REACTIONS OF 5-FORMYL- AND 5-ACYL-3,4-DIHYDRO-2*H*-PYRANS AND THEIR ANNELATED ANALOGS WITH NUCLEOPHILES

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Abstract. *β-Carbonyl-substituted dihydropyrans are highly useful heterocyclic compounds showing important application in organic synthesis. The increased susceptibility of the dihydropyran ring to the action of various nucleophiles makes these compounds valuable building blocks for the synthesis of a wide variety of hetero- and carbocyclic compounds. On the other hand, the presence of two non-equivalent electrophilic centers poses the problem of selectivity of reactions involving nucleophiles. This chapter will survey the reactivity of 5-formyl- and 5-acyl-3,4-dihydro-2H-pyrans and their annelated analogues with C-, N- and some other mono- and binucleophiles.*

Contents

1. Introduction

5-Formyl- and 5-acyl-3,4-dihydro-2*H*-pyrans and their benzo-condensed derivatives are promising starting compounds for the synthesis of a wide variety of heterocyclic systems. The presence of an oxyvinyl moiety conjugated to the electron-withdrawing group makes them masked equivalents of highly electrophilic β-ketoaldehydes. Since the majority of aldehydes of this type are unstable due to their high CH-acidity and carbonyl activity, it is difficult to use them in organic synthesis. At the same time, β-carbonyl-substituted dihydropyrans are stable compounds and retain a high reactivity.

The presence of two non-equivalent electrophilic centers in the structure of this type of heterocycles determines their chemical potential in reactions with mono- and binucleophiles. Such dihydropyran derivatives can be considered as push-pull compounds containing electron-donating and electron-withdrawing groups at the opposite ends of a double bond and as Michael acceptors. In particular, they can interact with various nucleophiles to form 1,4- and 1,2-addition products, which in the presence of the second nucleophilic center in the starting material may undergo *exo-trig* cyclization to give condensed heterocycles. If adducts of this type are unstable, they may further be subjected to recyclization with opening of the dihydropyran ring (Figure 1).

It should be noted that dihydropyran skeleton constitutes a key structural element in many natural compounds. Some examples of naturally occurring dihydropyrans bearing carbonyl group at C-5 position are presented (Figure 2). Among them there are polyketide trichodermatide C (**A**),[1] flavonoid

4-*O*-epidesmoflorin (**B**),[2] monoterpene alkaloid alstoniaphylline A (**C**),[3] macroline type indole alkaloids alstonerine (**D**),[4] alstophyllal (**E**),[5] alstonisine (**F**)[6] and others.

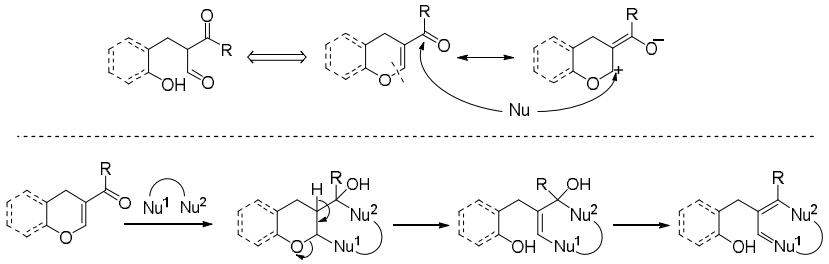


Figure 1. Reactivity of 5-formyl- and 5-acyl-3,4-dihydro-2*H*-pyrans and their benzo-condensed analogues.

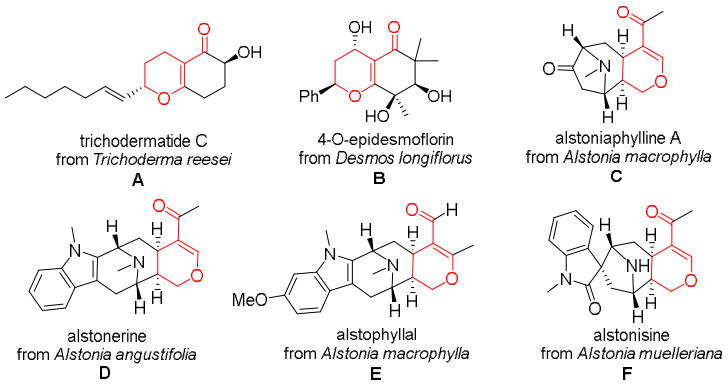


Figure 2. Selection of natural products containing carbonyl-substituted dihydropyran rings.

This chapter exclusively describes the transformations of dihydro-2*H*-pyrans and chromenes containing formyl- or acyl group in the β-position in relation to the oxygen atom. We do not consider 2-alkoxy-5-acyl-3,4-dihydro-2*H*-pyrans, which are essentially cyclic acetals, since their chemical transformations are largely different from dihydropyrans of above-mentioned type (Figure 3).

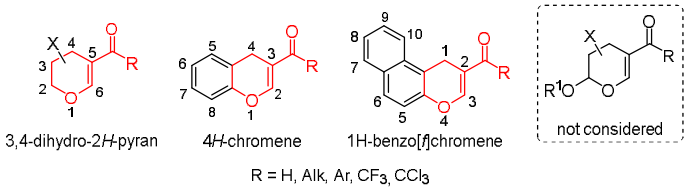


Figure 3. Considered β-carbonyl-substituted dihydropyrans and their benzo-condensed derivatives.

2. Reactions of 5-formyl- and 5-acyl-3,4-dihydro-2*H*-pyrans with nucleophiles

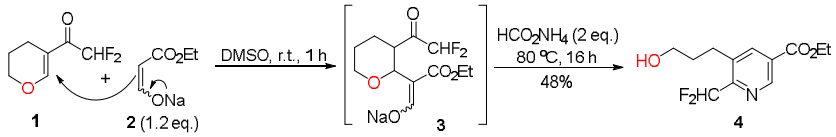
β-Carbonyl-substituted dihydropyrans are easily available compounds which can be prepared by various methods and fairly convenient building blocks to prepare a variety of heterocyclic compounds. Strong polarization of the C=C double bond in the pyran ring due to the presence of donor oxygen atom linked to one double-bonded carbon atom and acceptor acyl or formyl group on the other determines their synthetic potential in reactions with nucleophiles. The presence of two non-equivalent electrophilic centers causes the possibility of an initial attack by the nucleophile of either the C-6 atom (1,4-addition) or the carbonyl carbon atom (1,2-addition). Acyldihydropyrans like β-alkoxy vinyl ketones can be considered as

push-pull olefins, however, the presence of a six-membered ring significantly affects their reactivity in comparison with acyclic analogs. For example, β-ethoxyvinyl trifluoromethyl ketone ($EtOCH=CHCOCF_3$) is readily hydrolyzed by dilute acids to form trifluoroacetylacetaldehyde and ethanol, while 5-trifluoroacetyl-3,4-dihydro-2*H*-pyran does not react even at 70 °C with conc. HCl for eight hours.[7]

2.1. C-Nucleophiles

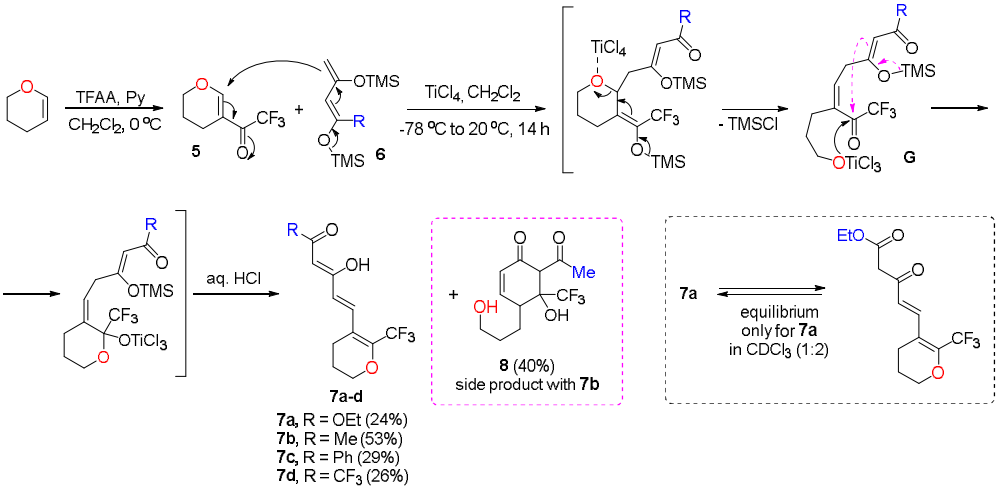
2.1.1. Enolates and CH-acids

The reactions of acyldihydropyrans with C-nucleophiles (CH-acids and carbanionic reagents) as well as with N-nucleophiles represent the most extensive class of transformations with their participation. The reaction of β-difluoroacetyldihydropyran **1** with the enolate of the 1,3-dicarbonyl compound **2** leads to the formation of the Michael adduct **3** which was treated with ammonium formate in a one-pot manner to form 2-difluoromethylpyridine **4** (Scheme 1).[8]



Scheme 1. Synthesis of 2-difluoromethylpyridine **4**.

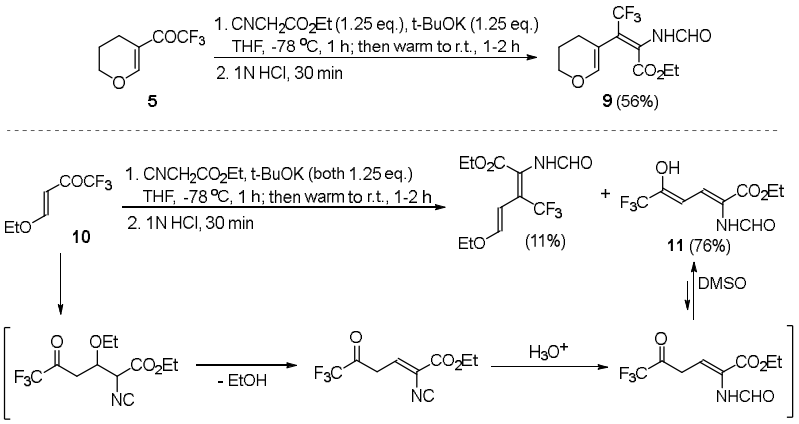
Treatment of 1-(3,4-dihydro-2*H*-pyran-5-yl)-2,2,2-trifluoroethan-1-one **5**, which is easily obtained by reacting 3,4-dihydro-2*H*-pyran and trifluoroacetic anhydride in the presence of pyridine, with 1,3-bis(trimethylsilyl) ethers **6** in the presence of $TiCl_4$ leads to 6-(trifluoromethyl)-3,4-dihydro-2*H*-pyrans **7** (Scheme 2). This cascade process involves the conjugate addition of 1,3-bis(trimethylsilyl) ether through the terminal carbon atom to dihydropyran, the subsequent opening of the pyran ring as a result of retro-Michael reaction, intramolecular nucleophilic addition of the alkoxide oxygen atom to the carbonyl group and dehydration. It should be noted that the compounds **7b-d** exist in the enol form in solution $CDCl_3$. For the dihydropyran **7a**, the ratio enol/ketone was 1:2. The synthesis of compound **7b** is accompanied by the formation of cyclohexenone **8** as a side product. It can be explained by the attack of the central carbon atom of 1,3-dicarbonyl moiety on the trifluoroacetyl group in the intermediate **G**.[9]



Scheme 2. $TiCl_4$-mediated recyclization of dihydropyran **5** with 1,3-bis(trimethylsilyl) ethers.

Trifluoroacetylated dihydropyran **5** by condensation with ethyl isocyanoacetate in the presence of *t*-BuOK produces exceptionally the Knoevenagel condensation product. The treatment of the isonitrile with

dilute hydrochloric acid leads to the corresponding formamides **9** (Scheme 3).[10] A similar pattern is observed in the case of acyclic α-substituted CF_3-enones. However, acyclic α-unsubstituted CF_3-enones **10** under the same conditions are mainly converted into Michael adducts **11** with the elimination of the alkoxy group. Apparently, in the case of cyclic enones, the β-position is sterically more hindered. As a result, the nucleophilic attack of the enolate anion is directed toward the carbonyl group.



Scheme 3. Reactions of β-trifluoroacetylated vinyl ethers with ethyl isocyanoacetate.

