Fluorinated Pyrones, Chromones and Coumarins

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Contents

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Abstract The synthesis, reactivity and applications of fluorinated α- and γ-pyrones, chromones and coumarins are reviewed. The literature data clearly indicate that these heterocycles are very attractive building blocks for the synthesis of various heterocyclic compounds containing the R^F group. This chapter reviews the significant advances in this area, highlighting new and interesting trifluoromethylated derivatives and their novel transformations. The bibliography includes 204 references.

Keywords Fluorinated heterocycles • 4-Pyrones • 2-Pyrones • Chromones • Coumarins

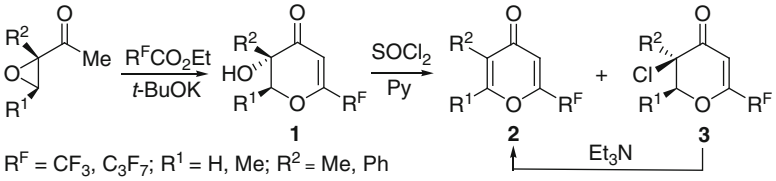
1 Fluorinated 4-Pyrones

4*H*-Pyran-4-ones (4-pyranones, 4-pyrones, γ-pyrones) containing polyfluoroalkyl substituents, especially the CF_3 group, serve as key precursors to a variety of fluorinated pyridine derivatives having a wide range of biological activities. For example, 2,6-bis(trifluoromethyl)-4-pyridols have been found useful as herbicides and fungicides as disclosed in patent literature [1a, b]. Certain 2-aryl-6-tri(di)fluoromethyl-4-pyrones selectively inhibit COX-2 in preference to COX-1 and are useful in the treatment of COX-2 mediated diseases, such as inflammation, pain, fever, and asthma with fewer side effects [1c]. Due to the powerful electron-withdrawing ability of R^F groups the insertion of polyfluoroalkyl substituents into the 2-position of 4-pyrone activates these molecules and dramatic differences in the reactivity of 2-alkyl(aryl)- and 2-(polyfluoroalkyl)-4-pyrones with respect to nucleophilic reagents are observed.

1.1 Synthesis of 2-(Polyfluoroalkyl)-4-Pyrones

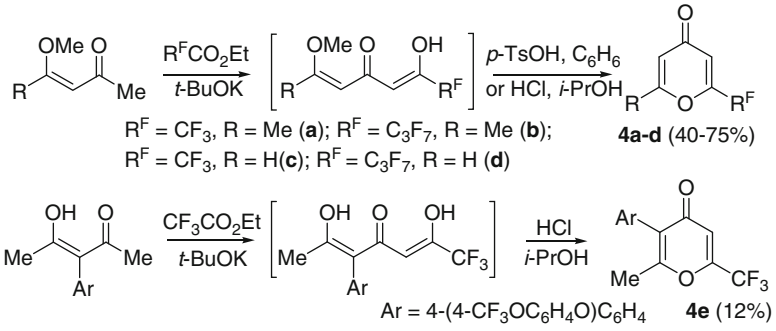
In addition to the considerable variety of methods for the synthesis of non-fluorinated γ-pyrones [2], Tyvorskii and co-workers have described three new procedures, which produced 2-(perfluoroalkyl)-4-pyrones. One of them is a convenient two-step synthesis of 5-substituted 2-(perfluoroalkyl)-4*H*-pyran-4-ones **2** by dehydration of 2,3-dihydro-3-hydroxy-6-(perfluoroalkyl)-4*H*-pyran-4-ones **1** prepared

by condensation of 2-acetyloxiranes with ethyl perfluoroalkanoates [3]. The reaction of dihydropyranones **1** with thionyl chloride in pyridine provides the desired pyrones **2** in 61–79 % yields with 10–15 % of chlorine-containing dihydropyrones **3**. Pure compounds **2** were prepared in good yields by the treatment of **1** with $SOCl_2$ followed by reflux of the crude products in Et_3N [4] (Scheme 1).



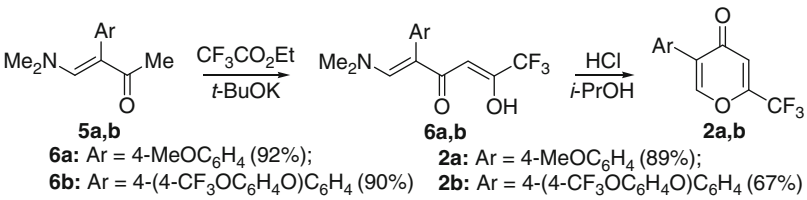
Scheme 1 Synthesis of pyrones **2**

Additionally, unsubstituted and 6-substituted 2-(perfluoroalkyl)-4*H*-pyran-4-ones **4** have been prepared using alkyl enolates derived from β-dicarbonyl compounds. The reaction of acetylacetone enol ether with ethyl perfluoroalkanoates in the presence of *t*-BuOK, followed by *p*-TsOH catalyzed cyclization in benzene afforded pyrones **4a,b** in 57–75 % yields. Similarly, the parent compounds **4c,d** were obtained from the formylacetone derivative in 40–64 % yields [4]. Analogue **4e** was accessible in low yield from the corresponding triketone [5] (Scheme 2).



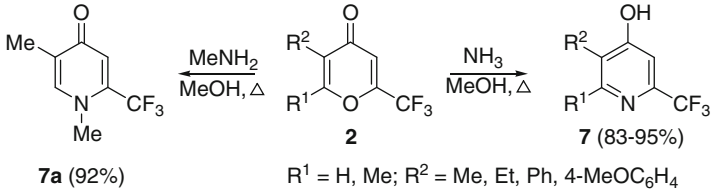
Scheme 2 Synthesis of pyrones **4**

The alternative way to 5-aryl substituted γ-pyrone **2a,b** is based on the readily available aminoenones **5a,b**. Reaction of **5a,b** with ethyl trifluoroacetate in the presence of *t*-BuOK afforded enamino diketones **6a,b** cyclized to pyrones **2a,b** [6]. Compounds **6b** and **2b** are starting materials for the preparation of 4-pyridones exhibited potent antimalarial activity [5] (Scheme 3).



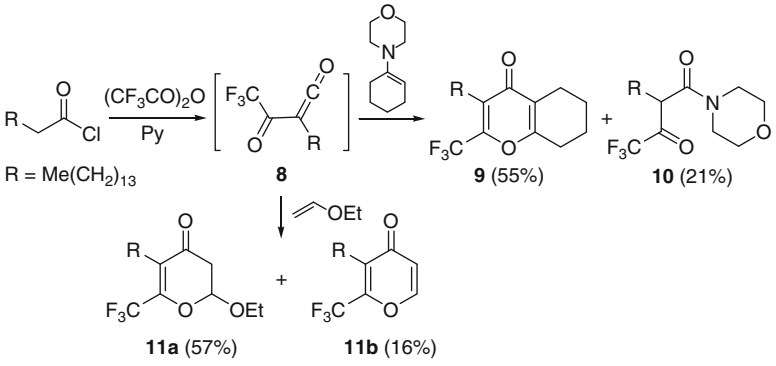
Scheme 3 Synthesis of pyrones **2a,b**

The ready availability of pyrones **2** and the enhanced reactivity at their α-position have made them the starting materials of choice for the synthesis of 2-(trifluoromethyl)-4-pyridinols **7** by reaction with ammonia or methylamine [6–8] (Scheme 4).



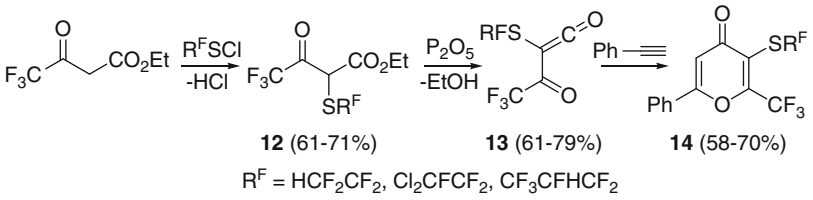
Scheme 4 Reactions of pyrones **2** with amines

Trifluoromethylated pyrones can also be prepared from acyl chlorides by reaction with pyridine and trifluoroacetic anhydride followed by capture of the intermediate trifluoroacyl ketene **8** with suitable reagents. Thus, addition of *N*-cyclohexenylmorpholine to the intermediate from palmitoyl chloride gave pyrone **9** as the major product, accompanied by amide **10**. Ethyl vinyl ether yielded pyrones **11a** and **11b** (through β-elimination of ethanol) [9] (Scheme 5).



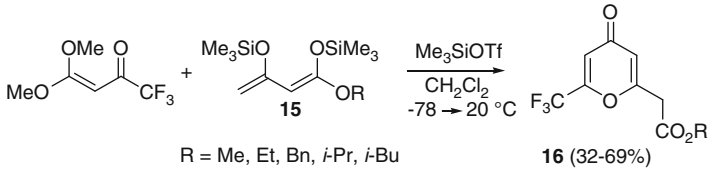
Scheme 5 Synthesis of pyrones **9** and **11**

Acylketene methodology [10] was also developed for the synthesis of 4-pyrones bearing a polyfluoroalkylthio substituent. The reaction of ethyl trifluoroacetoacetate with fluoroalkanesulfenyl chlorides afforded compounds **12** (Scheme 6).



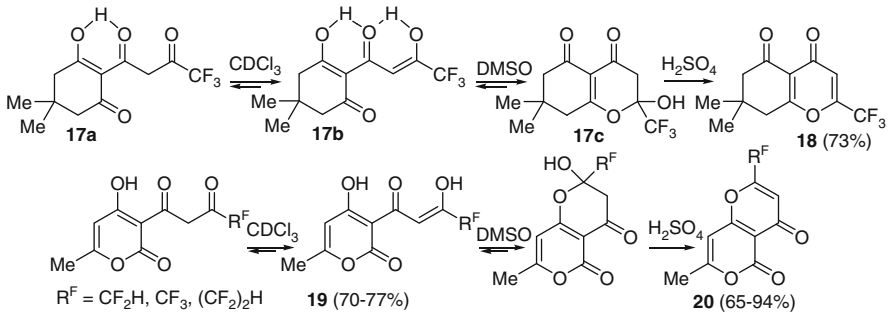
Scheme 6 Synthesis of pyrones **14**

The latter reacting with P_2O_5 gave rise to fluoroalkylthio(trifluoroacetyl)ketenes **13**, which were demonstrated to act as heterodienes in the Diels–Alder reaction with phenylacetylene to form 4-pyrones **14** [11]. Langer et al. reported that the Me_3SiOTf-mediated cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes **15** with 4,4-dimethoxy-1,1,1-trifluorobut-3-en-2-one resulted in the formation of trifluoromethylated pyran-4-ones **16** [12] (Scheme 7).



Scheme 7 Synthesis of pyrones **16**

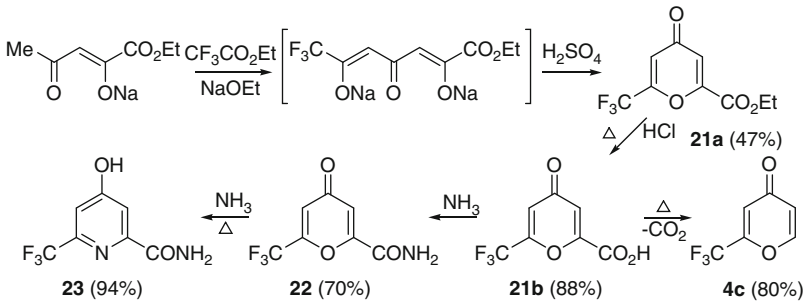
Condensation of 2-acetyldimedone with ethyl trifluoroacetate in the presence of LiH afforded tetraketone **17** in 65 % yield existing in $CDCl_3$ as an equilibrium mixture of **17a** and **17b**. In a mixture of DMSO-d_6 and CCl_4, **17** occurs as cyclic hemiketal **17c** (95 %) and open forms **17a** and **17b** (5 %). Treatment of **17** with concentrated H_2SO_4 at ~20 °C for 5 h afforded the carbofused 4-pyrone **18** [13] (Scheme 8).



Scheme 8 Synthesis of pyrones **18** and **20**

If dehydroacetic acid is used as the methylene component in the condensation with R^FCO_2Et under the same conditions, the reaction gives fluorine-containing pyrones **19**, which underwent cyclization to 2-(polyfluoroalkyl)-7-methylpyrano[4,3-b]pyran-4,5-diones (**20**) on treatment with H_2SO_4 [14].

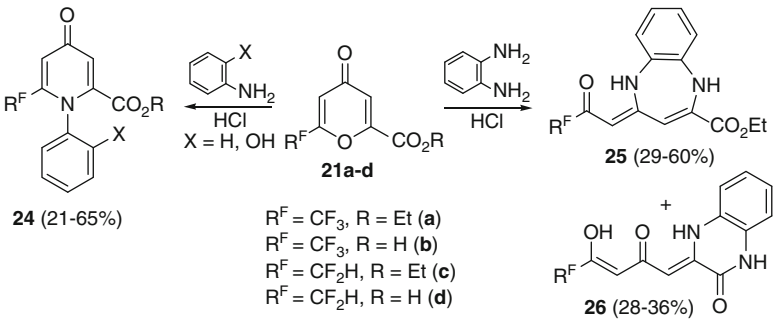
The reaction of ethyl 2,4-dioxopentanoate with ethyl trifluoroacetate in the presence of NaOEt leads to ester **21a**. This ester is smoothly hydrolyzed to acid **21b** by reflux in 20 % HCl, whereas its treatment with 20 % ammonia depending on conditions applied affords amides **22** and **23** in high yields [15]. Decarboxylation of 6-(trifluoromethyl) comanic acid (**21b**) gave 2-(trifluoromethyl)-4*H*-pyran-4-one (**4c**) [4, 16] (Scheme 9).



Scheme 9 Synthesis of pyrones **21** and **22**

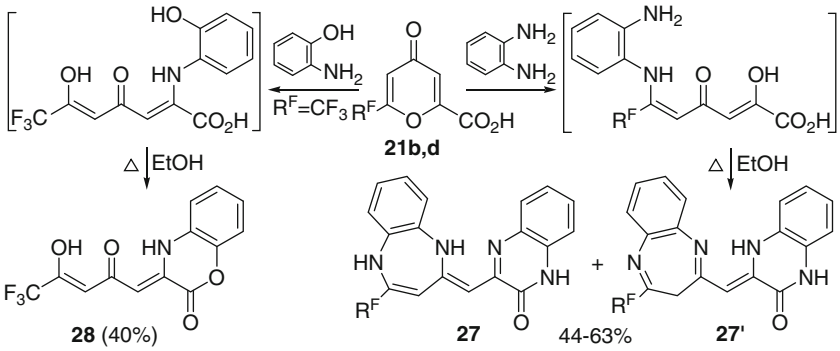
1.2 Reactions of 2-(Polyfluoroalkyl)-4-Pyrones

Obydennov and Usachev have reported [17] that 2-R^F-4-pyrones **21a–d** react with aniline and *o*-aminophenol under acidic conditions to give the corresponding 2-R^F-1-aryl-4-pyridones **24**. Their reaction with *o*-phenylenediamine in the presence of HCl gave R^F-bearing benzodiazepines **25** and quinoxalin-2-ones **26** (Scheme 10).



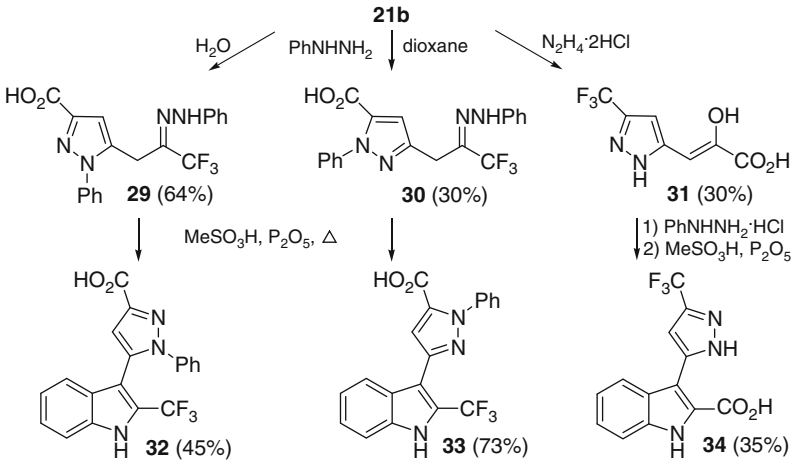
Scheme 10 Reactions of pyrones **21** with amines in the presence of an acid

In the absence of a strong acid, compounds **27** can be prepared as a mixture of two tautomers (R^F=CF_3, **27**: **27′** = 21: 79; R^F=CF_2H, **27**: **27′** = 65: 35) from the reaction of 6-R^F-comanic acids **21b,d** with *o*-phenylenediamine. To transform **27′** into more conjugated tautomers **27** the mixtures were heated in DMSO at 80–120 °C. Under the same conditions reaction of pyrone **21b** with *o*-aminophenol led to the formation of benzo[*b*][1,4]oxazin-2-one **28** [17] (Scheme 11).



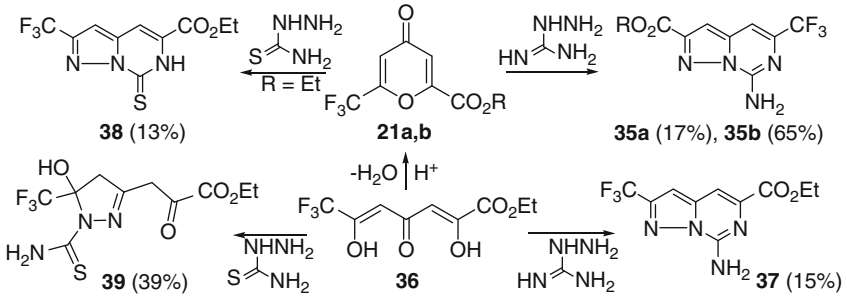
Scheme 11 Reactions of **21b,d** with amines in the absent of an acid

It was also reported that acid **21b** reacts regioselectively with phenylhydrazine in water to give 1-phenylpyrazole-3-carboxylic acid **29**. Similar reaction in dioxane leads to 1-phenylpyrazole-5-carboxylic acid **30**. A strong solvent influence on the reaction route was also found for 6-(trifluoromethyl)comanic acid derivatives **21a** and **22** [18]. The reaction of **21b** with $N_2H_4 \cdot 2HCl$ (2.2 equiv.) in water gave a mixture of regioisomeric pyrazoles from which 3-(trifluoromethyl)pyrazole **31** was isolated in 30 % yield. Phenylhydrazones **29** and **30** as well as phenylhydrazone from pyrazole **31** were converted into 3-(pyrazolyl)indoles **32** and **33**, and indole-2-carboxylic acid **34**, by heating in $MeSO_3H$ with P_2O_5 [19] (Scheme 12).



Scheme 12 Some reactions of pyrone **21b**

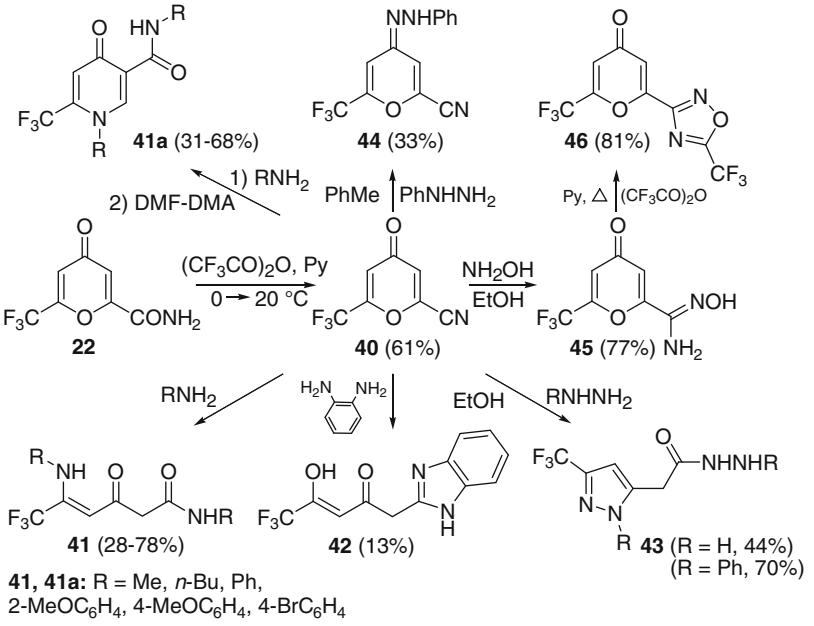
Pyrones **21a,b** react with aminoguanidine to give 5-CF_3-pyrazolo[1,5-*c*]pyrimidines **35a,b** as the major products, while the reaction of their precursor, ethyl 7,7,7-trifluoro-2,4,6-trioxoheptanoate (**36**), with the same polynucleophile gave regioisomeric 2-CF_3-pyrazolo[1,5-*c*]pyrimidines **37**. On the other hand, the reaction of **21a** and **36** with thiosemicarbazide affords **38** and **39** in low yield [20] (Scheme 13).



Scheme 13 Some reactions of **21a,b** and **36**

Dehydration of pyronecarboxamide **22** with trifluoroacetic anhydride in the presence of pyridine leads to the formation of 2-cyano-6-(trifluoromethyl)-4-pyrone (**40**) in 61 % yield. The reactions of this cyanopyrone with *N*-nucleophiles can proceed with or without substitution of the cyano group to give a wide range of novel trifluoromethylated compounds. Thus, cyanopyrone **40** easily reacted with aliphatic and aromatic amines in EtOH at −20 °C and *o*-phenylenediamine in

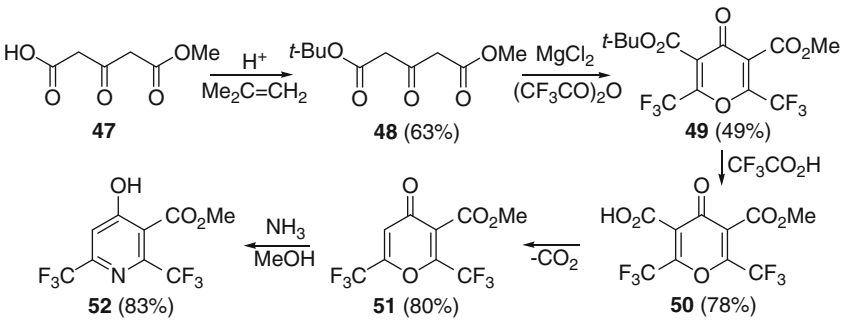
acetic acid to produce carbamoylated aminoenones **41** and benzimidazole **42**. Treatment of **41** with DMF-DMA in toluene under ambient conditions for 24 h gave 4-pyridone-3-carboxamides **41a** in 31–68 % yields. The regiochemistry of the reactions of **40** with hydrazine and phenylhydrazine in EtOH is similar to those observed in the case of the amine attack. These reactions afforded derivatives of 2-(3-trifluoromethylpyrazol-5-yl)acetic acid **43**, whereas the reaction with phenylhydrazine in toluene resulted in the formation of phenylhydrazone **44** in 33 % yield. The reaction between **40** and hydroxylamine in ethanol proceeds by the nucleophilic addition to the cyano group to give amidoxime **45**. Heating this compound with trifluoroacetic anhydride in the presence of pyridine gave pyrone **46** in high yield [21] (Scheme 14).



Scheme 14 Some reactions of pyrone **40**

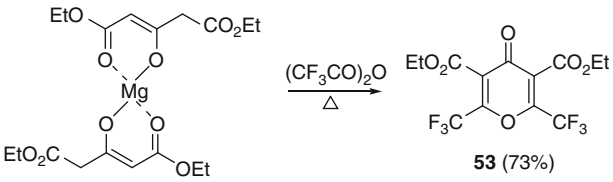
1.3 Synthesis and Reactions of 2,6-bis(Polyfluoroalkyl)-4-Pyrones

The first synthesis of 4-pyrone derivatives with two CF_3 groups was reported in 1988 by Lee and co-workers [22]. Acetone dicarboxylic acid monomethyl ester **47** reacted with isobutylene in sulfuric acid to form **48**. Subsequent reaction with $MgCl_2$ and trifluoroacetic anhydride led to pyrone **49**. This compound was converted to the monoester **50**, which gave pyrone **51**. The latter was reacted with ammonia in methanol to form 4-hydroxypyridine **52** [22] (Scheme 15).



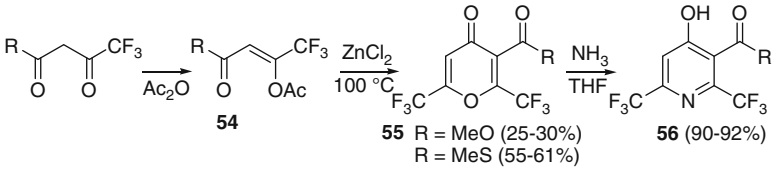
Scheme 15 Synthesis of compounds **49**–**52**

Diester **53** was obtained by the one-pot transformation of a magnesium diacetonedicarboxylate complex using trifluoroacetic anhydride [23] (Scheme 16).



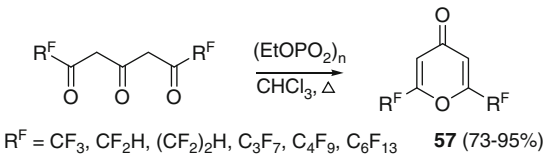
Scheme 16 Synthesis of pyrone **53**

Babu et al. reported that 3-acetoxy-4,4,4-trifluoro-2-butenoates (**54**) undergo self-condensation at 100 °C in presence of catalytic amounts of zinc chloride to yield 2,6-bis(trifluoromethyl)-4-pyrones **55**. These compounds were further converted to the corresponding pyridine derivatives **56** via ammonolysis [24] (Scheme 17).



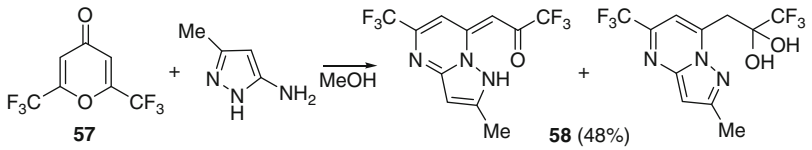
Scheme 17 Synthesis of pyrones **55**

A variety of procedures have been used to obtain the 2,6-bis(polyfluoroalkyl)-4-pyrones **57** from the corresponding 1,3,5-triketones [H_2SO_4, PPA, HCl/MeOH, $(Me_3SiO)_3PO$]. Ethyl polyphosphate appeared to be the most effective dehydrating agent with regard to the isolation and yield of products formed [25] (Scheme 18).



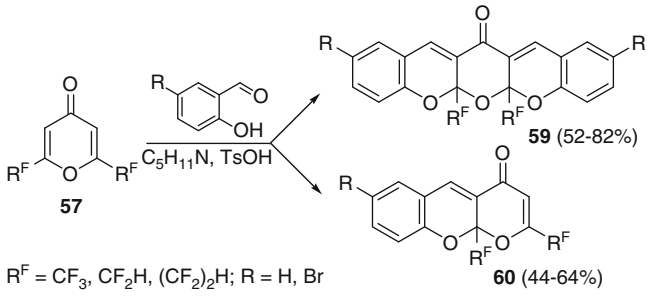
Scheme 18 Synthesis of pyrones **57**

Pyrazolo[1,5-*a*]pyrimidine **58** and its hydrated form were obtained by reaction of 5-amino-3-methylpyrazole with 2,6-bis(trifluoromethyl)-4-pyrone (**57**) [26] (Scheme 19).



Scheme 19 Synthesis of compounds **58**

Polyfluoroalkyl-substituted 4-pyrones **57** react with salicylaldehydes in the presence of piperidine and *p*-TsOH to give a wide variety of fused 2*H*-chromenes **59** and **60**. Compounds **59** were obtained as mixtures of the corresponding *trans*- and *cis*-isomers in variable proportions, depending on the nature of the starting materials and catalysts. This annulation proceeds by a tandem intermolecular oxa-Michael addition and subsequent intramolecular Mannich condensation [27] (Scheme 20).



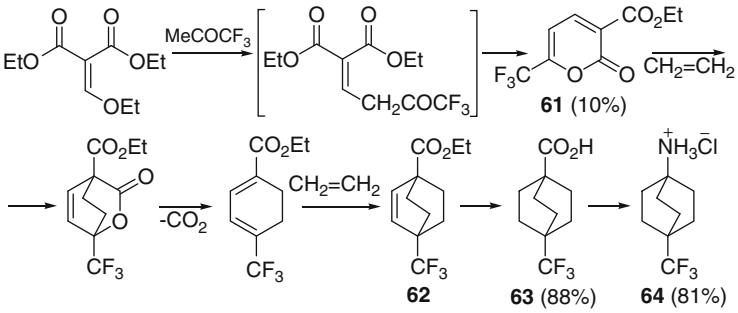
Scheme 20 Synthesis of compounds **59** and **60**

2 Fluorinated 2-Pyrones

Most reports concerning 2*H*-pyran-2-ones (α-pyrones) involve non-fluorinated derivatives, which perform important biological functions in nature and have unlimited synthetic potential for the construction of a variety of arenes and heteroarenes [28]. However, very few deal with 2-pyrones containing fluoroalkyl groups. It is evident that the C-2, C-4 and C-6 positions of the 2-pyranone ring are electrophilic in nature and prone to nucleophilic attack. The presence of polyfluoroalkyl substituents on the pyrone ring favours these reactions. At the same time, R^F-containing 2-pyrones behave as cyclic dienes in cycloadditions.

2.1 Synthesis and Reactions of 6-(Polyfluoroalkyl)-2-Pyrones

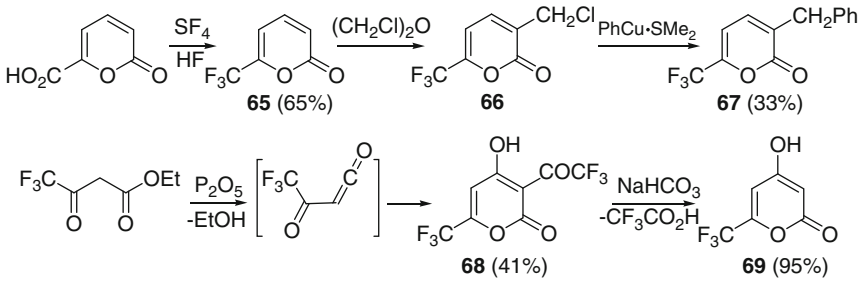
The ethyl 6-(trifluoromethyl)-2-pyrone-3-carboxylate (**61**) was prepared by condensation of trifluoroacetone with diethyl ethoxymethylenemalonate, followed by cyclization of intermediate diethyl β-acylethylidenemalonate. This pyrone was used for the preparation of cage derivatives to explore their usefulness as antiviral agents. Reaction of **61** with ethylene at high pressure afforded ester **62**. Hydrogenation of **62** yielded the corresponding alkyl bicyclo[2.2.2]octane-l-carboxylate, which was hydrolyzed to **63**. The latter was converted into bicyclo[2.2.2]octan-l-amine hydrochloride **64** via the Schmidt reaction [29] (Scheme 21).



Scheme 21 Synthesis of pyrone **61** and its derivatives

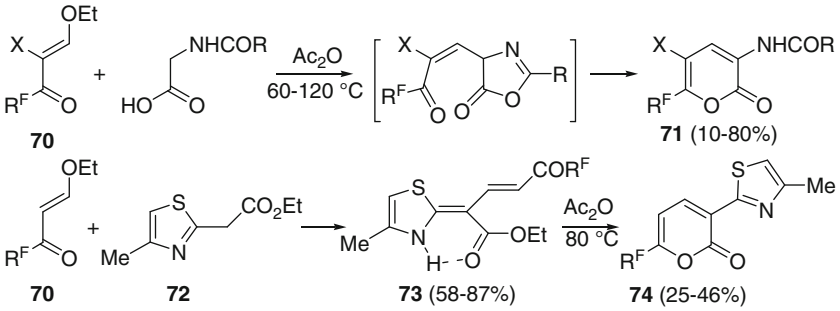
6-(Trifluoromethyl)-2-pyrone (**65**) was prepared in 65 % yield by reaction of 2-pyrone-6-carboxylic acid with SF_4–HF at 100 °C. Chloromethylation with bis(chloromethyl) ether and sulfuric acid at 75 °C gave an inseparable mixture of mono- and bis(chloromethyl)pyranones. However, when the mixture was treated with phenylcopper-dimethyl sulfide in THF at 35 °C, only **66** reacted, giving the desired pyrone **67** as one of the perspective inactivators of α-Chymotrypsin [30] (Scheme 22).

