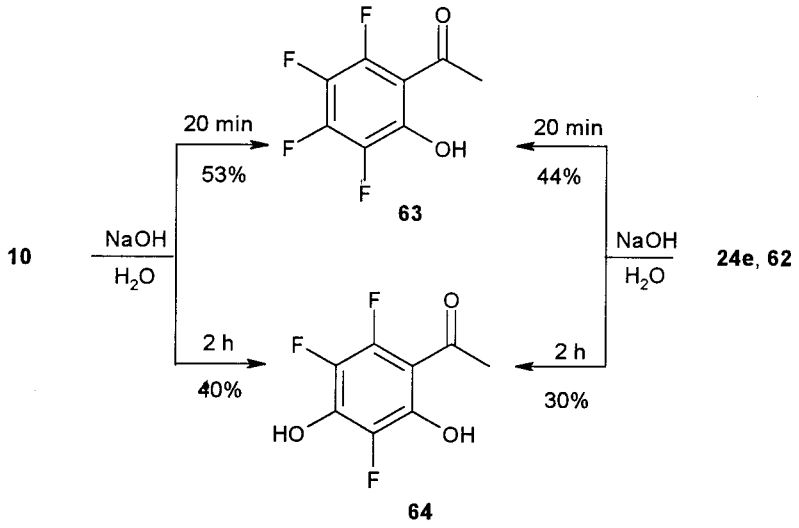


Scheme 30

In contrast, under these conditions the reaction of chromone (**5a**) with *N*-(2-hydroxyethyl)ethylenediamine affords 3-(3,4,5,6-tetrafluoro-2-hydroxybenzoylmethylidene)-4-hydroxyethylpiperazin-2-one (**62**) only (Scheme 30).[47]

Attempts to subject product (**62**) to further cyclization failed. Acid catalysis of the reaction causes hydrolysis of **62** to chromone (**11**). The starting piperazine (**62**) remains unchanged in refluxing in toluene even in the presence of *p*-toluenesulfonic acid; heating in alkaline medium results in acid cleavage of

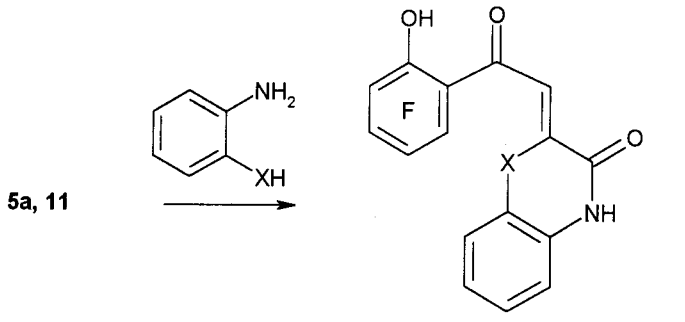
product (**62**) to 3,5,6-trifluoro-2,4-dihydroxyacetophenone (**63**) or 3,4,5,6-trifluoro-2-hydroxyacetophenone (**64**) depending on the reaction time (Scheme 31).[47]



Scheme 31

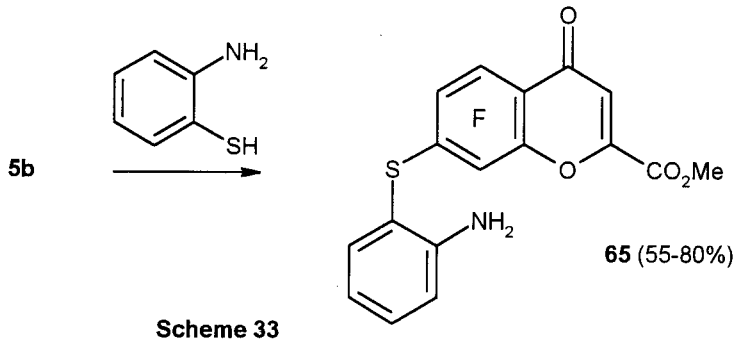
Under the same conditions piperazinone (**24e**) and aminoacrylic acid (**10**) are also subjected to cleavage to dihydroxy(hydroxy)polyfluoroacetophenones (**63,64**) (Scheme 31).[49]

2-Ethoxycarbonylchromone (**5a**) reacts with *o*-phenylenediamine to give the quinoxaline derivative (**25f**). The same product may be prepared by treatment of 2-carboxychromone (**11**) with *o*-phenylenediamine (Scheme 32).[45] Benzoxazinone (**29b**) with a hydroxytetrafluorophenyl moiety is derived from chromones (**5a**) and (**11**) on refluxing with *o*-aminophenol (Scheme 32).[25,32]