Treatment of 2-C-formyl glycals **12** with CH-acids in the presence of piperidinium acetate in boiling toluene results in the stable Knoevenagel products **13** (Scheme 4).[11,12] In addition to piperidinium acetate, Al_2O_3 in CH_2Cl_2 and anhydrous AcONa in ethanol were successfully used as a catalyst for the Knoevenagel reaction of formyl glycals with various CH-acids, to obtain exclusively *E*-isomers of **13**.[13] Reaction of malononitrile with 6-substituted 3,4-dihydro-2*H*-pyran-5-carbaldehyde **14** due to its lower carbonyl activity requires more harsh conditions for formation of the Knoevenagel product **15** (boiling chlorobenzene, 2 h).[14] The obtained Knoevenagel products may be easily converted to pyridine derivatives under the action of ammonia or aromatic amines. Moreover, acetonedicarboxylic acid esters **16** as 1,3-C,C-binucleophiles react with 2-formyl glycals **12a,b** and 2-hydroxyisophthalic acid esters **17** are formed as a result of the Knoevenagel condensation and Michael reaction (Scheme 4).[11]

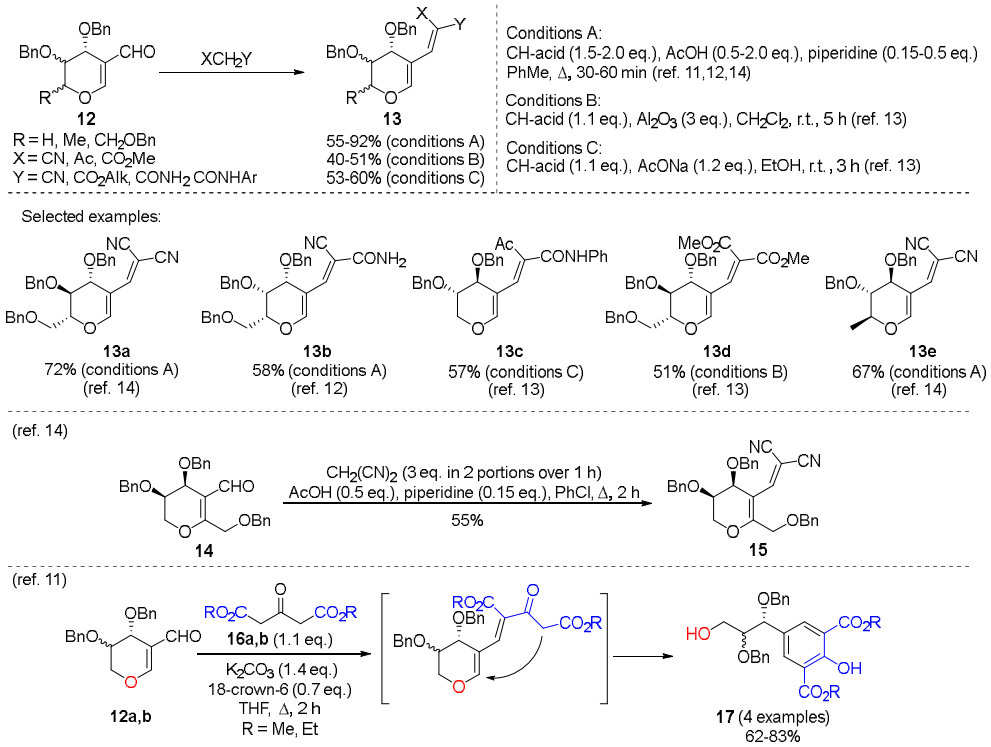
The cascade reaction of dihydropyrancarbaldehyde **18** and 4-hydroxycoumarin **19a** in the presence of EDTA, including the Knoevenagel condensation and 6π-oxa-electrocyclization of the intermediate **H**, results in the condensed coumarin **20**, most of which undergoes methanolysis with the opening of the tetrahydropyran ring under the reaction conditions (Scheme 5).[15]

Very recently Sagar and co-workers have described a microwave-assisted reaction of 2-C-formyl glycals **12c,d** and 4-hydroxycoumarins **19** or 4-hydroxyquinolones **21** that leads to pyrano[3,2-*c*]pyranones **22**[16] or pyrano[3,2-*c*]quinolones **23**[17] possessing, respectively, anticancer and selective antiproliferative activities at micromolar levels. This cascade process proceeds *via* subsequent 1,2-addition of heterocyclic enol to glycal carbonyl group, dehydration and further 6π-elecrocyclization of the 1-oxatriene intermediate (Scheme 6).

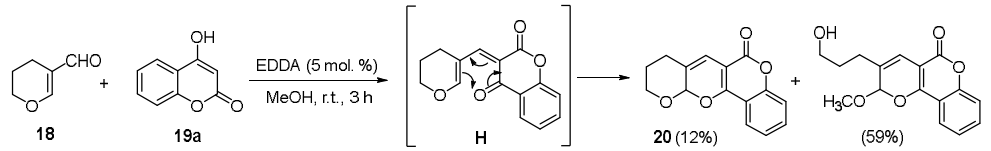
2.1.2. Organometallic compounds

The selectivity between 1,2- and 1,4-addition to α,β-unsaturated carbonyl compounds is often explained by the concept of soft and hard acids and bases. As a rule, organolithium compounds as hard nucleophiles react by 1,2-addition mechanism, and softer cuprate reagents give the Michael addition products. The Grignard reagents lie somewhere between them. In reactions that proceed by kinetic control with organometallic reagents having a highly localized negative charge, a charge-controlled 1,2-addition can be expected. In contrast, in additions of nucleophiles having charge dislocalization where the reaction is

frontier orbital controlled, a 1,4-addition is expected. Besides, the nature of the nucleophile, steric factor and solvent can affect the regioselectivity of the process.



Scheme 4. Reactions of formyl glycals with CH-acids.



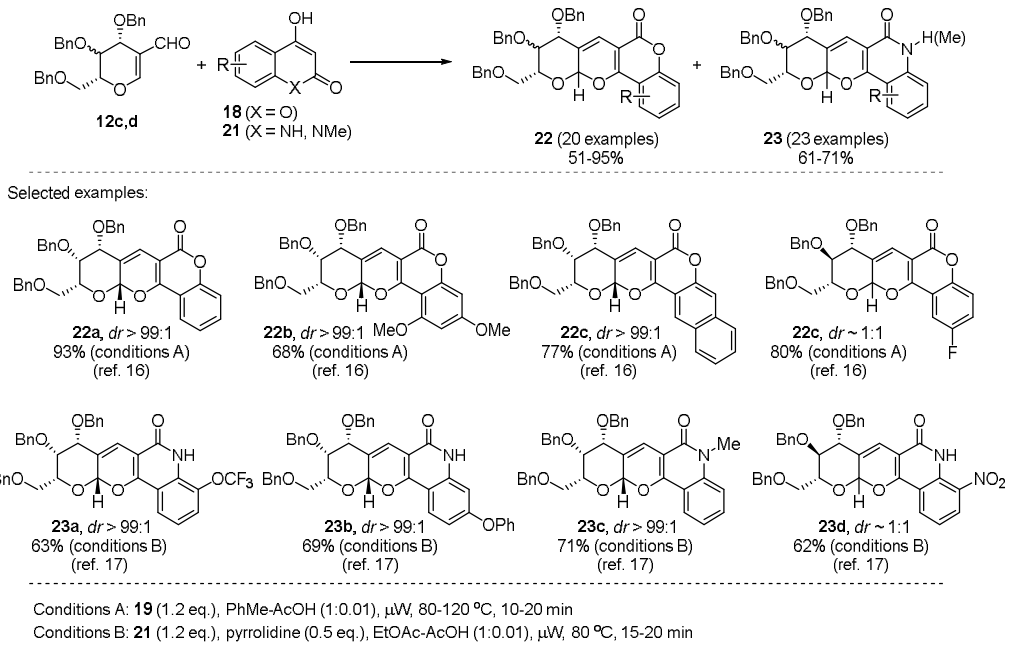
Scheme 5. Cascade reaction of dihydropyrancarbaldehyde and 4-hydroxycoumarin.

It was shown that β-trifluoroacetyldihydropyran **5** with acetylenide generated *in situ* from phenylacetylene and butyllithium gives the corresponding propargyl alcohol **24** through addition to the carbonyl group (Scheme 7).[18] At the same time, in the presence of anhydrous $ZnCl_2$ and Et_3N, the initially formed 1,4-addition product after hydrolysis turns into tetrahydropyranol **25** as a result of the opening of the tetrahydropyran ring and the intramolecular 1,2-addition.

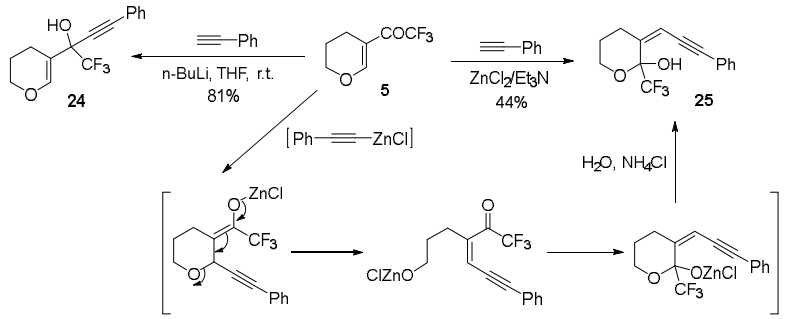
The addition of methyl bromoacetate or allyl bromide to 5-trifluoroacetyl-3,4-dihydro-2*H*-pyran **5** in diethyl ether in the presence of zinc dust leads to the formation of tertiary alcohols **26** through the intermediate generation of organozinc compounds (Scheme 8).[1,19]

The reaction of phenylmagnesium bromide with β-trifluoroacetyldihydropyran **5** in diethyl ether gives *cis*-tetrahydropyran **27** and hemiacetal **28** as a minor product. The formation of the latter is explained by the presence of an equilibrium between the initially formed enolate and its acyclic form, which can be attacked by nucleophile on the carbonyl carbon atom. It is worth noting that a similar ratio of products is also observed while using other aryl- and alkylmagnesium bromides, however the reaction with *n*-butyllithium

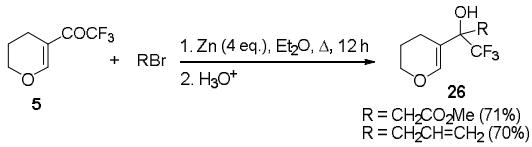
proceeds differently and leads to the formation of a mixture of 1,4- and 1,2-addition products **29-31**, including alcohol **32** as the reduction product (Scheme 9).[20]



Scheme 6. Synthesis of pyranoquinolones and pyranocoumarins.



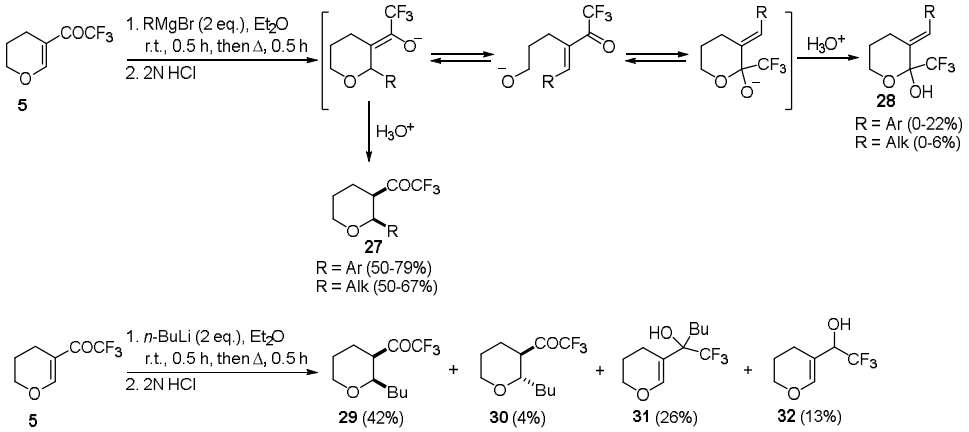
Scheme 7. Reactions of β-trifluoroacetyldihydropyran with acetylenides.



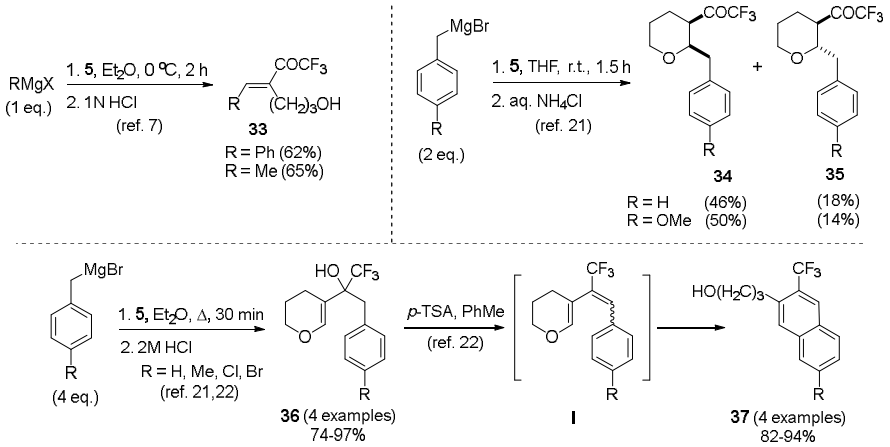
Scheme 8. 5-Trifluoroacetyl-3,4-dihydro-2*H*-pyran as a substrate in Barbier-type reaction.