Dealkoxylation of trifluoroacetoacetic ester by P_2O_5 leads to trifluoroacetylketene, which quickly dimerizes to hexafluorodehydroacetic acid **68**. The reaction of **68** with $NaHCO_3$ leads to the formation of 2-pyrone **69** [31] (Scheme 22).



Scheme 22 Synthesis of pyrones **67**–**69**

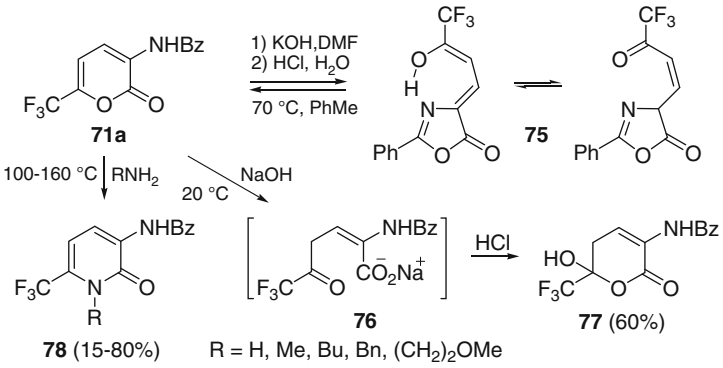
Gerus et al. reported that heating of β-alkoxyvinyl ketones **70** and *N*-acylglycines in acetic anhydride gave the corresponding 3-(acylamino)-6-(polyfluoroalkyl)-2*H*-pyran-2-ones (**71**) [32]. Reactions of thiazole **72** with enones **70** gave products **73** in good to high yields as a result of acylvinylation of the active methylene group. Products **73** were cyclized to pyrones **74** by heating in acetic anhydride [33] (Scheme 23).



Scheme 23 Synthesis of pyrones **71** and **74**

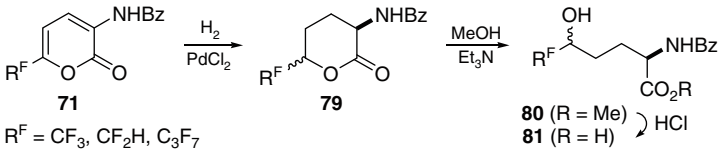
The reactions of 2*H*-pyran-2-one **71a** with *O*– and *N*-nucleophiles were studied and a series of trifluoromethyl-containing oxazolone and pyridone derivatives were synthesized. The oxazolone **75**, which can exist in two tautomeric forms, can be obtained by heating of **71a** with KOH in DMF and subsequent acidification. When **71a** was dissolved in aqueous 1N NaOH, a yellow solution of salt **76** was formed.

After acidification of the solution with HCl, hydroxypyrone **77** precipitated. The pyridones **78** were obtained by heating **71a** with ammonia or alkylamines [32, 34] (Scheme 24).



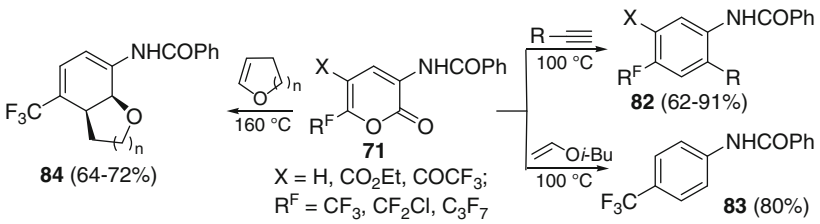
Scheme 24 Some reactions of pyrone **71a**

The key step of the synthesis of new δ-(polyfluoroalkyl)-δ-hydroxy-α-amino acids **81** was the hydrogenation of 2*H*-pyran-2-ones **71** to the tetrahydropyrones **79**, which were transformed into the corresponding benzoylamino acid esters **80** by methanolysis. In all cases mixtures of diastereomeric esters **80** were formed, careful treatment of which with 15 % HCl gave a mixture of the diastereomeric benzoylamino acids **81**. The latter are of interest as analogues of 2-amino-5-hydroxyvaleric acid and glutamic acid [35] (Scheme 25).



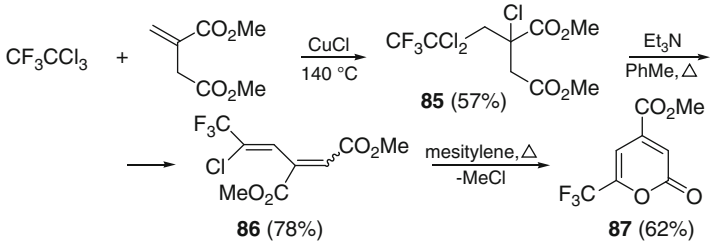
Scheme 25 Reduction of pyrones **71**

The propensity of α-pyrones to undergo the Diels-Alder reaction makes them useful for syntheses of highly substituted aromatics and biphenyls. A practical method for the regioselective synthesis of the *N*-benzoyl-4-(polyfluoroalkyl)anilines **82** by thermal Diels–Alder cycloaddition of **71** with fluorostyrenes and acetylenes was described. Free 4-(polyfluoroalkyl)anilines were smoothly formed in good yields by DBU-assisted deprotection. In the case of the reactions of pyrone **71a** with isobutyl vinyl ethers and cyclic vinyl ethers, compounds **83** and **84** were obtained, respectively [36] (Scheme 26).



Scheme 26 Diels-Alder reaction of pyrones **71**

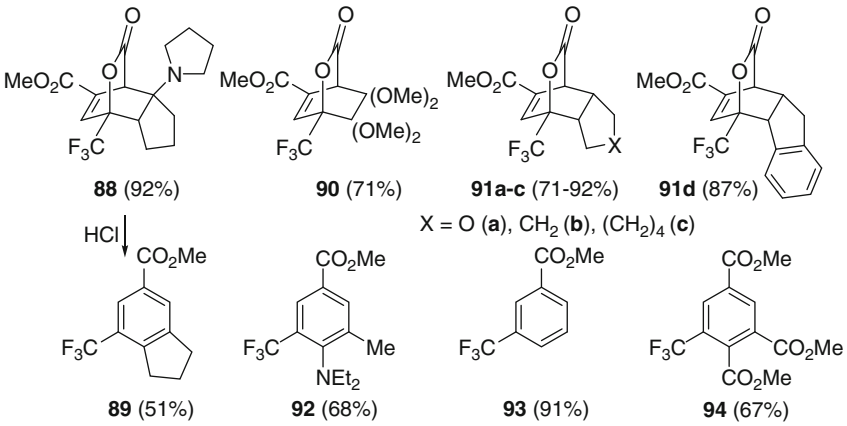
The Cu-catalysed (3–6 mol%) addition of 1,1,1-trichloro-2,2,2-trifluoroethane to methyl itaconate leads to the 1: 1 adduct **85** in 57 % yield. Double HCl elimination with triethylamine affords the diene **86** (*Z*/*E* = 17:83). Refluxing of **86** in mesitylene leads to elimination of MeCl and formation of **87** in 62 % yield [37] (Scheme 27).



Scheme 27 Synthesis of pyrone **87**

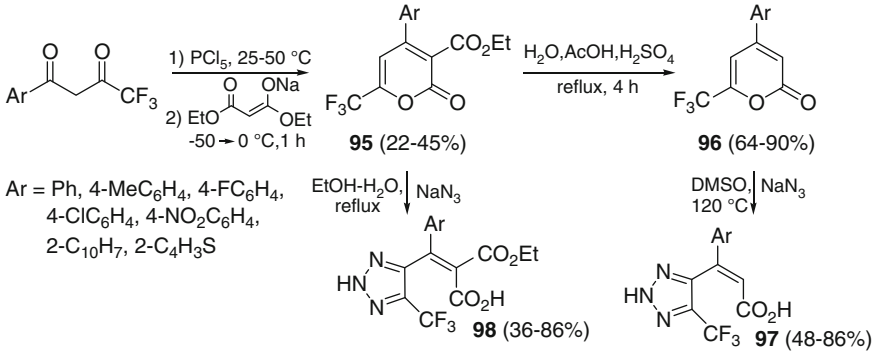
The presence of the carbomethoxy and trifluoromethyl groups in the diene system of the pyrone **87** increases its electrophilicity and its ability to undergo Diels-Alder reactions with inverse electron demand. The reaction of **87** with 1-(*N*-pyrrolidino)-1-cyclopentene at 30 °C gives rise to the tricyclic lactone **88**. When **88** is treated with HCl/dioxane, the indane derivative **89** is obtained. This compound was prepared directly in the reaction of **87** with l-(trimethylsilyloxy)cyclopentene at 180 °C in 90 % yield. More reactive tetramethoxyethylene adds at 100 °C to **87** to afford **90**. With 2,5-dihydrofuran at 130 °C, **91a** is formed as the sole isomer. Endo-adducts of this type result also with cyclopentene (**91b**, 120 °C), cyclooctene (**91c**, 150 °C), and indene (**91d**, 80 °C). All four possible regio- and stereoisomers can be identified in the reaction of **87** with vinylacetate at 150 °C (79 % yield) (Scheme 28).

Another feature of 2-pyrone **87** is its ability to undergo Diels-Alder reactions with acetylenes. The cycloadducts decarboxylate spontaneously to form benzene rings bearing the CF_3 group. The substitution pattern is determined by the regioselectivity of the [4 + 2] cycloaddition step. Thus, the reaction of **87** with 1-(*N,N-diethylamino*)-1-propyne takes place at 0 °C to produce **92** as a single isomer. Less electron rich acetylenes require heating at 140–200 °C. Treatment of **87** with acetylene at 200 °C leads to **93**, while with dimethyl acetylenedicarboxylate triester **94** is formed [37] (Scheme 28).



Scheme 28 Products obtained from pyrone **87**

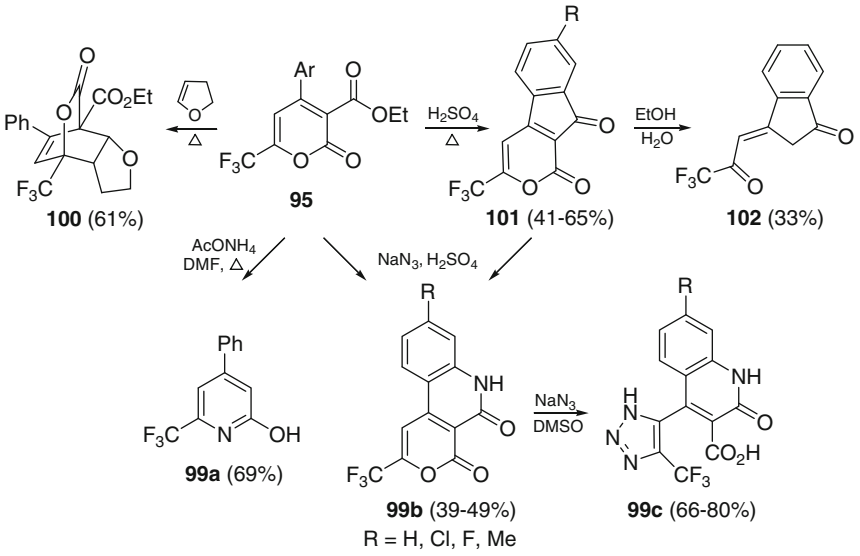
Our group reported that treatment of 1-aryl-4,4,4-trifluorobutane-1,3-diones with PCl_5 and then with sodium diethyl malonate afforded ethyl 4-aryl-6-(trifluoromethyl)-2-oxo-2*H*-pyran-3-carboxylates (**95**) in moderate yields. These compounds can be converted in high yields to 2*H*-pyran-2-ones **96** by refluxing in aqueous acetic acid with H_2SO_4 [38]. Pyrones **95** and **96** react with sodium azide to produce highly functionalized (*Z*)-CF_3-1,2,3-triazoles **97** and **98** [39a] (Scheme 29).



Scheme 29 Synthesis of pyrones **95** and **96** and their reaction with NaN_3

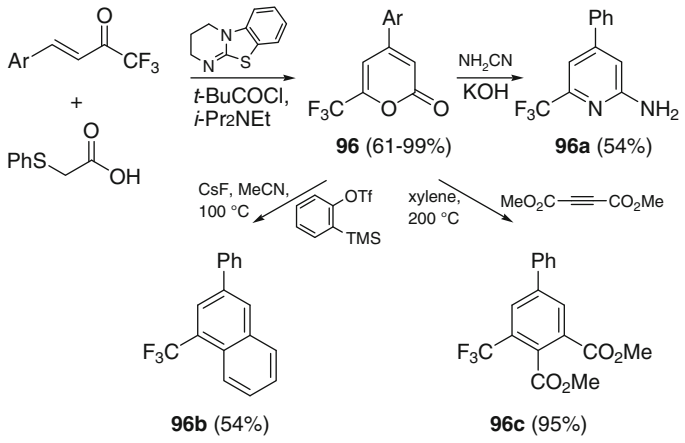
The reaction of **95** (Ar=Ph) with NH_4OAc in refluxing aqueous DMF, involving loss of the ethoxycarbonyl group at the 3-position, afforded the pyridinol derivative **99a**, while the solvent-free inverse electron-demand Diels-Alder reaction with 2,3-dihydrofuran gave bicyclic lactone **100** in 61 % yield. Treatment of **95** with H_2SO_4 at 110–125 °C afforded the intramolecular Friedel-Crafts acylation products **101**, which are the first representatives of a novel polynuclear fused heterocyclic system. Due to the presence of antiaromatic cyclopentadienone fragment compound **101** (R=H) showed high reactivity to weak nucleophiles such as water leading to the formation of **102** [38a]. 2-(Trifluoromethyl)-6*H*-pyrano[3,4-*c*]quinoline-4,5-diones

99b can be obtained from pyrones **95** and **101** via the Schmidt reaction in moderate yields. When pyranocarbostyrils **99b** were heated in DMSO with NaN_3 at 120 °C for 3 h, triazoles **99c** were obtained in good yields and presumably arise via ring-opening of the initially formed fused intermediate [38b] (Scheme 30).



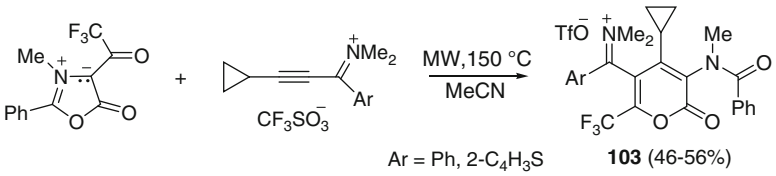
Scheme 30 Some reactions of pyrones **95**

Very recently, the concise synthesis of a range of disubstituted 2-pyrones **96** from (thiophenyl)acetic acids and readily available trifluoromethyl enones via an isothiourea mediated one-pot Michael addition/lactonization/thiol elimination sequence has been demonstrated. Derivatization of these reactive pyrones to generate additional high-value products was next investigated and compounds **96a–c** were prepared in good yields [39b] (Scheme 31).



Scheme 31 Synthesis and some reactions of pyrones **96**

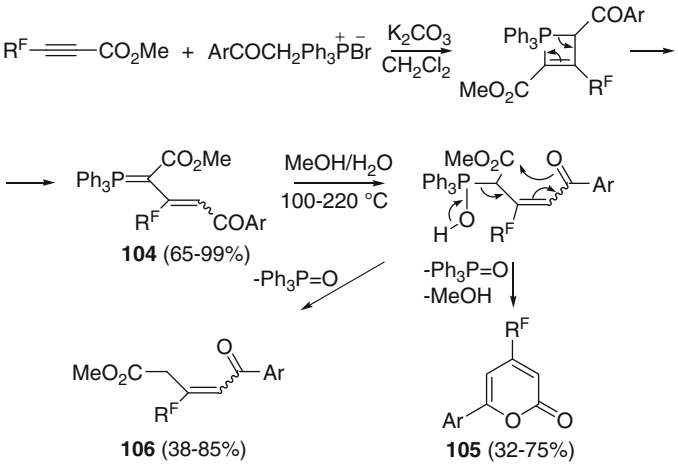
Gerster and Maas reported that heating 4-trifluoroacetyl-substituted münchnone and the propyne iminium triflates in acetonitrile solution at 150 °C (closed vessel) under microwave irradiation furnished the (6-oxo-2-trifluoromethyl-6*H*-pyran-3-yl) arylidene iminium salts **103** [40] (Scheme 32).



Scheme 32 Synthesis of pyrones **103**

2.2 *Synthesis of 4-(Perfluoroalkyl)-2-Pyrones*

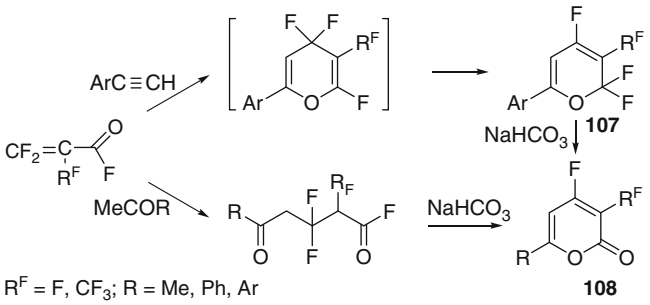
In contrast to 6-(perfluoroalkyl)-2-pyrones, only one method for the preparation of 4-(perfluoroalkyl)-2-pyrones has been described [41]. It was established that the reaction of methyl 2-perfluoroalkynoates with aroylmethyltriphenyl phosphonium bromide in the presence K_2CO_3 in dichloromethane at room temperature gave methyl 4-aroyl-2-triphenylphosphoranylidene-3-(perfluoroalkyl)-3-butenoates **104** in excellent yields. 6-Aryl-4-(perfluoroalkyl)-2-pyrones **105** and methyl 4-aroyl-3-(perfluoroalkyl)-3-butenoates **106** were obtained in moderate to high yield by hydrolysis of phosphoranes **104** with hot aqueous methanol in a sealed tube. The butenoates **106** were isolated chromatographically as mixtures of *Z* and *E* isomers, the ratios of which were estimated by ^{1}H NMR. Reaction mechanism was proposed to account for the formation of products **104–106** [41] (Scheme 33).



Scheme 33 Synthesis of pyrones **105**

2.3 Miscellaneous

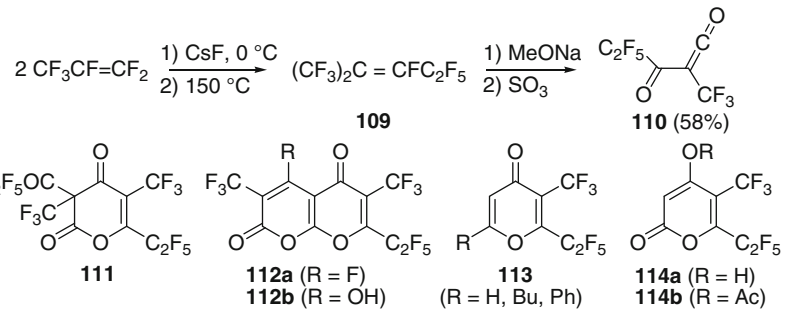
Fluorinated α-pyrones were obtained from perfluoroacryloyl fluoride and perfluoromethacryloyl fluoride by reaction with arylacetylenes and methyl ketones. The arylacetylene route involves a [4 + 2] cycloadduct, followed by a 1,3 fluoride ion shift to **107** and hydrolysis to the pyrone **108**. The methyl ketone route may involve addition of enols to the fluorinated double bond, ring closure through the enol form of the resulting 1,5-diketone, and loss of HF [42a] (Scheme 34).



Scheme 34 Synthesis of pyrones **108**

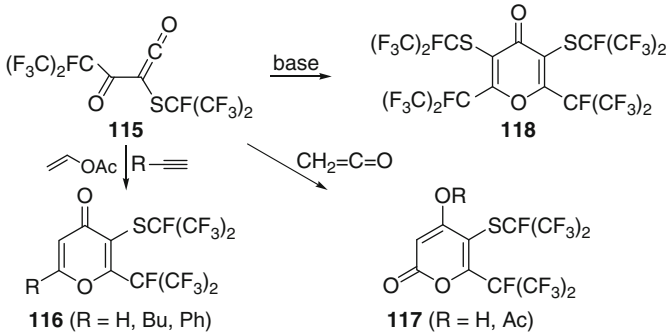
The synthesis and chemistry of perfluoroacylketene **110** are described by England [42b]. Hexafluoropropene dimerizes under CsF catalysis. Heating the resulting mixture in a sealed vessel to 150 °C yields the thermodynamic dimer **109**, from which compound **110** was prepared in good yield (Scheme 35).

Cesium fluoride catalyst in tetraglyme without heating caused the acylketene **110** to dimerize to **111**. When heated with catalytic amounts of cesium fluoride in tetraglyme **110** gave the pyronopyrone **112a** (from 3 mol of **110** with loss of 2 mol of C_2F_5COF). Hydrolysis of **112a** by sulfuric acid gave **112b**. The acylketene **110** also reacted with phenyl- and butylacetylenes to give pyrones **113**. Although acetylene was not reacted with **110**, the corresponding product **113** (R=H) was obtained by reaction with vinyl acetate with simultaneous loss of acetic acid. Compound **110** added readily to the C=C bond in ketene with proton migration to give a mixture of hydroxypyrone **114a** and the acetylated product **114b**. These products could be interconverted by hydrolysis of **114b** in sulfuric acid and by acetylation of **114a** with ketene [42b] (Scheme 35).



Scheme 35 Products obtained on the basis of acylketene **110**

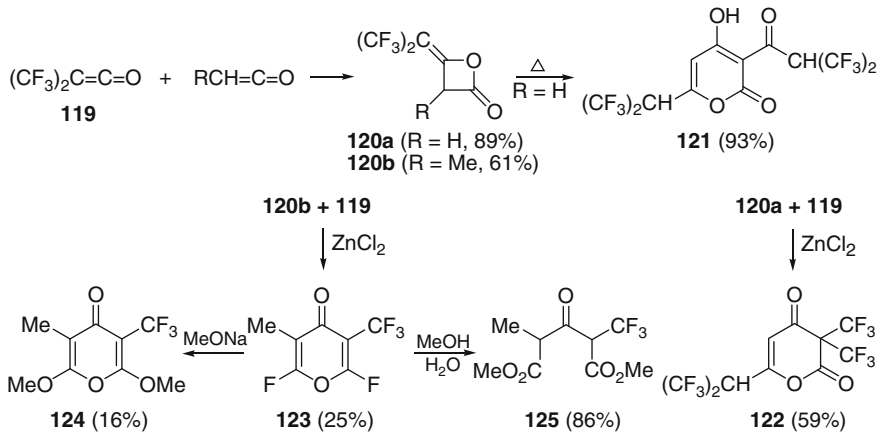
The chemistry of compound **115**, prepared from the reaction of hexafluoropropene with sulfur and potassium fluoride in DMF, is similar to **110**. Diels-Alder addition of **115** to vinyl acetate was accompanied by loss of acetic acid to give the parent pyrone **116** (R=H). The reaction of **115** with butyl- and phenylacetylenes gave **116** (R=Bu, Ph). Addition of **115** to the C=C bond of ketene was accompanied by a 1,3 hydrogen shift to produce the hydroxypyrone and its acetylated product **117**. In the presence of a weak base such as dimethylacetamide or dimethylpropionamide, **115** underwent a self-condensation reaction with loss of CO_2 to give the pyrone **118**; this reaction was not observed for **110** [43] (Scheme 36).



Scheme 36 Products obtained on the basis of acylketene **115**

England and Krespan reported that ketene **119** reacted exothermically with ketene at very low temperature to give β-lactone **120a**, which was readily dimerized by base to give α-pyrone **121**, a reaction analogous to the formation of dehydroacetic acid from diketene. Lactone **120a** also reacted with another equivalent of ketene **119** in the presence of zinc chloride as catalyst to give the insertion product **122**. Methylketene, like ketene, reacted with **119** to give a mixed lactone **120b**, the reaction of which with another mole of **119** in the presence of zinc chloride gave γ-pyrone **123**. Reaction of **123** with sodium methoxide replaced two fluorine atoms to give the dimethoxypyrone **124**, methanol gave the keto diester **125** [44] (Scheme 37).

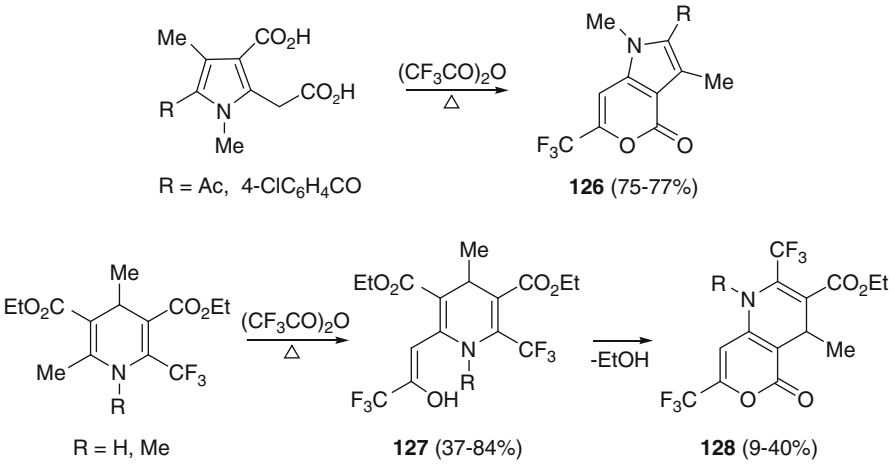
A synthetic entry to 2-acyl-1,3-dimethyl-6-(trifluoromethyl)-1*H*-pyrano[4,3-*b*]pyrrol-4-ones **126** in high yields has been developed via ring closure of pyrrole-2-acetic



Scheme 37 Products obtained on the basis of ketene **119**

acid derivatives with trifluoroacetic anhydride at reflux [45a]. Under the same conditions trifluoromethylated dihydropyridinecarboxylates were converted via compounds **127** into pyrano[4,3-*b*]pyridine-3-carboxylates **128** in low yields [45b] (Scheme 38).

The butenolide, 3-(trifluoromethyl)-2*H*-furo[2,3-*c*]pyran-2-one, was obtained by treatment of 3-iodo-2*H*-furo[2,3-*c*]pyran-2-one with trifluromethyltriethylsilane in the presence of copper iodide and potassium fluoride in 1-methyl-2-pyrrolidinone [45c].



Scheme 38 3,4-Fused pyrones **126** and **128**

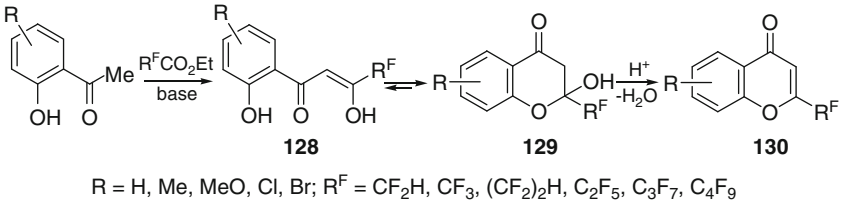
3 Fluorinated Chromones

Chromones (4*H*-chromen-4-ones, 4*H*-1-benzopyran-4-ones) are naturally occurring oxygen-containing heterocycles which perform important biological functions in nature [46]. Many chromone derivatives, including flavones and 2-(trifluoromethyl)

chromones, exhibit various types of biological activity and find use as valuable synthetic intermediates in the preparation of pharmacologically relevant products and new heterocyclic systems [47–49]. There are a number of methods available for preparing chromones, however, the most common methods involve Claisen condensation of 2-hydroxyacetophenones with esters or Baker-Venkataraman rearrangement of 2-acyloxyacetophenones. The ensuing diketone is then cyclized under strongly acidic conditions to furnish chromones. These compounds possess two strong electrophilic centers (carbon atoms C-2 and C-4) and their reactions with nucleophiles start predominantly with attack of the C-2 atom (1,4-addition) and are accompanied by pyrone ring-opening to form an intermediate capable of undergoing intramolecular heterocyclizations. Alternatively, the initial attack can also occur at C-4 (1,2-addition) [46].

3.1 Synthesis of 2-(Polyfluoroalkyl)Chromones

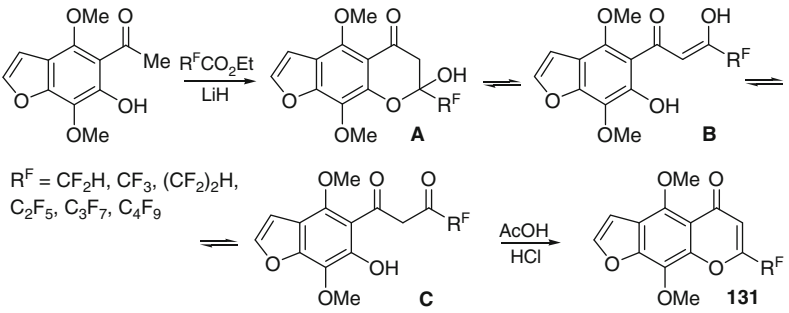
The first representatives of 2-(trifluoromethyl)chromones were obtained in 1951 by condensation of substituted 2-hydroxyacetophenones with ethyl trifluoroacetate in the presence of sodium followed by dehydration of the initially formed β-diketones in an acid medium [50]. It has long been considered [51] that these diketones have a linear keto-enol structure **129a**; however, subsequently, it has been found on the basis of ^{1}H NMR data [52] that they exist as cyclic semiketals **129b** both in solutions and in crystals. Cyclisation is facilitated by the presence of the electron-withdrawing trifluoromethyl group in the side chain and the hydroxy group in the *ortho*-position of the benzene ring. Refluxing of 2-hydroxychromanones **129b** in ethanol [50] or acetic acid [53, 54] in the presence of concentrated HCl results in 2-(polyfluoroalkyl)chromones **130** (Scheme 39).



Scheme 39 Synthesis of 2-R^F-chromones **130**

Modification of natural products by replacing an alkyl group by a polyfluoroalkyl group has long attracted the attention of researchers, because the electron-withdrawing effect of the fluorinated substituent entails electron density redistribution in the molecule and thus changes its reactivity with respect to nucleophilic reagents [55]. In this connection, of obvious interest is the synthesis of 7-(polyfluoroalkyl)norkhellins **131** [56, 57], which are fluorinated analogues of natural furochromone khellin (active substance of the plant *Ammi visnaga L.*, known for its therapeutic properties since antiquity), because it opens up the way for the

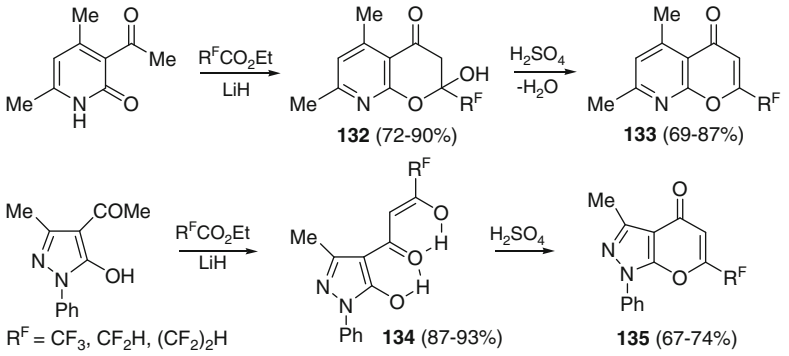
preparation of a broad range of fluorine-containing heterocycles that incorporate the benzofuran fragment and are potentially biologically active (Scheme 40).



Scheme 40 Synthesis of fluorokhellins **131**

Fluorokhellins **131** were prepared by the reaction of khellinone with R^FCO_2Et in the presence of LiH followed by dehydration of the condensation products, which exist as furochromanones **A** in crystals and in DMSO-d_6 solutions. In $CDCl_3$, these compounds (except for R^F=CF_3) are mixtures of tautomers **A–C**. Irrespective of length of the fluoroalkyl group, cyclic form **A** predominates (50–78 %), while the content of the diketone form **C** usually does not exceed 8 % [57].