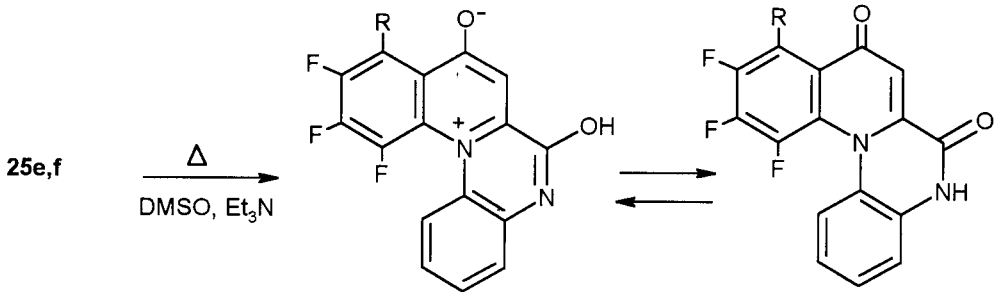
Scheme 32

2-Methoxycarbonylchromone (**5b**) with *o*-aminothiophenol forms 7-(2-aminothiophenol)-5,6,8-trifluoro-2-methoxycarbonylchromone (**65**) as a result of nucleophilic displacement of the fluorine atom at the C7 position of heterocycle (Scheme 33).[15]



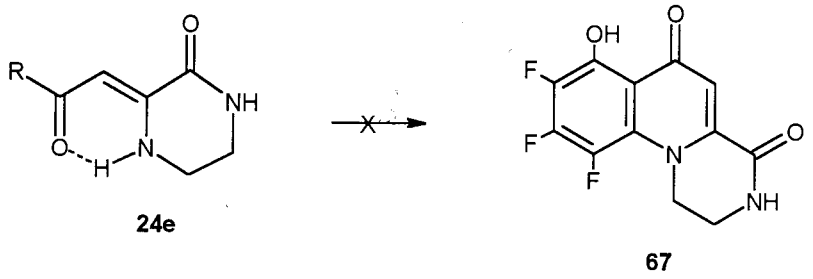
Scheme 33

Heating quinoxalones (**25f**) and (**25e**) in DMSO in the presence of triethylamine results in products derived by heterocyclization, namely 4-substituted 1,2,3-trifluoro-(5*H*)-5-oxoquinolino[1,2-*a*]-8*H*-quinoxalin-7-ones (**66a,b**) (Scheme 34).[45] The driving force for these processes is probably the aromatic character of the presumed zwitterionic intermediate.



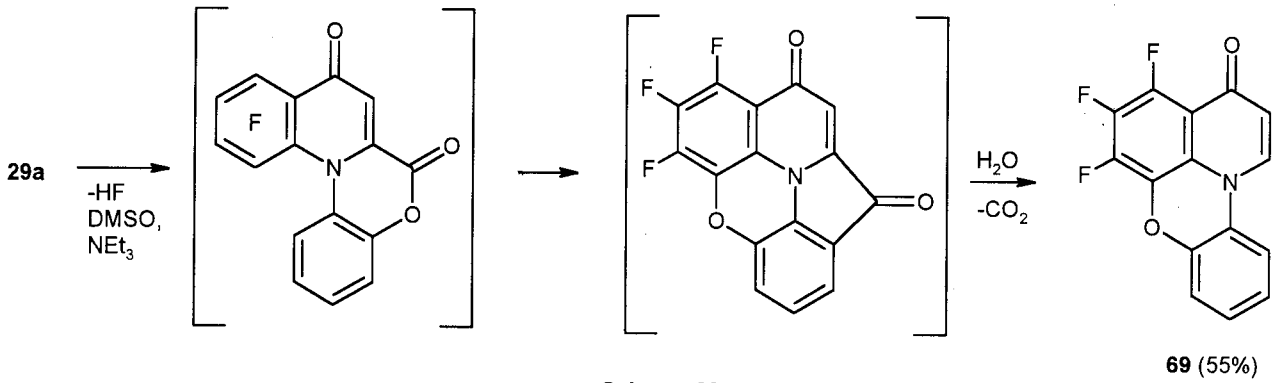
Scheme 34

In this context, it is interesting to note that piperazinone (**24e**) does not form the corresponding heterocyclic system (**67**), neither under these conditions nor upon heating in the presence of LiH or K_2CO_3. This is likely due to the absence of any aromatic character of its possible isomers (Scheme 35).[45]



Scheme 35

Benzoxazine derivative (**29a**) also undergoes cyclization on heating in DMSO to form 4,5,6-trifluoro-3*H*-pyrido[3,2,1-*k,l*]phenoxazin-3-one (**68**) as the final product (unlike the above-mentioned transformation of quinoxalines (**25e,f**) to quinolinequinoxalone (**66**) (Scheme 36)). The formation of product (**68**) is likely to occur through the intermediates shown in Scheme 36.[50]



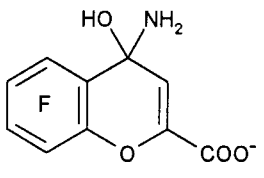
Scheme 36

Summing up the data on the interaction of 2-ethoxycarbonyl- (**5a**) and 2-carboxy chromones (**11**) with dinucleophiles it can be assumed that the reaction mechanism is different at the first stages although the end products may be similar (for example, in the reaction with *o*-phenylenediamine).