It was described that the ketone **5** reacts with phenyl- and methylmagnesium bromides with the formation of acyclic products **33**.[7] These results are somewhat in contrast with the above-mentioned details. The ketone **5** reacts with the excess benzylmagnesium bromide in THF or in a mixture THF-diethyl ether to form mainly 1,4-addition product **34** and **35**.[21] At the same time, replacement of the solvent to ether leads to

1,2-addition product **36**, which can be converted into naphthalene derivatives **37** under action of *p*-toluenesulfonic acid *via* diene intermediate **I** (Scheme 10).[22] Allylmagnesium bromide in diethyl ether was attached exclusively by the carbonyl group (yield 82%).



Scheme 9. Reactions of β-trifluoroacetyldihydropyran with organometallic compounds.

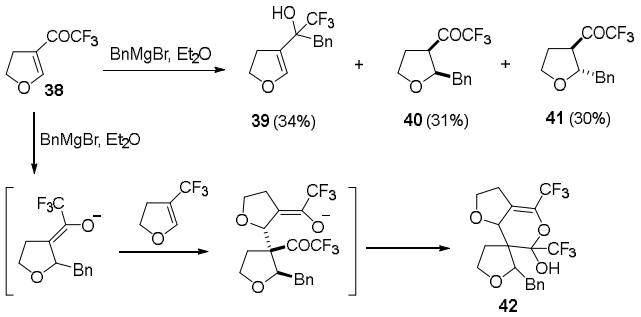


Scheme 10. Reactions of β-trifluoroacetyldihydropyran with Grignard reagents.

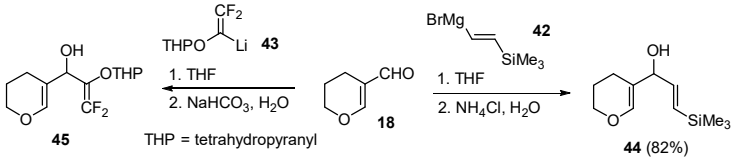
For comparison, β-trifluoroacetyldihydrofuran **38** reacts with benzylmagnesium bromide less selectively with the formation of three isomeric products **39–41**. In addition, the spiro-product **42** was also isolated with low yield as a result of the conjugate addition of enolate to the starting ketone and further hemiketalization (Scheme 11).[21]

The addition of (vinylsilyl)magnesium bromide **42**, as well as α-lithiated difluorovinyl ether **43** to dihydropyran-5-carbaldehyde **18** proceeds exclusively as 1,2-addition with the formation of secondary alcohols **44**,[23] **45**,[24] the oxidation of which provides substrates for the Nazarov cyclization reaction (Scheme 12).

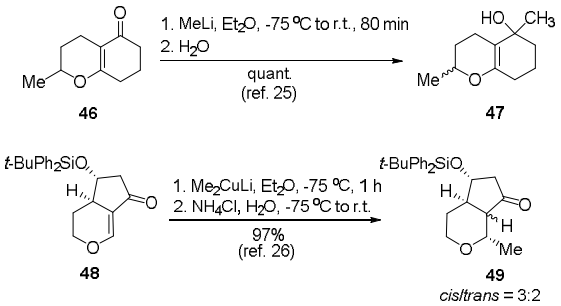
In the reaction of bicyclic pyranoketone **46** with methyllithium, only the 1,2-addition product **47** was isolated (Scheme 13).[25] The reaction of ketone **48** with lithium dimethylcuprate proceeds as 1,4-addition.[26]



Scheme 11. Reaction of β-trifluoroacetyldihydrofuran with benzylmagnesium bromide.



Scheme 12. 1,2-Addition of organometallic compounds to dihydropyran-5-carbaldehyde.



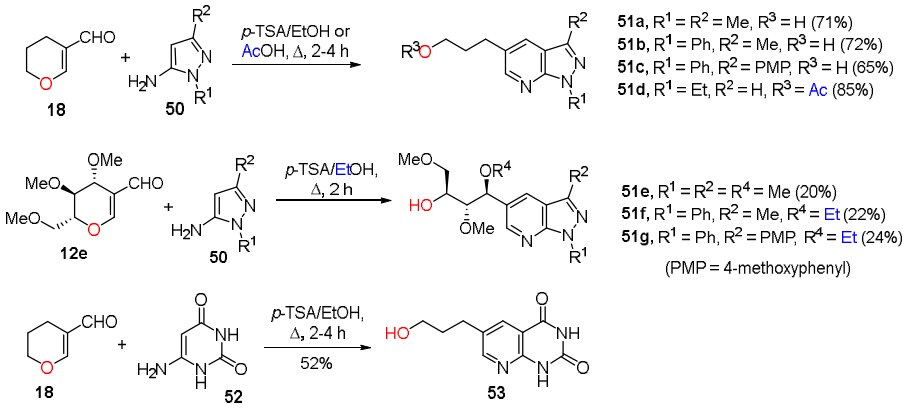
Scheme 13. Bicyclic pyranoketones in 1,2- and 1,4-addition reactions.

2.1.1. 1,3-C,N-Binucleophiles

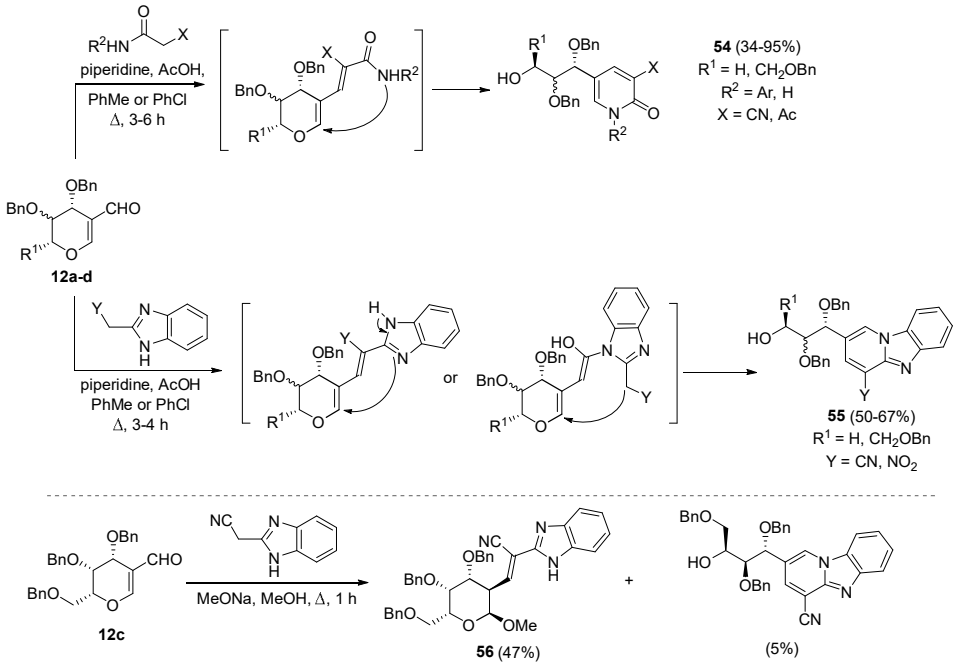
Acid-catalyzed condensation of 3,4-dihydro-2*H*-pyran-5-carbaldehyde **18** with N-substituted pyrazole-5-amines **50** leads to pyrazolo[3,4-*b*]pyridines **51a-d** in good yields. The reaction does not proceed at room temperature and the use of acetic acid as a solvent is accompanied by acylation of the hydroxyl group (**51d**).[27] At the same time, the reaction of 2-C-formyl glycal **12e** with aminopyrazoles **50** leads to the corresponding pyrazolo[3,4-*b*]pyridines **51e-g** in low yields; while conjugated with the pyridine ring N-phenyl substituent makes the α-methoxy group of the side chain of the product a better leaving group, which leads to its replacement with the ethoxy group from the solvent under the reaction conditions (**51f,g**). Dihydropyrancarbaldehyde **18** reacts with 6-aminouracil **52**, which can be regarded as heterocyclic enamine, to form pyrido[2,3-*d*]pyrimidine-2,4-dione **53** by the related mechanism (Scheme 14).

N-Arylamides of cyanoacetic and acetoacetic acids or cyanoacetamide act as 1,3-C,N-binucleophiles in the piperidinium acetate-mediated reaction with 2-C-formyl glycals **12** to form 2-pyridones **54**. The intermediate Knoevenagel adduct could not be isolated under reaction conditions.[11,14,20] The reaction of formyl glycals **12** with 2-cyanomethyl- and 2-nitromethylbenzimidazoles leads to benzo[4,5]imidazo[1,2-*a*]pyridines **55**. Due to the presence of two non-equivalent nucleophilic centers in benzimidazoles (methylene carbon atom and endocyclic nitrogen atom), the first stage of heterocyclization can be either the Knoevenagel condensation or nucleophilic addition of benzimidazole nitrogen to the carbonyl group. However, in this case, the same product is formed regardless of the direction of the initial

attack.[11] Using methanol as a solvent in the presence of MeONa leads to the product of the Knoevenagel condensation **56**, formation of which accompanies 1,6-addition of methanol (Scheme 15).[28]



Scheme 14. Reactions of β-formyldihydropyrans with heterocyclic enamines.



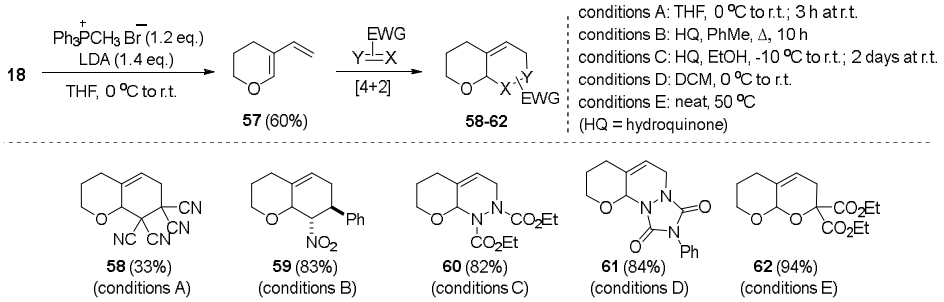
Scheme 15. Reactions of β-formyldihydropyrans with methylene active N-nucleophiles.

2.1.1. Miscellaneous C-nucleophiles

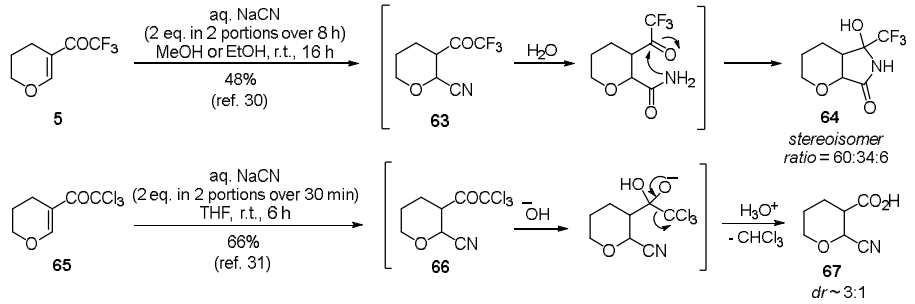
Wittig olefination of the aldehyde **18** with methylene triphenylphosphorane gives an electron-enriched diene **57**, which easily reacts with electron-deficient carbo- and heterodienophiles (Scheme 16).[29]

The reaction of β-trifluoroacetyldihydropyran **5** with NaCN in aqueous alcohol leads to pyrrolidinone **64** as a result of subsequent Michael addition of cyanide ion, partial hydrolysis of the nitrile group of the adduct **63** and nucleophilic 5-*exo*-*trig* cyclization of the formed amide fragment with the carbonyl group.[30]

Under similar conditions, β-trichloroacetyldihydropyran **65** reacts with NaCN to produce both diastereomers of 2-cyanotetrahydropyran-3-carboxylic acid **67** through the formation of the Michael adduct **66**, which in contrast to trifluoroacetyl adduct **63** undergoes subsequent haloform cleavage (Scheme 17).[31]

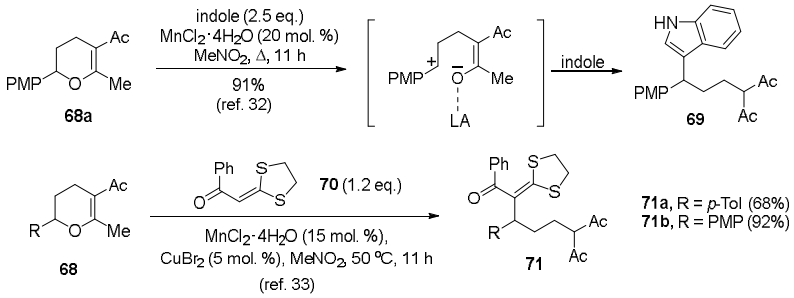


Scheme 16. Wittig synthesis of 5-vinyl-3,4-dihydropyran and its cycloaddition reactions with electron-deficient dienophiles.



Scheme 17. Contrasting behavior of 5-trifluoro- and 5-trichloroacetyl-3,4-dihydropyrans toward aqueous NaCN.