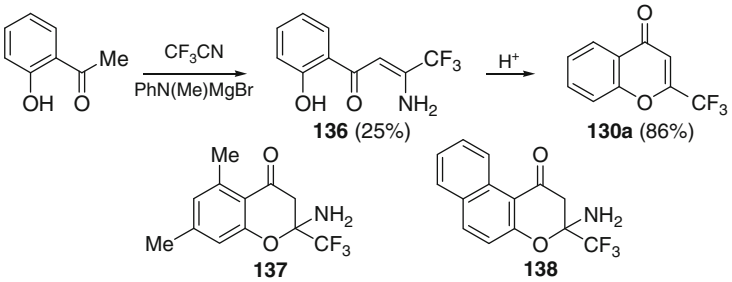
If 2-hydroxyacetophenone analogues such as 3-acetyl-4,6-dimethyl-2-pyridone and 4-acetyl-5-hydroxy-3-methyl-1-phenylpyrazole are used as the methylene component in the condensation with R^FCO_2Et in the presence of LiH in THF or dioxane, the reaction gives the corresponding R^F-containing β-diketones **132** and **134**, whose dehydration under the action of concentrated H_2SO_4 affords 8-aza-2-(polyfluoroalkyl) chromones **133** [58] and 6-(polyfluoroalkyl)-3-methyl-1-phenylpyrano[2,3-*c*] pyrazol-4(1*H*)-ones **135** [59] (Scheme 41).



Scheme 41 Synthesis of compounds **133** and **135**

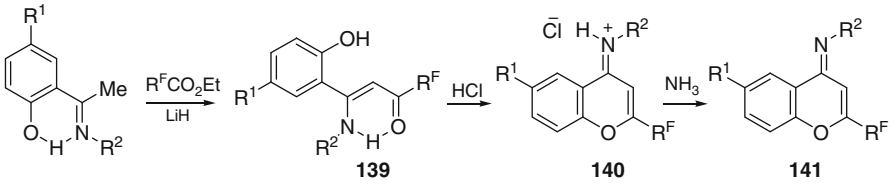
Recently, 2-(trifluoromethyl)chromones **130** have been prepared by the reaction of 2-hydroxyacetophenones with trifluoroacetic anhydride in pyridine (80 °C, 3 h, yields

79–98 %) [60]. Due to the low solubility of phenolates, derivatives hydroxylated at the benzene ring are synthesized using the Kostanecki–Robinson method. Thus, 7-hydroxy-2-(trifluoromethyl)chromone was obtained in 68 % yield by heating 2,4-dihydroxyacetophenone with trifluoroacetic anhydride and sodium trifluoroacetate [49]. In addition to these protocols, other methods for the synthesis of chromones **130** have also been developed. For example, the reaction of 2-hydroxyacetophenone with trifluoroacetonitrile affords aminoenone **136**. Unlike diketones **128**, this compound exists in the open form as *Z*-isomer having a coplanar *s-cis*-conformation stabilised by an intramolecular hydrogen bond [61]. However, the products of condensation of CF_3CN with sterically hindered 2-hydroxy-4,6-dimethylacetophenone and 1-acetyl-2-naphthol exist predominantly as 2-aminochroman-4-ones **137** and **138** due to unfavourable interactions between the vinylic hydrogen atom and the *ortho*-substituent in the benzene ring [62]. In an acid medium, compounds **136–138** are converted into **130** in high yields (Scheme 42).



Scheme 42 Precursors **136–138**

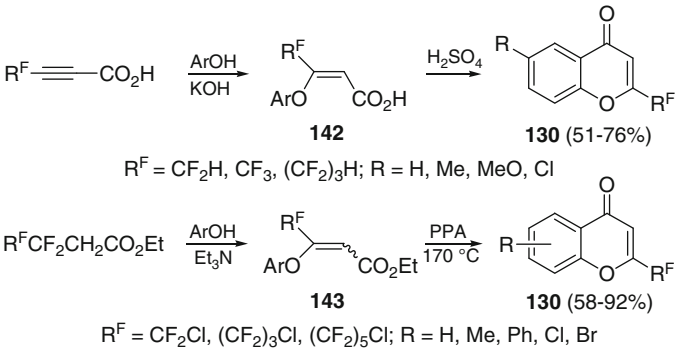
The condensation of ketimines, prepared from 2-hydroxyacetophenones and primary amines, with R^FCO_2Et in the presence of LiH yields aminovinyl ketones **139** with γ-arrangement of the NHR and R^F groups, which exist only in the open form. In an ethanol solution of HCl, these compounds cyclise to 2-(polyfluoroalkyl)-4*H*-chromene-4-iminium salts **140**, which can be neutralised with ammonia to form 2-(polyfluoroalkyl)-4*H*-chromene-4-imines **141**. On treatment with aqueous acetic acid, compounds **139** and **141** are hydrolysed to chromanones **129**, which can be easily converted into chromones **130** [63] (Scheme 43).



$R^F = CF_3, H(CF_2)_2$; $R^1 = H, Me$; $R^2 = CH_2Ph$, *i*-Pr, $(CH_2)_2OH$

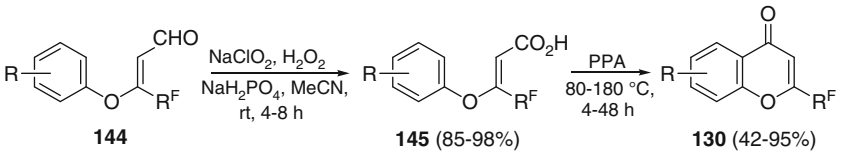
Scheme 43 Synthesis of chromone imines **141**

The reactions of polyfluoroalk-2-ynoic acids with a fivefold excess of ArOH and KOH in an aqueous solution are stereoselective and result in (*Z*)-β-(polyfluoroalkyl)-β-aryloxyacrylic acids **142**. On treatment with concentrated H_2SO_4, these compounds are converted into 2-R^F-chromones **130** [64]. A similar approach to the synthesis of 2-R^F-chromones **130** has been described in a study [65], in which ethyl 2,2-dihydropolyfluorocarboxylates were used as the starting substrates. They were made to react with phenols in the presence of Et_3N in MeCN at 60 °C, which gave ethers **143**, most often, as mixtures of *Z*- and *E*-isomers. When heated with polyphosphoric acid (PPA) at 170 °C, they were converted into chromones **130** in high yields (Scheme 44).



Scheme 44 Syntheses of chromones **130**

The oxidation of enals **144** using sodium chlorite and hydrogen peroxide under mild conditions gave the corresponding acids **145**. When acids **145** were treated with polyphosphoric acid at high temperatures, the desired chromones **130** were obtained in predominantly very high yields [66] (Scheme 45).



Scheme 45 Synthesis of chromones **130**

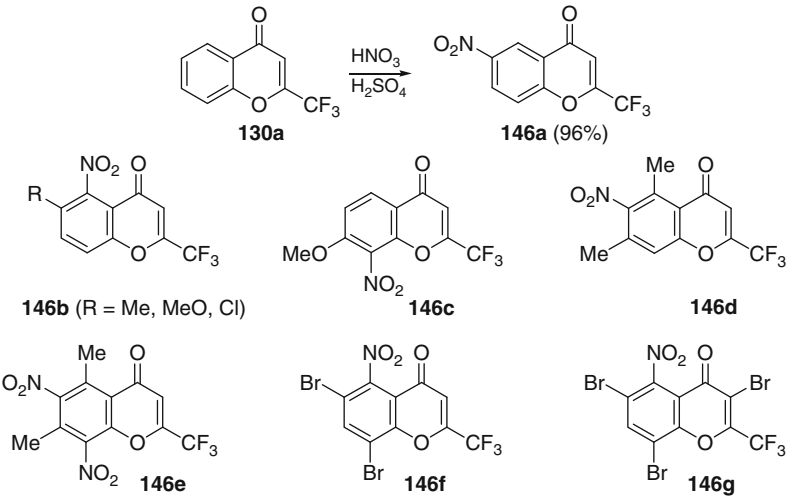
3.2 Reactions of 2-(Polyfluoroalkyl)Chromones

In recent years, our research group has examined the chemistry of 2-(polyfluoroalkyl) chromones **130** and a number of features of these compounds important from the synthetic standpoint have been found. This allowed chromones **130** to be

recommended as readily accessible highly reactive substrates for the synthesis of various heterocyclic derivatives including R^F-containing compounds with a potential biological activity [46b]. The NMR, vibrational, electronic, and structural properties of 6-nitro- and 6-amino-2-(trifluoromethyl)chromones were discussed and assigned with the assistance of DFT calculations [67a].

3.2.1 Nitration and Hydrogenation

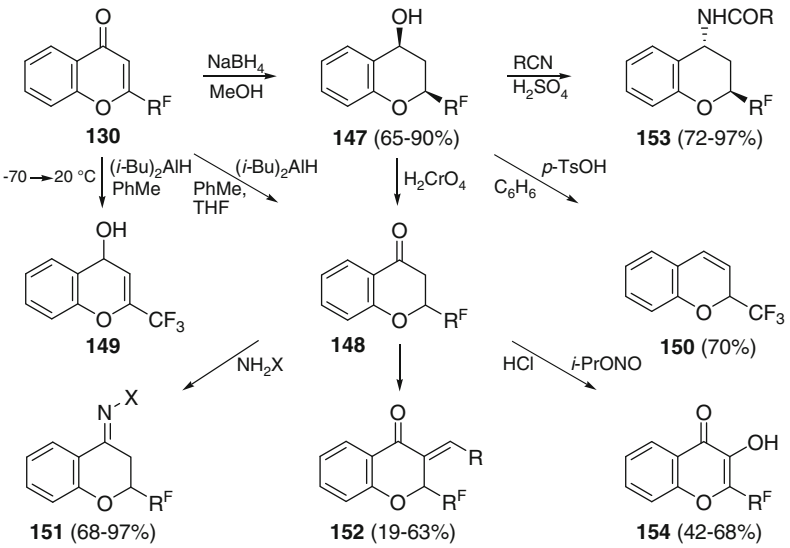
2-(Trifluoromethyl)chromone **130a** unsubstituted in the benzene ring, like its non-fluorinated analogues, is smoothly nitrated at the 6-position yielding 6-nitro-2-(trifluoromethyl)chromone (**146a**). On heating with a mixture of nitric and sulfuric acids, 6-, 7- and 8-substituted 2-(trifluoromethyl)chromones are nitrated into the positions, which is in line with the directing effect of substituents, giving rise to the corresponding nitro derivatives **146b–g** [54, 67–69] (Scheme 46).



Scheme 46 Some 2-CF_3-chromone derivatives

Reduction of 2-(polyfluoroalkyl)chromones **130** by sodium borohydride in methanol gives *cis*-2-(polyfluoroalkyl)chroman-4-oles **147** in high yields, which were easily oxidized under the action of chromic acid into 2-(polyfluoroalkyl) chroman-4-ones **148**. Selective reduction of chromone **130a** can be achieved by using of diisobutylaluminium hydride. In this case, 2-(trifluoromethyl)chroman-4-one (**148a**, R^F=CF_3) and 2-(trifluoromethyl)-4*H*-chromen-4-ol (**149**) were obtained. Dehydration of chromanol **147a** (R^F=CF_3) gave 2-(trifluoromethyl)-2*H*-chromene (**150**) [70]. Chromanones **148**, which easily react at both the carbonyl carbon atom and α-methylene group, are of interest as the starting materials for the preparation of novel R^F-containing chromans derivatives. Thus, they react with hydroxylamine,

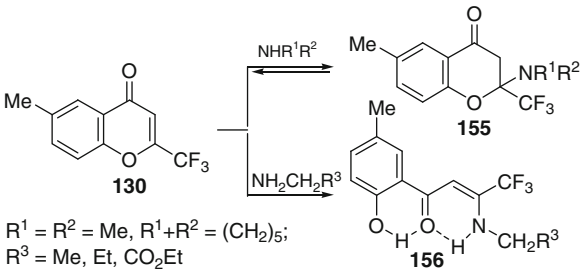
hydrazine hydrate, benzaldehyde on reflux in ethanol and with an excess of dimethylformamide dimethylacetal to give oximes and hydrazones **151** as well as methylidene derivatives **152** [70]. Application of the Ritter reaction conditions to chroman-4-ols **147** gave 4-(acylamino)-2-(polyfluoroalkyl)chromans (**153**) in excellent yields. This reaction was stereoselective and chromanes **153** were obtained as mixtures of *trans*- and *cis*-isomers (*trans*/*cis* = 84/16–94/6) without the formation of any side products [71]. Treatment of an alcoholic solution of **148** with an excess of isopropyl nitrite and concentrated hydrochloric acid at 0–80 °C for 3 h gave 3-hydroxychromones **154** in good yields [72] (Scheme 47).



Scheme 47 Some reactions of **130** and **148**

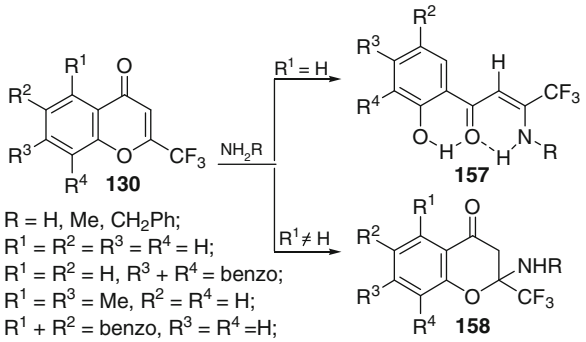
3.2.2 Reactions with Mono-, Di- and Triamines

In 1981, an attempt at using 6-methyl-2-(trifluoromethyl)chromone (**130**) as a protective group in the peptide synthesis was made, which showed for the first time that secondary amines (dimethylamine and piperidine) add reversibly to the C-2 atom without opening of the pyrone ring to give unstable compounds **155** (in the case of sterically hindered diethylamine, the reaction does not proceed). However, even mere mixing of 6-methylchromone **130** with primary amines (ethyl- and propylamines) induces opening of the pyrone ring to give aminoenones **156**. A similar transformation takes place for ethyl glycinate in MeCN [73]. Subsequently, the significance of the steric factor in the reactions of **130** with ammonia and primary amines was also demonstrated for other examples (Scheme 48).



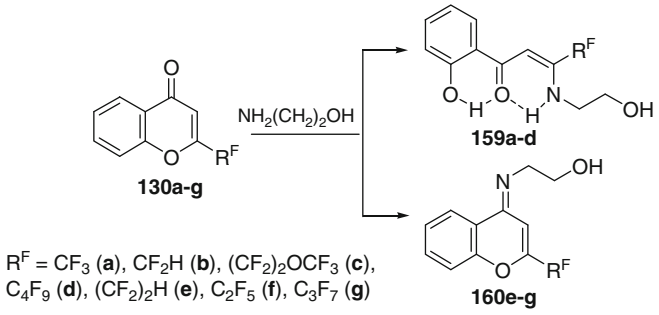
Scheme 48 Reactions of chromones **130** with amines

The nature of the substituent at the 5-position of the chromone system influences the form of existence of the reaction products, which can be either ring or open. The attack by the amine on the C-2 atom of **130** for R^1=H is accompanied by the pyrone ring opening and yields aminoenones **157**; when $R^1 \neq H$, the process stops after the nucleophilic addition of the amine to give stable chromanones **158** [74] (Scheme 49).



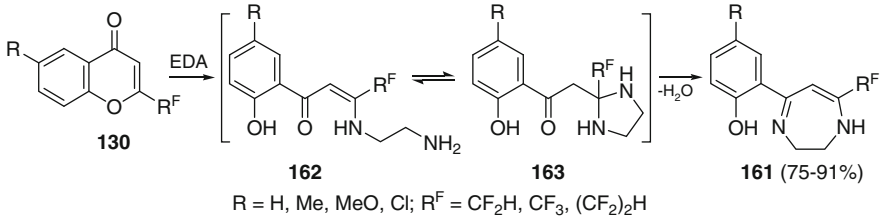
Scheme 49 Reactions with primary amines

A change in the direction of nucleophilic attack has been found in a study of the reaction between chromones **130a–g** unsubstituted in the benzene ring and 2-aminoethanol at room temperature. This amine easily yields aminovinyl ketones **159a–d**, however the reaction with **130e–g** leads to imines **160e–g** [75, 76] (Scheme 50).



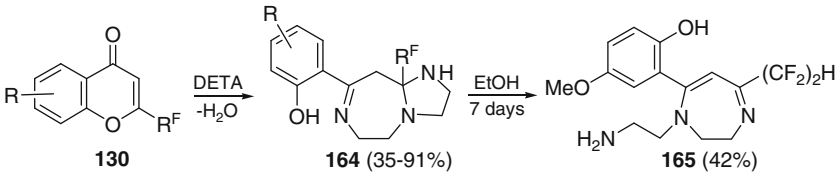
Scheme 50 Reactions with ethanolamine

Unlike non-fluorinated chromones, whose reactions with ethylenediamine (EDA) give complex mixtures of products [77], the reactions of 2-R^F-chromones **130** give rise to 5-(2-hydroxyaryl)-7-(polyfluoroalkyl)-2,3-dihydro-1*H*-1,4-diazepines (**161**) in excellent yields. The reaction is accompanied by opening of the pyrone ring with the initial formation of aminovinyl ketones **162** (in equilibrium with imidazolidines **163**) and cyclization to dihydrodiazepines **161** [78, 79]. Compounds **161** exist in $CDCl_3$ as the 1*H*-7-R^F-tautomers due to the formation of an intramolecular hydrogen bond between the phenolic proton and the imine nitrogen atom of the heterocycle. This conclusion was based on the values of the $^3J_{H,F}$ coupling constants, which are 2.8–4.5 Hz for molecules with the HCF_2CF_2–C(X)=C fragments, where X=O, N [80] (Scheme 51).



Scheme 51 Synthesis of dihydrodiazepines **161**

With diethylenetriamine (DETA), chromones **130** are converted into 5-(2-hydroxyaryl)-7-(polyfluoroalkyl)-1,4,8-triazabicyclo[5.3.0]dec-4-enes (**164**) (35–91 %), which represent the cyclic form of dihydrodiazepines containing a 2-aminoethyl group at the nitrogen atom located most closely to the fluorinated group. The first step is nucleophilic addition of the primary amino group to the C-2 atom accompanied by opening of the pyrone ring yielding *N*-substituted aminovinyl ketones, which further cyclise to triazabicyclic products **164** with participation of both electrophilic centres [81]. It should be emphasised that the formation of **164** is typical only of 2-R^F-chromones and R^F-aminovinyl ketones [82], where the R^F group substantially increases the reactivity of the carbon atom that carries this group. On keeping in ethanol for a week, compound **164** (R^F=$(CF_2)_2H$, R=MeO) isomerises into dihydrodiazepine **165** [83] (Scheme 52).

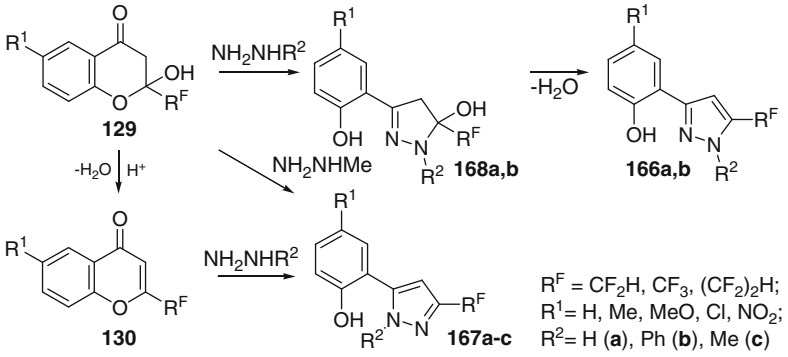


Scheme 52 Synthesis of compounds **164** and **165**

Thus, the reaction of 2-R^F-chromones with amines usually starts with the attack by the amino group on the C-2 atom. In the case of secondary amines or in the presence of a substituent at the 5-position, the reaction can stop after 1,4-nucleophilic addition; however, in most cases, it is accompanied by pyrone ring opening giving the corresponding aminovinyl ketones, whose structural features and subsequent transformations provide a variety of products. An exception is the reaction of 2-R^F-chromones with 2-aminoethanol pointing to the possibility of an attack by the amine on the carbonyl group.

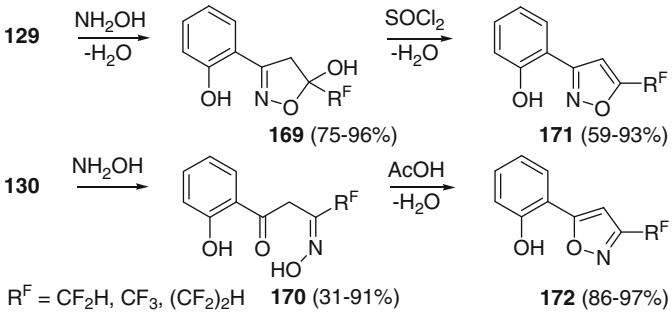
3.2.3 Reactions with Hydrazines, Hydroxylamine, Amidines and Sodium Azide

The reactions of chromanones **129** and chromones **130** with hydrazine hydrate resulted in the formation of 3(5)-(2-hydroxyaryl)-5(3)-polyfluoroalkylpyrazoles that have a planar conformation and mainly exist as 1*H*-5-R^F-tautomers **166a** in $CDCl_3$ and as 1*H*-3-R^F-tautomers **167a** in DMSO. The reaction with phenylhydrazine allows one to synthesise regioisomeric 5-R^F-pyrazole **166b** from **129** and 3-R^F-pyrazoles **167b** from **130**. With methylhydrazine, only the 3-R^F-regioisomers **167c** are formed. Under mild conditions, the reaction of **129** with hydrazines can be arrested after the formation of dihydropyrazoles **168** [84a]. Reactions of CF_3-pyrazole **166a** (R^1=H) with various 2-chloro-3-nitropyridines via nucleophilic aromatic substitution followed by denitrocyclization gave benzo[*f*]pyrazolo[1,5-*d*]pyrido[3,2-*b*][1,4]oxazepines in 50–60 % yields (Scheme 53).



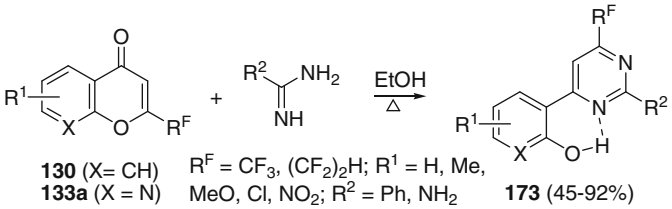
Scheme 53 Reactions with hydrazines

The reaction of chromanones **129** with hydroxylamine gave oximes existing in the ring isoxazoline form **169** [53]. Under similar conditions, chromones **130** react at the C-2 atom rather than at the oxo group and give isomeric oximes **170**, which do not tend to cyclise, unlike the aliphatic analogues [85]. The change in the direction of the nucleophilic attack on passing from **129** to **130** makes it possible to obtain regioisomeric 5-R^F-isoxazoles **171** (refluxing of **169** in toluene with $SOCl_2$) and 3-R^F-isoxazoles **172** (refluxing of **170** in AcOH with HCl) (Scheme 54). Azachromones **133** react with amines, hydrazines and hydroxylamine similarly [86].



Scheme 54 Reactions with hydroxylamine

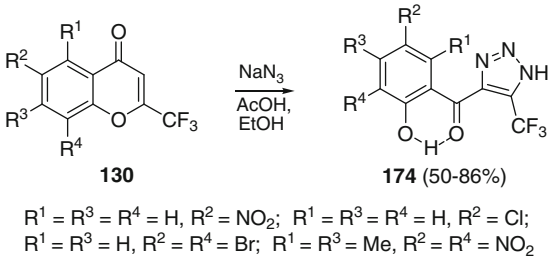
Substituted 2-R^F-chromones are effective in the reaction with amidines to create R^F-containing pyrimidine derivatives. Reflux of chromones **130** with benzamidine hydrochloride or guanidinium nitrate in the presence of KOH yielded the pyrimidines **173** in moderate to high yields [87] (Scheme 55).



Scheme 55 Reactions with amidines

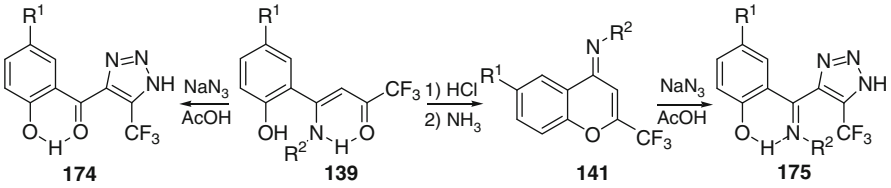
The reaction is applicable to the 8-aza-5,7-dimethyl-2-(trifluoromethyl)chromone (**133a**) to afford the corresponding pyrimidines with 2-pyridone substituent [87].

Salicyloyltriazoles **174** were prepared by the reaction of 2-CF_3-chromones **130** with sodium azide. It should be noted that on replacement of the CF_3 group by H, CF_2H or $(CF_2)_2H$, the reaction does not take place. Furthermore, without an electron-withdrawing group at the 6-position the reaction slows down to such an extent that 2-(trifluoromethyl)chromone **130a** is recovered unchanged [88] (Scheme 56).



Scheme 56 Reactions of chromones **130** with sodium azide

The reactivity of the pyrone ring with respect to NaN_3 can be increased by replacement of the C=O group by the C=NR group. It was shown [88] that the presence of an electron-withdrawing group in the benzene ring is not obligatory for chromene-4-imines **141**, and they easily react with NaN_3 in the presence of AcOH to give aryltriazolylketone imines **175** due to protonation of C=N bond (Scheme 57).

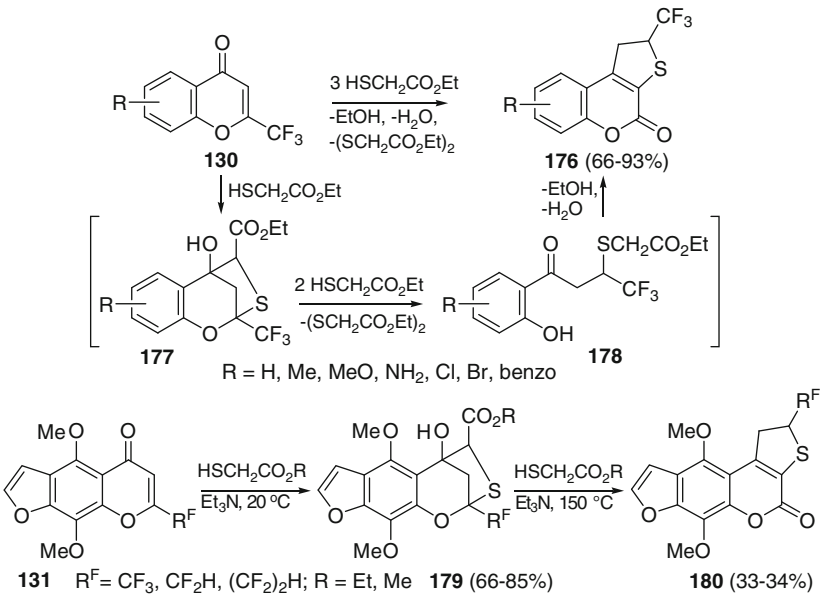


Scheme 57 Reactions with sodium azide

Hydrolysis of imines **175** affords triazoles **174**, which could not be synthesised from the corresponding 2-CF_3-chromones. Since the transformations **139** → **141** and **141** → **174** proceed via common iminium intermediate **140**, it comes as no surprise that aminovinyl ketones **139** are converted under these conditions into triazoles **174** as easily as chromene-4-imines **141** [88].

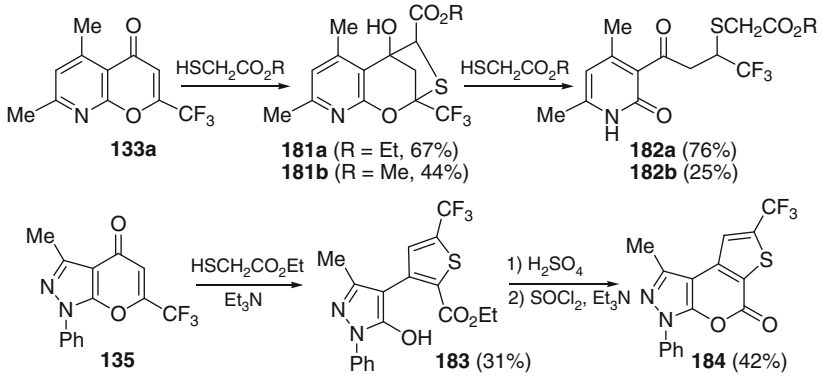
3.2.4 Reactions with Alkyl Mercaptoacetates

One of the most unexpected reactions of 2-CF_3-chromones **130** is the reaction with ethyl mercaptoacetate in the presence of Et_3N, which results in **176** and diethyl 3,4-dithiaadipate via redox process. This reaction can be accomplished only with 2-CF_3-chromones. Most likely, it starts with the formation of **177**, subsequent reductive opening leads to **178** cyclizing to dihydrothienocoumarin **176** [89]. The reaction of alkyl mercaptoacetates with fluorokhellins **131** stops after the formation of products **179**. Only under rigorous conditions (sealed tube, 150 °C), norkhellins **131** were converted into **180** [57, 90] (Scheme 58).



Scheme 58 Reactions of **130** and **131** with ethyl mercaptoacetate

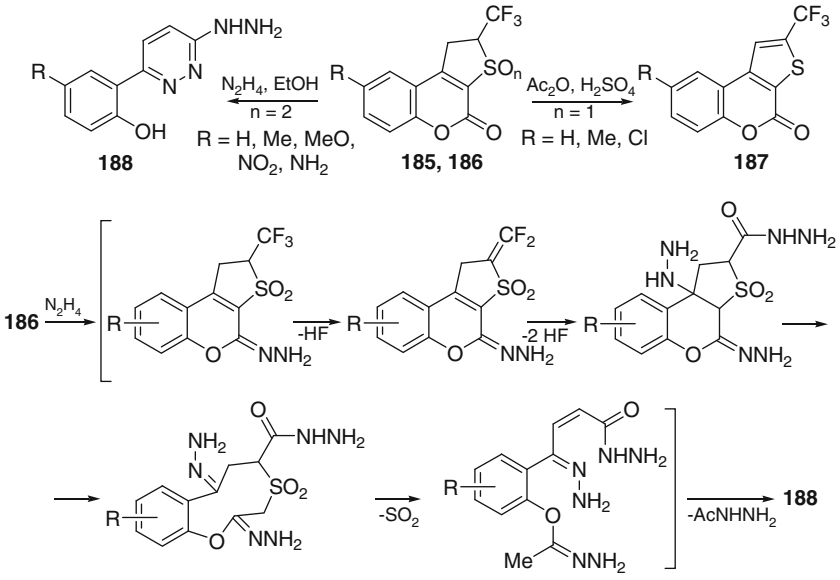
The reaction of 8-aza-5,7-dimethyl-2-(trifluoromethyl)chromone (**133a**) with alkyl mercaptoacetates afforded bicycles **181a**,**b**. When the reaction time and the amount of Et_3N were increased, acyclic derivatives **182a**,**b** were isolated [91]. A similar reaction of pyranopyrazole **135** proceeds at the C-6 atom followed by pyrone ring opening and intramolecular condensation of the aldol type to give compound **183**, from which heterofused coumarin **184** was obtained [59] (Scheme 59).



Scheme 59 Reactions of **133a** and **135** with ethyl mercaptoacetate

Selective oxidation of dihydrothienocoumarins **176** gives rise to highly reactive substrates, namely, sulfoxides **185** (NO_2, $CHCl_3$) and sulfones **186** (H_2O_2, AcOH). Under Pummerer rearrangement conditions, sulfoxides **185** produce thienocoumarins

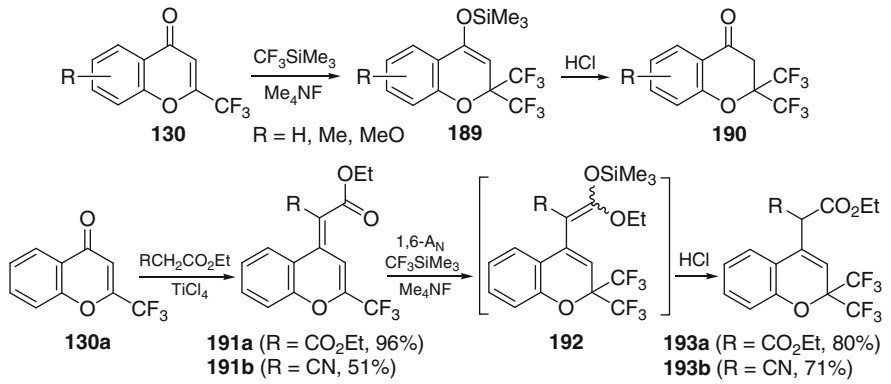
187 [89b]. Sulfones **186** are transformed into 3-hydrazino-6-(2-hydroxyaryl)pyridazines **188** by the action with hydrazine hydrate [92]. Previously, these pharmaceutically valuable products providing the basis for a series of 3-hydrazinopyridazine drugs [93], were synthesised in seven steps starting from phenols and succinic anhydride [94]. Multistep mechanism of this transformation is given below (Scheme 60).