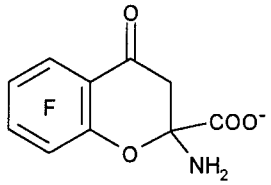
The first reaction step of ester (**5**) with *N*-dinucleophiles possibly involves the attack of the amino group at the electrophilic center C9 of the chromone system in accordance with a charge controlled process. The formation of *N*-methylamide (**49**) in the reaction of ester (**5**) with methylamine confirms this supposition. However, the attack of nucleophiles can also take place at the C7 center in an excess of methylamine in accordance with an orbital controlled process. Orbital control may predominate in: a) the reaction of 2-ethoxycarbonylchromone (**5a**) with cyclohexylamine in dioxane resulting in the formation of the 7-substituted products (**50, 8**) (Scheme 24); b) the interaction of chromone (**5a**) with ethylenediamine in DMSO resulting in compound (**60**) (Scheme 29). This is probably due to the specific solvation of the starting reagents by the solvent similarly to that proceeding in the reaction of 5-aryl-2,3-dihydrofurane-2,3-diones with aromatic amines in dioxane.[51]

In the next step the second aminogroup of the *N*-nucleophile (ethylenediamine, *o*-phenylenediamine, *o*-aminophenol) attacks the nearest atom (C2) of the chromone system (**5**), followed by cleavage of the heterocyclic ring and the formation of new heterocycles (piperazinone (**24e**), quinoxalinone (**25f**), benzoxazinone (**29b**)) (Scheme 29,32). This is obviously due to thermodynamic factors.

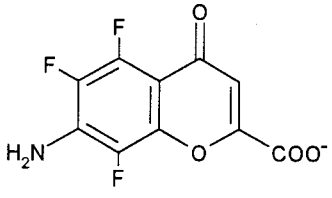
In contrast to 2-ethoxycarbonylchromone (**5**), 2-carboxychromone (**11**) reacts with equimolar amount of the primary amine to furnish salts (**53**) (Scheme 26). The reaction of chromonecarboxylate with an excess of amine proceeds in different ways: heating in dioxane results in resinification of the reaction mass, while in aqueous media the reversible interaction of the anion with the amino group of a primary amine at the electrophilic centers C2 and C4 of the chromone takes place. When the reaction occurs at the carbon atom C2 of the chromone, two pathways are possible: a) the addition of the amine to double bond C2=C3 (products **57** and **58** (Scheme 27)); or b) the formation of 2-aminoacrylic acid derivatives (compounds **10**, **54**, **56**) due to opening of the chromone heterocycle similarly to that occurring in the reaction with ammonia or cyclohexylamine (Scheme 26). However, the products of cyclohexylamine addition undergo identical transformations upon heating in dioxane to form more stable salts.



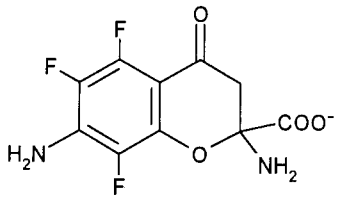
Δ H=−1313.94



ΔH=−1388.47



ΔH=−1128



ΔH=−1217

If the process is kinetically controlled the attack at the C4 center is possible in accordance with charge control since the charge at this atom is the highest apart from the C9 carbon. However, the attack of the amine nucleophile at the C2 atom of the carboxylic anion, like 2-ethoxycarbonylchromone, is not kinetically controlled. Actually, calculations of model systems have shown that the attack of a nucleophile at the C2 atom of fluorinated carboxylic anions results in more stable reaction products than attack at nucleophilic centers C4 and C7. This follows from comparison of products formation enthalpies (ΔH= kJ·mol^{-1}).[45]

The formation of the corresponding carboxylic anion followed by the attack of a nucleophile at atom C2 of the chromone (an excess of hydrazine or second amino group of *o*-phenylenediamine) is also

characteristic of the interaction of 2-carboxychromone (**11**) with hydrazines and *o*-phenylenediamine. The further course of the reaction depends on the thermodynamic stability of the final end products, similarly to that for non-fluorinated aroylpyruvic acids.

VIII. **Conclusion**

In the present work, we have shown that fluorinated acyl(aroyl)pyruvates have the reactivity of both α- and β-dicarbonyl compounds similarly to their non-fluorinated analogues. Thus, acyl(aroyl)pyruvates react with hydrazines and hydroxylamine at the β-dicarbonyl fragment to form the corresponding pyrazoles or isoxazoles similarly to β-diketones and β-keto esters. As in the cases of α-dicabonyl compounds, polyfluoroacyl(aroyl)pyruvates react with diamines (ethylenediamine, ethanolamine, *o*-phenylenediamine, *o*-aminophenol, *o*-aminothiophenol) at the α-keto ester fragment to give piperazinone, morpholinone, quinoxalinone, benzoxazinone and benzothiazinone derivatives.

The introduction of fluorine atoms into the molecule of aroylpyruvate greatly changes its reactivity resulting in the formation of heterocycles which are not found for the non-fluorinated analogues – chromones, quinolones, cinnolones. The latter may be subjected to different transformations in reactions with HO-, HN- and HS-nucleophiles to afford novel heterocyclic systems.

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