Ring opening of the dihydropyran **68a** catalyzed by Mn(II) as a Lewis acid and the nucleophilic attack of the formed carbocation by indole lead to substituted acetylacetone **69** in high yield.[32] Similarly, dihydropyrans **68** react with α-oxoketene dithioacetal **70** as a nucleophile to yield acetylacetone derivatives **71** (Scheme 18).[33]

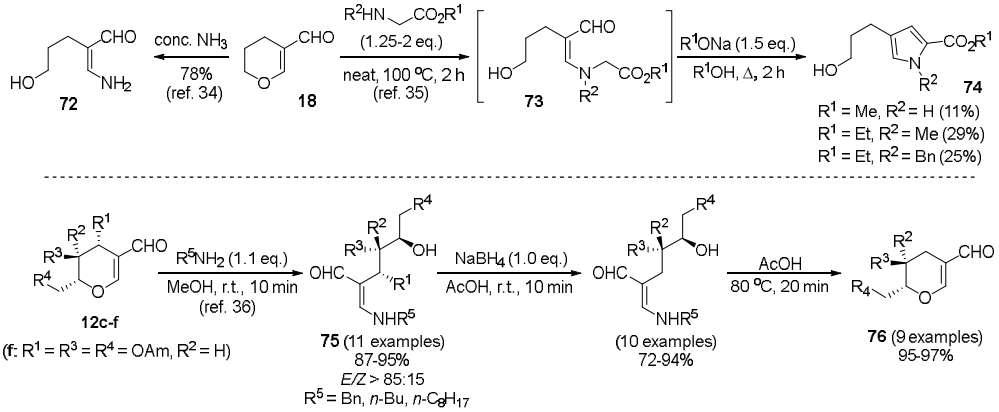


Scheme 18. Manganese(II)-catalyzed synthesis of acetylacetone derivatives from 2-aryl-5-acetyl-3,4-dihydropyrans.

2.2. N-Nucleophiles

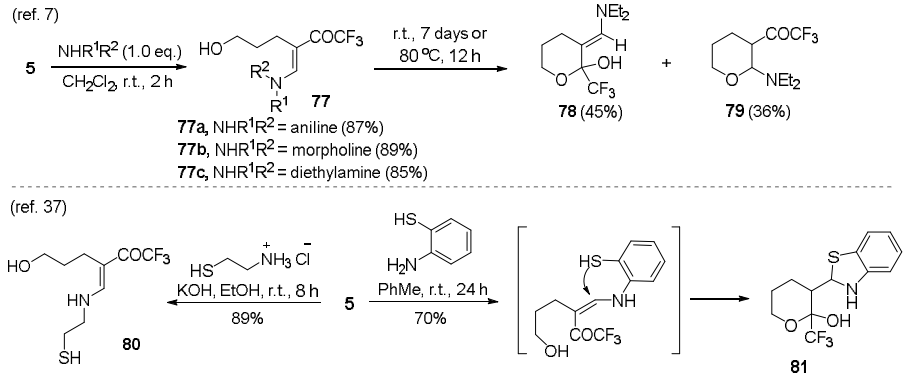
2.2.1. Amines

The reaction of 3,4-dihydropyran-5-carbaldehyde **18** with ammonia is also accompanied with the dihydropyran ring opening to give 3-amino-2-(3-hydroxypropyl)acrolein **72**.[34] Condensation of the aldehyde **18** with glycine esters proceeds similarly, resulting in the enaminal **73**, which can also be converted into substituted pyrrole **74** in one-pot manner.[35] The reaction of related C-2-formyl glycals with primary amines in methanol stereoselectively leads to the β-enaminals **75** with a ratio of *E*/*Z*-isomers in the range from 85:15 to 93:7.[36] The above-described synthesis of β-enaminals **75** and their subsequent regioselective reduction with sodium borohydride in acetic acid and acid-mediated cyclization may be considered as a convenient and efficient sequence for the indirect deoxygenation of C-2-formyl glycals **12** to 3-deoxy-C-2-formyl glycals **76** (Scheme 19).



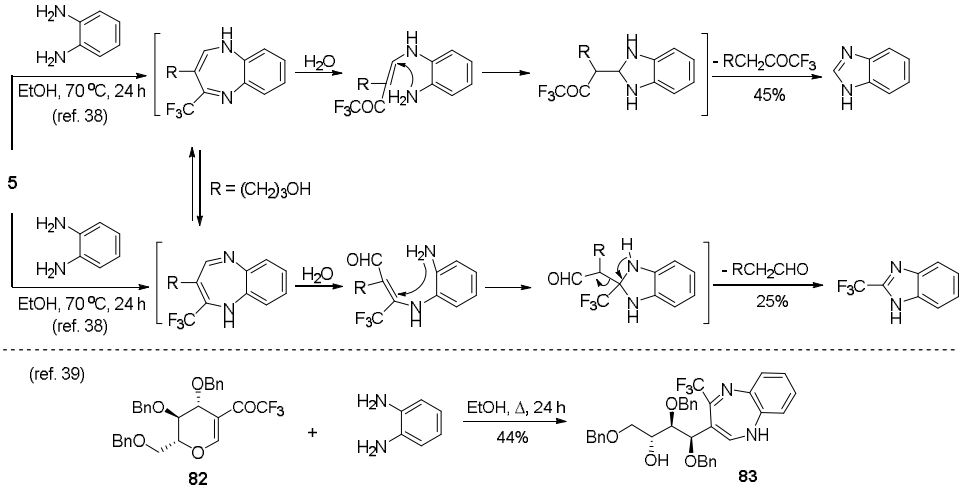
Scheme 19. β-Formyldihydropyrans ring opening in reactions with ammonia, amines and glycine esters. Three-step 3-deoxygenation of C-2-formyl glycals.

β-Trifluoroacetyldihydropyran **5** reacted with aniline, morpholine and diethylamine in the same way with the ring opening and formation of *E*-enaminoketones **77** (Scheme 20).[7] Compound **77c** was unstable and spontaneously converted into cyclic hemiketal **78** and hemiaminal ether **79** in the ratio 5:4 at room temperature per week, and at 80 ºC this process ended in 12 hours. In the case of reaction of pyran **5** with 2-aminoethanethiol, only *E*-enaminoketone **80** was isolated in high yield. The condensation with 2-aminothiophenol led to cyclic hemiketal **81** along with 7% of di(2-aminophenyl)disulfide as a result of oxidation of the starting 2-aminothiophenol.[37]



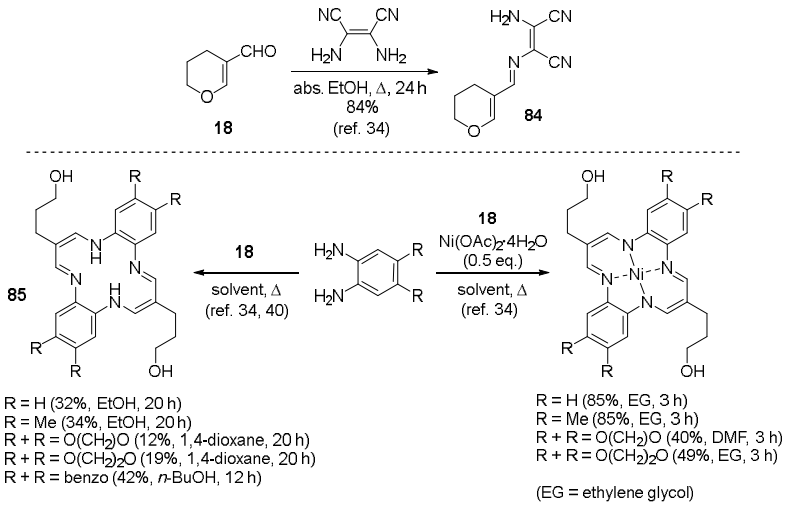
Scheme 20. Reactions of 5-trifluoroacetyl-3,4-dihydro-2*H*-pyran with amines.

However, the reaction of *o*-phenylenediamine with trifluoroacetyldihydropyran **5** gives a mixture of benzimidazole (major product) and 2-trifluoromethylbenzimidazole (minor product).[38] It is assumed that the reaction proceeds through the formation of isomeric benzodiazepines, its hydrolytic opening followed by intramolecular Michael addition and the decay of the adducts to yield the observed products. On the other hand, the reaction of 2-C-trifluoroacetyl glycal **82** with *o*-phenylenediamine as 1,4-N,N-binucleophile stops at the stage of benzodiazepine **83** (Scheme 21).[39]



Scheme 21. Reactions of β-trifluoroacetyldihydropyrans with *o*-phenylenediamine.

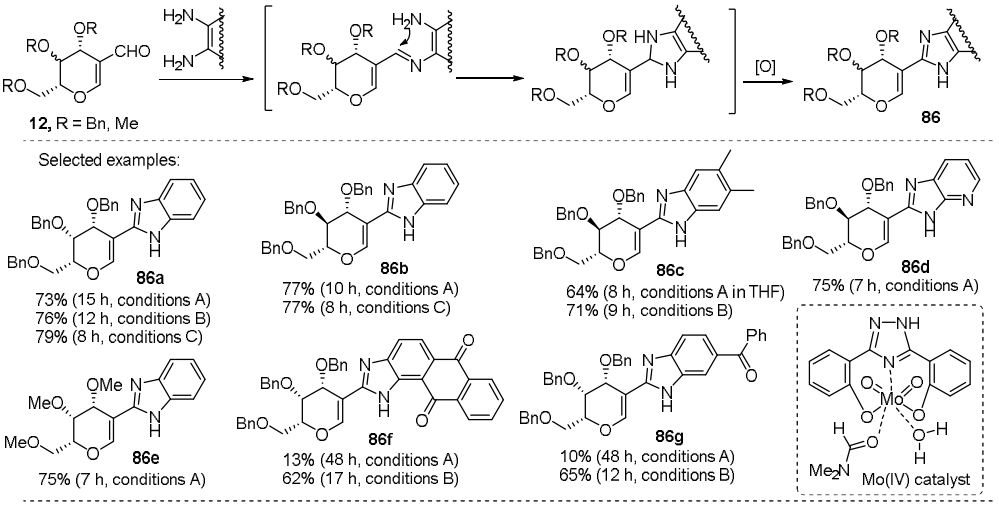
The carbaldehyde **18** reacts with 1,2-diamines in a completely different manner. For example, the reaction with diaminomaleonitrile leads to the azomethine **84** without pyran ring opening, while the reaction with *o*-phenylenediamines proceeds via ring opening with the formation of macrocyclic 5,14-dihydrodibenzo[*b,i*][1,4,8,11]tetraazacyclotetradecine **85** (Scheme 22).[34,40]



Scheme 22. Reactions of 3,4-dihydropyran-5-carbaldehyde with diaminomaleonitrile and *o*-phenylenediamines.

It should be noted that the yields of macrocycles can be significantly increased by using nickel(II) acetate due to the template effect.

However, various (2-benzimidazolyl)glycals **86** were obtained by the reaction of 2-C-formyl glycals with aromatic 1,2-diamines in the presence of atmospheric oxygen under the action of the catalytic system $VO(acac)_2$-$Ti(OBu)_4$ as a result of two successive nucleophile additions of both 1,2-diamine nitrogens on the exocyclic carbon of glycal, followed by oxidative aromatization (Scheme 23).[41] In addition to *o*-phenylenediamine, this protocol appeared suitable for its methylated analogs and pyridine-2,3-diamine, but it led to unsatisfactory results when using *o*-phenylenediamines with electron-withdrawing acyl substituents. The use of anhydrous $CeCl_3$ as co-catalyst allowed to overcome this limitation and avoid the use of stoichiometric amount of $VO(acac)_2$. The usefulness of Mo(IV) complex as catalyst was also shown in this reaction.[42]



Conditions A: 1,2-diamine (1.3 eq.), O_2 (air), $VO(acac)_2$ (100 mol. %), $Ti(OBu)_4$ (20 mol. %), $MgSO_4$, CH_2Cl_2, r.t. (ref. 41)
Conditions B: 1,2-diamine (1.3 eq.), O_2 (air), $CeCl_3$ (5 mol. %), $VO(acac)_2$ (30 mol. %), $Ti(OBu)_4$ (10 mol. %), $MgSO_4$, THF, 55 °C (ref. 41)
Conditions C: 1,2-diamine (1.1 eq.), O_2 (air), Mo(IV) catalyst (8 mol. %), $MgSO_4$, THF, r.t. (ref. 42)

Scheme 23. Oxidative synthesis of glycal-based chiral benzimidazoles from 2-formyl glycals and aromatic 1,2-diamines.