Scheme 60 Synthesis of hydrazinopyridazines **188**

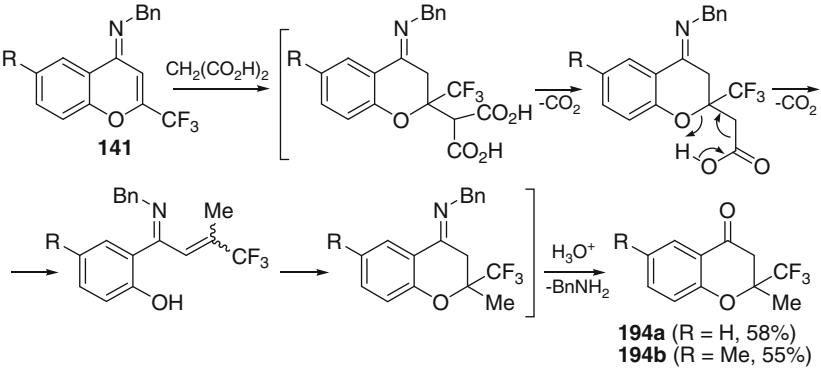
3.2.5 Reactions with *C*-Nucleophiles

Trimethyl(trifluoromethyl)silane (Ruppert's reagent) easily reacts with α,β-unsaturated carbonyl compounds yielding the corresponding trifluoromethylated alcohols [95]. The reaction of CF_3SiMe_3 with 2-CF_3-chromones **130** is the first example of preparative 1,4-trifluoromethylation of the α,β-enone system, which leads to trimethylsilyl ethers **189** giving after acid hydrolysis 2,2-bis(trifluoromethyl)chroman-4-ones **190** [96]. Chromone **130a** reacts with ethyl malonate and ethyl cyanoacetate to give methylidene derivatives of 4*H*-chromene **191a,b**. Subsequent reaction with CF_3SiMe_3 in the presence of Me_4NF involves nucleophilic 1,6-addition to the conjugated systems to produce, through acid hydrolysis of intermediate **192**, 2*H*-chromenes **193a,b** [97] (Scheme 61).



Scheme 61 Reactions with Ruppert's reagent

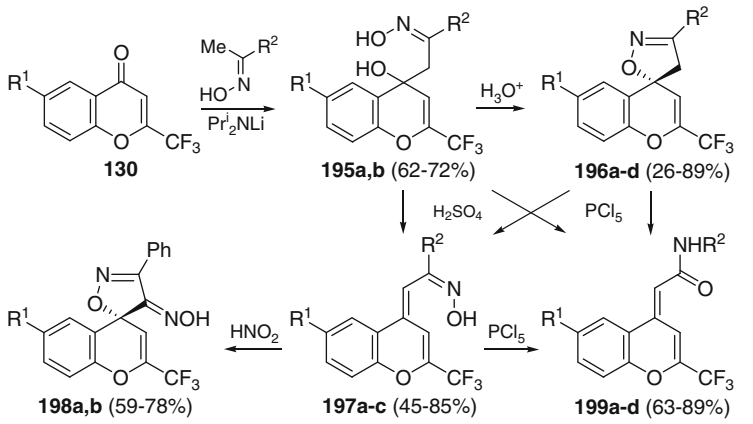
2-Methyl-2-(trifluoromethyl)chroman-4-ones **194a,b** were obtained in good yields by reaction of chromene-4-imines **141** with malonic acid, which acts as methylating agent via addition-decarboxylation-hydrolysis sequence [98] (Scheme 62).



Scheme 62 Reactions with malonic acid

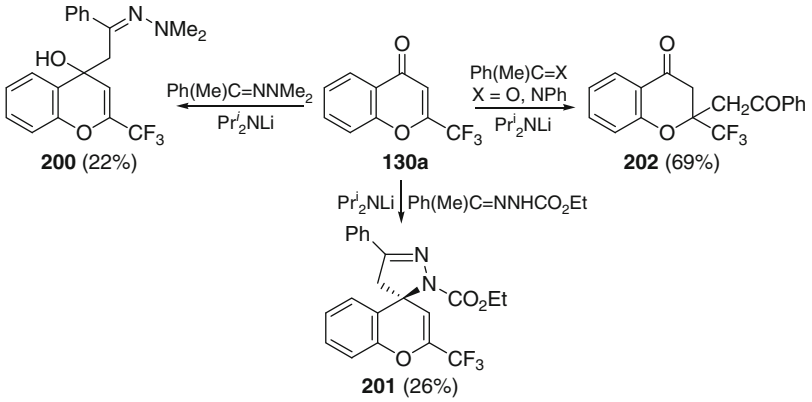
The reactions of 2-CF_3-chromones **130** with dilithiooximes proceed via nucleophilic 1,2-addition to give β-hydroxy oximes **195a–d** and, on acidification, 4*H*-chromene-4-spiro-5′-isoxazolines **196a–d**. The isoxazoline ring in **196** undergoes opening under the action of concentrated H_2SO_4, yielding oximes **197a–c**. Their nitrosation leads to **198a,b**, while the Beckmann rearrangement, to α,β-unsaturated amides **199**. The latter are also formed from **196** using PCl_5 [99] (Scheme 63).

Analogous reactions of acetophenone dimethylhydrazone and acetophenone ethoxycarbonylhydrazone with chromone **130a** gave β-hydroxy hydrazone **200** and spiropyrazoline **201**, which are also 1,2-adducts. In contrast, acetophenone and



Scheme 63 Products from **130** and dilithiooximes

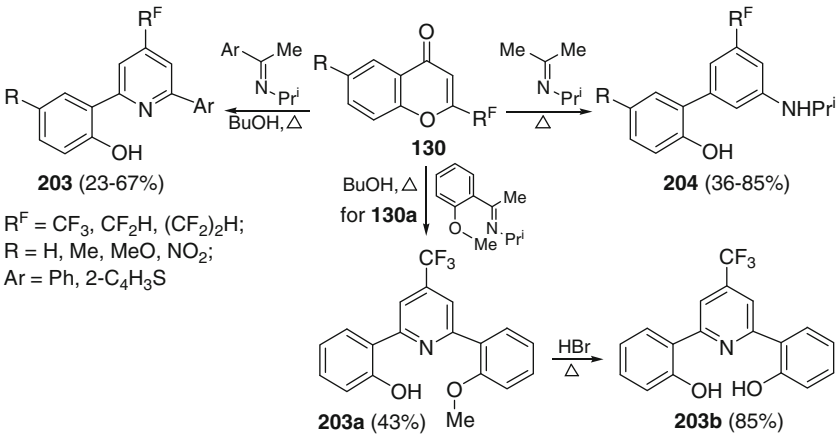
acetophenone anil behaved differently under the same conditions giving via 1,4-addition chromanone **202** [99, 100] (Scheme 64).



Scheme 64 Reactions of **130a** with hydrazones, acetophenone anil and acetophenone

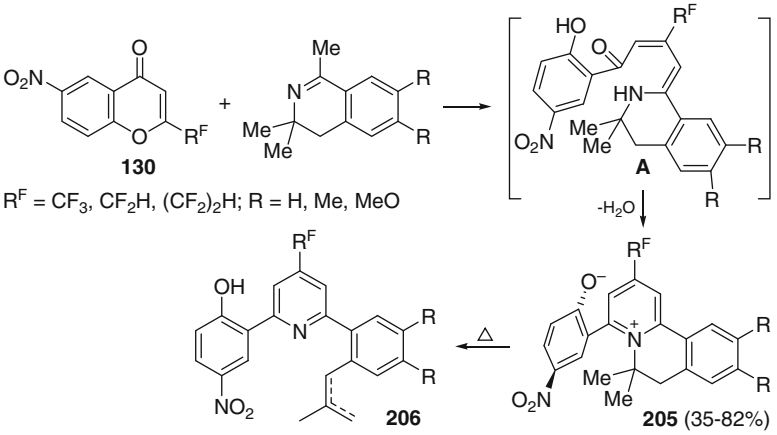
It was also found that 2-R^F-chromones **130** react with *N*-(1-arylethylidene)-2-propanamines to afford pyridines **203** in moderate yields. Using this reaction, pyridine **203a** was obtained, demethylation of which to 2,6-bis(2-hydroxyphenyl)-4-(trifluoromethyl)pyridine (**203b**) was achieved by heating with 48 % HBr at 200 °C [87]. When a mixture of chromones **130** with (isopropylidene)isopropylamine was refluxed without solvent for 10 h, anilines **204** were obtained [101] (Scheme 65).

The reaction of 6-nitro-2-R^F-chromones **130** with 1,3,3-trimethyl-3,4-dihydroisoquinolines affords chiral zwitter-ions **205** in 35–82 % yields. This reaction is typical only for 6-nitro derivatives and includes the nucleophilic attack of the



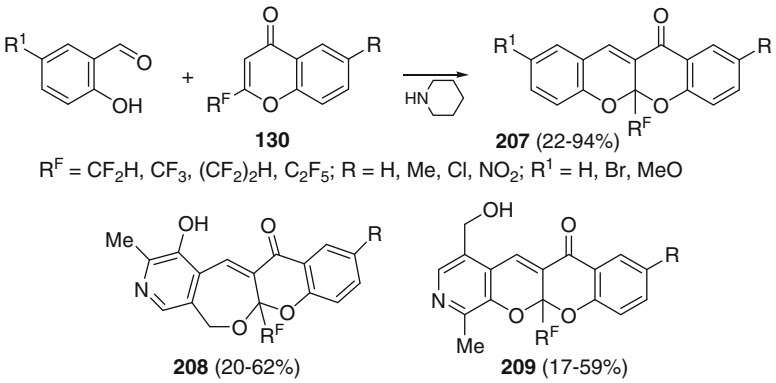
Scheme 65 Reactions of **130** with imines

enamine tautomer of dihydroisoquinoline to C-2 atom of **130** followed by ring opening and intramolecular cyclization at the keto group with elimination of H_2O. Cleavage of the Me_2C–N bond, resulting in the formation of isomers **206**, takes place on heating or in the presence of H_2SO_4 [102] (Scheme 66).



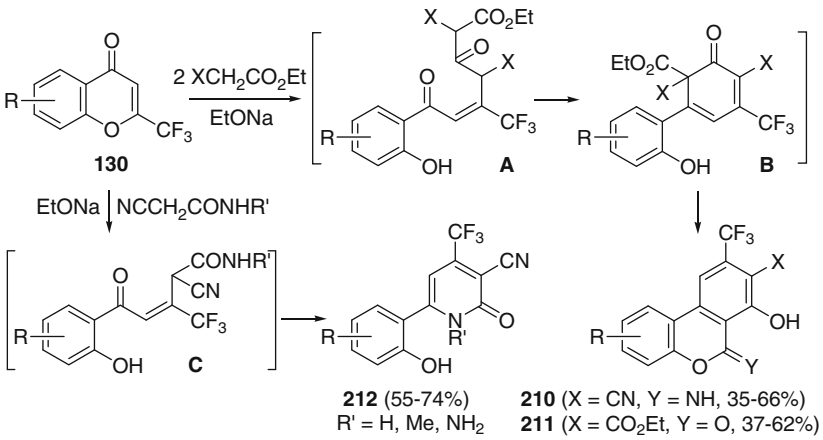
Scheme 66 Reactions of **130** with 3,4-dihydroisoquinolines

We also found that 2-R^F-chromones **130** react with salicylaldehydes in the presence of piperidine to afford **207** via oxa-Michael addition followed by intramolecular Mannich condensation [27]. Treatment of **130** with pyridoxal hydrochloride in the presence of NaOH (2.6 equiv.) gave oxepines **208** in moderate yields. In this case, the reaction proceeded at the alcoholic hydroxyl. Interestingly, using 1.3 equiv. of NaOH, it was possible to obtain **209** [103] (Scheme 67).



Scheme 67 Reactions of **130** with salicylaldehydes

Recently, Sosnovskikh et al. reported that 2-(trifluoromethyl)chromones **130** reacted with two molecules of ethyl cyanoacetate, yielding benzo[*c*]chromene-8-carbonitriles **210**. A similar base-mediated reaction of **130** with diethyl malonate gave carboxylates **211**. These products are formed through nucleophilic attack followed by Claisen condensation (intermediate **A**), intramolecular cyclization and dehydration (intermediate **B**), and then by aromatization (after hydrolysis and decarboxylation) through involvement of the phenolic hydroxy group. At the same time, chromone **130a** reacts with cyanoacetamide, *N*-methyl cyanoacetamide, and cyanoacetohydrazide in the presence of sodium ethoxide, affording 2-pyridones **212** in good yields [104] (Scheme 68).



Scheme 68 Reactions of **130** with active methylene compounds

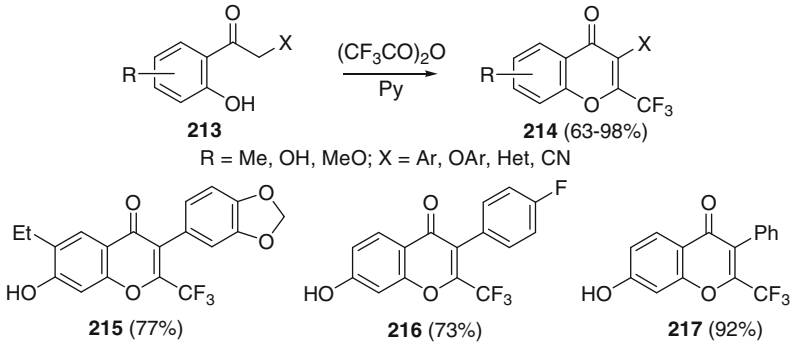
In conclusion, it should be noted that the trifluoromethyl group occupies a special place among polyfluorinated substituents, because the most interesting and peculiar transformations with *N*-, *S*- and *C*-nucleophiles can be carried out only for

2-CF_3-chromones and their derivatives. Most of the reaction described in this chapter are typical only for 2-R^F-chromones and does not occur when the R^F group is replaced by the methyl or trichloromethyl group [46b].

3.3 3-Substituted 2-(Polyfluoroalkyl)Chromones

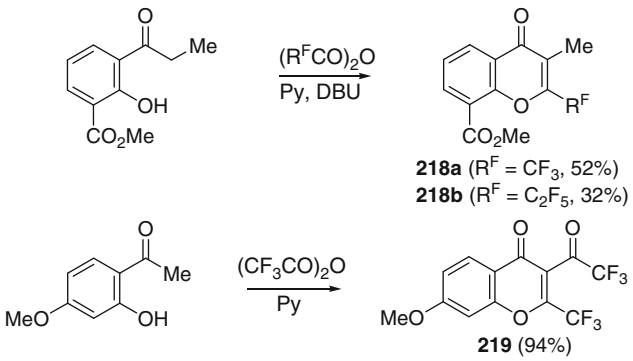
3.3.1 Synthesis of 3-Substituted 2-(Trifluoromethyl)Chromones

Preparation of 3-aryl and 3-hetaryl-2-(trifluoromethyl)chromones **214** was achieved by reaction of trifluoroacetic anhydride with pyridine solutions of ketones **213** [105]. This simple and effective procedure was also used for the synthesis of 7-hydroxy-2-(trifluoromethyl)chromone-3-carbonitrile (**214**, X=CN), from which 7-hydroxy-2-(trifluoromethyl)chromone-3-carboxamide (**214**, X=$CONH_2$) was obtained. These compounds are useful for preventing allergic and asthmatic symptoms [106]. The same procedure was employed for the preparation of isoflavones **215** and **216** which are potent dual PPARα and γ agonists [107]. By heating ω-phenylresacetophenone with $(CF_3CO)_2O$ and sodium trifluoroacetate isoflavone **217** was prepared with the intent to study antihypertensive activity [48]. The reactions of isoflavones containing a trifluoromethyl group at the 2-position have been reviewed previously [108] (Scheme 69).



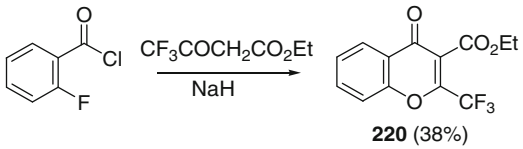
Scheme 69 Synthesis of 3-substituted 2-CF_3-chromones

2-Hydroxy-3-(methoxycarbonyl)propiophenone is easily converted into chromones **218a,b** through DBU assisted Baker-Venkataraman reaction with perfluoroalkanoyl anhydrides in pyridine [109]. The strength of the trifluoroacetic anhydride as acylating agent and the electron delocalization toward the carbonyl oxygen promoted by the *para*-methoxyl group favor the over trifluoracetylation of an intermediate, which ultimately produce **219** in excellent yield [60] (Scheme 70).



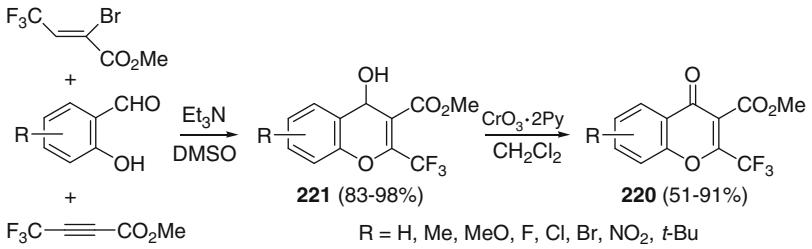
Scheme 70 Synthesis of 3-substituted 2-R^F-chromones

The reaction of *o*-fluorobenzoyl chloride with β-ketoesters in the presence of NaH has been proposed as a method for the synthesis of 2-methylchromone-3-carboxylic acid and its esters. In particular, this reaction proved to be suitable for the preparation of ethyl 2-(trifluoromethyl)chromone-3-carboxylate (**220**) [110] (Scheme 71).



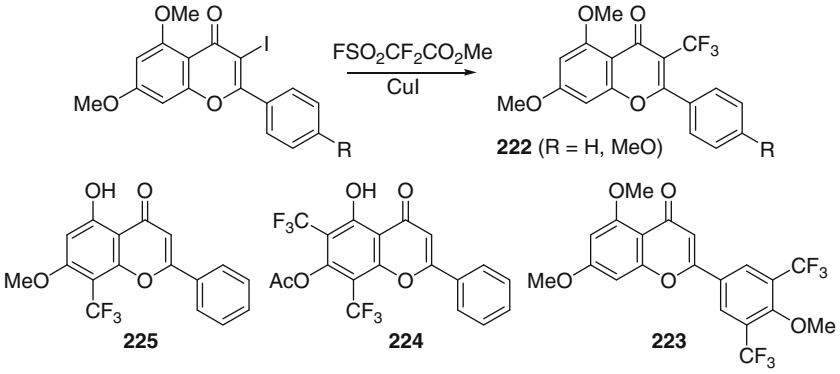
Scheme 71 Synthesis of chromone **220**

Derivatives of 4-hydroxy-2-(trifluoromethyl)-4*H*-chromene **221** were obtained via condensation of salicylaldehydes with methyl (*Z*)-2-bromo-4,4,4-trifluoro-2-butenoate [111] or methyl 2-perfluoroalkynoates [112]. Treatment of **221** with Sarrett reagent in CH_2Cl_2 generated chromones **220** in high yields [111] (Scheme 72).



Scheme 72 Synthesis of compounds **220** and **221**

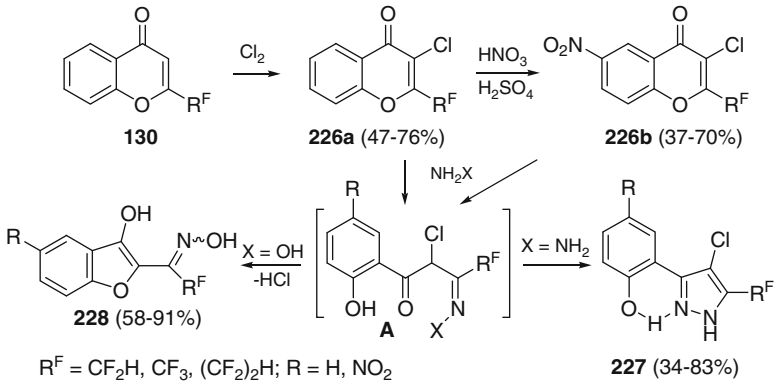
3-(Trifluoromethyl)flavonoid derivatives **222** were prepared by trifluoromethylation of 3-iodoflavonoids with $FSO_2CF_2CO_2Me$/CuI. Other C ring and B ring trifluoromethylated flavones were also prepared. All the compounds were tested for their effect on the U2OS cell cycle. Bistrifluoromethylated apigenin derivative **223** showed the strongest activity [113]. Chrysin derivatives **224** and **225** were tested in vitro against human gastric adenocarcinoma cell line (SGC-7901) and colorectal adenocarcinoma (HT-29) cells [114] (Scheme 73).



Scheme 73 Trifluoromethylated flavones

3.3.2 Reactions of 3-Substituted 2-(Polyfluoroalkyl)Chromones

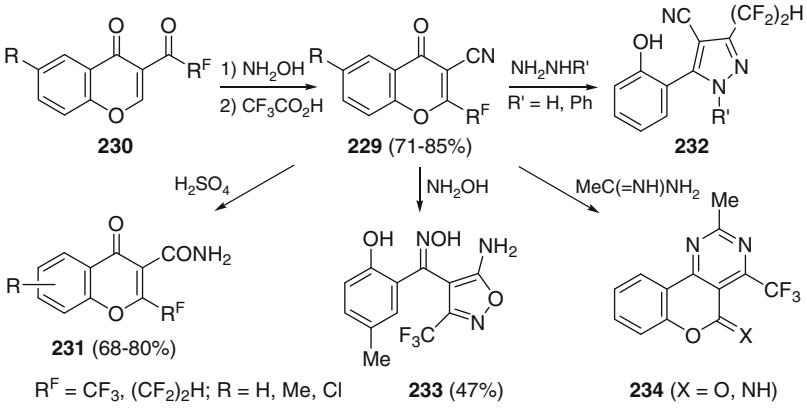
When treated with chlorine in the light (CCl_4, ~60 °C, 1 h), chromones **130** add a chlorine molecule at the double bond of the pyrone ring and, after elimination of HCl, they are converted into 3-chlorochromones **226a**, which are readily nitrated to give 3-chloro-6-nitrochromones **226b** [67, 115] (Scheme 74).



Scheme 74 Reactions of chromones **226** with hydrazine and hydroxylamine

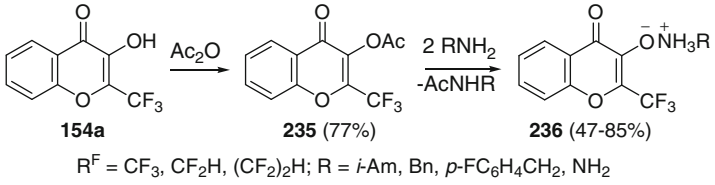
3-Chlorochromones **226** react with hydrazine dihydrochloride to give 4-chloropyrazoles **227** in good yields [115]. It is the first example of a reaction of 3-halochromone with a nucleophile with retention of the halogen atom in the reaction product. When chromones **226** are refluxed with hydroxylamine, contraction of the pyrone ring to the furan ring, typical of 2-unsubstituted 3-halochromones, takes place to give benzofurans **228** [116]. The reactions involve intermediate **A** resulting from the attack of the NH_2 group on the C-2 atom with the pyrone ring opening. This is followed by either an intramolecular Ad_N-E reaction between the C=O and NH_2 groups (X=NH_2) or nucleophilic substitution of the phenolic hydroxyl for the chlorine atom (X=OH) [116] (Scheme 74).

When 3-cyano-2-(polyfluoroalkyl)chromones **229**, prepared from 3-(polyfluoroacyl)chromones **230** (see Sect. 3.4.1), were treated with H_2SO_4, amides **231** were obtained in high yields. Heterocyclization of **229** with hydrazines, hydroxylamine and acetamidine resulted in pyrazoles **232**, 5-aminoisoxazole oxime **233**, and pyrimidin-5-ones **234** in variable yields [117] (Scheme 75).



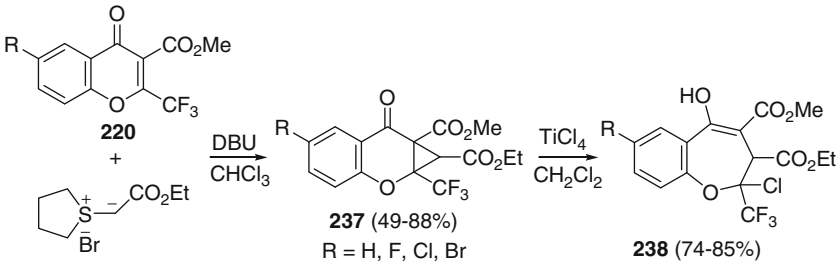
Scheme 75 Some reactions of chromones **229**

We found that **154a** smoothly reacts with an excess of MeI (refluxing acetone) and Ac_2O–Py to produce the expected 3-methoxy- and 3-acetoxy-2-(trifluoromethyl) chromones in high yields. Treatment of **235** with primary amines and hydrazine gave only the corresponding ammonium salts **236** [72] (Scheme 76).



Scheme 76 Acetylation of chromone **154a**

Chromones **220** were converted to 2-trifluoromethyl-substituted benzoxepins **238** through cyclopropanation and Lewis acid-catalyzed ring opening of **237** [111] (Scheme 77).

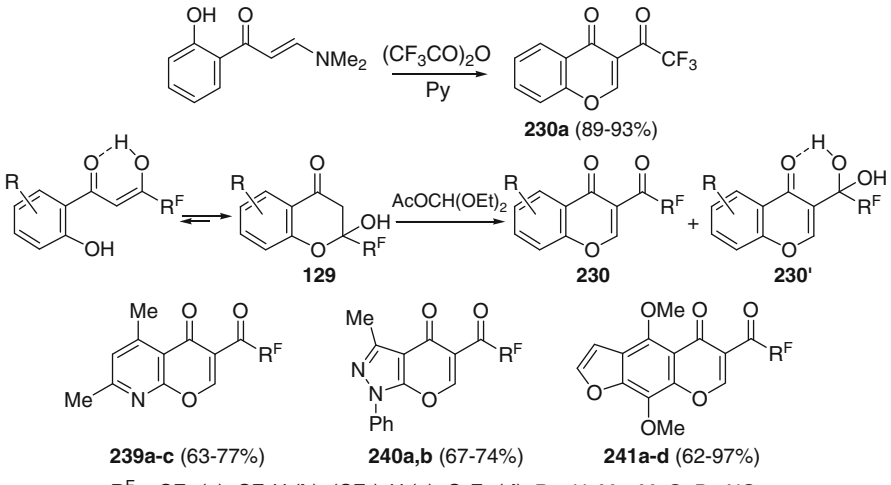


Scheme 77 Synthesis of compounds **237** and **238**

3.4 3-(Polyfluoroacyl)- and 2-(Trifluoroacetyl)Chromones

3.4.1 Synthesis and Reactions of 3-(Polyfluoroacyl)Chromones

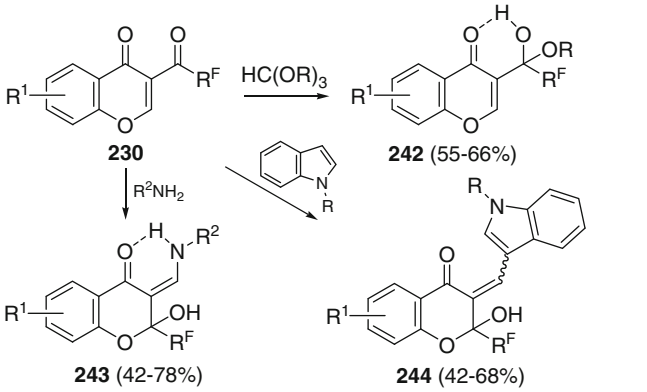
3-(Polyfluoroacyl)chromones **230** containing a β-dicarbonyl fragment and a masked formyl group are highly reactive R^F-containing building blocks [118]. There has been only two reports on the preparation of **230** by trifluoroacetylation of 3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one with trifluoroacetic anhydride or *N*-(trifluoroacetyl)imidazole [119] and by formylation of 2-hydroxy-2-(polyfluoroalkyl)chroman-4-ones **129** using diethoxymethyl acetate [120] (Scheme 78).



Scheme 78 Synthesis of 3-(polyfluoroacyl)chromones **230** and their heteroanalogs

It should be taken into account that these compounds easily add a water molecule at the carbonyl group and exist as a mixture with their hydrates **230′** [121]. Pure **230a** was obtained from a mixture of keto and hydrate forms using P_2O_5 [122]. Heteroanalogues **239–241** were obtained similarly in high yields [59, 121, 123].

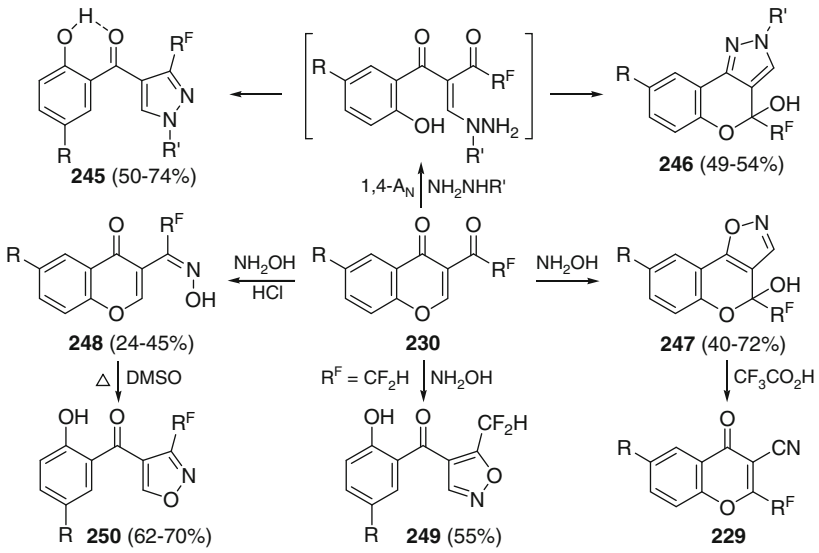
As expected, the reaction of chromones **230** with alkyl orthoformates catalyzed with HCl or *p*-TsOH resulted in the formation of hemiketals **242**. The reaction of **230** with primary amines afforded chromanones **243** in good yields [121] (Scheme 79).



Scheme 79 Reactions of **230** with amines and indoles

Chromones **230** smoothly react with indole and *N*-methylindole in refluxing pyridine resulting in the formation of **244** as mixtures of *Z*- and *E*-isomers [124]. These reactions include the nucleophilic 1,4-addition of the amine or indole with concomitant opening of the pyrone ring and subsequent intramolecular cyclization of the intermediate at the R^FCO group [125].

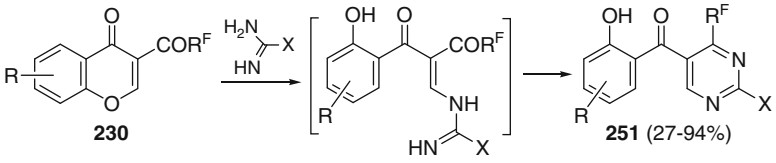
Reactions of 3-(polyfluoroacyl)chromones **230** with hydrazine hydrate and methylhydrazine proceed via nucleophilic 1,4-addition followed by opening of the pyrone ring and heterocyclization at polyfluroacyl group into 4-(2-hydroxyaroyl)-3-(polyfluoroalkyl) pyrazoles **245** or aroyl group into 4-(polyfluoroalkyl)-2,4-dihydrochromeno[4,3-*c*] pyrazol-4-oles **246** [126] (Scheme 80).