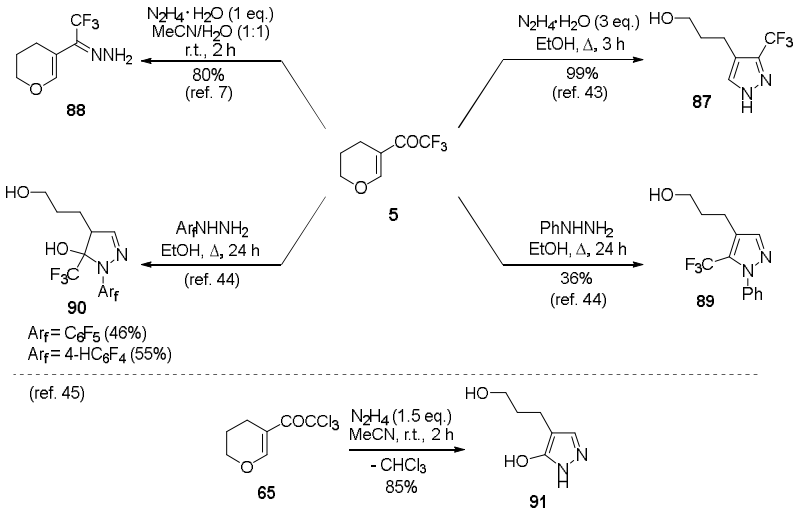
2.2.2. 1,2-N,N- and 1,2-N,O-Binucleophiles

The reactions of 5-formyl- and 5-acyl-3,4-dihydro-2*H*-pyrans with unsubstituted hydrazine, alkyl- and arylhydrazines, carbohydrazides as 1,2-N,N-binucleophiles usually result in pyrazole derivatives. In some cases, the formation of regioisomers is possible.

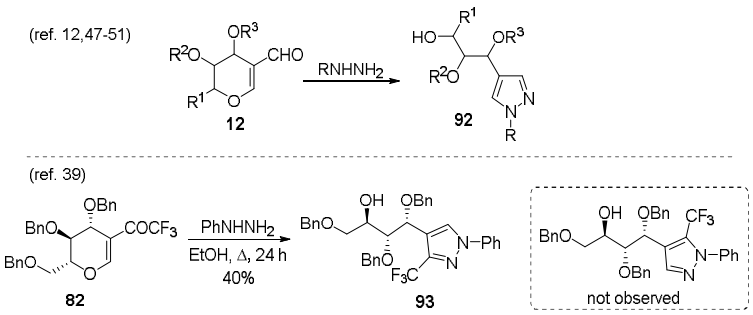
The treatment of β-trifluoroacetyldihydropyran **5** with hydrazine hydrate in boiling ethanol gives pyrazole **87** in almost quantitative yield (Scheme 24).[43] At the same time, the 1,2-addition of hydrazine to dihydropyran **5** leading to hydrazone **88** was also described.[7] The treatment of β-trifluoroacetyldihydropyran **5** with phenylhydrazine in boiling ethanol leads to 5-trifluoromethyl-substituted pyrazole **89**. The reaction with tetra- and pentafluorophenylhydrazines stops at the stage of pyrazolines **90**.[44] This fact can be explained by the different basicity of hydrazines. In the latter case, the CF_3 group also appears in the fifth position. Cyclocondensation of 5-trichloroacetyl-3,4-dihydro-2*H*-pyran **65** under the action of anhydrous hydrazine is accompanied by the cleavage of haloform-type with the formation of 5-hydroxy-1*H*-pyrazole **91**.[45] The ease of haloform cleavage is due to the greater stability of the trichloromethyl anion compared to trifluoromethyl one.[46]

Various formyl glycals **12** were introduced into this transformation in order to obtain substituted pyrazoles **92** (Scheme 25). The reaction was carried out with hydrazine hydrate, methylhydrazine and

arylhydrazines in different solvents at room temperature, under conventional heating or without solvent with microwave activation.[12,47-49] Yields are usually above 70%. It is noted that the reaction time increases from 3-6 min to 6-9 h with conventional convective heating without solvent at 90 ºC.[50] However, aryl hydrazines are less reactive compared to hydrazine.[51] In the case of trifluoroacetyl glycal **82** and phenylhydrazine, the formation of two regioisomeric pyrazoles is possible, however, only the 3-CF_3-derivative **93** was isolated. This indicates that the initial attack of the nucleophilic nitrogen atom of the amino group is directed at the carbonyl carbon atom.[39]



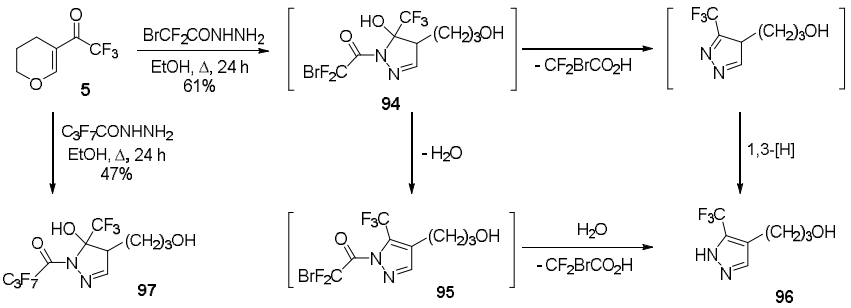
Scheme 24. Reactions of β-trihalogenacetyldihydropyrans with hydrazines.



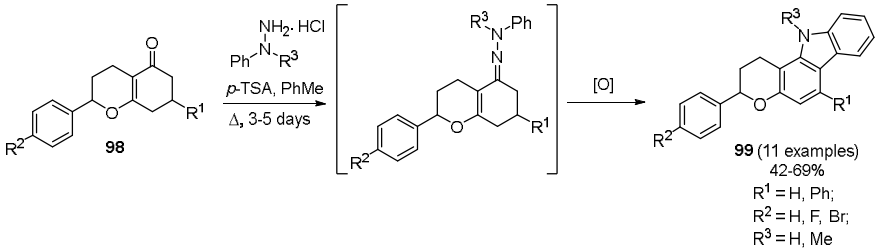
Scheme 25. Synthesis of pyrazoles from glycals and hydrazines.

N-Unsubstituted pyrazole **96** is formed in the reaction of β-trifluoroacetyldihydropyran **5** with bromodifluoroacetic acid hydrazide in boiling ethanol (Scheme 26). It can be explained either by elimination of the carboxylic acid from pyrazoline **94** and the subsequent hydrogen schift, or by dehydration of pyrazoline **94** followed by hydrolysis of *N*-acylpyrazole **95**. However, perfluorobutanoic acid hydrazide under the mentioned conditions gives pyrazoline **97**. The resulting pyrazolines can be dehydrated into pyrazoles by the action of P_2O_5 or PCl_3 in chloroform or $SOCl_2$ in the presence of pyridine.[44]

The reaction of bicyclic pyranoketones **98** with phenylhydrazine and *N*-methyl-*N*-phenylhydrazine hydrochlorides under the conditions of the Fischer indole synthesis proceeds completely differently with the formation of pyranocarbazoles **99** through the hydrazone stage (Scheme 27).[52]



Scheme 26. Reactions of β-trifluoroacetyldihydropyran with carboxylic acid hydrazides.



Scheme 27. Synthesis of 1,2,3,11-tetrahydropyrano[3,2-*a*]carbazoles.

It has been shown that the nature of the solvent and the possibility of the formation of intermolecular hydrogen bonds can significantly influence the regioselectivity of the interaction of acyldihydropyrans with methylhydrazine.[53] In aprotic dipolar solvents, the regioisomer **101a** is predominantly formed, whereas only the product **102a** was isolated in protic solvents. In non-polar toluene, the reaction almost does not proceed (Scheme 28). One of the reasons for this behavior may be a change in the sterical availability of electrophilic centers in acetyldihydropyran **100** due to the formation of an intermolecular hydrogen bond.

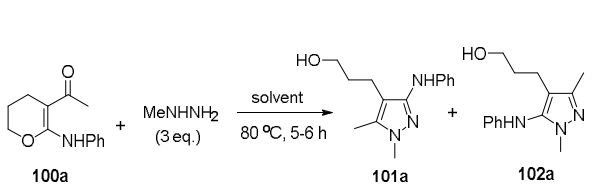
The treatment of β-trifluoroacetyldihydropyran **82** with an ethanolic solution of hydroxylamine leads to dihydroisoxazole **103**, the dehydration of which gives 5-trifluoromethylisoxazole **104**.[39] In the reaction of dichloromethylketone **105** with conc. aqueous solution of hydroxylamine, 5-hydroxy-5-dichloromethyl-4,5-dihydroisoxazole **106** was isolated. It undergoes intramolecular dehydration under the action of conc. H_2SO_4 at 30 °C with the formation of bicyclic dihydroisoxazole **107**. Besides, tetrahydropyran-3-carbonitrile **108** was obtained at a higher temperature as a result of the protonation of the isoxazole oxygen, cleavage of C–O bond and formation of the corresponding oxime. Then the carbonyl group of this oxime is attacked by the hydroxyl group of the side chain and, finally, closure of the pyran ring and dehydration lead to nitrile **108** (Scheme 29).[54]

It was shown that dihydropyrans **5** and **65** under the action of hydroxylamine hydrochloride in aqueous pyridine turn into a mixture of similar products with a predominance of the derivatives of tetrahydropyran **110** at a higher temperature (Scheme 30).[55]

The addition of hydroxylamine to a carbonyl carbon was described,[7] whereby using of hydroxylamine hydrochloride leads exclusively to oxime **111**, while when adding potassium hydroxide to hydrochloride 2-hydroxy-2-(trifluoromethyl)tetrahydro-2*H*-pyran-3-carbonitrile **112** was also isolated in 34% yield (Scheme 31). The authors explain the formation of the latter product either by conjugate addition of NH_2OH with subsequent opening of the pyran cycle, hemiketalization, isomerization to the oxime and its dehydration to the nitrile, or by addition of hydroxide anion, hemiketalization, isomerization to the aldehyde, formation of the oxime and its dehydration.

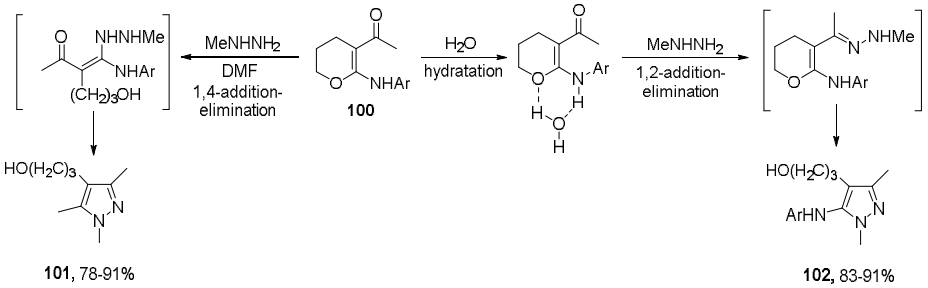
The reaction of the enaminone **100** with hydroxylamine in aqueous DMF at 100 °C leads to the regioselective formation of 3-arylaminoisoxazoles **113**. The reaction in water, ethanol or methanol proceeds much slower. At the same time, carrying out the reaction in water in the presence of KOH and

tetrabutylammonium bromide (TBAB) provides access to 5-arylaminoisoxazoles **114**. In the presence of KOH, deprotonation of hydroxylamine occurs and it reacts as O-nucleophile with attack of the β-position of the enaminone. 5-Arylamino-substituted isomers **114** are formed as a result of vinyl nucleophilic substitution S_NVin, intramolecular cyclization and dehydration. In the absence of KOH, a stronger nucleophilic center in hydroxylamine is a nitrogen atom (Scheme 32).[56]

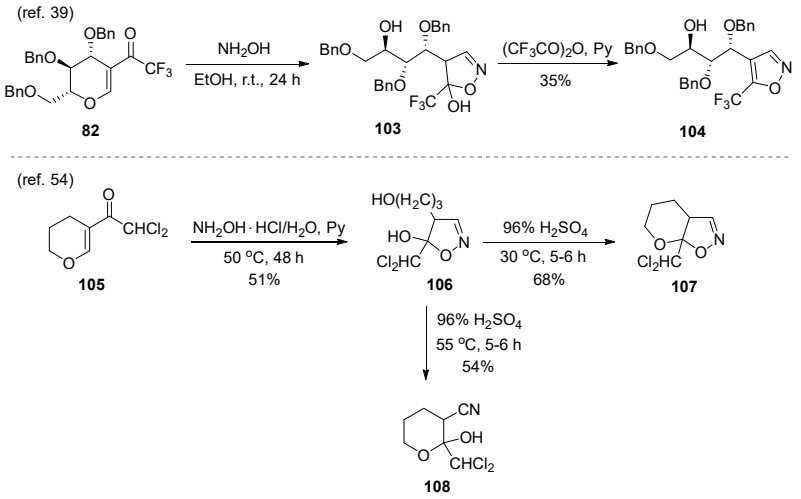


Solvent	Yield, %[a]	
	101a	**102a**
$MeNO_2$	69	12
MeCN	76	10
DMSO	81	trace
DMF	85	trace
PhMe[b]	trace	trace
H_2O[c]	0	94
MeOH	0	91
EtOH	0	87
t-BuOH	trace	84

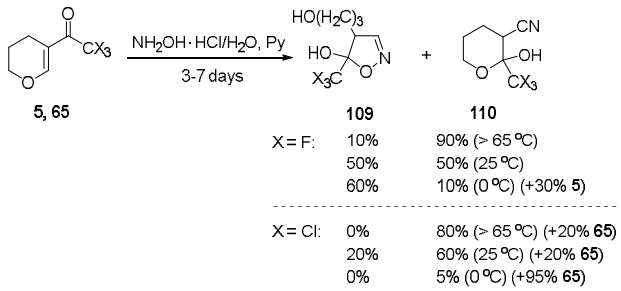
[a] Isolated yields.
[b] Recovered 84% of unreacted **100a**.
[c] In the presense of TBAB (10 mol. %).



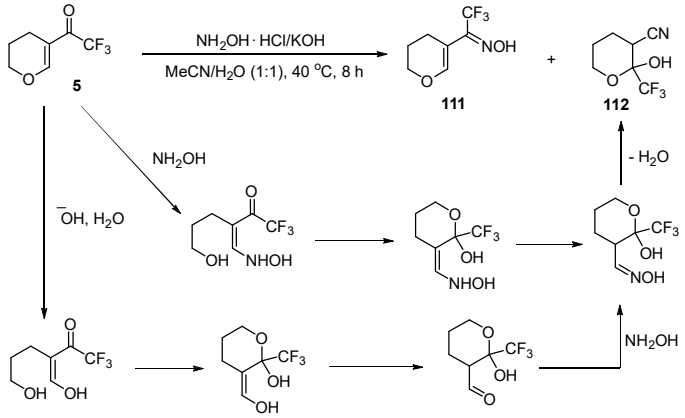
Scheme 28. The regioselectivity of the interaction of α-phenylamino-β-acetyldihydropyran with methylhydrazine.



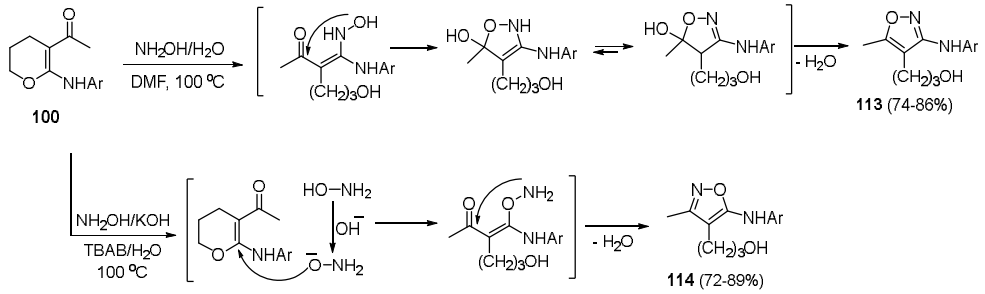
Scheme 29. Synthesis and transformations of 5-hydroxy-4,5-dihydroisoxazoles.



Scheme 30. Competition between dihydroisoxazole and tetrahydropyran formation.



Scheme 31. Reaction of β-trifluoroacetyldihydropyran with hydroxylamine.

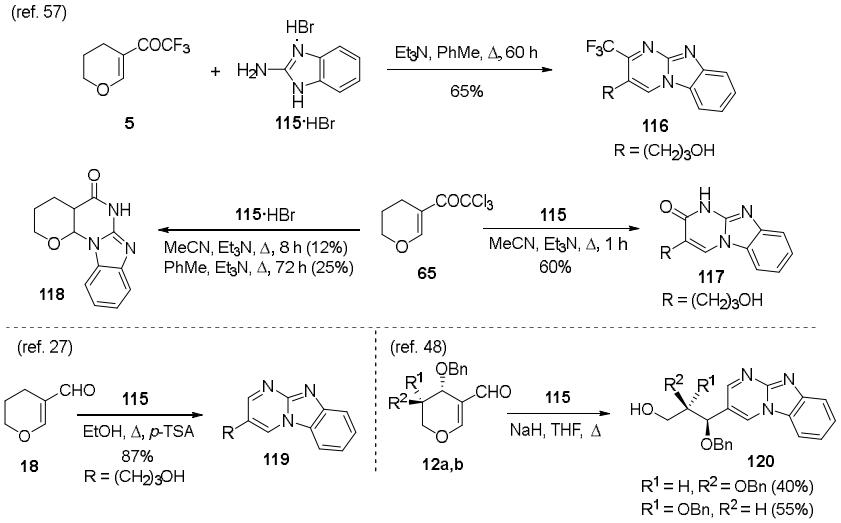


Scheme 32. Synthesis of 3- and 5-arylaminoisoxazoles.

2.2.3. 1,3-N,N-Binucleophiles

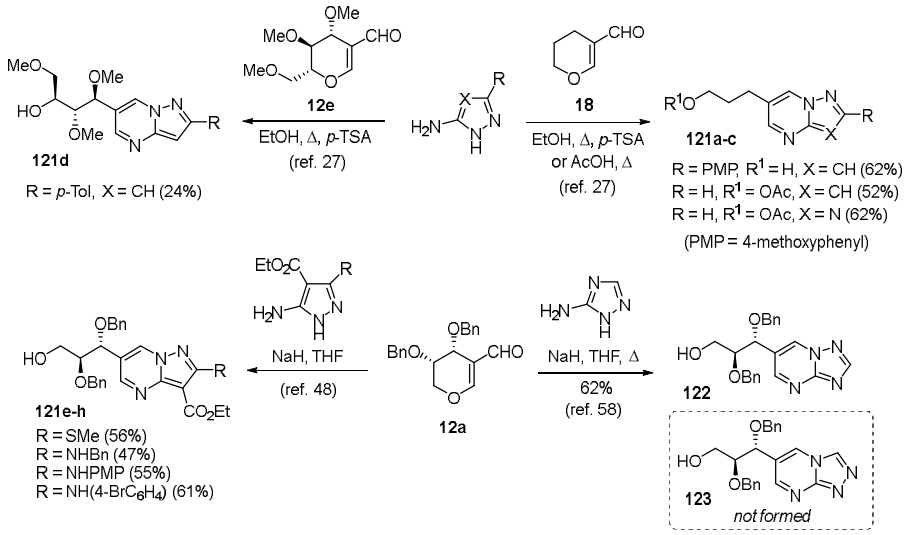
Condensation of 2-aminobenzimidazole **115** hydrobromide with β-trifluoroacetyldihydropyran **5** in boiling toluene in the presence of Et_3N leads to the regioselective formation of 2-trifluoromethylpyrimido[1,2-*a*]benzimidazole **116** (Scheme 33). The authors believe that triethylamine hydrobromide formed *in situ* facilitates dehydration at the last stage of heterocyclization.[57] The interaction of 5-trichloroacetyl-3,4-dihydro-2*H*-pyran **65** with 2-aminobenzimidazole or its hydrobromide is accompanied by cleavage of the trichloromethyl group. In the case of the free base, pyrimido[1,2-*a*]benzimidazol-2(1*H*)one **117** is formed, and only tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyrano[3,2-*e*]pyrimidinone **118** was isolated while using hydrobromide. Carbaldehyde **18** reacts with 2-aminobenzimidazole in the presence of *p*-TSA to give

benzo[4,5]imidazo[1,2-*a*]pyrimidine **119**.[27] 2-C-Formyl glycals react with 2-aminobenzimidazole in the presence of NaH in boiling THF in the same way.[48]



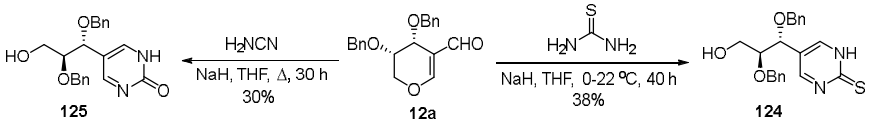
Scheme 33. Reactions of β-acyldihydropyrans with 2-aminobenzimidazole and its hydrobromide.

In the condensation of dihydropyrancarbaldehyde **18** or 2-C-formyl glycals **12a,e** with 5-aminopyrazoles, pyrazolo[1,5-*a*]pyrimidines **121** were obtained both under the catalysis of *p*-TSA and in the presence of NaH (Scheme 34). Despite the possibility of the formation of isomeric [1,2,4]triazolo[4,3-*a*]pyrimidines **122** and [1,2,4]triazolo[1,5-*a*]pyrimidines **123** only the latter have been isolated in the reaction with 3-amino-1,2,4-triazole.[27,48,58]



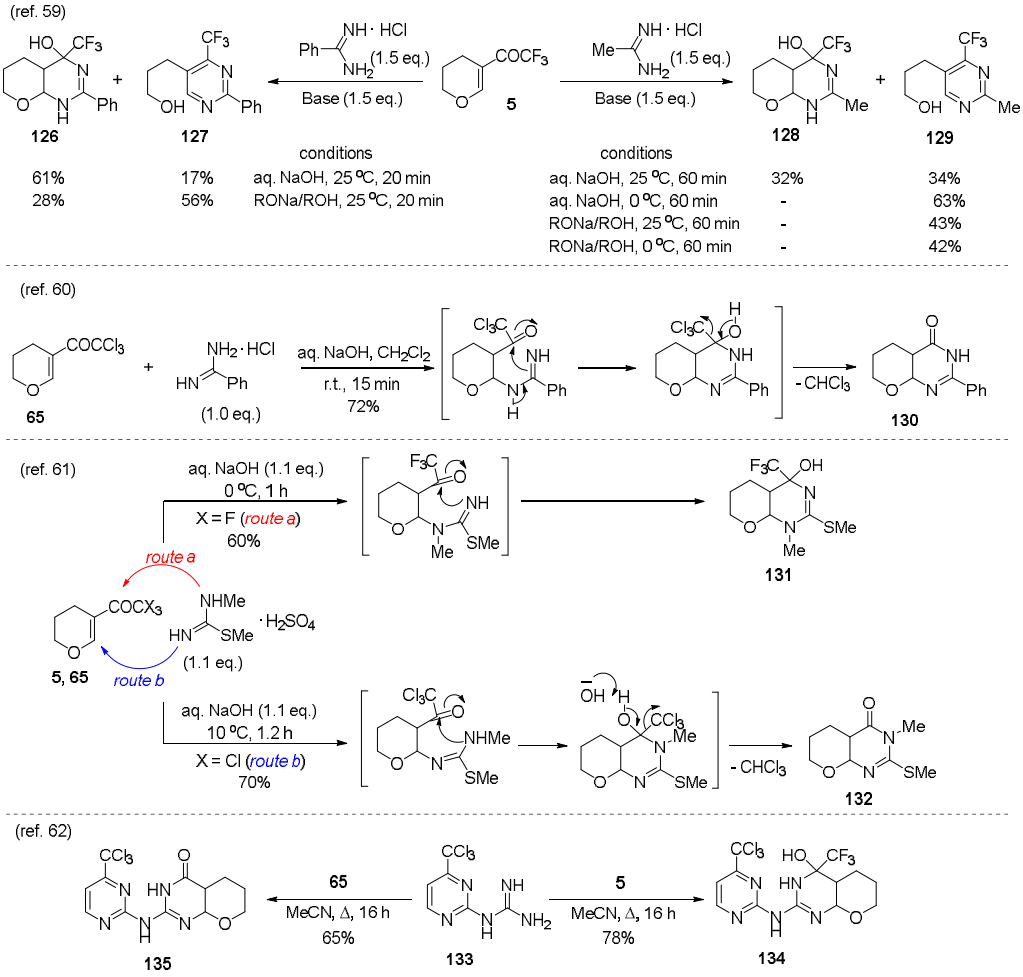
Scheme 34. Reactions of β-formyldihydropyrans with 5-aminopyrazoles and 3-amino-1,2,4-triazole.

The reaction of O-benzylated 2-formyl-*L*-arabinal **12a** with thiourea in the presence of NaH leads to pyrimidine-2-thione **124**. Pyrimidin-2-one **125** was isolated in moderate yield in the reaction of **12a** with cyanamide as a result of attack of the cyanamide amino group on the carbonyl carbon atom, hydrolysis of nitrile group to amide and intramolecular vinyl substitution S_NVin (Scheme 35).[58]



Scheme 35. Synthesis of pyrimidine-2-thiones.

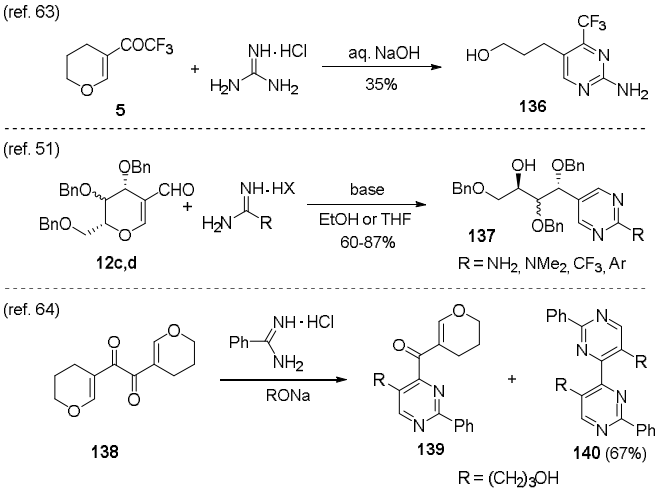
It was shown that the ratio of pyrano[2,3-*d*]pyrimidin-4-ols **126**, **127** and pyrimidines **128**, **129** as products in the reaction of amidines and trifluoroacetyldihydropyran **5** strongly depends on the conditions and the nature of the amidine (Scheme 36).