R^F = CF$_2$H, CF$_3$, (CF$_2$)$_2$H; R = H, Me, Cl, NO$_2$; R' = H, Me

Scheme 80 Reactions of **230** with hydrazines and hydroxylamine

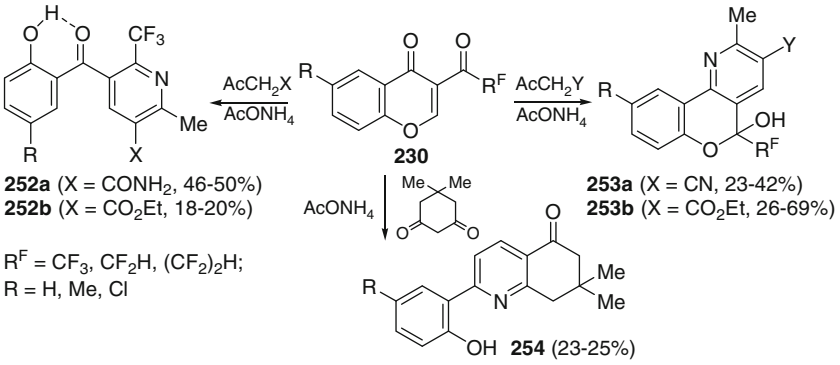
Similar reaction of **230** with hydroxylamine proceeds via 1,4-addition and subsequent cyclization to **247** in good yields. On treatment with trifluoroacetic acid, the isoxazole ring of this fused heterocyclic system opens to give 3-cyano-2-R^F-chromones **229** (see Sect. 3.3.2). On the other hand, oximation of **230** with hydroxylamine hydrochloride occurs either at the C=O group connected to the R^F group or at the C-2 atom to give chromones **248** and isoxazole **249**, respectively. The former were converted to isoxazoles **250** by heating in DMSO [127] (Scheme 80). Treatment of chromones **230** with amidine and guanidine gave 5-salicyloyl-4-(polyfluoroalkyl) pyrimidines **251** in variable yields, from which the corresponding 4-(trifluoromethyl) pyrimidine-5-carboxylic acids, a new class of potent ryanodine receptor activators, were obtained under Dakin reaction conditions [128] (Scheme 81).



R^F = CF$_2$H, CF$_3$, (CF$_2$)$_2$H, C$_3$F$_7$; R = H, Me, MeO; X = H, Me, Ph, NH$_2$, NMe$_2$

Scheme 81 Reactions of **230** with amidines

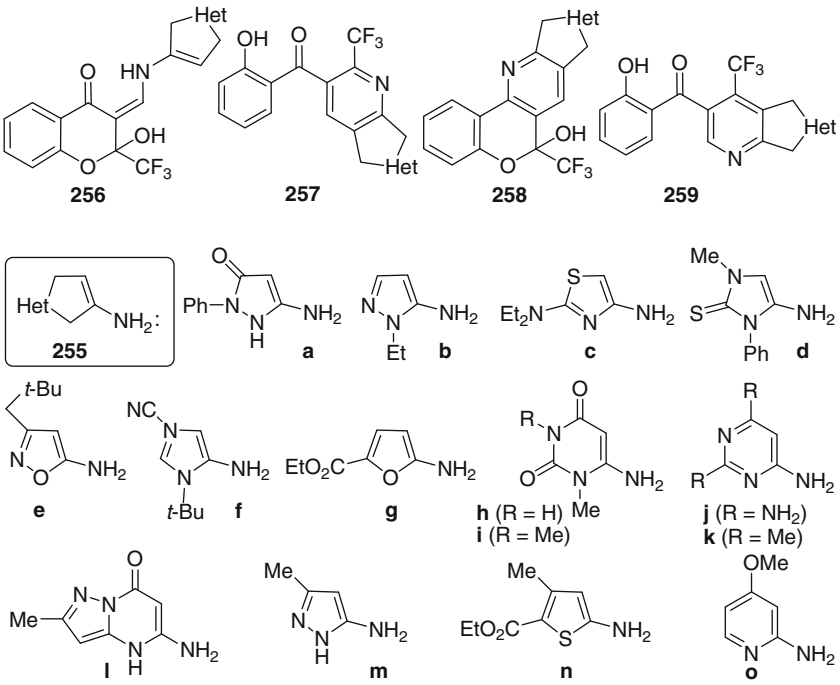
Reactions of chromones **230** with acetoacetamide and ethyl acetoacetate in ethanol in the presence of ammonium acetate proceed at the C-2 atom of the chromone system with pyrone ring-opening and subsequent cyclization to **252**. Similar reaction with β-aminocrotononitrile gave 5-hydroxy-2-methyl-5-(polyfluoroalkyl)-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitriles (**253a**) [129]. Three-component reaction between chromones **230**, dimedone, and $AcONH_4$ is accompanied by detrifluoroacetylation and leads to **254** in low yields [130] (Scheme 82).



Scheme 82 Reactions of **230** with active methylene compounds

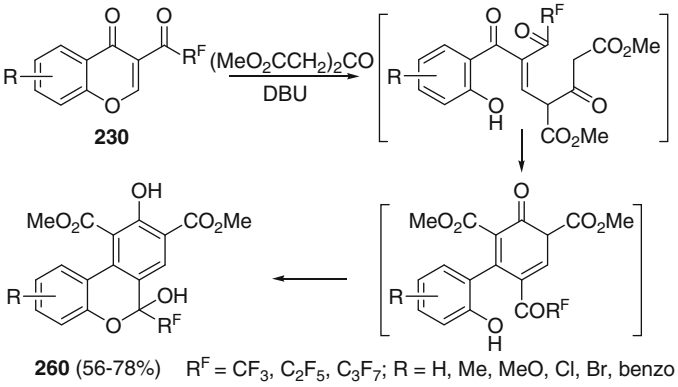
Chromone **230a** reacts with heterocyclic amines **255** giving four types of products, depending on the nature of the 1,3-*C,N*-dinucleophile and the solvent. The reaction of heterocycles **255a**,**i,j,l** with **230a** gave the corresponding fused pyridines **257** as the main products, while in the case of **255e–h** the formation of chromeno[4,3-b]pyridines **258** was preferred. At the same time, aminoheterocycles **255b,k,m–o** in DMF gave mainly chromanones **256**. Reactions of **255a–e**, performed in glacial acetic acid yielded preferably products **257** and **259**, which represent fused pyridines with a trifluoromethyl group located in the α- or γ-position. It clearly appears that the less aromatic heterocycles **255a–j,l** have a proclivity to form fused pyridines **257**–**259** [131] (Scheme 83).

While enamines react with chromones **230** mainly at the R^FCO group to produce pyridine derivatives, reactions of dimethyl acetonedicarboxylate with **230** took an entirely different course and gave a series of 6*H*-benzo[*c*]chromenes **260** in good yields. This heterocyclic system certainly is the product of the primary 1,4-addition



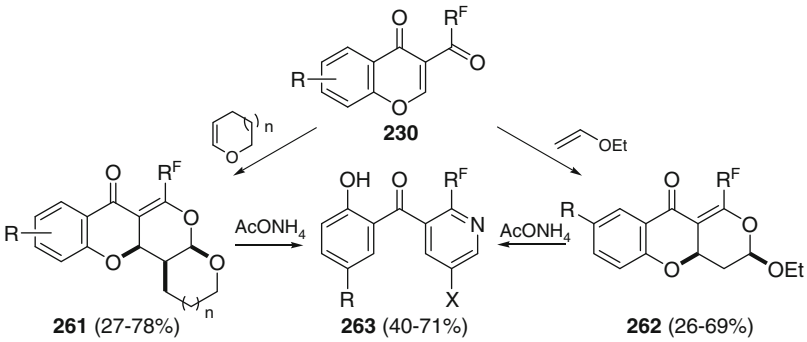
Scheme 83 Products **256**–**259** from chromones **230** and aminoheterocycles **255**

followed by the pyrone ring-opening, attack of the second CH_2 group to the carbonyl bound with the aromatic cycle, and ring-closure involving the phenolic hydroxyl and R^FCO group [132] (Scheme 84).



Scheme 84 Reaction of chromones **230** with dimethyl acetonedicarboxylate

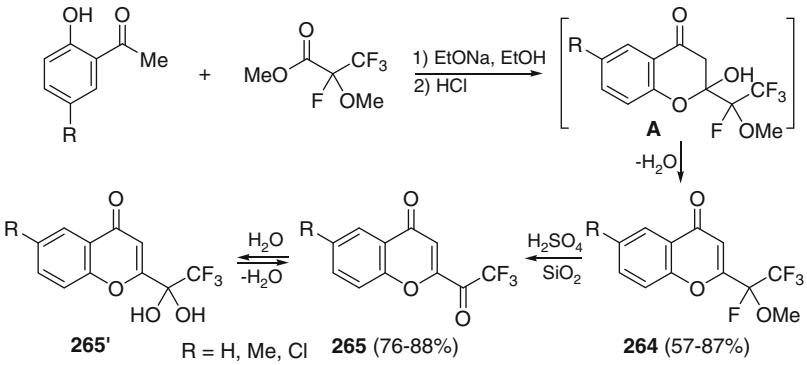
3-(Polyfluoroacyl)chromones **230** undergo heterodiene cycloaddition to 3,4-dihydro-2*H*-pyran, 2,3-dihydrofuran and ethyl vinyl ether under mild conditions, producing novel fused pyranes **261** and **262** with high stereoselectivity and in good yields. Some of these pyranes were transformed into 2-R^F-containing pyridines on treatment with ammonium acetate in ethanol [133] (Scheme 85).



Scheme 85 Hetero-Diels-Alder reaction of chromones **230**

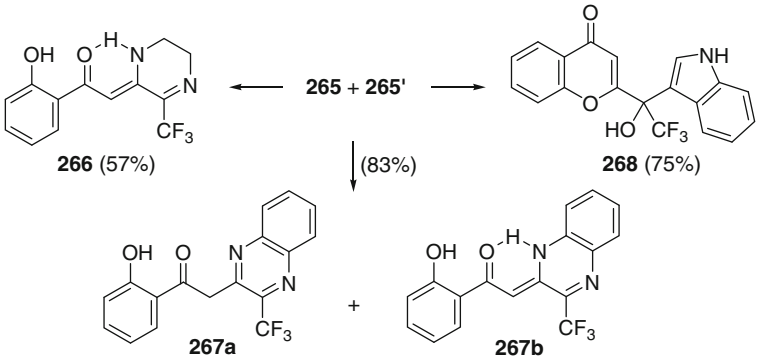
3.4.2 Synthesis and Reactions of 2-(Trifluoroacetyl)Chromones

We found that methyl 2-methoxytetrafluoropropionate reacted with 2-hydroxyacetophenones under Claisen reaction conditions (NaOEt or LiH) affording chromones **264** in high yields. Deprotection of chromones **265** was carried out using 96 % H_2SO_4 and SiO_2, to afford 2-(trifluoroacetyl)chromones **265**, which were prone to form hydrates [134] (Scheme 86).



Scheme 86 Synthesis of 2-(trifluoroacetyl)chromones **265**

Chromone **265** (R=H) behaves as a latent 1,2-diketone, having a masked aroyl fragment at the 3-position, and reacts with ethylenediamine and *o-phenylenediamine* to give **266** and **267a,b** (two tautomeric forms) in good yields. This chromone reacted smoothly with indole to produce the expected adduct **268**. These results clearly indicate that C-2 of **265**, due to the electron-withdrawing effect of the CF_3CO group, is very susceptible to nucleophilic attack [134] (Scheme 87).



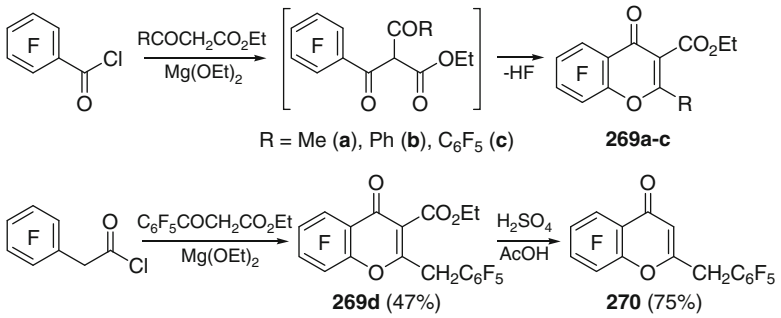
Scheme 87 Some reactions of 2-(trifluoroacetyl)chromones **265**

4 Ring-Fluorinated Chromones and Coumarins

4.1 Synthesis of Ring-Fluorinated Chromones and Coumarins

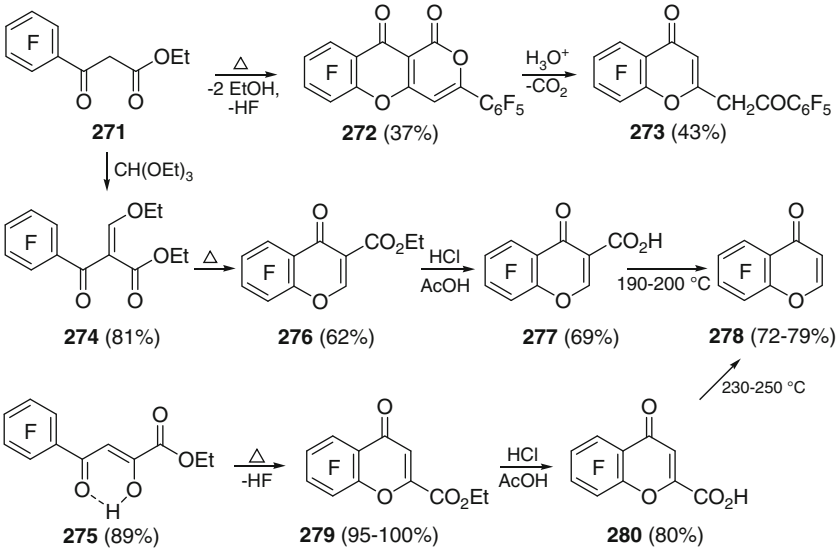
Ring-fluorinated chromone carboxylic acids are very interesting compounds being oxygen analogues of the fluoroquinolone antibiotics. It is well-known that polyfluoroaryl β-dicarbonyl compounds are useful in this area because the nucleophilic replacement of their *ortho*-fluorine atom leads to the formation of chromone structures. Such behaviour has been found in the reactions of pentafluoroaromatic β-ketoesters [135] and β-diketones [135, 136] and also in the synthesis of 2-substituted 3-ethoxycarbonyl-5,6,7,8-tetrafluorochromones **269a–d** through the reaction of pentafluorobenzoyl and pentafluorophenylacetyl chlorides with β-ketoesters in the presence of magnesium ethoxide. On hydrolysis, **269d** gave 2-pentafluorobenzyl-5,6,7,8-tetrafluorochromone (**270**) [135, 137] (Scheme 88).

Saloutin et al. reported [138] that the self-condensation of ethyl pentafluorobenzoylacetate (**271**) on refluxing without any catalyst leads to the formation of compound **272** in 37 % yield, acid hydrolysis of which gave 2-pentafluorobenzoylmethyl-5,6,7,8-tetrafluorochromone (**273**). Other routes for preparing some new ring-fluorinated chromones have been performed from the 2-ethoxymethylene pentafluorobenzoylacetic ester (**274**) and also via intramolecular cyclization of ethyl pentafluorobenzoylpyruvate (**275**). The reaction of ester **271** with ethyl orthoformate results in the



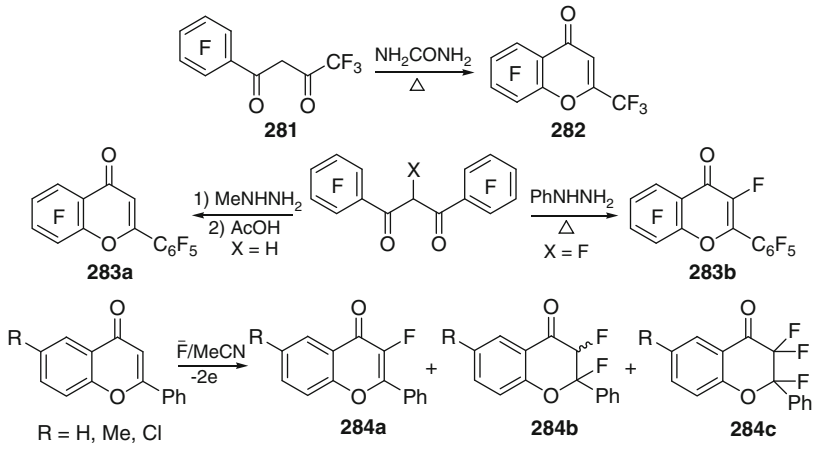
Scheme 88 Synthesis of chromones **269** and **270**

formation of compound **274**, which was refluxed with water to form 3-ethoxycarbonyl-5,6,7,8-tetrafluorochromone (**276**). The latter was hydrolyzed under acidic conditions to give carboxylic acid **277**, sublimation of which produced 5,6,7,8-tetrafluorochromone (**278**). This compound was derived directly from ester **276** in boiling acetic acid [138]. Pentafluoroacetophenone reacts with diethyl oxalate in the presence of LiH to give ethyl pentafluorobenzoylpyruvate (**275**), which can be isolated through its copper(II) chelate. Ester **275** is stable at room temperature, but is converted by heat to give 2-ethoxycarbonyl-5,6,7,8-tetrafluorochromone (**279**) in quantitative yield. The latter under acidic hydrolysis gave tetrafluorochromone (**280**), sublimation of which at 230–250 °C produced chromone **278** [138]. Pentafluoroacetophenone also reacts with Vilsmeier reagent to give chromone **278** and its 3-formyl derivative depending on the conditions [139] (Scheme 89).



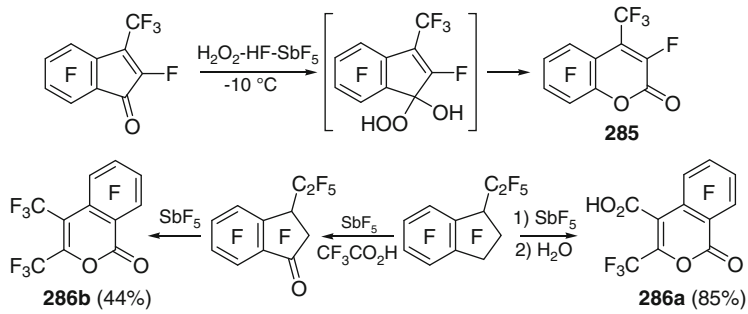
Scheme 89 Synthesis of chromones **273**, **278** and **280**

Heating diketone **281**, containing an easily replaceable fluorine atom in the *ortho*-position to the carbonyl group, with urea results in 2-(trifluoromethyl)-5,6,7,8-tetrafluorochromone (**282**) [140]. Perfluoroflavones **283a,b** were obtained from the reactions of bis(pentafluorobenzoyl)- and fluorobis(pentafluorobenzoyl)-methanes with methyl- and phenylhydrazines [136]. 3-Fluoroflavone **284a** and its 6-substituted derivatives were prepared from appropriate flavones by electrochemical fluorination with $Et_4NF \cdot 4HF$ or $Et_3N \cdot 3HF$. Anodic fluorination of flavones affords mono- (**284a**), di- (**284b**) and tri- (**284c**) fluoro derivatives, whose ratio depends on the type of salt used and the temperature of electrolysis. 3-Fluoroflavones **284a** are formed upon dehydrofluorination of **284b** under the action of Et_3N, while trifluoro derivatives **284c** are the products of further fluorination of **284a**. The yields of **284a** vary over a broad range (25–63 %) [141] (Scheme 90).



Scheme 90 Some ring-fluorinated chromones

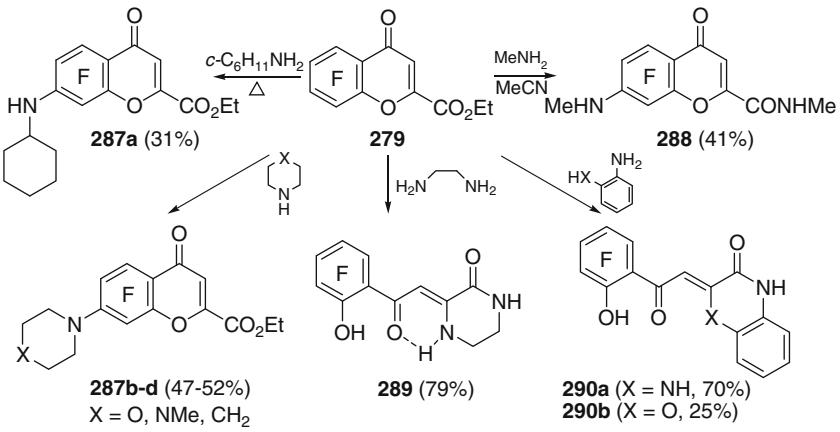
Formation of perfluoro-4-methylcoumarin **285** has been reported from perfluoro-3-methylindenone, in which the carbonyl group is involved in reaction with H_2O_2 in the HF–SbF_5 system [142a]. Perfluoro-1-ethylindan heated with excess of SiO_2 in SbF_5 at 75 °C and then treated with water, gives isocoumarin **286a** in high yield. Perfluoro-3-ethylindan-1-one is converted, under the action of SbF_5 at 70 °C, to perfluoro-3,4-dimethylisocoumarin **286b** [142b, c] (Scheme 91).



Scheme 91 Some ring-fluorinated coumarins

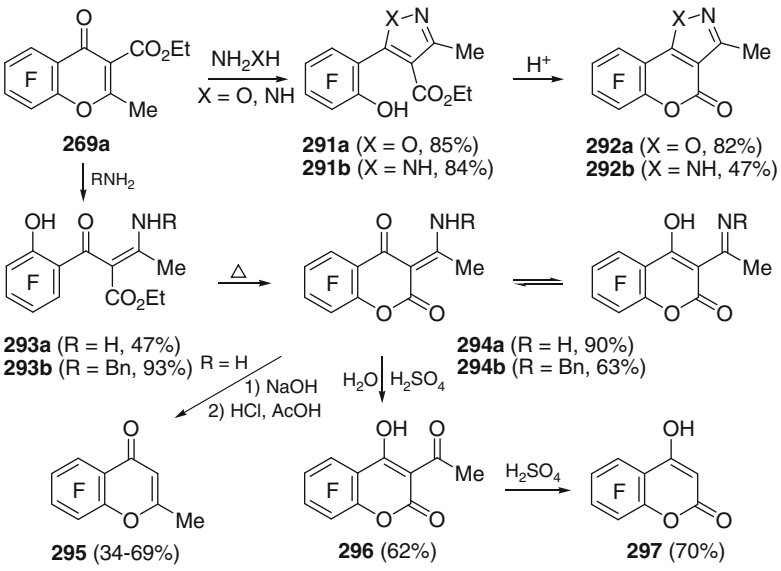
4.2 Reactions of Ring-Fluorinated Chromones and Coumarins

The reactions of chromones with amines is known to afford the corresponding aminoenones at the C-2 atom [46]. In contrast, chromone **279** reacts with cyclohexylamine, morpholine, *N*-methylpiperazine, and piperidine without pyrone ring opening to give compounds **287a–d**. Similar reaction with methylamine furnishes compound **288**, which results from reaction at the ethoxycarbonyl group and nucleophilic displacement of the fluorine atom at the 7-position of the heterocycle. At the same time, ammonia and aniline does not react with **279**. The reaction of **279** with ethylenediamine gave piperazinone **289** [143]. Refluxing of **279** with *o-phenylenediamine* in toluene for 18 h in the presence of $BF_3 \cdot Et_2O$ results in the formation of quinoxalinone **290a** [144]. On treatment with *o*-aminophenol chromone **279** gave benzoxazinone **290b** in low yield [145, 146] (Scheme 92).



Scheme 92 Reactions of chromone **279** with amines

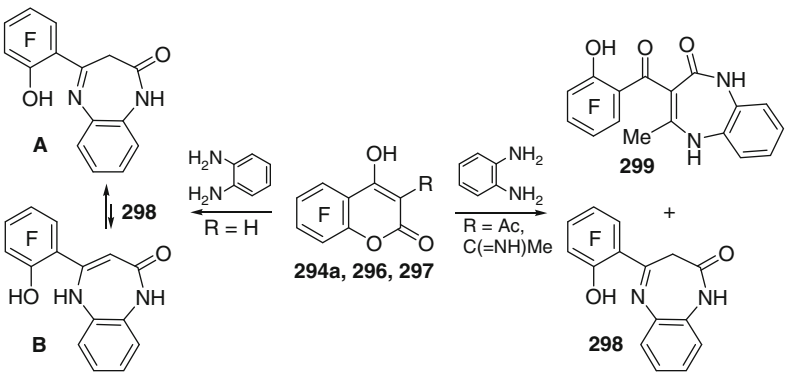
The reaction of chromone **269a** with hydroxylamine affords isoxazole **291a**, which could only arise from addition of the *N*-nucleophile at the C-2 position of the heterocycle. This compound was subjected to cyclization on refluxing under acidic conditions to give benzopyranoisoxazole **292a**. A similar reaction of chromone **269a** with hydrazine hydrate gave the corresponding pyrazole **291b**. When **291b** was heated with a boiling mixture of concentrated acetic and hydrochloric acids, benzopyranopyrazole **292b** was obtained [147a]. Chromone **269a** also reacts with ammonium hydroxide at room temperature to give a mixture of aminoenone **293a** and its cyclic derivative **294a**. The latter can be derived from **293a** by refluxing with ammonium hydroxide. When **269a** was heated with ammonium hydroxide, only **294a** was obtained. Similar reaction of **269a** with benzylamine also proceeds at the C-2 position and gives substituted aminoenone **293b**, which was then subjected to cyclization to produce coumarin **294b** without any catalyst or solvent at 100 °C. Both keto-enamino and imino-enol isomers are possible in structures **293** and **294**, however keto-enamino form is preferred [147b, c]. Under acidic conditions, aminoenone **293a** was hydrolyzed to give 2-methyl-5,6,7,8-tetrafluorochromone (**295**), which was also obtained from 3-carboxy-2-methyl-5,6,7,8-tetrafluorochromone and compound **294a** by alkaline and subsequent acidic treatment. When **294a** was treated with diluted H_2SO_4, coumarin **296** was obtained. The latter was treated with concentrated H_2SO_4 to give 4-hydroxy-5,6,7,8-tetrafluorocoumarin (**297**) [147a] (Scheme 93).



Scheme 93 Some derivatives of chromone **269a**

4-Hydroxycoumarin **297** was found to react with *o*-phenylenediamine on refluxing in toluene to form product **298** existing as a mixture of tautomers **A** and **B**. Under similar conditions, 3-acetyl-4-hydroxycoumarin **296** reacts with *o*-phenylenediamine

to form a mixture of products from which benzodiazepine-2-one **299** and compound **298** can be isolated. The former was also obtained in 65 % yield by the reaction of 3-acetimidoyl-4-hydroxycoumarin **294a** [148a] (Scheme 94).



Scheme 94 Reactions of 4-hydroxycoumarins with *o*-phenylenediamine

The reactions of 4-hydroxy-5,6,7,8-tetrafluorocoumarine derivatives with ammonia and morpholine involve aromatic nucleophilic substitution of fluorine atoms at the 7-position as the main process [148b].

5 Fluorinated Coumarins

Derivatives of 2*H*-1-benzopyran-2-one, also known as coumarins, are prominent natural products possessing a wide range of valuable physiological activities. Many coumarin derivatives exert anticoagulant, antitumor, antiviral, antiinflammatory and antioxidant effects, as well as antimicrobial and enzyme inhibition properties [47a, 149]. In addition, they represent useful synthetic building blocks in organic and medicinal chemistry, and have also found application as photosensitisers, fluorescent and laser dyes [150]. 7-Amino-4-(trifluoromethyl)coumarins, the important class of laser dyes for the "blue-green" region, are strongly fluorescent in polar solvents, and their fluorescence properties depend on the electron-donating ability of the 7-amino group [151].

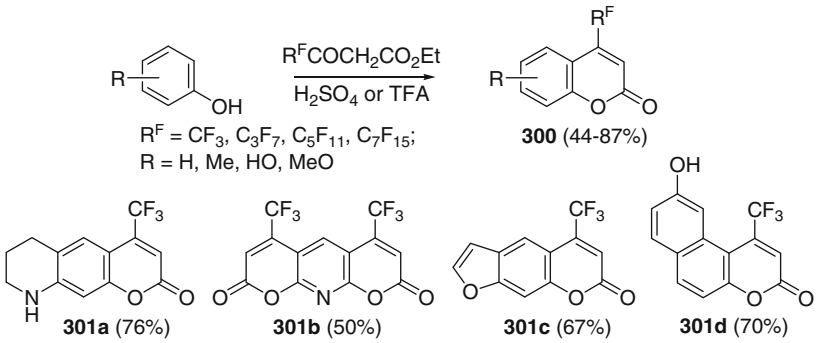
5.1 Synthesis and Application of Polyfluoroalkylated Coumarins

5.1.1 3-Unsubstituted 4-(Polyfluoroalkyl)Coumarins

Coumarins have been synthesized by several routes, including Pechmann, Perkin, Knoevenagel and Wittig reactions. The reaction of various phenols with β-ketoesters in the presence of an acid catalyst, an example of the Pechmann reaction, has been

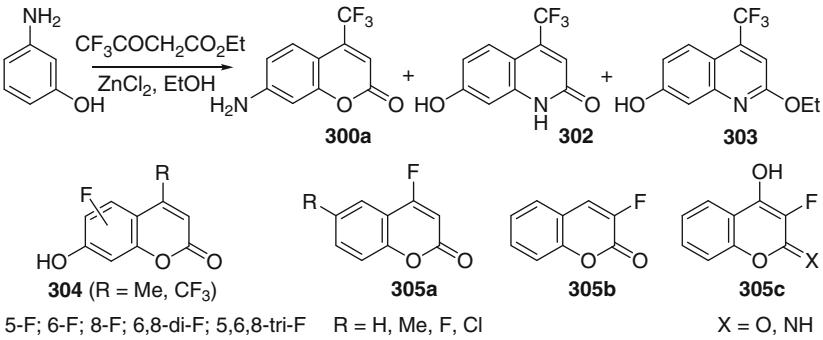
extensively used in the synthesis of 4-substituted coumarins. With ethyl 4,4,4-trifluoroacetoacetate [152] and electron-rich phenols, the reaction affords, almost invariable, 4-(trifluoromethyl)coumarins **300** bearing different electron-donating substituents at the benzene ring [50, 153, 154].

Various derivatives of 7-hydroxy- and 7-amino-4-(trifluoromethyl)coumarins **300** are readily prepared by the Pechmann reaction using zinc chloride as the condensing agent [155]. Recently, there have been reports on the use of $ZrCl_4$ [156], AgOTf and molecular iodine [157], $InCl_3$ [158], $Sc(OTf)_3$ [159] and $TiCl_4$ [160] as Lewis acids for the synthesis of 4-CF_3-coumarins **300**. A 30-membered library of 4-substituted coumarins has been synthesized in a microwave-assisted Pechmann reaction using neat trifluoroacetic acid both as an acidic reagent and a reaction medium [161]. Fused 4-(trifluoromethyl)coumarins **301a–d**, including 4-CF_3-psoralen **301c**, were obtained in the presence of an acid catalyst such as $ZnCl_2$, methanesulfonic acid or sulfuric acid [162–165] (Scheme 95).



Scheme 95 Some representatives of 4-(trifluoromethyl)coumarins

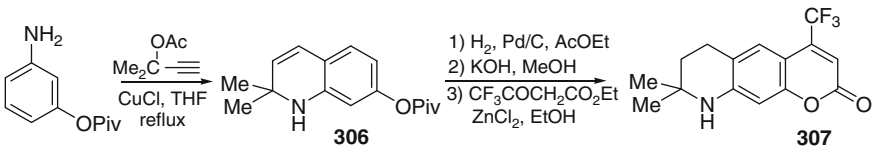
Synthesis and purification of 7-amino-4-(trifluoromethyl)courmarin (**300a**) (R = 7–NH_2, R^F=CF_3, Coumarin 151) from 3-aminophenol by the Pechmann reaction was first reported in 1980 [166]. Two byproducts, 7-hydroxy-4-(trifluoromethyl-2-quinolone (**302**) and 2-ethoxy-7-hydroxy-4-(trifluoromethyl)quinoline (**303**), were also isolated and identified. The synthesis of benzene ring fluorinated 7-hydroxy-4-methyl- and 7-hydroxy-4-(trifluoromethyl)coumarins **304** in 45–80 % yields was reported by Sun et al. by the condensation of fluorinated resorcinols with ethyl acetoacetate and ethyl trifluoroacetoacetate in methanesulfonic acid at ~20 °C [167]. 4-Fluorocoumarins **305a** were obtained from the corresponding 4-chlorocoumarins by a halogen-exchange reaction [168a]. The reaction of (*Z*)-2-fluoro-3-methoxyprop-2-enoyl chloride with phenol gave 3-fluorocoumarin **305b** [168b]. Dmowski reported facile preparation of 3-fluoro-4-hydroxycoumarins **305c** by treatment of *o*-hydroxy-2,3,3,3-tetrafluoropropiophenone with aqueous KOH and NH_3 [168c, d] (Scheme 96).