Scheme 36. Synthesis of dihydropyrimidines and tetrahydropyrimidines.

The condensation was carried out either under the action of a 1M aqueous NaOH or with an alcohol solution of sodium alkoxide, and proceeds with almost a complete predominance of aromatic pyrimidines in alcohol reaction media.[59] β-Trichloroacetyldihydropyran **65** in the reaction with benzamidine hydrochloride in aqueous NaOH gives dihydropyrimidine **130** in good yield as a result of subsequent Michael addition, intramolecular cyclization and elimination of trichloromethyl group. In fact, the last two stages of this cascade process are a type of haloform cleavage in the intramolecular version.[60] The presence of two non-equivalent N-nucleophilic centers in 1,2-dimethylisothiourea leads to the fact that in reaction with β-alkoxyvinyl trihalomethyl ketones both *N*-methyl-2-methylthiotetrahydropyrimidines and *N*-methyl-2-methylthiodihydropyrimidines may be formed primarily depending on the nature of the halogen.[61] In the case of β-trifluoroacetyldihydropyran **5**, the C-6 position is attacked by the nitrogen atom linked to the methyl group (*path a*); an attack by a nitrogen atom of an unsubstituted imino group (*path b*) is observed for trichloroacetyl derivative **65**, followed by haloform cleavage in both cases. Dihydropyrans **5**, **65** react with 4-(trichloromethyl)-2-guanidinopyrimidine **133** similarly with diastereoselective formation of dipyrimidin-2-ylamines **134**, **135** (Scheme 36).[62]

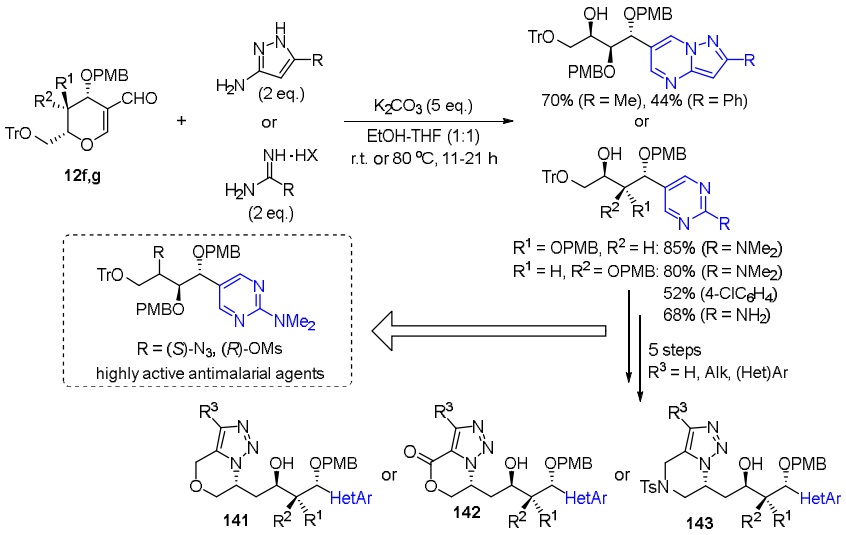
The reaction of the ketone **5** and guanidine hydrochloride in aqueous NaOH passes predictably and yields 4-trifluoromethyl-2-aminopyrimidine **136**.[63] A large series of pyrimidines **137** was obtained from 2-C-formyl glycals and salts of substituted benzamidines, guanidines and trifluoroacetimidate in the presence of a base (K_2CO_3, *n*-BuLi).[51] Both mono- **139** and bipyrimidines **140** may be obtained from 1,2-bis(3,4-dihydro-2*H*-pyran-5-yl)ethane-1,2-dione **138** and benzamidine depending on the reaction conditions (Scheme 37).[64]



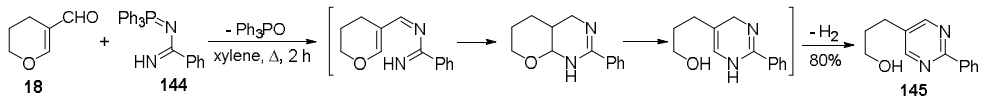
Scheme 37. Synthesis of pyrimidines from 2-C-formyl glycals or 3-acyldihydropyrans.

Lim and Park described new molecular frameworks **141-143** which contain both fused triazoles from one side of a single molecule and pyrazole, pyrimidine or pyrazolopyrimidine scaffolds from another side as two distinct privileged substructures connected with a stereochemically enriched vicinal diol linker,[49] which was further utilized for the expansion of molecular-shape diversity, from 2-C-formyl glycals and 1,3-binucleophiles on the first stage. Among described intermediates pyrimidines with excellent antimalarial potency and high selectivity were identified (Scheme 38).[65]

A special case is the condensation of the aldehyde **18** with (triphenylphosphanylidene)benzimidamide **144** to form pyrimidine **145**. The authors believe that the mechanism of the process includes the aza-Wittig reaction, the 6π-electrocyclization of the azatriene intermediate, the opening of the tetrahydropyran ring, and the dehydrogenation of dihydropyrimidine (Scheme 39).[66]



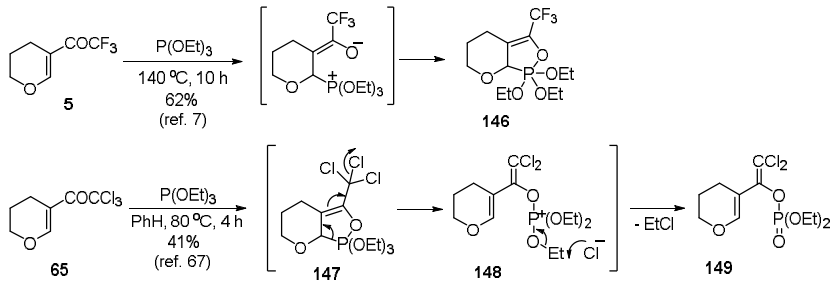
Scheme 38. Construction of molecular frameworks based on reactions of 2-C-formyl glycals and 1,3-N,N-binucleophiles.



Scheme 39. β-Formyldihydropyran in cascade aza-Wittig reaction/6π-electrocyclization.

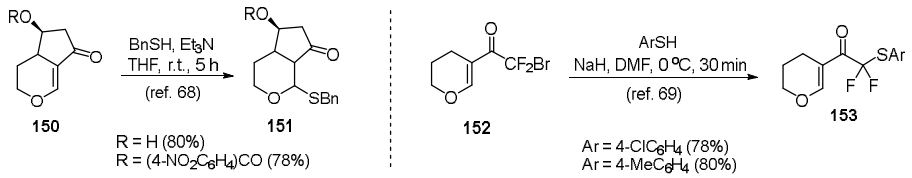
2.3. Miscellaneous nucleophiles

In the reaction of β-trifluoroacetyldihydropyran **5** with an excess of triethylphosphite, cyclophosphorane **146** is formed as a product of the formal [4+1]-cycloaddition.[7] The reaction of β-trichloroacetyldihydropyran **65** with triethylphosphite also proceeds through [1,2]oxaphospholo[3,4-*b*]pyran **147**, which is revealed by the C–P bond with the elimination of chloride ion, followed by dealkylation of formed diene **148** which in turn yields phosphate **149** (Scheme 40).[67] This transformation is related to the Perkow reaction.



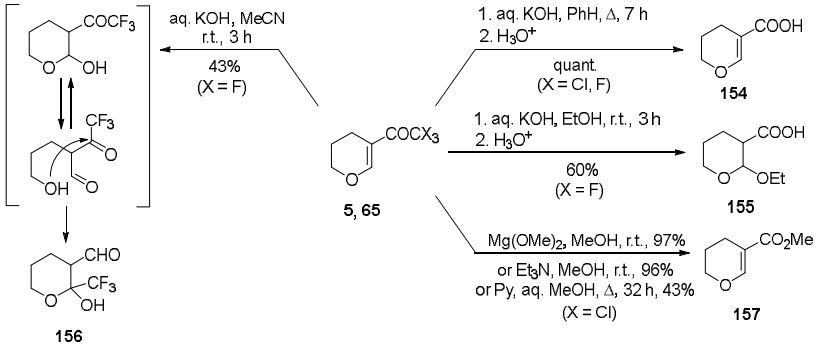
Scheme 40. Reactions of carbonyl-substituted dihydropyrans with triethylphosphite.

Bicyclic acyldihydropyrans **150** react with benzyl mercaptan in the presence of triethylamine to form Michael adducts **151**.[68] In the reaction with sodium thiophenolate, the carbon atom bonded to the bromine acts as the center for the nucleophilic attack in bromodifluoroacetyldihydropyran **152**. The reaction proceeds *via* the $S_{RN}1$ mechanism and involves the stage of one-electron transfer (Scheme 41).[69]



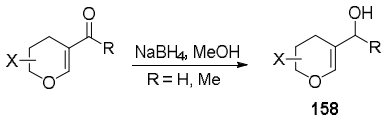
Scheme 41. Reactions of carbonyl-substituted dihydropyrans with benzyl mercaptan and thiophenols.

Heating of β-acyldihydropyranes **5**, **65** in boiling benzene in the presence of aqueous KOH leads to the product of the haloform cleavage 3,4-dihydro-2*H*-pyran-5-carboxylic acid **154**. Carrying out the reaction in ethanol in addition to haloform cleavage is accompanied by the 1,4-addition of ethanol (compound **155**). In aqueous acetonitrile, initially formed Michael adduct underwent further recyclization to form tetrahydro-2*H*-pyran-2-ol **156**.[7,70] Using of methanol as a solvent for haloform cleavage with various bases leads to methyl 3,4-dihydro-2*H*-pyran-5-carboxylate **157** (Scheme 42).[71]



Scheme 42. Products of haloform cleavage of β-acyldihydropyrans.

The reduction of β-carbonyl-substituted dihydropyrans with $NaBH_4$ in methanol selectively proceeds as 1,2-addition without using $CeCl_3$ to form the corresponding allyl alcohols **158**.[72] The 2-C-hydroxymethyl glycals obtained in this way are valuable substrates for the chemistry of carbohydrates with enormous synthetic possibilities, which were described in detail in the recent review (Scheme 43).[73]



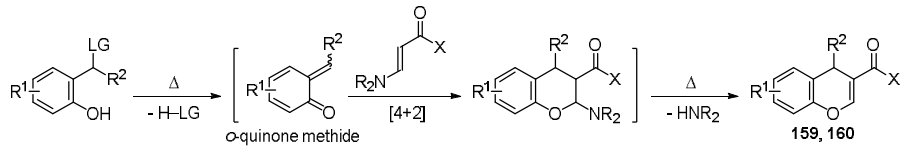
Scheme 43. Reduction of β-carbonyl-substituted dihydropyrans with $NaBH_4$.

3. Reactions of carbonyl-containing 4*H*-chromenes and their annelated analogs with nucleophiles

Despite the fact that chemical properties of 3-acyl-4*H*-chromenes seem similar in shape to those of well studied 3-formylchromones[74] and 3-acylchromones,[75] their chemistry is represented in only a few papers. At the same time, the transformations of 3-trifluoroacetyl-4*H*-chromenes and their annelated analogues have not been studied at all before our works.

Due to the low availability of 4*H*-chromenes **159** and 1*H*-benzo[*f*]chromenes **160** containing a carbonyl group in the β-position to the oxygen atom of the pyran cycle, their properties have been studied to a much lesser extent. The presence in their structure of two electron-deficient fragments (α-carbon atom of dihydropyran cycle and carbonyl carbon atom) allows to consider them as 1,3-bielectrophils, but the conjugation of the carbonyl group with the oxygen atom of the heterocycle reduces its electrophilic activity.

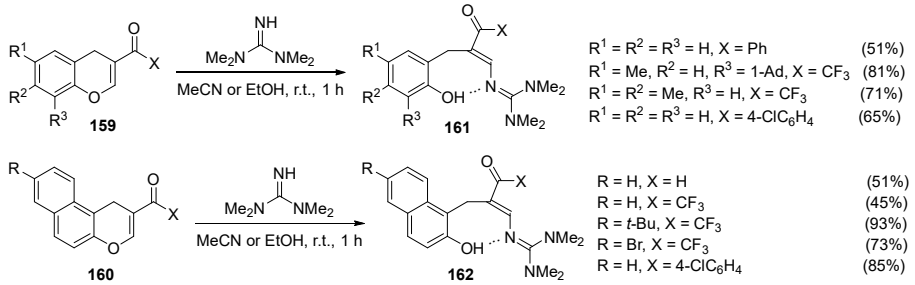
In recent years, however, a number of effective approaches to 4*H*-chromenes **159**, **160** containing formyl and various acyl (such as trifluoroacetyl, aroyl, cynnamoyl) substituents at the C-3 position have been developed[76] based on cycloaddition between highly polirized (push-pull) α-amino-β-carbonyl-substituted ethylenes and *in situ* generated *o*-quinone methides[77] with subsequent elimination of amine from intermediate 2-aminochroman (Scheme 44).