Scheme 96 Some representatives of fluorinated coumarins

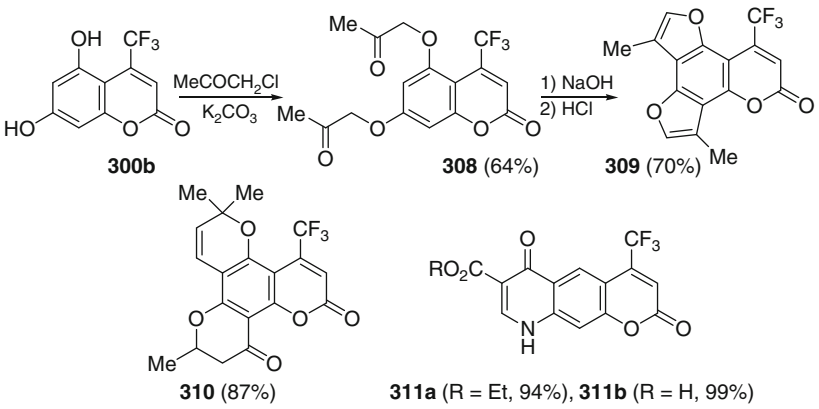
Reaction of 3-aminophenylpivalate with 3-acetoxy-3-methyl-l-butyne in the presence of CuCl afforded the corresponding propargyl aniline, which could be cyclized to **306** by treatment with catalytic CuC1 in refluxing THF. Reduction of the olefin by catalytic hydrogenation, deprotection of the phenol, and Pechmann cyclization using ethyl trifluoroacetoacetate mediated by zinc chloride in ethanol, afforded coumarin **307**, the 1-oxa version of 4-(trifluoromethyl)-2(1*H*)-piperidino[3,2-*g*]quinolinone, typified by the lead human androgen receptor antagonist LG120907. A series of 4-(trifluoromethyl)-2*H*-pyrano[3,2-g]quinolin-2-ones was prepared and tested for the ability to modulate the transcriptional activity of the human androgen receptor [169] (Scheme 97).

It was shown that the base-catalyzed cyclization of **308**, prepared from **300b** and chloroacetone, gave difurocoumarin **309** in high yield [170]. Coumarin **300b** was



Scheme 97 Synthesis of coumarin **307**

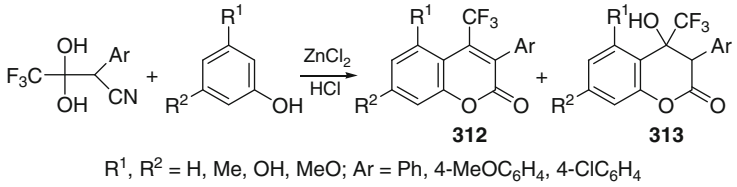
also reacted with crotonic acid in the presence of PPA to offer the corresponding angular chromanone, which was further condensed with 1,1-diethoxy-3-methyl-2-butene under microwave irradiation to produce the target tetracyclic dipyranocoumarin **310** as a potential anti-HIV-1 agent [171]. Reaction of 7-aminocoumarin **300a** with diethyl ethoxymethylenemalonate led to the condensation intermediate (the Gould-Jacobs reaction), thermal cyclization of which gave the desired tricyclic ester **311a**. This ester was hydrolyzed to the corresponding benzopyranopyridine carboxylic acid **311b**, which was found to possess high antimicrobial activity against Gram-positive microorganism [172] (Scheme 98).



Scheme 98 Some derivatives of 4-(trifluoromethyl)coumarin

5.1.2 3-Substituted 4-(Trifluoromethyl)Coumarins

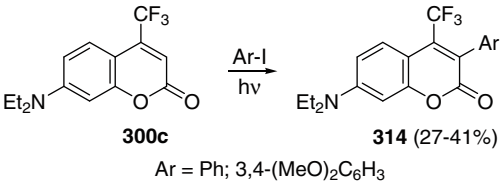
Resorcinol and 5-methylresorcinol react with 3-oxo-2-aryl-4,4,4-trifluorobutyronitrile using $ZnCl_2$ in dibutyl ether under the Hoesch reaction conditions to give a low yield of coumarins **312**. However, the related reaction with *m*-methoxyphenol was found to produce poor yields of **312** and **313** [173] (Scheme 99).



Scheme 99 Synthesis of coumarins **312**

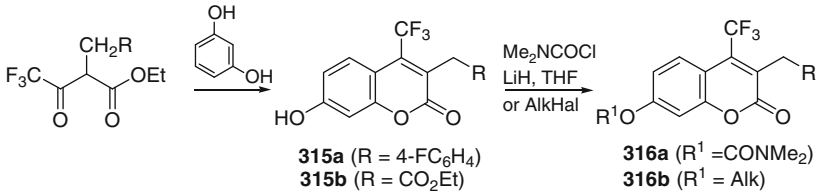
3-Aryl-7-(diethylamino)-4-(trifluoromethyl)coumarins **314** were synthesized as a result of the photoreaction of 7-(diethylamino)-4-(trifluoromethyl)coumarin (**300c**) with iodobenzene and 3,4-dimethoxyiodobenzene in acetonitrile. It was established that the electron-withdrawing CF_3 group and addition of triethylamine accelerate photosubstitution [174] (Scheme 100).

Ethyl 2-(*p*-fluorobenzyl)trifluoroacetoacetate reacted with resorcinol in 70 % sulfuric acid at 100 °C to provide coumarin **315a**. Upon treatment with *N,N-dimethylcarbamoyl* chloride in the presence of NaH, this compound was readily converted into the corresponding *N,N*-dimethylcarbamate **316a**, which was tested as a TNF-α inhibitor [175]. A similar reaction of resorcinol with diethyl



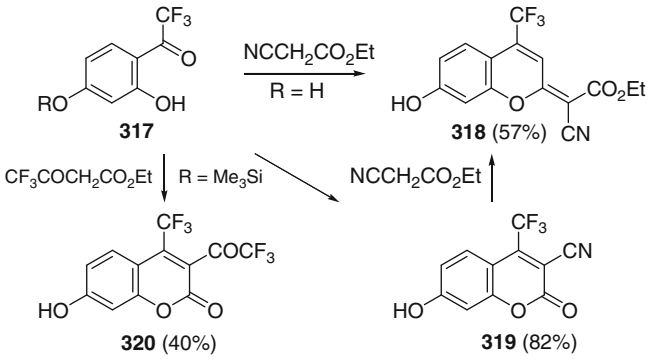
Scheme 100 Synthesis of coumarins **314**

trifluoroacetosuccinate in PPA gave compound **315b**, from which **316b** as CYP2C9 substrates responsible for the metabolism of drugs were obtained [176] (Scheme 101).



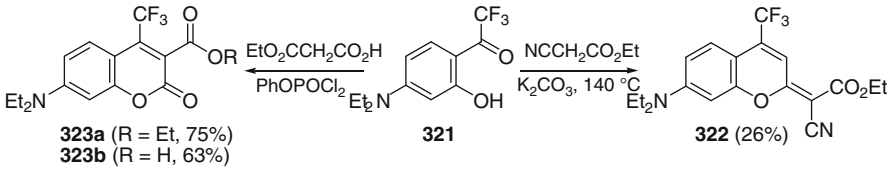
Scheme 101 Synthesis of coumarins **315** and **316**

Voznyi et al. reported that condensation of 4-(trifluoroacetyl)resorcinol **317** (R=H) with cyanoacetic ester occurs at 100–150 °C and is accompanied by closure of the pyrane ring and formation **318** as a result of condensation of **319** with cyanoacetic ester, followed by hydrolysis of the cyano group and decarboxylation [177]. When the trimethylsilyl derivative **317** (R=Me_3Si) was heated with cyanoacetic ester, it was possible to increase the yield of compound **319** from 10–12 % to 79–82 %. The synthesis of **320** was realized by a similar method [178] (Scheme 102).



Scheme 102 Synthesis of coumarins **318**–**320**

Similarly, reaction of **321** with cyanoacetic ester and potassium carbonate gave the benzopyrane **322**. When ketone **321** was treated with monoethyl malonate, triethylamine and phenyl phosphorodichloridate, the required coumarin **323a** was obtained and subsequent alkaline hydrolysis gave the acid **323b** [179] (Scheme 103).



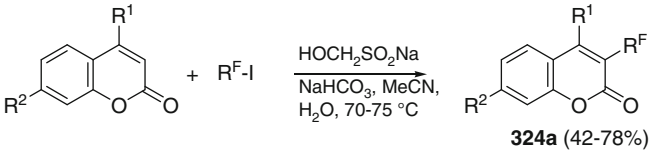
323a (R = Et, 75%)
323b (R = H, 63%)

321

322 (26%)

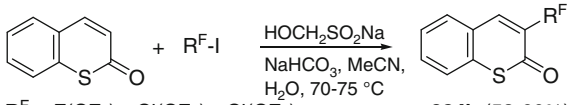
Scheme 103 Synthesis of coumarins **322** and **323**

Huang et al. reported that coumarins and thiocoumarin react with perfluoroalkyl iodides in the presence of sodium hydroxymethanesulfinate (Rongalite) to give 3-(polyfluoroalkyl)coumarins **324a,b** selectively and under mild conditions. A free-radical mechanism was proposed for the reaction [180]. The regioselective reaction of 3-unsubstituted coumarins with bis(perfluoroalkanoyl)peroxides also affords 3-(perfluoroalkyl)coumarins **324c**. Though the introduction of perfluoroalkyl groups into the 3-position of coumarins lowers the fluorescence intensities, the derivatives **324c** are much more stable towards UV irradiation than 3-unsubstituted coumarins [181] (Scheme 104).



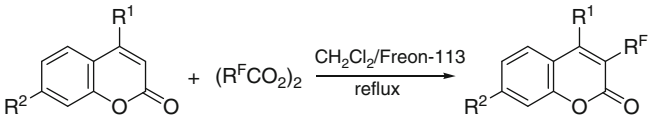
324a (42-78%)

R^F = $F(CF_2)_6$, $F(CF_2)_7$, $F(CF_2)_8$, $Cl(CF_2)_4$, $Cl(CF_2)_6$, $Cl(CF_2)_8$;
R^1 = H, Me; R^2 = H, OH, NEt_2



R^F = $F(CF_2)_6$, $Cl(CF_2)_4$, $Cl(CF_2)_6$

324b (53-60%)



324c (21-67%)

R^F = CF_3, C_3F_7, C_7F_{15}; R^1 = H, Me, CF_3; R^2 = H, Me, OH, MeO, NH_2, NMe_2, NEt_2

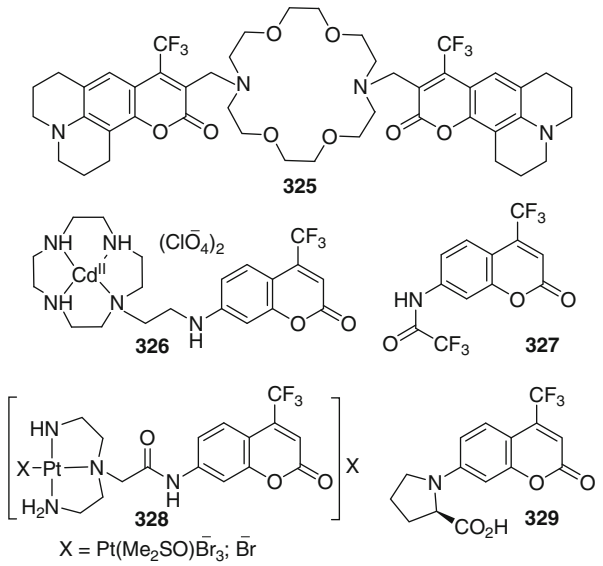
Scheme 104 Synthesis of 3-(polyfluoroalkyl)coumarins **324**

5.1.3 Applications of 7-Amino-4-(Trifluoromethyl)Coumarin Derivatives

7-Amino-4-(trifluoromethyl)coumarin (**300a**) is strongly fluorescent in polar solvents and its ^{19}F NMR spectrum shows only a singlet peak without any coupling to intramolecular protons. Thus, coumarin **300a** has been utilized as a reporter group that is active in both fluorescence measurement and ^{19}F magnetic resonance imaging [182].

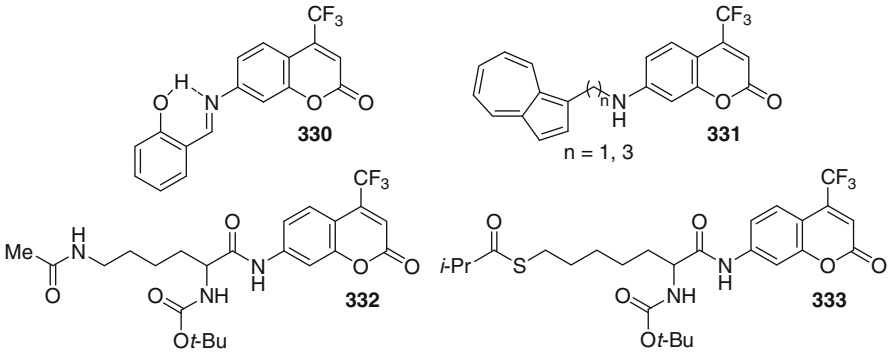
The photophysical properties of fluoroionophores composed of a laser dye, Coumarin 153, linked to azacrowns have been reported. The changes in the photophysical properties upon complexation with alkali and alkaline-earth metal cations are due to the direct interaction between the cation and the carbonyl group of the coumarin. Of particular interest is the bis-coumarin **325**, which exhibits specific changes in quantum yield according to the size of the cation [183]. Mizukami et al. reported a novel fluorescent anion sensor **326** that works in neutral aqueous solution for bioanalytical application. This molecule contains 7-amino-4-(trifluoromethyl)coumarin (**300a**) as a fluorescent reporter and Cd(II)-1,4,7,10-tetraazacyclododecane as an anion host. In neutral aqueous solution, Cd(II) of **326** is coordinated by the four nitrogen atoms of cyclen and the aromatic amino group of coumarin [184]. A colorimetric and fluorescent cyanide probe based on 4-(trifluoromethyl)coumarin **327** displays rapid response and high selectivity for cyanide over other common anions [185]. In order to develop coordination complexes that can be used as selective probes, fluorescent agents and inorganic medicinal agents, the design, synthesis, characterization and X-ray structure of new water-soluble monofunctional Pt(II) complexes with useful spectroscopic properties for assessing metal binding to biomolecules were investigated. Complex **328** was designed to allow the fluorophore group, coumarin **300a**, to be attached to metal centers through the diethylenetriamine moiety [186]. Proline-substituted coumarin derivatives, such as compound **329**, were prepared and used as environment-sensitive fluorescence probes. Phosphorylation and dephosphorylation of tyrosine derivatives labeled with the coumarin–proline conjugate induced marked changes in fluorescence intensity allowing phosphatase activity to be monitored [187] (Scheme 105).

A coumarin-based derivative **330**, a highly selective and sensitive turn-on fluorogenic probe for the detection of hydrosulfate anion in aqueous solution, has been designed and synthesized. This compound exhibits a unique fluorescence change in the presence of the HSO_4^- ion and with high selectivity over other anions [188]. Compounds **331** were synthesized from 1-azulenecarboxaldehyde and 7-amino-4-(trifluoromethyl)coumarin (**300a**) and a very fast vibrational cooling process of azulene was studied by the transient absorption method using molecular integrated systems with a molecular thermometer. This is the first attempt to use the



Scheme 105 Useful derivatives of 7-amino-4-(trifluoromethyl)coumarin

molecular heater–molecular thermometer integrated system for investigating the thermalization process from the solvent side [189] (Scheme 106).

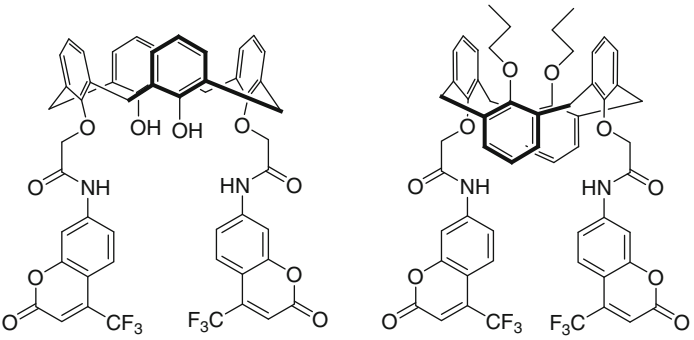


Scheme 106 Useful derivatives of 7-amino-4-(trifluoromethyl)coumarin

To probe the steric requirements for deacylation, lysine-derived small molecule substrates, including coumarin derivative **332**, were synthesized and their structure-reactivity relationships with various histone deacetylases were examined. It was found that compound **332**, prepared from the corresponding lysine derivative and coumarin **300a** in pyridine in the presence of $POCl_3$, is selectively deacetylated by HDAC6 in preference to HDAC1 and HDAC3. This indicated that the structure of

N-Boc and trifluoromethyl coumaryl amide of **332** is selectively recognized by HDAC6 [190]. Suzuki et al. have identified novel HDAC6-selective inhibitors whose designs were based on the structure of the HDAC6-selective substrate **332**. Thus, compound **333**, in which the acetamide of **332** is replaced by a thioester function, was obtained from the corresponding bromide and thioisobutyric acid under alkaline conditions [191] (Scheme 106).

Novel calix[4]arene-based anion sensor **334** with two coumarin units attached via amido functions acting also as binding sites was described. This compound may be considered as a potential fluorescent chemosensor for F^-. Reference calixarene **335** was also synthesized and its 1,3-alternate conformation was deduced from the ^1H NMR spectrum [192] (Scheme 107).

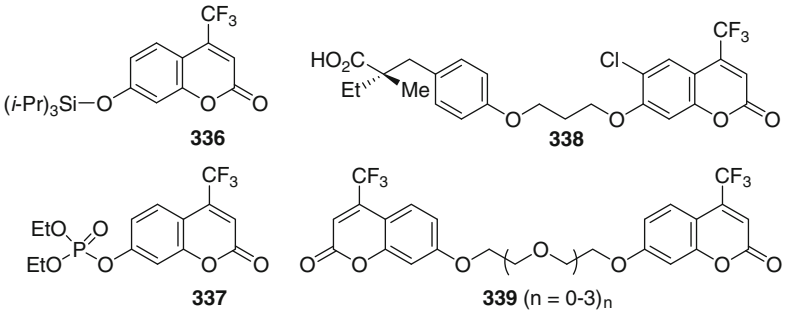


Scheme 107 Useful derivatives of 7-amino-4-(trifluoromethyl)coumarin

5.1.4 Applications of 7-Hydroxy-4-(Trifluoromethyl)Coumarin Derivatives

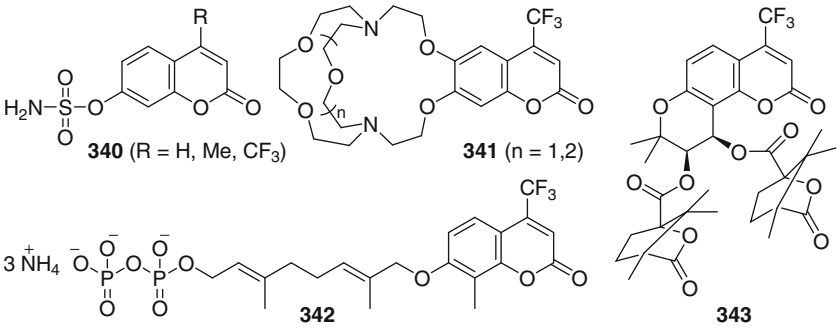
One-step reaction of 7-hydroxy-4-(trifluoromethyl)coumarin (**300c**) with TIPS-Cl provided compound **336** in 67 % yield, which was used to detect fluoride anions in organic and aqueous media, utilizing the specific affinity of fluoride anion to silicon [193]. Eighteen new fluorogenic analogues of organophosphorus nerve agents were synthesised and characterised. They included analogues of tabun, sarin, cyclosarin, and soman, with the 7-hydroxy-4-(trifluoromethyl)coumarin leaving group, for example, compound **337**. These analogues inhibited acetylcholinesterase effectively in vitro and therefore have potential as tools for the identification of novel organophosphatases in biological systems [194]. A series of potent and highly subtype-selective PPARα agonists was identified through a systematic SAR study. Based on the results of superior in vivo efficacy in the two animal models, coumarin **338** was

characterized in pharmacokinetic studies in three preclinical animal species. It exhibited low plasma clearance, good oral bioavailability, and no significant off-target activity was observed for **338**. Unfortunately, the results for the stability studies of compound **338** indicated the lactone ring stability issues [195]. Bis-4-(trifluoromethyl)-7-hydroxycoumarins **339** (n = 0, 1) ended mono and diethyleneglycols were prepared starting from bis(3-hydroxyphenyl)glycols by Pechmann condensation using ethyl trifluoroacetoacetate. Accordingly, coumarin **300c** was converted to bis-coumarin ended three and tetraethylenglycol derivatives **339** (n = 2, 3) by reacting with three and tetraethyleneglycols dichlorides in Na_2CO_3/DMF. The Li^+, Na^+ and Rb^+ metal/ligand selectivities of cation binding behaviour of products in acetonitrile were studied with steady state fluorescence spectroscopy [196] (Scheme 108).



Scheme 108 Useful derivatives of 7-hydroxy-4-(trifluoromethyl)coumarin

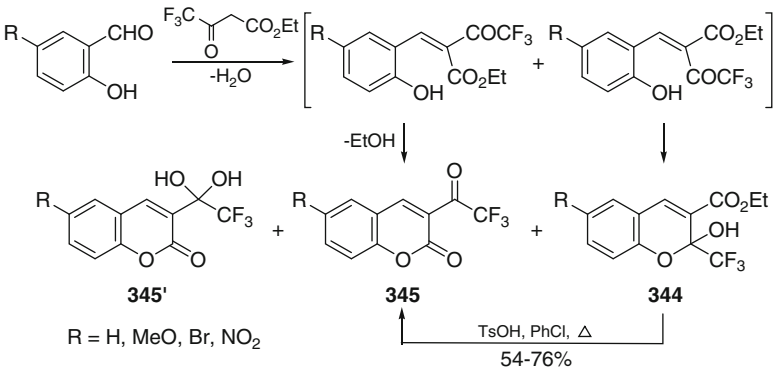
Woo et al. synthesized and examined coumarin sulfamates **340**, of which 4-methylcoumarin 7-*O*–sulfamate was found to be the most effective nonsteroidal E1-STS inhibitors [197]. The coupling between the fluorescence properties of the (trifluoromethyl)coumarino fluorophore and the protolytic state of the ion binding moiety of two fluorescent cryptands **341** is investigated. The experimental results obtained with **341** indicate that the diprotonated state of the fluorescent cryptands exhibit a comparatively high quantum yield around 0.6 and are characterized by a single lifetime around 5.4 ns [198]. Coumarin **342**, a fluorescent analogue of farnesyl pyrophosphate (FPP), was prepared and utilized to study ligand interactions with *E. coli* UPPs [199]. To explore the structural requirements of (+)-*cis-khellactone* derivatives as novel anti-HIV agents, 24 monosubstituted 3′,4′-di-*O*-(*S*)-camphanoyl-(+)-*cis*-khellactone derivatives, including compound **343**, were synthesized asymmetrically [200]. The metabolism of 7-benzyloxy-4-(trifluoromethyl)coumarin to 7-hydroxy-4-(trifluoromethyl)coumarin (**300a**) was studied in human liver microsomal preparations and in cDNA-expressed human cytochrome P450 (CYP) isoforms [201] (Scheme 109).



Scheme 109 Useful derivatives of 7-hydroxy-4-(trifluoromethyl)coumarin

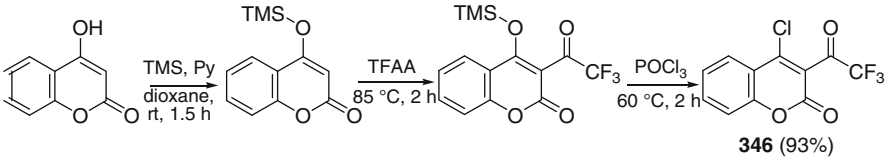
5.2 *Synthesis and Reactions of 3-(Trifluoroacetyl)Coumarins*

A series of ethyl 2-hydroxy-2-(trifluoromethyl)-2*H*-chromene-3-carboxylates (**344**) was obtained in high yields via the Knoevenagel condensation of salicylaldehydes with ethyl trifluoroacetoacetate in the presence of piperidinium acetate. The subsequent recyclization of these chromenes proceeds smoothly in refluxing chlorobenzene in the presence of *p*-toluenesulfonic acid affording 3-(trifluoroacetyl) coumarins (**345**) in good yields [202]. These compounds were also prone to the facile and reversible covalent hydrate formation [120] (Scheme 110).



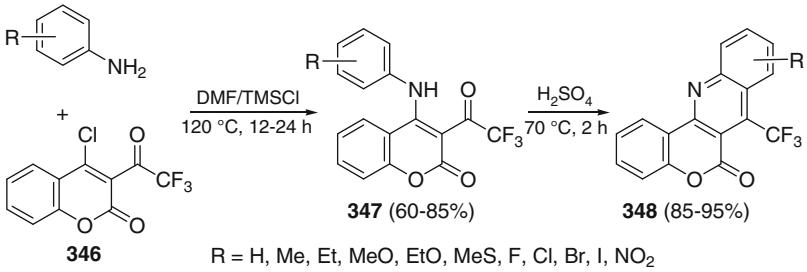
Scheme 110 Synthesis of 3-(trifluoroacetyl)coumarins **345**

4-Chloro-3-(trifluoroacetyl)coumarin (**346**) was synthesized via direct TMSCl-mediated acylation of 4-hydroxycoumarin with trifluoroacetic anhydride (TFAA) followed by the treatment with $POCl_3$ [203] (Scheme 111).



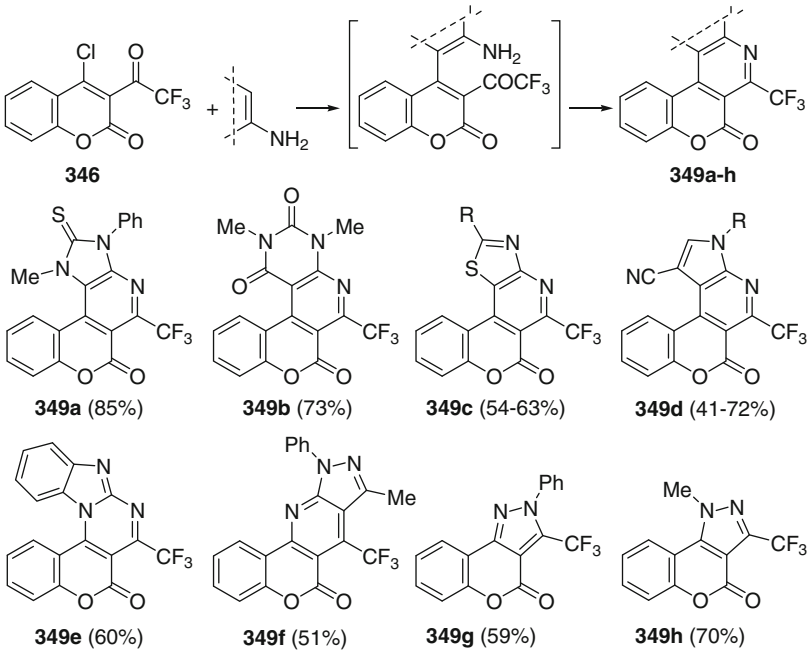
Scheme 111 Synthesis of 4-chloro-3-(trifluoroacetyl)coumarin **346**

Iaroshenko et al. reported that the reaction of **346** with anilines is a two-step method, which affords via substitution products **347** a set of 7-(trifluoromethyl)-6*H*-chromeno[4,3-*b*]quinolin-6-ones (**348**) in concentrated H_2SO_4 at 70 °C in high yields [203] (Scheme 112).



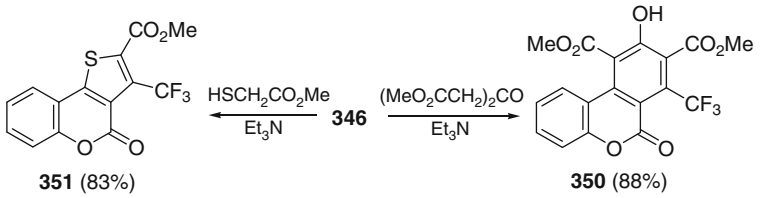
Scheme 112 Reaction of coumarin **346** with anilines

Coumarin **346** also reacts with electron-rich aminoheterocycles, dimethyl 1,3-acetonedicarboxylate, hydrazines, alkyl thioglycolates, and methyl sarcosinate to give a variety of 3,4-heteroannulated coumarins **349a–h** with an excellent regioselectivity and in moderate to high yields (41–85 %) [204] (Scheme 113).



Scheme 113 Products from coumarin **346** and aminoheterocycles

Treatment of **346** with dimethyl 1,3-acetonedicarboxylate in dioxane in the presence of triethylamine at reflux gave the expected benzo[*c*]coumarin **350**, whereas the reaction with methyl thioglycolate in dichloromethane at room temperature resulted in the formation of thienocoumarin **351** [204] (Scheme 114).



Scheme 114 Synthesis of compounds **350** and **351**

6 Conclusion

Analysis of the published data demonstrates that of the diverse fluorine-containing pyrones, chromones and coumarins, 2-(trifluoromethyl)-4-pyrones and 2-(polyfluoroalkyl)chromones, as well as 3-(polyfluoroacyl)chromones and chromones with the

perfluorinated benzene ring have now been studied most comprehensively. Data on 3-fluoro- and 3-(trifluoromethyl)chromones and coumarins are quite scarce. Despite the ready accessibility of polyfluoroalkylated pyrones and chromones, these compounds have long remained out of sight of chemists engaged in synthesis, and their systematic study has started only in recent years. Nevertheless, it is already clear that these compounds and, in particular, trifluoromethylated analogues of natural oxygen-containing heterocycles are valuable substrates for the synthesis of diverse partially fluorinated heterocycles with a potential biological activity. Indeed, a polyfluoroalkyl group present at the C-2 atom of the pyrone system entails dramatic changes in the reactivity of this ring, which is manifested as a bunch of new transformations uncharacteristic of non-fluorinated analogues. In addition, the introduction of a polyfluoroacyl group into the 3-position of the chromone system also changes crucially the reactivity of the pyrone ring with respect to nucleophiles and stipulates the broad synthetic potential of 2-unsubstituted 3-(polyfluoroacyl)chromones. The diversity of properties of these compounds is due to the fact that, being actually highly reactive geminally activated alkenes with a good leaving group at the β-carbon atom, they acquire the ability to undergo additional reactions related to opening and transformation of the γ-pyrone ring.

References

1. (a) Lee LF, Stikes GL, Molyneaux JM, Sing YL, Chupp JP, Woodard SS (1990) A novel dehydrofluorination of 2-(trifluoromethyl)dihydro-3,5-pyridinedicarboxylates to 2-(difluoromethyl)-3,5-pyridinedicarboxylates. J Org Chem 55:2812–2871; (b) Lee LF, Miller ML (1986) 2,6-Substituted pyridine compounds. EP 0182769; (c) Crespo MIC, Mayorga JMJ, Julia JLM, Gras JF (2003) 2-Phenylpyran-4-one derivatives. US 0232880
2. (a) Cavalieri LF (1947) The chemistry of the monocyclic α- and γ-pyrones. Chem Rev 41:525–584; (b) Ross WJ, Todd A, Clark BP, Morgan SE, Baldwin JE (1981) The synthesis and rearrangement of epoxypyrones. Tetrahedron Lett 22:2207–2208; (c) Clark BP, Ross WJ, Todd A (1984) 2,4,6-Trioxohexanoic acids and esters thereof as intermediates. UK 2123813; (d) Hobuß D, Laschat S, Baro A (2005) Concise two-step synthesis of γ-pyrone from acetone. Synlett:123–124; (e) Chou S-Y, Chen S-F (1997) Synthesis of 2-hydroxymethyl-3,5-dimethyl-4-methoxypyridine: a key intermediate for omeprazole. Heterocycles 45:77–85; (f) Koreeda M, Akagi H (1980) A convenient synthesis of substituted γ-pyrones. Tetrahedron Lett 21:1197–1200; (g) Honma Y, Oda K, Hashiyama T, Hanamoto K, Nakai H, Inoue H, Ishida A, Takeda M, Ono Y, Tsuzurahara K (1983) Antiallergic agents. 2. *N*-(1*H*-Tetrazol-5-yl)-6-phenyl-2-pyridinecarboxamides. J Med Chem 26:1499–1504; (h) Torii S, Tanaka H, Anoda T, Simizu Y (1976) A convenient preparation of maltol, ethylmaltol, and pyromeconic acid from 2-alkyl-6-methoxy-2*H*-pyran-3(6*H*)-ones. Chem Lett:495–498
3. Tyvorskii VI, Stanishevskii LS, Tishchenko IG (1976) Synthesis of 3-hydroxy-6-perfluoroalkyl-2,3-dihydro-4-pyrones. Khim Geterotsikl Soedin 1575; Chem Abstr (1977) 86:139750
4. (a) Tyvorskii VI, Bobrov DN, Kulinkovich OG, De Kimpe N, Tehrani KA (1998) New synthetic approaches to 2-perfluoroalkyl-4*H*-pyran-4-ones. Tetrahedron 54:2819–2826; (b) Tyvorskii VI, Bobrov DN (1997) New method for the synthesis of 4-hydroxy-2-trifluoromethylpyridine. Chem Heterocycl Compd 33:995–996
5. Yeates CL, Batchelor JF, Capon EC, Cheesman NJ, Fry M, Hudson AT, Pudney M, Trimming H, Woolven J, Bueno JM, Chicharro J, Fernández E, Fiandor JM, Gargallo-Viola D, de las

Heras FG, Herreros E, León ML (2008) Synthesis and structure–activity relationships of 4-pyridones as potential antimalarials. J Med Chem 51:2845–2852
6. Tyvorskii VI, Bobrov DN, Kulinkovich OG, Aelterman W, De Kimpe N (2000) Synthesis of 3-(trifluoromethyl)benzo[*c*][1,6]naphthyridines from substituted 4*H*-pyran-4-ones via 4-amino-5-aryl-2-(trifluoromethyl)pyridines. Tetrahedron 56:7313–7318
7. Tyvorskii VI, Bobrov DN, Kulinkovich OG, Tehrani KA, De Kimpe N (2001) Synthesis of 5-alkyl-4-amino-2-(trifluoromethyl)pyridines and their transformation into trifluoromethylated 1*H*-pyrazolo[4,3-*c*]pyridines. Tetrahedron 57:2051–2055
8. Tyvorskii VI, Bobrov DN (1998) Synthesis and transformations of 4-hydroxy-5-methyl-2-trifluoromethylpyridine. Chem Heterocycl Compd 34:679–682
9. Boivin J, El Kaim L, Zard SZ (1995) Trifluoromethyl ketones from carboxylic acids. Part II. A versatile access to trifluoromethylated heterocycles. Tetrahedron 51:2585–2592
10. Morita Y, Kamakura R, Takeda M, Yamamoto Y (1997) Convenient preparation of trifluoroacetyl Meldrum's acid and its use as a building block for trifluoromethyl-containing compounds. Chem Commun 1997:359–360
11. Serdyuk RN, Sizov AY, Ermolov AF (2003) Polyfluoroalkylthiotrifluoroacetylketenes. Russ Chem Bull 52:1854–1858
12. Langer P, Bunescu A, Reimann S, Lubbe M, Spannenberg A (2009) Synthesis of trifluoromethyl-substituted arenes, cyclohexenones and pyran-4-ones by cyclocondensation of 1,3-bis(silyloxy)-1,3-butadienes with 4,4-dimethoxy-1,1,1-trifluorobut-3-en-2-one: influence of the Lewis acid on the product distribution. J Org Chem 74:5002–5010
13. Sosnovskikh VY, Usachev BI, Bogdanov EA (2001) Trifluoroacetylation of 2-acetyldimedone. Russ Chem Bull 50:568–569
14. Sosnovskikh VY, Usachev BI, Blinov AG, Kodess MI (2001) New derivatives of dehydroacetic acid: synthesis of 2-polyfluoroalkyl-7-methylpyrano[4,3-*b*]pyran-4,5-diones. Mendeleev Commun 11:36–38
15. Usachev BI, Bizenkov IA, Sosnovskikh VY (2007) Trifluoroacetylation of ethyl 2,4-dioxopentanoate. The first synthesis of 4-oxo-6-(trifluoromethyl)-4*H*-pyran-2-carboxylic acid and its derivatives. Russ Chem Bull 56:558–559
16. Usachev BI, Usachev SA, Röschenthaler G-V, Sosnovskikh VY (2010) First synthesis of 4-oxo-6-trifluoromethyl-4*H*-thiopyran-2-carboxylic acid and its derivatives. Russ Chem Bull 59:845–847
17. Obydennov DL, Usachev BI (2012) Reactions of 6-(tri- and 6-(difluoromethyl))comanic acids and their ethyl esters with aniline and its 2-substituted derivatives. J Fluor Chem 141:41–48
18. Usachev BI, Obydennov DL, Kodess MI, Sosnovskikh VY (2009) Regioselective solvent-sensitive reactions of 6-(trifluoromethyl)comanic acid and its derivatives with phenylhydrazine. Tetrahedron Lett 50:4446–4448
19. Usachev BI, Obydennov DL, Sosnovskikh VY (2012) Regioselective synthesis of trifluoromethylated 3-(pyrazolyl)indoles on the basis of 6-(trifluoromethyl)comanic acid. J Fluor Chem 135:278–284
20. Usachev BI, Obydennov DL, Sosnovskikh VY (2012) Regioselective synthesis of 2- and 5-(trifluoromethyl)pyrazolo[1,5-*c*]pyrimidines on the basis of 7,7,7-trifluoro-2,4,6-trioxoheptanoic and 6-(trifluoromethyl)comanic acids. Izv Acad Nauk Ser Khim:1580–1586
21. (a) Usachev BI, Obydennov DL, Röschenthaler G-V, Sosnovskikh VY (2012) 2-Cyano-6-(trifluoromethyl)-4*H*-pyran-4-one: a novel versatile CF_3-containing building block. J Fluor Chem 137:22–26; (b) Obydennov DL, Sidorova ES, Usachev BI, Sosnovskikh VY (2013) A novel, two-step synthesis of 4-pyridone-3-carboxamides from 2-cyano-4-pyrones. Tetrahedron Lett 54:3085–3087
22. Lee LF, Spear KL, Ruminski PG, Dhingra OP (1988) Pyridine gametocides. EP 0276204
23. Mihovilovic MD, Spreitzer H (2005) Diastereoselective synthesis of cis-2,6-disubstituted perhydro-4-pyranones using elevated pressure hydrogenation. Monatsh Chem 136:1197–1203

24. Babu S, Pozzo MJ (1991) Trifluoromethyl substituted 4-pyrones via self-condensation of trifluoroacetoacetates. J Heterocycl Chem 28:819–821
25. (a) Yachevskii DS, Chizhov DL, Pashkevich KI, Charushin VN (2004) Synthesis of 2,6-bis-polyfluoroalkyl-4*H*-pyran-4-ones. Arkivoc xi:71–76; (b) Yachevskii DS, Chizhov DL, Ratner VG, Pashkevich KI (2001) Synthesis of bis(polyfluoroalkyl)-1,3,5-triketones. Russ Chem Bull 50:1233–1237
26. Yachevskii DS, Chizhov DL, Charushin VN (2006) Synthesis of regioisomeric polyfluoroalkylpyrazolo[1,5-*a*]pyrimidines. Russ J Org Chem 42:142–144
27. Sosnovskikh VY, Korotaev VY, Chizhov DL, Kutyashev IB, Yachevskii DS, Kazheva ON, Dyachenko OA, Charushin VN (2006) Reaction of polyhaloalkyl-substituted chromones, pyrones, and furanones with salicylaldehydes as a direct route to fused 2*H*-chromenes. J Org Chem 71:4538–4543
28. Goel A, Ram VJ (2009) Natural and synthetic 2*H*-pyran-2-ones and their versatility in organic synthesis. Tetrahedron 65:7865–7913
29. Whitney JG, Gregory WA, Kauer JC, Roland JR, Snyder JA, Benson RE, Hermann EC (1970) Antiviral agents. I. Bicyclo[2.2.2]octan- and -oct-2-enamines. J Med Chem 13:254–260
30. Boulanger WA, Katzenellenbogen JA (1986) Structure-activity study of 6-substituted 2-pyranones as inactivators of α-chymotrypsin. J Med Chem 29:1159–1163
31. German LS, Sterlin SR, Cherstkov VF (1982) Hexafluorodehydroacetic acid. Russ Chem Bull 31:1476–1477
32. Gerus II, Tolmachova NA, Vdovenko SI, Fröhlich R, Haufe G (2005) A convenient synthesis and chemical properties of 3-acylamino-6-polyfluoroalkyl-2*H*-pyran-2-ones. Synthesis 2005:1269–1278
33. Tolmachova NA, Gerus II, Vdovenko SI, Haufe G, Kirzhner YA (2007) Synthesis of new polyfluoroalkyl-containing pyrones, pyridones and pyrido[1,2-*a*]benzazoles from fluorinated β-alkoxyenones. Synthesis 2007:3797–3806
34. Tolmachova NA, Dolovanyuk VG, Gerus II, Kondratov IS, Polovinko VV, Bergander K, Haufe G (2011) Catalytic hydrogenation of 3-amino-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-ones and its use in the synthesis of trifluoromethyl-containing mimetics of ornithine and thalidomide. Synthesis 2011:1149–1156
35. Tolmachova NA, Gerus II, Dolovanyuk VG, Vdovenko SI, Kondratov IS, Haufe G (2009) Synthesis of new δ-(polyfluoroalkyl)-δ-hydroxy-α-amino acids. Eur J Org Chem 2009:5012–5019
36. Tolmachova NA, Gerus II, Vdovenko SI, Essers M, Fröhlich R, Haufe G (2006) Thermal Diels–Alder reactions of 3-(benzoylamino)-6-(polyfluoroalkyl)pyran-2-ones – new synthesis of *p*-(polyfluoroalkyl)anilines. Eur J Org Chem 2009:4704–4709
37. (a) Martin P, Streith J, Rihs G, Winkler T, Belluš D (1985) A new electrophilic 2-pyrone bearing a CF_3-group, its preparation and its [4+2] cycloaddition reactions. Tetrahedron Lett 26:3947–3950; (b) Martin P, Steiner E, Streith J, Winkler T, Belluš D (1985) Convenient approaches to heterocycles via copper-catalyzed additions of organic polyhalides to activated olefines. Tetrahedron 41:4057–4078
38. (a) Usachev BI, Obydennov DL, Röschenthaler G-V, Sosnovskikh VY (2008) Convenient synthesis of ethyl 4-aryl-6-(trifluoromethyl)-2-oxo-2*H*-pyran-3-carboxylates and 4-aryl-6-(trifluoromethyl)-2*H*-pyran-2-ones: novel highly reactive CF_3-containing building blocks. Org Lett 10:2857–2859; (b) Usachev SA, Usachev BI, Sosnovskikh VY (2014) Synthesis of 3-(trifluoromethyl)indeno[2,1-*c*]pyran-1,9-diones from 4-aryl-3-carbethoxy-6-(trifluoromethyl)-2-pyrones and their reaction with sodium azide leading to new carbostyril derivatives. Tetrahedron 70:60–66
39. (a) Usachev BI, Usachev SA, Röschenthaler G-V, Sosnovskikh VY (2011) A simple and convenient synthesis of 3-[5-(trifluoromethyl)-1,2,3-triazol-4-yl]cinnamic acids from 4-aryl-6-(trifluoromethyl)-2*H*-pyran-2-ones and sodium azide. Tetrahedron Lett 52:6723–6725; (b) Yeh P-P, Daniels DSB, Cordes DB, Slawin AMZ, Smith AD (2014) Isothiourea-mediated one-pot synthesis of trifluoromethyl substituted 2-pyrones. Org Lett 16:964–967

40. Gerster H, Maas G (2008) Diverse reactivities of acetylenic iminium salts toward 1,3-oxazolium-5-olates (Münchnones). Z Naturforsch 63b:384–394
41. (a) Cao W, Ding W, Huang T, Huang H, Wei C (1998) Convenient syntheses of 4-perfluoroalkyl-6-(α-thienyl)-2-pyranones and methyl 4-(α-thienacyl)-3-perfluoroalkyl-3-butenoates. J Fluor Chem 91:99–101; (b) Cao W, Ding W, Liu R, Huang T, Cao J (1999) Facile syntheses of 4-perfluoroalkyl-6-(α-furyl)-2-pyranones and methyl 4-(α-furoyl)-3-perfluoroalkyl-3-butenoates. J Fluor Chem 95:135–140; (c) Cao W, Ding W, Wang L, Song L, Zhang Q (2001) Convenient synthesis of 4-perfluoroalkyl-6-(2-naphthyl)-2-pyranones. J Fluor Chem 109:201–204
42. (a) England DC, Donald EA, Weigert FJ (1981) Fluorinated pyrones and cyclobutenecarboxylates. J Org Chem 46:144–147; (b) England DC (1981) Fluoroketenes. 10. Synthesis and chemistry of a perfluoroacylketene and a related perfluorovinyl ketone. J Org Chem 46:147–153
43. England DC (1981) Fluoroketenes. 11. Synthesis and chemistry of a perfluoroacylketene and related compounds containing a perfluoroisopropyl sulfide group. J Org Chem 46:153–157
44. England DC, Krespan CG (1970) Fluoroketenes. VI. Cycloadditions of cumulenes to bis(trifluoromethyl)ketene. J Org Chem 35:3322–3327
45. (a) Gizur T, Harsányi K (1994) Regioselective acetylation of some N-methylpyrrole derivatives with isopropenyl acetate and different acetic anhydrides. J Heterocycl Chem 31:361–365; (b) Chupp JP (1990) Derivation of fluorine-containing pyridine dicarboxylates. IV. N-Substituted dihydropyridine derivatives. J Heterocycl Chem 27:1697–1704; (c) Sun K, Chen Y, Wagerle T, Linnstaedt D, Currie M, Chmura P, Song Y, Xu M (2008) Synthesis of butenolides as seed germination stimulants. Tetrahedron Lett 49:2922–2925
46. (a) Ellis GP (1977) Chromenes, chromanones and chromones in the chemistry of heterocyclic compounds, vol. 31. Wiley, New York; (b) Sosnovskikh VY (2003) Synthesis and reactions of halogen-containing chromones. Russ Chem Rev 72:489–516
47. (a) Horton DA, Bourne GT, Smythe ML (2003) The combinatorial synthesis of bicyclic privileged structures or privileged substructures. Chem Rev 103:893–930; (b) De Meyer N, Haemers A, Mishra L, Pandey H-K, Pieters LAC, Berghe DAV, Vlietinck AJ (1991) 4′-Hydroxy-3-methoxyflavones with potent antipicornavirus activity. J Med Chem 34:736–746; (c) Xue H, Lu X, Zheng P, Liu L, Han C, Hu J, Liu Z, Ma T, Li Y, Wang L, Chen Z, Liu G (2010) Highly suppressing wild-type HIV-1 and Y181C mutant HIV-1 strains by 10-chloromethyl-11-demethyl-12-oxo-calanolide A with druggable profile. J Med Chem 53:1397–1401; (d) Prykhod'ko AO, Dubinina GG, Khilya VP, Yarmoluk SM (2004) Antiproliferative activities of some 7-hydroxy-3-aryloxy-2-trifluoromethyl-4*H*-4-chromenone derivatives against 60 human cancer cell lines. Biopolim Klitina 20:159–163, Chem Abstr (2004) 142:190331; (e) Chosh CK (2006) 2-Methyl-4-oxo-4*H*-1-benzopyran-4-one as a synthon in heterocyclic chemistry. J Heterocycl Chem 43:813–820
48. Wu ESC, Loch JT III, Toder BH, Borrelli AR, Gawlak D, Radov LA, Gensmantel NP (1992) Flavones. 3. Synthesis, biological activities, and conformational analysis of isoflavone derivatives and related compounds. J Med Chem 35:3519–3525
49. Bolós J, Gubert S, Anglada L, Planas JM, Burgarolas C, Castelló JM, Sacristán A, Ortiz JA (1996) 7-[3-(1-piperidinyl)propoxy]chromenones as potential atypical antipsychotics. J Med Chem 39:2962–2970
50. Whalley WB (1951) Organic fluoro-compounds. Some trifluoromethyl-chromones and -coumarins. J Chem Soc:3235–3238
51. Pashkevich KI, Saloutin VI, Postovskii IY (1981) Fluorine-containing β-diketones. Uspekhi Khim 50:325–354
52. (a) Morera E, Ortar G (1981) Ring-chain isomeric transformations. The cyclohemiketal structure of 4,4,4-trifluoro-1-(2-hydroxyphenyl)-1,3-butanediones. Tetrahedron Lett 22:1273–1276; (b) Bayer V, Pastor RE, Cambon AR (1982) Synthese de F-alkyl-2 chromones et mise en evidence de leurs intermediaires reactionnels. J Fluor Chem 20:497–505
53. Sosnovskikh VY, Sizov AY, Usachev BI (2002) 2-Polyfluoroalkylchromones. 10. Synthesis of regioisomeric 3-(2-hydroxyaryl)-5-polyfluoroalkyl- and 5-(2-hydroxyaryl)-3-polyfluoro-

alkylisoxazoles and determination of their structures by ^{1}H, ^{19}F, and ^{13}C NMR spectroscopy. Russ Chem Bull 51:1270–1279
54. Sosnovskikh VY, Usachev BI (2001) 2-Polyfluoroalkylchromones. 6. Synthesis of substituted 2-morpholino-2-trifluoromethylchroman-4-ones. Russ Chem Bull 50:453–455
55. Welch JT (1987) Advances in the preparation of biologically active organofluorine compounds. Tetrahedron 43:3123–3197
56. Sosnovskikh VY, Kutsenko VA (2000) Synthesis of 7-trifluoromethyl- and 7-trichloromethylnorkhellins. Mendeleev Commun 10:238–239
57. Sosnovskikh VY, Usachev BI, Vorontsov II (2003) 7-Polyfluoroalkylnorkhellins: synthesis and reactions with alkyl mercaptoacetates. Tetrahedron 59:2549–2554
58. Sosnovskikh VY, Barabanov MA (2003) The first synthesis of 8-aza-2-polyfluoroalkylchromones. J Fluor Chem 120:25–28
59. Sosnovskikh VY, Barabanov MA, Usachev BI, Irgashev RA, Moshkin VS (2005) Synthesis and some properties of 6-di(tri)fluoromethyl- and 5-di(tri)fluoroacetyl-3-methyl-1-phenylpyrano[2,3-c]pyrazol-4(1*H*)-ones. Russ Chem Bull 54:2846–2850
60. Castañeda ICH, Ulic SE, Védova COD, Metzler-Nolte N, Jios JL (2011) One-pot synthesis of 2-trifluoromethylchromones. Tetrahedron Lett 52:1436–1440
61. Sosnovskikh VY, Ovsyannikov IS (1993) Condensation of trichloro- and trifluoroacetonitrile with 4-hydroxy-4-methyl-2-pentanone and 2′-hydroxyacetophenone. Zhurn Organ Khim 29:89–93
62. (a) Sosnovskikh VY (1998) Condensation of nitriles of polyhalogenated carboxylic acids and benzonitrile with 2-hydroxy-4,6-dimethylacetophenone. Russ Chem Bull 47:354–356; (b) Sosnovskikh VY (1996) Condensation of acetylnaphthols with trifluoro- and trichloroacetonitriles. The first example of ring-chain isomerism in the aromatic β-hydroxyoxoenamine series. Mendeleev Commun 6:189–190
63. Sosnovskikh VY, Usachev BI (2004) Synthesis of 3-alkylamino-3-(2-hydroxyaryl)-1-polyfluoroalkylprop-2-en-1-ones and 2-polyfluoroalkyl-4*H*-chromen-4-imines. Russ Chem Bull 53:383–392
64. Tamura K, Ishihara T, Yamanaka H (1994) Synthesis of 2-polyfluoroalkylated thiochromones and chromones. J Fluor Chem 68:25–31
65. Huang W-Y, Liu Y-S, Lu L (1994) A facile synthesis of fluoroalkylated chromones and their analogues from 2,2-dihydropolyfluoroalkanoates. J Fluor Chem 66:263–270
66. Kharrat SE, Kharrat RE, Laurent P, Blancou H (2007) Synthesis of 3-trifluoromethyl- and 3-perfluoroalkyl-substituted 3-aryloxy- and 3-heteroaryloxypropenoic acids and of the cyclization products, 2-trifluoromethyl-and 2-perfluoroalkyl-4*H*-chromen-4-ones. Synthesis 2007:3542–3552
67. (a) Jiménez LPA, Echeverría GA, Piro OE, Ulic SE, Jios JL (2013) Vibrational, electronic, and structural properties of 6-nitro- and 6-amino-2-trifluoromethylchromone: an experimental and theoretical study. J Phys Chem A 117:2169–2180; (b) Sosnovskikh VY, Usachev BI (2000) 2-Polyfluoroalkylchromones. 5. Nitration and chlorination of 2-trifluoromethylchromone. Russ Chem Bull 49:2074–2076
68. Sosnovskikh VY, Usachev BI, Kodess MI (2002) 2-Polyfluoroalkylchromones. 12. Nitration of 5,7-dimethyl-2-polyhaloalkylchromones and complete assignment of signals in the ^{1}H and ^{13}C NMR spectra of 5,7-dimethyl-2-trifluoromethylchromone and its mono- and dinitro derivatives. Russ Chem Bull 51:1817–1828
69. Sosnovskikh VY, Usachev BI (2002) 2-Polyfluoroalkylchromones. 13. Synthesis and nitration of 6,8-dibromo-2-trifluoromethylchromone. Russ Chem Bull 51:1954–1956
70. Sosnovskikh VY, Irgashev RA, Usachev BI (2009) Synthesis and some properties of 2-(polyfluoroalkyl)chroman-4-ols and 2-(polyfluoroalkyl)chroman-4-ones. Russ Chem Bull 58:2465–2473
71. Sosnovskikh VY, Irgashev RA, Levchenko AA (2009) Stereoselective synthesis of *cis*-2-(polyfluoroalkyl)chroman-4-ols and *trans*-4-acylamino-2-(polyfluoroalkyl)chromans. Arkivoc iv:125–135
72. Irgashev RA, Sosnovskikh VY, Sokovnina AA, Röschenthaler G-V (2010) The first synthesis of 3-hydroxy-2-(polyfluoroalkyl)chromones and their ammonium salts. 3-hydroxychromone in the Mannich reaction. J Heterocycl Chem 47:944–948

73. Kemp DS, Hanson G (1981) New protective groups for peptide synthesis. 4. Chromone-derived protection for amine and carboxyl functions. J Org Chem 46:4971–4975
74. (a) Sosnovskikh VY, Kutsenko VA, Yachevskii DS (1999) Steric factor in reactions of substituted 2-trifluoromethylchromones with ammonia and primary amines. Mendeleev Commun:204–205; (b) Sosnovskikh VY, Usachev BI (2001) 2-Polyfluoroalkylchromones. 8. 2-Trifluoromethyl- and 6-nitro-2-trifluoromethylchromones in reactions with amines. Russ Chem Bull 50:1426–1429
75. Sosnovskikh VY, Usachev BI (2000) Unexpected influence of tetra- and pentafluoroethyl groups on the direction of reactions of 2-polyfluoroalkylchromones with 2-aminoethanol. Mendeleev Commun 10:240–241
76. Sosnovskikh VY, Usachev BI, Safronov AP (2001) 2-Polyfluoroalkylchromones. 7. Reactions of 6-substituted 2-tetra- and 2-pentafluoroetylchromones with 2-aminoethanol. Russ Chem Bull 50:1314–1316
77. Owczarek M, Kostka K (1991) Studies in the group of chromone derivatives. Part XVII. Transformations of chromone and its methyl derivatives with ethylenediamine. Pol J Chem 65:345–352
78. Sosnovskikh VY, Kutsenko VA (1999) Reactions of 2-polyfluoroalkylchromones with aliphatic amines. Russ Chem Bull 48:812–814
79. Sosnovskikh VY, Kutsenko VA (1999) Reactions of aromatic and heteroaromatic β-amino-β-polyfluoroalkylvinyl ketones with ethylenediamine. A new synthesis of N,N′-unsubstituted imidazolidines. Russ Chem Bull 48:540–551
80. (a) Sosnovskikh VY (2001) Spin-spin coupling constant $^3J_{H,F}$ of the 1,1,2,2-tetrafluoroethyl group as a useful tool for recognition of regioisomeric and tautomeric pairs of organofluoric compounds. Russ Chem Bull 50: 1223–1227; (b) Sosnovskikh VY (2003) Spin-spin coupling constant $^3J_{H,F}$ as a reliable criterion for recognition of individual regioisomeric and tautomeric pairs of $H(CF_2)_2$-containing isoxazoles and pyrazoles. Russ Chem Bull 52:2087–2094
81. (a) Sosnovskikh VY, Yatluk YG, Kutsenko VA (1999) Novel synthesis of 1,4,8-triazabicyclo[5.3.0]dec-4-ene derivatives. Russ Chem Bull 48:1800–1801; (b) Sosnovskikh VY, Vorontsov II, Kutsenko VA (2001) 2-Polyfluoroalkylchromones. 9. Synthesis and structures of 5-(2-hydroxyaryl)-7-polyfluoroalkyl-1,4,8-triazabicyclo[5.3.0]dec-4-enes. Russ Chem Bull 50:1430–1438
82. (a) Sosnovskikh VY, Kutsenko VA, Yatluk YG (1999) Simple synthesis of 1,4,8-triazabicyclo[5.3.0]dec-4-ene derivatives from β-amino-β-polyfluoroalkylvinyl ketones and diethylenetriamine. Russ Chem Bull 48:1395–1396; (b) Sosnovskikh VY, Kutsenko VA, Yatluk YG (2000) Reactions of β-amino-β-polyfluoroalkylvinyl ketones with diethylenetriamine. Simple synthesis of 1,4,8-triazabicyclo[5.3.0]dec-4-ene derivatives. Russ Chem Bull 49:1426–1429
83. Sosnovskikh VY, Vorontsov II, Kutsenko VA, Yatluk YG (2000) Unexpected isomerization in the series of fluorine-containing 2,3-dihydro-1*H*-1,4-diazepines with a 2-aminoethyl group at one of the nitrogen atoms. Mendeleev Commun 10:56–58
84. (a) Sosnovskikh VY, Barabanov MA, Sizov AY (2002) 2-Polyfluoroalkylchromones. 11. Synthesis and structures of 5-hydroxy-3-(2-hydroxyaryl)-5-polyfluoroalkyl-Δ^2-pyrazolines and 3(5)-(2-hydroxyaryl)-5(3)-polyfluoroalkylpyrazoles. Russ Chem Bull 51:1280–1291; (b) Sapegin AV, Kalinin SA, Smirnov AV, Dorogov MV, Krasavin M (2014) New tetracyclic 1,4-oxazepines constructed via practically simple tandem condensation strategy from readily available synthons. Tetrahedron 70:1077–1083
85. Sosnovskikh VY, Mel'nikov MY, Pogozhikh SA (1999) Reactions of 3,3-dialkyl-2,3-dihydro-6-trifluoromethyl-4-pyrones with hydroxylamine. Synthesis and structures of 5-(1,l-dialkyl-2-hydroxyethyl)-5-hydroxy-3-trifluoromethyl-Δ^2-isoxazolines. Russ Chem Bull 48:1323–1328
86. Sosnovskikh VY, Barabanov MA, Usachev BI (2003) Reactions of 5,7-dimethyl-2-polyfluoroalkyl-8-azachromones with N-nucleophiles. Russ Chem Bull 52:1758–1767
87. Sosnovskikh VY, Usachev BI, Sizov AY, Barabanov MA (2004) A simple one-pot synthesis of 2,6-disubstituted 4-(polyfluoroalkyl)pyridines and -pyrimidines by reaction of 2-polyfluoroalkylchromones with aromatic methyl ketimines and amidines. Synthesis 2004:942–948

88. Sosnovskikh VY, Usachev BI (2002) A convenient synthesis of 4(5)-(2-hydroxyaroyl)-5(4)-trifluoromethyl-1,2,3-triazoles from 2-trifluoromethylchromones and chromen-4-imines. Mendeleev Commun 12:75–76
89. (a) Sosnovskikh VY, Usachev BI, Sevenard DV, Lork E, Röschenthaler G-V (2001) Unexpected synthesis of dihydrothienocoumarin derivatives from 2-trifluoromethylchromones and ethyl mercaptoacetate. Tetrahedron Lett 42:5117–5119; (b) Sosnovskikh VY, Usachev BI, Sevenard DV, Lork E, Röschenthaler G-V (2003) Synthesis of 2-(trifluoromethyl)-1,2-dihydro-4H-thieno[2,3-*c*]chromen-4-ones and 2-(trifluoromethyl)-4*H*-thieno[2,3-*c*]chromen-4-ones from 2-trifluoromethylchromones and ethyl mercaptoacetate. Tetrahedron 59:2625–2630
90. Sosnovskikh VY, Usachev BI (2001) Reactions of 7-polyfluoroalkylnorkhellins with alkyl mercaptoacetates: a simple synthesis of dihydrothienopsoralens and benzofuran derivatives of 2-oxa-7-thiabicyclo[3.2.1]octane. Tetrahedron Lett 42:5121–5122
91. (a) Sosnovskikh VY, Barabanov MA, Usachev BI (2003) A novel redox reaction between 8-aza-5,7-dimethyl-2-trifluoromethylchromone and alkyl mercaptoacetates. Org Lett 5:2501–2504; (b) Sosnovskikh VY, Barabanov MA, Usachev BI (2004) A novel redox reaction between 8-aza-5,7-dimethyl-2-trifluoromethylchromone and alkyl mercaptoacetates. Facile synthesis of CF_3-containing 2-pyridone derivatives. J Org Chem 69:8297–8304
92. Sosnovskikh VY, Usachev BI, Vorontsov II (2002) Unusual reaction of 2-(trifluoromethyl)-1,2-dihydro-3λ^6-thieno[2,3-*c*]chromen-3,3,4-triones with hydrazine as a new route to 3-hydrazinopyridazine derivatives. J Org Chem 67:6738–6742
93. Pinza M, Pifferi G (1994) Synthesis and biotransformation of 3-hydrazinopyridazine drugs. Farmaco 49:683–692
94. Coates WJ, Roe AM, Slater RA (1977) Dihydropyridazinones. GB 1488330
95. (a) Prakash GKS, Yudin AK (1997) Perfluoroalkylation with organosilicon reagents. Chem Rev 97:757–786; (b) Singh RP, Shreeve JM (2000) Nucleophilic trifluoromethylation reactions of organic compounds with (trifluoromethyl)trimethylsilane. Tetrahedron 56:7613–7632; (c) Langlois BR, Billard T (2003) Some recent results in nucleophilic trifluoromethylation and introduction of fluorinated moieties. Synthesis:185–194
96. (a) Sosnovskikh VY, Sevenard DV, Usachev BI, Röschenthaler G-V (2003) The first example of a preparative 1,4-perfluoroalkylation using (perfluoroalkyl)trimethylsilanes. Tetrahedron Lett 44:2097–2099; (b) Sevenard DV, Sosnovskikh VY, Kolomeitsev AA, Königsmann MH, Röschenthaler G-V (2003) Regioselective 1,4-trifluoromethylation of α,β-enones using 'protect-in-situ' methodology. Tetrahedron Lett 44:7623–7627; (c) Sosnovskikh VY, Usachev BI, Sevenard DV, Röschenthaler G-V (2003) Regioselective nucleophilic 1,4-trifluoromethylation of 2-polyfluoroalkylchromones with (trifluoromethyl)trimethylsilane. Synthesis of fluorinated analogs of natural 2,2-dimethylchroman-4-ones and 2,2-dimethylchromenes. J Org Chem 68:7747–7754
97. Sosnovskikh VY, Usachev BI, Permyakov MN, Sevenard DV, Röschenthaler G-V (2006) First example of regioselective nucleophilic 1,6-addition of trimethyl(trifluoromethyl)silane to 4*H*-chromene derivatives. Russ Chem Bull 55:1687–1689
98. Sosnovskikh VY, Usachev BI (2002) A simple and efficient synthesis of 2-methyl-2-trifluoromethylchroman-4-ones from 2-trifluoromethyl-4*H*-chromen-4-imines and malonic acid. Synthesis 2002:2341–2343
99. (a) Sosnovskikh VY, Usachev BI, Sizov AY, Kodess MI (2004) Novel chemical modifications at the 4-position of chromones. Synthesis and reactivity of 4*H*-chromene-4-spiro-5′-isoxazolines and related compounds. Tetrahedron Lett 45:7351–7354; (b) Sosnovskikh VY, Sizov AY, Usachev BI, Kodess MI, Anufriev VA (2006) Spiro[4*H*-chromene-4,5′-isoxazolines] and related compounds: synthesis and reactivities. Russ Chem Bull 55: 535–542
100. Sosnovskikh VY, Usachev BI, Sizov AY (2004) Synthesis of 2-aroylmethyl-2-polyfluoroalkylchroman-4-ones. Russ Chem Bull 53:1776–1777
101. Sosnovskikh VY, Usachev BI, Sizov AY (2004) A novel and simple synthesis of substituted anilines by reaction of 2-polyfluoroalkylchromones with (isopropylidene)isopropylamine. Synlett 2004:1765–1766

102. Sosnovskikh VY, Usachev BI, Sizov AY, Vorontsov II, Shklyaev YV (2003) Reaction of 2-polyfluoroalkylchromones with 1,3,3-trimethyl-3,4-dihydroisoquinolines and methylketimines as a direct route to zwitterionic axially chiral 6,7-dihydrobenzo[*a*]quinolizinium derivatives and 2,6-diaryl-4-polyfluoroalkylpyridines. Org Lett 5:3123–3126
103. Sosnovskikh VY, Korotaev VY, Barkov AY, Sokovnina AA, Kodess MI (2012) Reaction of 2-(trifluoromethyl)chromones with pyridoxal: formation of 1-benzopyranooxepino- and 1-benzopyranopyranopyridines. J Fluor Chem 141:58–63
104. Sosnovskikh VY, Safrygin AV, Anufriev VA, Eltsov OS, Iaroshenko VO (2011) Reactions of 2-(trifluoromethyl)chromones with cyanoacetamides, ethyl cyanoacetate and diethyl malonate. Unexpected synthesis of benzo[*c*]coumarin derivatives. Tetrahedron Lett 52:6271–6274
105. (a) Khilya VP, Grishko LG, Shevchenko LI, Barvinok LI, Dymovich VA, Sabo V (1973) Synthesis and properties of heterocyclic analogs of isoflavones. Chem Heterocycl Compd 9:1091–1097; (b) Khilya VP, Sabo V, Grishko LG, Vikhman DV, Babichev FS, Dymovich VA (1975) Chemistry of heteroanalogs of isoflavones II. Synthesis and properties of thiazole analogs of isoflavones. Chem Heterocycl Compd 11:898–903; (c) Khilya VP, Grishko LG, Sokolova TN (1975) Chemistry of heteroanalogs of isoflavones III. Synthesis of benzimidazole and benzothiazole analogs of isoflavones. Chem Heterocycl Compd 11:1353–1355
106. Klutchko S, Brown RE, Von Strandtmann M (1976) Substituted chromone-3-carbonitriles, carboxamides and carboxylic acids useful for preventing asthmatic symptoms. US 3937837
107. Matin A, Gavande N, Kim MS, Yang NX, Salam NK, Hanrahan JR, Roubin RH, Hibbs DE (2009) 7-Hydroxybenzopyran-4-one derivatives: a novel pharmacophore of peroxisome proliferator-activated receptor α and -γ (PPARα and γ) dual agonists. J Med Chem 52:6835–6850
108. Frasinyuk MS, Khilya VP (1999) Preparation and reactions of isoflavone heteroanalogs. Chem Heterocycl Compd 35:3–22
109. Riva C, De Toma C, Donadel L, Boi C, Pennini R, Motta G, Leonardi A (1997) New DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) assisted one-pot synthesis of 2,8-disubstituted 4*H*-1-benzopyran-4-ones. Synthesis 1997:195–201
110. Coppola GM, Dodsworth RW (1981) An improved synthesis of 2-methylchromone-3-carboxylic acid and its esters. Synthesis 1981:523–524
111. Wen L, Zhang H, Lin H, Shen Q, Lu L (2012) A facile synthetic route to 2-trifluoromethyl-substituted polyfunctionalized chromenes and chromones. J Fluor Chem 133:171–177
112. Lu L, Wei J, Chen J, Zhang J, Deng H, Shao M, Zhang H, Cao W (2009) A simple and convenient synthesis of 2-(perfluoroalkyl)-4*H*-chromenes from salicyl N-tosylimines or salicylaldehydes and methyl 2-perfluoroalkynoates. Tetrahedron 65:9152–9156
113. Wang C-L, Li H-Q, Menga W-D, Qing F-L (2005) Trifluoromethylation of flavonoids and anti-tumor activity of the trifluoromethylated flavonoid derivatives. Bioorg Med Chem Lett 15:4456–4458
114. (a) Zheng X, Meng W-D, Xu Y-Y, Cao J-G, Qing F-L (2003) Synthesis and anticancer effect of chrysin derivatives. Bioorg Med Chem Lett 13:881–884; (b) Zheng X, Cao J-G, Meng W-D, Qing F-L (2003) Synthesis and anticancer effect of B-ring trifluoromethylated flavonoids. Bioorg Med Chem Lett 13:3423–3427
115. Sosnovskikh VY, Usachev BI, Sizov AY (2003) 2-Polyfluoroalkylchromones. 14. Synthesis of 4-chloro-3(5)-(2-hydroxyaryl)-5(3)-polyfluoroalkylpyrazoles. Russ Chem Bull 52:508–510
116. Sosnovskikh VY, Usachev BI, Sizov AY (2003) 2-Polyfluoroalkylchromones. 15. Transformation of 3-chloro-2-(polyfluoroalkyl)chromones into benzofuran derivatives by hydroxylamine. Russ Chem Bull 52:984–988
117. Sosnovskikh VY, Moshkin VS, Kodess MI (2008) Reactions of 3-(polyfluoroacyl)chromones with hydroxylamine: synthesis of novel R^F-containing isoxazole and chromone derivatives. Tetrahedron 64:7877–7889
118. Isakova VG, Khlebnikova TS, Lakhvich FA (2010) Chemistry of fluoro-substituted β-diketones and their derivatives. Russ Chem Rev 79:849–879
119. Yokoe I, Maruyama K, Sugita Y, Harashida T, Shirataki Y (1994) Facile synthesis of 3-substituted chromones from an enaminoketone. Chem Pharm Bull 42:1697–1699

120. Sosnovskikh VY, Irgashev RA (2005) A novel and convenient synthesis of 3-(polyhaloacyl) chromones using diethoxymethyl acetate. Synlett 2005:1164–1166
121. (a) Sosnovskikh VY, Irgashev RA, Barabanov MA (2006) 3-(Polyhaloacyl)chromones and their hetero analogues: synthesis and reactions with amines. Synthesis:2707–2718; (b) Sosnovskikh VY, Irgashev RA, Barabanov MA, Moshkin VS (2006) Reactions of 3-polyfluoroacylchromones with primary amines. Russ Chem Bull 55:593–594
122. Semeniuchenko V, Khilya V, Groth U (2009) Nucleophilic homogeneous hydrogenation by iridium complexes. Synlett 2009:271–275
123. Sosnovskikh VY, Irgashev RA (2006) 6-Polyfluoroacyl- and 6-trichloroacetylnorkhellins: synthesis and reaction with aromatic amines. Heteroat Chem 17:99–103
124. Sosnovskikh VY, Irgashev RA (2007) Synthesis of 3-(azolylmethylene)chroman-4-ones via addition of indoles and *N*-methylpyrrole to 3-(polyfluoroacyl)chromones. Lett Org Chem 4:344–351
125. Sosnovskikh VY, Irgashev RA (2006) Reactions of 3-(polyfluoroacyl)chromones with indole and *N*-methylindole. Russ Chem Bull 55:2294–2295
126. Sosnovskikh VY, Irgashev RA, Moshkin VS, Kodess MI (2008) Reaction of 3-(polyfluoroacyl)chromones with hydrazines: new regioselective synthesis of R^F-containing pyrazoles. Russ Chem Bull 57:2146–2155
127. (a) Sosnovskikh VY, Moshkin VS, Irgashev RA (2006) Reactions of 3-(polyfluoroacyl)chromones with hydroxylamine. The first synthesis of 3-cyano-2-(polyfluoroalkyl)chromones. Tetrahedron Lett 47:8543–8546; (b) Sosnovskikh VY, Moshkin VS, Kodess MI (2008) Reactions of 3-(polyfluoroacyl)chromones with hydroxylamine: synthesis of novel R^F-containing isoxazole and chromone derivatives. Tetrahedron 64:7877–7889
128. Kotljarov A, Irgashev RA, Iaroshenko VO, Sevenard DV, Sosnovskikh VY (2009) 3-(Polyfluoroacyl)chromones and their hetero analogues as valuable substrates for syntheses of 4-(polyfluoroalkyl)pyrimidines. Synthesis 2009:3233–3242
129. Sosnovskikh VY, Irgashev RA, Kodess MI (2008) One-pot three-component reaction of 3-(polyfluoroacyl)chromones with active methylene compounds and ammonium acetate: regioselective synthesis of novel R^F-containing nicotinic acid derivatives. Tetrahedron 64:2997–3004
130. Sosnovskikh VY, Irgashev RA, Demkovich IA (2008) Three-component synthesis of partially hydrogenated quinolines from 3-substituted chromones, dimedone, and ammonium acetate. Russ Chem Bull 57:2210–2213
131. (a) Kotljarov A, Iaroshenko VO, Volochnyuk DM, Irgashev RA, Sosnovskikh VY (2009) Reactions of 3-(polyfluoroacyl)chromenones with heterocyclic amines: novel synthesis of polyfluoroalkyl-containing fused pyridines. Synthesis:3869–3879; (b) Iaroshenko VO, Sevenard DV, Kotljarov A, Volochnyuk DM, Tolmachev AO, Sosnovskikh VY (2009) A convenient synthesis of fluorinated pyrazolo[3,4-*b*]pyridine and pyrazolo[3,4-*d*]pyrimidine nucleosides. Synthesis:731–740
132. Iaroshenko VO, Savych I, Villinger A, Sosnovskikh VY, Langer P (2012) Reactions of 3-acylchromones with dimethyl 1,3-acetonedicarboxylate and 1,3-diphenylacetone: one-pot synthesis of functionalized 2-hydroxybenzophenones, 6*H*-benzo[*c*]chromenes and benzo[*c*] coumarins. Org Biomol Chem 10:9344–9348
133. (a) Sosnovskikh VY, Irgashev RA, Khalymbadzha IA, Slepukhin PA (2007) Stereoselective hetero-Diels–Alder reaction of 3-(trifluoroacetyl)chromones with cyclic enol ethers: synthesis of 3-aroyl-2-(trifluoromethyl)pyridines with ω-hydroxyalkyl groups. Tetrahedron Lett 48:6297–6300; (b) Sosnovskikh VY, Khalymbadzha IA, Irgashev RA, Slepukhin PA (2008) Stereoselective hetero-Diels–Alder reaction of 3-(polyfluoroacyl)chromones with enol ethers. Novel synthesis of 2-R^F-containing nicotinic acid derivatives. Tetrahedron 64:10172–10180
134. Irgashev RA, Sosnovskikh VY, Kalinovich N, Kazakova O, Röschenthaler G-V (2009) Methyl 2-methoxytetrafluoropropionate as a synthetic equivalent of methyl trifluoropyruvate in the Claisen condensation. The first synthesis of 2-(trifluoroacetyl)chromones and 5-aryl-2-hydroxy-2-(trifluoromethyl)furan-3(2H)-ones. Tetrahedron Lett 50:4903–4905

135. Osadchii SA, Barkhash VA (1970) Synthesis and some reactions of polyfluoro aromatic β-diketone. Zhurn Organ Khim 6:1627–1636; Chem Abstr (1970) 73:109623
136. Osadchii SA, Barkhash VA (1971) Reaction of polyfluoro aromatic β-diketones with hydrazines. Zhurn Organ Khim 7:1215–1220; Chem Abstr (1971) 75:98491
137. (a) Vorozhtsov NN Jr, Barkhash VA, Prudchenko AT, Khomenko TI (1965) Synthesis of polyfluorinated chromones and flavones. Dokl Akad Nauk SSSR 164:1046–1049; Chem Abstr (1966) 64:11372; (b) Filler R, Rao YS, Biezais A, Miller FN, Beaucaire VD (1970) Polyfluoroaryl β-dicarbonyl compounds. J Org Chem 35:930–935
138. Saloutin VI, Skryabina ZE, Bazyl' IT, Chupakhin ON (1993) Novel fluorinated chromones. J Fluor Chem 65:37–41
139. Vlasov VM, Yakobson GG (1969) Aromatic fluoro derivatives. XXXV. Formylation of pentafluoroacetophenone. Izv Akad Nauk SSSR Ser Khim:893–896
140. Dilli S, Robards K (1978) By-product formation in the synthesis of chromium(III) chelates of β-diketones. Aust J Chem 31:1833–1837
141. (a) Hou Y, Higashiya S, Fuchigami T (1998) Selective anodic fluorination of flavones. Synlett:973–974; (b) Hou Y, Higashiya S, Fuchigami T (1999) Electrolytic partial fluorination of organic compounds. 32. Regioselective anodic mono- and difluorination of flavones. J Org Chem 64:3346–3349
142. (a) Chuikov IP, Karpov VM, Platonov VE (1992) Fluoroindenes. 13. Transformations of polyfluorinated indenes and 1-alkylideneindans in the H_2O_2-HF-SbF_5 system. Russ Chem Bull 41:1104–1110; (b) Zonov YV, Karpov VM, Platonov VE (2007) Reaction of perfluoro-1-ethylindan with SiO_2/SbF_5 and skeletal transformations of perfluoro-3-ethylindan-1-one under the action of SbF_5 and SiO_2/SbF_5. J Fluor Chem 128:1065–1073; (c) Zonov YV, Karpov VM, Platonov VE (2012) Synthesis and skeletal rearrangements of perfluorinated 4-alkyl- and 4-phenyltetralin-1-ones under the action of antimony pentafluoride. J Fluor Chem 135:159–166
143. Saloutin VI, Bazyl' IT, Skryabina ZE, Chupakhin ON (1994) Interaction of 2-ethoxycarbonyl(carboxy)-5,6,7,8-tetrafluorochromones with *N*-nucleophiles. Izv Acad Nauk Ser Khim:904–907
144. Saloutin VI, Bazyl' IT, Skryabina ZE, Shurov SN, Perevalov SG (1995) Interaction of 5,6,7,8-tetrafluoro-2-ethoxycarbonyl(carboxy)chromones with hydrazine and ortho-phenylenediamine. Zhurn Organ Khim 31:718–725
145. Saloutin VI, Perevalov SG, Skryabina ZE (1996) Ethyl (pentafluorobenzoyl)pyruvate and its derivatives in the reactions with ortho-aminophenol. Zhurn Organ Khim 32:1386–1389
146. (a) Saloutin VI, Burgart YV, Kappe CO, Chupakhin ON (2000) Perfluorinated acyl(aroyl) pyruvates as building blocks for the synthesis of heterocycles. Heterocycles 52:1411–1434; (b) Saloutin VI, Burgart YV, Chupakhin ON (1999) Fluorine-containing 2,4-dioxo acids in the synthesis of heterocyclic compounds. Russ Chem Rev 68:203–214
147. (a) Saloutin VI, Skryabina ZE, Bazyl' IT, Kisil' SP (1999) Interaction of 3-ethoxycarbonyl(carboxy)-substituted 5,6,7,8-tetrafluorochromones with *N*-nucleophiles: synthesis of fluorocoumarins. J Fluor Chem 94:83–90; (b) Shcherbakov KV, Burgart YV, Kodess MI, Saloutin VI (2012) Structure of 5,6,7,8-tetrafluoro-4-hydroxycoumarins. Chem Heterocycl Compd 48:1297–1306; (c) Shcherbakov KV, Burgart YV, Saloutin VI (2013) Features of reactions of polyfluorinated ethyl 4-oxo-2-pnenyl-4*H*-chromene-3-carboxylates with *N*-nucleophiles. Russ J Org Chem 49:719–729
148. (a) Burgart YV, Shcherbakov KV, Saloutin VI, Chupakhin ON (2004) 5,6,7,8-Tetrafluoro-4-hydroxycoumarin derivatives in reactions with *o*-phenylenediamine. Russ Chem Bull 53:1237–1239; (b) Bazyl' IT, Kisil' SP, Sharapko AE, Burgart YV, Saloutin VI, Chupakhin ON (1998) Reactions of 5,6,7,8-tetrafluoro-4-hydroxycoumarin and its derivatives with N-nucleophiles. Russ J Org Chem 34:363–368
149. Riveir ME, De Kimpe N, Moglioni A, Vázquez R, Monczor F, Shayo C, Davio C (2010) Coumarins: old compounds with novel promising therapeutic perspectives. Curr Med Chem 17:1325–1338

150. (a) Zahradnik M (1992) The production and application of fluorescent brightening agents. Wiley, Chichester; (b) Maeda M (1984) Laser dyes. Academic, New York
151. (a) Jones II G, Jackson WR, Choi C, Bergmark WR (1985) Solvent effects on emission yield and lifetime for coumarin laser dyes. Requirements for a rotatory decay mechanism. J Phys Chem 89:294–300; (b) Cisse L, Djande A, Capo-Chichi M, Delatre F, Saba A, Tine A, Aaron J-J (2011) Revisiting the photophysical properties and excited singlet-state dipole moments of several coumarin derivatives. Spectrochim Acta Part A 79:428–436; (c) Xu B, Yang J, Jiang X, Wang Y, Sun H, Yin J (2009) Ground and excited states calculations of 7-phenylamino-substituted coumarins. J Mol Struct 917:15–20
152. Zhu S, Song L, Jin G, Dai B, Hao J (2009) Recent progress on the synthesis of trifluoromethylated heterocyclic compounds based on ethyl 4,4,4-trifluoroacetoacetate and its derivatives. Curr Org Chem 13:1015–1027
153. Bayer V, Pastor R, Cambon A (1982) Synthese et etude spectrale de F-alkyl-4 coumarines. J Fluor Chem 20:187–202
154. Pastor RE, Fabron J, Cambon A, Hu Y-C (1987) Étude en résonance magnétique nucléaire du ^{13}C des F-méthyl-4 coumarines. Can J Chem 65:1356–1360
155. Bissell ER, Larson DK, Croudace MC (1981) Some 7-substituted 4-(trifluoromethyl)coumarins. J Chem Eng Data 26:348–350
156. Smitha G, Reddy CS (2004) $ZrCl_4$-catalyzed Pechmann reaction: synthesis of coumarins under solvent-free conditions. Synth Commun 34:3997–4003
157. Wu J, Diao T, Sun W, Li Y (2006) Expeditious approach to coumarins via Pechmann reaction catalyzed by molecular iodine or AgOTf. Synth Commun 36:2949–2956
158. Bose DS, Rudradas AP, Babu MH (2002) The indium(III) chloride-catalyzed von Pechmann reaction: a simple and effective procedure for the synthesis of 4-substituted coumarins. Tetrahedron Lett 43:9195–9197
159. Jung K, Park Y-J, Ryu J-S (2008) Scandium(III) triflate-catalyzed coumarin synthesis. Synth Commun 38:4395–4406
160. Valizadeha H, Shockravi A (2005) An efficient procedure for the synthesis of coumarin derivatives using $TiCl_4$ as catalyst under solvent-free conditions. Tetrahedron Lett 46:3501–3503
161. Katkevičs M, Kontijevskis A, Mutule I, Sūna E (2007) Microwave-promoted automated synthesis of a coumarin library. Chem Heterocycl Compd 43:151–159
162. Hammond PR, Atkins RL (1975) 2-Keto-4-trifluoromethyl-9-methyl-6,7,8,9-tetrahydro-2*H*-pyrano[3,2-*g*]quinoline, an efficient, stable laser dye. J Heterocycl Chem 12:1061
163. Atkins RL, Bliss DE (1978) Substituted coumarins and azacoumarins. Synthesis and fluorescent properties. J Org Chem 43:1975–1980
164. (a) Zhang B-L, Wang F-D, Yue J-M (2006) A new efficient method for the total synthesis of linear furocoumarins. Synlett:567–570; (b) Zhang B-L, Fan C-Q, Dong L, Wang F-D, Yue J-M (2010) Structural modification of a specific antimicrobial lead against *Helicobacter pylori* discovered from traditional Chinese medicine and a structure–activity relationship study. Eur J Med Chem 45:5258–5264
165. Dichtel WR, Hecht S, Fréchet JMJ (2005) Functionally layered dendrimers: a new building block and its application to the synthesis of multichromophoric light-harvesting systems. Org Lett 7:4451–4454
166. Bissell ER, Mitchell AR, Smith RE (1980) Synthesis and chemistry of 7-amino-4-(trifluoromethyl)coumarin and its amino acid and peptide derivatives. J Org Chem 45:2283–2287
167. Sun W-C, Gee KR, Haugland RP (1998) Synthesis of novel fluorinated coumarins: excellent UV-light excitable fluorescent dyes. Bioorg Med Chem Lett 8:3107–3110
168. (a) Bertram H-J, Böhm S, Born L (1991) Eine neue Reaktion von 4-hydroxycumarinen und synthese von 4-fluorcumarinen. Synthesis:937–938; (b) Shi G, Wang Q, Schlosser M (1996) Versatile 2-fluoroacrylic building blocks for the synthesis of fluorinated heterocyclic compounds. Tetrahedron 52:4403–4410; (c) Dmowski W (1982) Synthesis and intramolecular cyclisation of ortho-hydroxy-2,3,3,3-tetrafluoropropiophenone. Formation of 3-fluoro-4-

hydroxycoumarin. J Fluor Chem 20:589–598; (d) Dmowski W (1983) Synthesis of fluorinated derivatives of 4-hydroxycoumarin and chromone. Synthesis:396–397
169. Edwards JP, Higuchi RI, Winn DT, Pooley CLF, Caferro TR, Hamann LG, Zhi L, Marschke KB, Goldman ME, Jones TK (1999) Nonsteroidal androgen receptor agonist based on 4-(trifluoromethyl)-2*H*-pyrano[3,2-*g*]quinolin-2-one. Bioorg Med Chem Lett 9:1003–1008
170. Traven VF, Podkhalyuzina NY, Kanevskii DS (2003) Synthesis of new difurocoumarins. Chem Heterocycl Compd 39:866–871
171. Ma T, Liu L, Xue H, Li L, Han C, Wang L, Chen Z, Liu G (2008) Chemical library and structure–activity relationships of 11-demethyl-12-oxo calanolide a analogues as anti-HIV-1 agents. J Med Chem 51:1432–1446
172. Trkovnik M, Ivezić Z (2000) Synthesis of some new coumarin-quinolone carboxylic acids. J Heterocycl Chem 37:137–141
173. Nishiwaki T, Kikukawa H (1994) 3-Oxo-4,4,4-trifluorobutyronitriles as building blocks of trifluoromethyl substituted heterocycles. 2. Heterocyclization to 3-aryl-4-trifluoromethyl-2*H*-1-benzopyran-2-ones under Hoesch reaction conditions. J Heterocycl Chem 31:889–892
174. Kirpichenok MA, Mel'nikova LM, Denisov LK, Grandberg II (1990) Photochemical reactions of 7-aminocoumarins. 6. Reaction of 7-dialkylaminocoumarins with halo derivatives. Chem Heterocycl Compd 26:858–862
175. Cheng J-F, Chen M, Wallace D, Tith S, Arrhenius T, Kashiwagi H, Ono Y, Ishikawa A, Sato H, Kozono T, Sato H, Nadzan AM (2004) Discovery and structure–activity relationship of coumarin derivatives as TNF-α inhibitors. Bioorg Med Chem Lett 14:2411–2415
176. Bambal RB, Elliott RL (2004) 7-Alkoxycoumarins as CYP2C9 substrates and activity assay. US 6756209
177. Voznyi YV, Yufit DS, Pavlov VA, Struchkov YT (1989) Synthesis, structure, and lasing properties of 4-trifluoromethyl-7-hydroxy-2-cyanocarbethoxymethylene-2*H*-1-benzopyran. Russ Chem Bull 38:823–827
178. Voznyi YV, Dekaprilevich MO, Yufit DS, Struchkov YT (1992) Synthesis of 4-trifluoromethyl-7-hydroxycoumarin derivatives. Structure of 3-cyano-4-trifluoromethyl-7-acetoxycoumarin. Russ Chem Bull 41:1072–1075
179. Corrie JET, Munasinghe VRN, Retting W (2000) Synthesis and fluorescence properties of substituted 7-aminocoumarin-3-carboxylate derivatives. J Heterocycl Chem 37:1447–1455
180. (a) Huang B, Liu J, Huang W (1990) Direct perfluoroalkylation of coumarins by perfluoroalkyl iodides in the presence of sodium hydroxymethanesulphinate (Rongalite). J Chem Soc Chem Commun:1781–1782; (b) Huang B-N, Liu J-T, Huang W-Y (1994) Studies on sulfinatodehalogenation. 30. Synthesis of 3-perfluoroalkylated coumarins, thiocoumarins and 2-quinolones by direct perfluoroalkylation with perfluoroalkyl iodides and sodium hydroxymethanesulfinate. J Chem Soc Perkin 1:101–104
181. (a) Matsui M, Shibata K, Muramatsu H, Sawada H, Nakayama M (1991) Synthesis of 3-perfluoroalkylated coumarins. Synlett:113–114; (b) Matsui M, Shibata K, Muramatsu H, Sawada H, Nakayama M (1992) Synthesis, fluorescence, and photostabilities of 3-(perfluoroalkyl)coumarins. Chem Ber 125:467–471
182. Mizukami S, Takikawa R, Sugihara F, Shirakawa M, Kikuchi K (2009) Dual-function probe to detect protease activity for fluorescence measurement and ^{19}F MRI. Angew Chem Int Ed 48:3641–3643
183. Bourson J, Pouget J, Valeur B (1993) Ion-responsive fluorescent compounds. 4. Effect of cation binding on the photophysical properties of a coumarin linked to monoaza- and diaza-crown ethers. J Phys Chem 97:4552–4557
184. Mizukami S, Nagano T, Urano Y, Odani A, Kikuchi K (2002) A fluorescent anion sensor that works in neutral aqueous solution for bioanalytical application. J Am Chem Soc 124:3920–3925
185. Li H, Li B, Jin L-Y, Kan Y, Yin B (2011) A rapid responsive and highly selective probe for cyanide in the aqueous environment. Tetrahedron 67:7348–7353

186. Ndinguri MW, Fronczek FR, Marzilli PA, Crowe WE, Hammer RP, Marzilli LG (2010) Exploring water-soluble Pt(II) complexes of diethylenetriamine derivatives functionalized at the central nitrogen. Synthesis, characterization, and reaction with 5′-GMP. Inorg Chim Acta 363:1796–1804
187. Choi K, Park B, Han S-Y, Ahn HC (2011) Fluorescence probes for tyrosine dephosphorylation based on coumarin–proline conjugates. Chem Lett 40:290–291
188. Kim HJ, Bhuniya S, Mahajan RK, Puri R, Liu H, Ko KC, Lee JY, Kim JS (2009) Fluorescence turn-on sensors for HSO_4^-. Chem Commun 2009:7128–7130
189. (a) Okazaki T, Hirota N, Nagata T, Osuka A, Terazima M (1999) High temporally and spatially resolved thermal energy detection after nonradiative transition in solution using a molecular heater–molecular thermometer integrated system. J Am Chem Soc 121:5079–5080; (b) Okazaki T, Hirota N, Nagata T, Osuka A, Terazima M (1999) Spatially resolved thermalization dynamics of electronically photoexcited azulene probed by a molecular integrated thermometer. J Phys Chem A 103:9591–9600
190. Heltweg B, Dequiedt F, Marshall LB, Brauch C, Yoshida M, Nishino N, Verdin E, Jung M (2004) Subtype selective substrates for histone deacetylases. J Med Chem 47:5235–5243
191. (a) Suzuki T, Kouketsu A, Itoh Y, Hisakawa S, Maeda S, Yoshida M, Nakagawa H, Miyata N (2006) Highly potent and selective histone deacetylase 6 inhibitors designed based on a small-molecular substrate. J Med Chem 49:4809–4812; (b) Itoh Y, Suzuki T, Kouketsu A, Suzuki N, Maeda S, Yoshida M, Nakagawa H, Miyata N (2007) Design, synthesis, structure-selectivity relationship, and effect on human cancer cells of a novel series of histone deacetylase 6-selective inhibitors. J Med Chem 50:5425–5438
192. Lee SH, Kim HJ, Lee YO, Vicens J, Kim JS (2006) Fluoride sensing with a PCT-based calix[4]arene. Tetrahedron Lett 47:4373–4376
193. Sokkalingam P, Lee C-H (2011) Highly sensitive fluorescence "Turn-On" indicator for fluoride anion with remarkable selectivity in organic and aqueous media. J Org Chem 76:3820–3828
194. Timperley CM, Casey KE, Notman S, Sellers DJ, Williams NE, Williams NH, Williams GR (2006) Synthesis and anticholinesterase activity of some new fluorogenic analogues of organophosphorus nerve agents. J Fluor Chem 127:1554–1563
195. Desai RC, Metzger E, Santini C, Meinke PT, Heck JV, Berger JP, MacNaul KL, Cai T-Q, Wright SD, Agrawal A, Moller DE, Sahoo SP (2006) Design and synthesis of potent and subtype-selective PPARα agonists. Bioorg Med Chem Lett 16:1673–1678
196. Tuncer H, Erk Ç (2006) The synthesis of chromophore ended glycoles, Part IV. Bis-coumarin derivatives ended polyglycols. J Heterocycl Chem 43:1135–1139
197. (a) Woo LWL, Purohit A, Reed MJ, Potter BVL (1996) Active site directed inhibition of estrone sulfatase by nonsteroidal coumarin sulfamates. J Med Chem 39:1349–1351; (b) Woo LWL, Howarth NM, Purohit A, Hejaz HAM, Reed MJ, Potter BVL (1998) Steroidal and nonsteroidal sulfamates as potent inhibitors of steroid sulfatase. J Med Chem 41:1068–1083
198. Buet P, Kastenholz F, Grell E, Käb G, Häfner A, Schneider FW (1999) Trifluorocoumarino cryptands as photoprotonic molecules: basic features and theoretical considerations. J Phys Chem A 103:5871–5881
199. Chen AP-C, Chen Y-H, Liu H-P, Li Y-C, Chen C-T, Liang P-H (2002) Synthesis and application of a fluorescent substrate analogue to study ligand interactions for undecaprenyl pyrophosphate synthase. J Am Chem Soc 124:15217–15224
200. Xie L, Takeuchi Y, Cosentino LM, Lee K-H (1999) Anti-AIDS agents. 37. Synthesis and structure–activity relationships of (3′*R*,4′*R*)-(+)-*cis*-khellactone derivatives as novel potent anti-HIV agents. J Med Chem 42:2662–2672
201. Renwick AB, Surry D, Price RJ, Lake BG, Evans DC (2000) Metabolism of 7-benzyloxy-4-trifluoromethylcoumarin by human hepatic cytochrome P450 isoforms. Xenobiotica 30:955–969

202. Chizhov DL, Sosnovskikh VY, Pryadeina MV, Burgart YV, Saloutin VI, Charushin VN (2008) The first synthesis of 4-unsubstituted 3-(trifluoroacetyl)coumarins by the Knoevenagel condensation of salicylaldehydes with ethyl trifluoroacetoacetate followed by chromene–coumarin recyclization. Synlett 2008:281–285
203. Iaroshenko VO, Ali S, Babar TM, Dudkin S, Mkrtchyan S, Rama NH, Villinger A, Langer P (2011) 4-Chloro-3-(trifluoroacetyl)coumarin as a novel building block for the synthesis of 7-(trifluoromethyl)-6*H*-chromeno[4,3-*b*]quinolin-6-ones. Tetrahedron Lett 52:373–376
204. Iaroshenko VO, Erben F, Mkrtchyan S, Hakobyan A, Vilches-Herrera M, Dudkin S, Bunescu A, Villinger A, Sosnovskikh VY, Langer P (2011) 4-Chloro-3-(trifluoroacetyl)- and 4-chloro-3-(methoxalyl)coumarins as novel and efficient building blocks for the regioselective synthesis of 3,4-fused coumarins. Tetrahedron 67:7946–7955