R^1 = Alk, Hal, EDG, EWG, (het)areno; R^2 = H, (het)aryl; LG = Cl, OH, NMe_2; X = H, Ar, (*E*)-(CH=CH)–Ar, CF_3

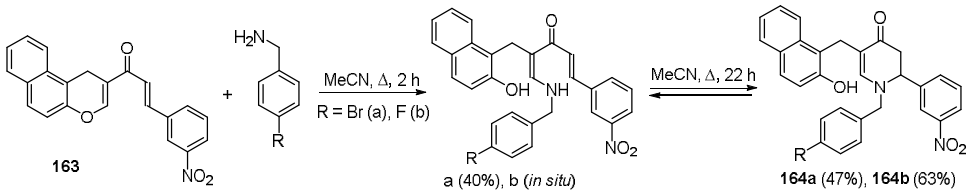
Scheme 44. Synthesis of β-carbonyl-substituted 4*H*-chromenes.

It was found that 3-formyl- and 3-acyl-4*H*-chromenes **159**, **160** react with 1,1,3,3-tetramethylguanidine (TMG) at room temperature with the opening of the pyran ring and formation of 2-(3-oxoprop-1-en-1-yl)guanidines **161**, **162** through successive aza-Michael addition and retro-oxo-Michael reaction (Scheme 45).[78] This transformation imposes a limitation on the use of TMG as an organic base in the presence of β-carbonyl-substituted 4*H*-chromenes.



Scheme 45. Reactions of 3-formyl- and 3-acyl-4*H*-chromenes with 1,1,3,3-tetramethylguanidine.

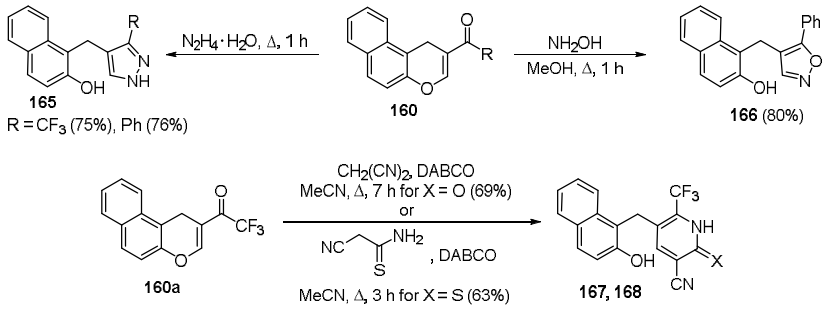
It should be noted that there is no information in the scientific periodicals about reactions of 3-acyl- and 3-formylchromenes with simple nucleophiles such as amines and ammonia, but only reaction of 2-cinnamoyl-1*H*-benzo[*f*]chromene **163** with 4-halobenzylamines, in which *N*-(4-halobenzyl)-2,3-dihydropyridin-4(1*H*)-ones **164** are formed as a result of the double Michael addition of the amine to the cross-conjugated dienaminone fragment and the opening of the pyran ring (Scheme 46).[76d]



Scheme 46. Interaction of 3-(3-nitrophenyl)-1-(1*H*-benzo[*f*]chromen-2-yl)prop-2-en-1-one with benzylamines.

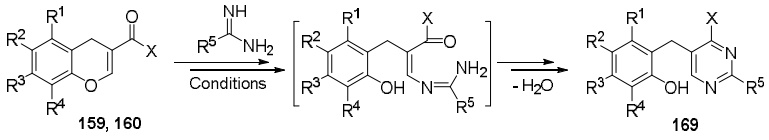
The reaction of carbonyl-substituted 4*H*-chromenes with 1,2-binucleophiles opens the way to 2-hydroxybenzylated five-membered heterocycles (Scheme 47). For example, 2-benzoyl- and

2-trifluoroacetyl-1*H*-benzo[*f*]chromens **160** in the reaction with hydrazine hydrate and hydroxylamine as 1,2-binucleophiles give substituted pyrazoles **165** and isoxazole **166** in good yields. The reaction of chromenes with methylene-active nitriles allows to obtain 2-hydroxybenzylated pyridine derivatives. In particular, the reaction of 2-trifluoroacetyl-1*H*-benzo[*f*]chromen **160a** with malononitrile or cyanothioacetamide in the presence of DABCO leads to cyanopyridone **167** and cyanopyridinethione **168** in good yields through a series of transformations involving the Dimroth rearrangement.[76a]



Scheme 47. Reactions of 2-acyl-1*H*-benzo[*f*]chromenes with binucleophiles.

The reaction of carbonyl-substituted 4*H*-chromenes with various amidines, guanidine and amidinothiourea as 1,3-binucleophiles leads to 5-(2-hydroxybenzyl)pyrimidines **169** (Scheme 48).[79]



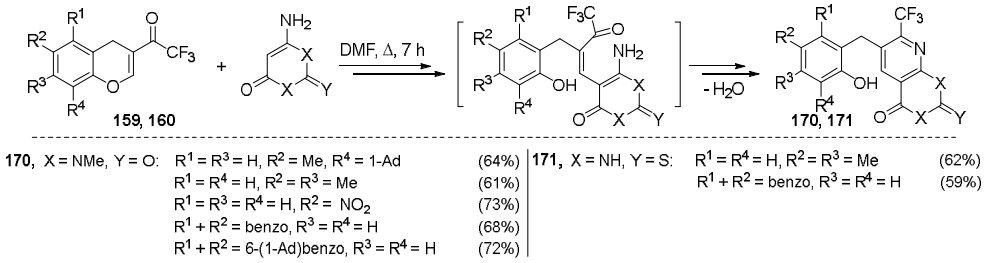
Scope

Entry		R^5	X	yield **169** (%)
1	$R^1 = R^2 = R^3 = R^4 = H$:	1-Ad	Ph	77
2		Ph	Ph	68
3	$R^1 = R^4 = H$, $R^2 = R^3 = Me$:	Ph	CF_3	65
4		4-MeC_6H_4	CF_3	68
5		1-Ad	CF_3	48
6		NH_2	CF_3	74
7	$R^1 = R^3 = H$, $R^2 = Me$, R^4 = 1-Ad:	1-Ad	CF_3	90
8		NH_2	CF_3	86
9	$R^1 + R^2$ = benzo, $R^3 = R^4 = H$:	Ph	H	74
10		Ph	4-ClC_6H_4	89
11		Ph	CF_3	64
12		NH_2	H	48
13		4-MeC_6H_4	CF_3	70
14		1-Ad	CF_3	71
15		$NH(C=S)NH_2$	CF_3	39
16		NH_2	CF_3	48

Conditions: amidine hydrochloride (1 eq.), DBU (1.1 eq.), MeCN, Δ, 6 h (entries 1-5, 7, 9-11, 13, 14)
guanidinium carbonate (2 eq.), Py, Δ, 8 h (entries 6, 8, 12, 16)
amidinothiourea (1.14 eq.), MeCN, Δ, 12 h (entry 15)

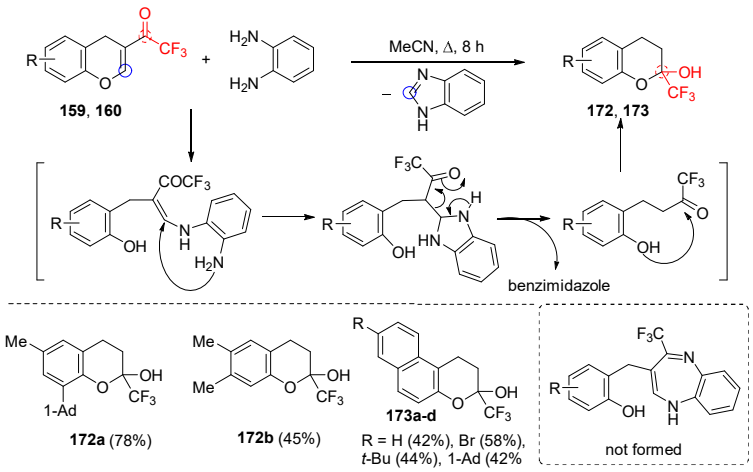
Scheme 48. Recyclization of carbonyl-substituted 4*H*-chromenes and 1*H*-benzo[*f*]chromenes by the action of amidines and guanidine.

It was found that 6-amino-1,3-dimethyluracil and 6-aminothiouracil as 1,3-C,N-binucleophils react with 3-trifluoroacetyl-4*H*-chromenes **161** to give 7-trifluoromethyl-substituted pyrido[2,3-*d*]pyrimidine-2,4-diones **162** and **163** containing 2-hydroxybenzyl or 2-hydroxynaphthalen-1-ylmethyl unit in the C-6-position (Scheme 49).[80] The reaction proceeds in regioselective manner with the bond formation between the α-carbon of 4*H*-chromens and the nucleophilic C-5-carbon of 6-amino(thio)uracils due to the Michael reaction with subsequent disclosure of the pyran ring and nucleophilic addition at the carbonyl group.



Scheme 49. Reactions of trifluoroacetylchromenes with 6-aminouracils: synthesis of pyrido[2,3-*d*]pyrimidines.

A number of unique transformations of trifluoroacetylchromenes in reactions with some other binucleophiles related to the specific nature of the trifluoroacetyl group was also discovered. One of these transformations was found in the reaction of trifluoroacetylchromenes as structural analogues of β-alkoxyvinyl trifluoromethyl ketones with *o*-phenylenediamine as a 1,4-binucleophile. Instead of trifluoromethyl-substituted benzodiazepines, 2-(trifluoromethyl)chroman-2-ols **172** and 2,3-dihydro-1*H*-benzo[*f*]chromen-3-ols **173** along with benzimidazole were isolated. In this case, trifluoroacetylchromenes play the role of 1,1-bielectrophiles rather than 1,3-bielectrophiles (Scheme 50).[81]

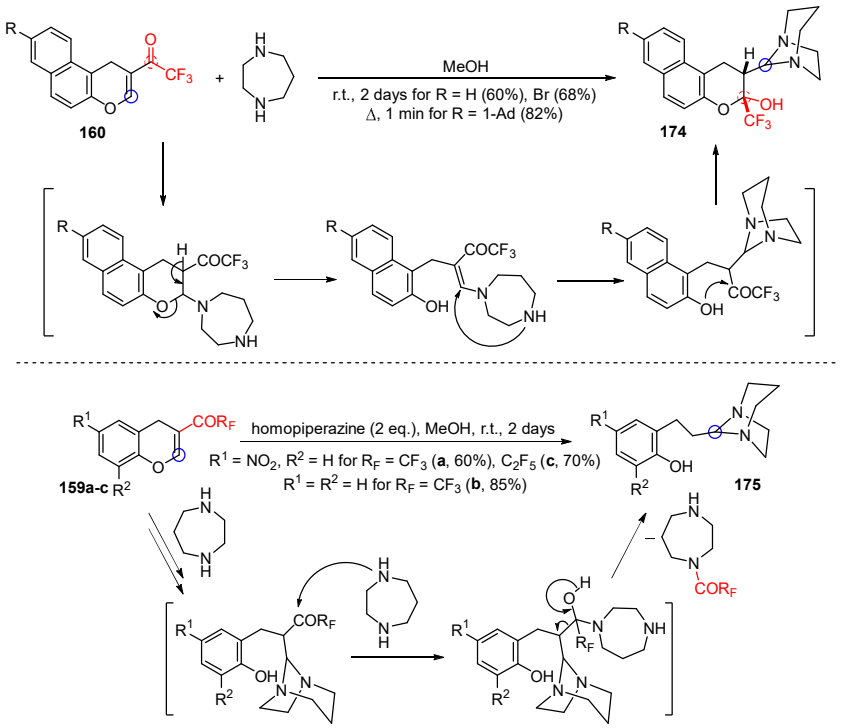


Scheme 50. Rearrangement of trifluoroacetylchromenes in trifluoromethylchromenols.

The proposed rearrangement mechanism includes the following steps: aza-Michael reaction/addition of one of the *o*-phenylenediamine amino groups to chromene, a retro-oxa-Michael reaction/opening of dihydropyran ring, repeated aza-Michael reaction, a retro-Mannich reaction accompanied by elimination of benzimidazole, and intramolecular addition at the carbonyl group (hemiketalization). In addition, it was noted that the use of ethylenediamine instead of *o*-phenylenediamine leads to a complex mixture of products

containing chromanols **172**, **173** as the main component. Reaction of chromenes **159**, **160** with *o*-aminothiophenol in the presence of air also results in chromanols in low yields along with bis(2-aminophenyl)disulfide as the product of oxidative dimerization of *o*-aminothiophenol.

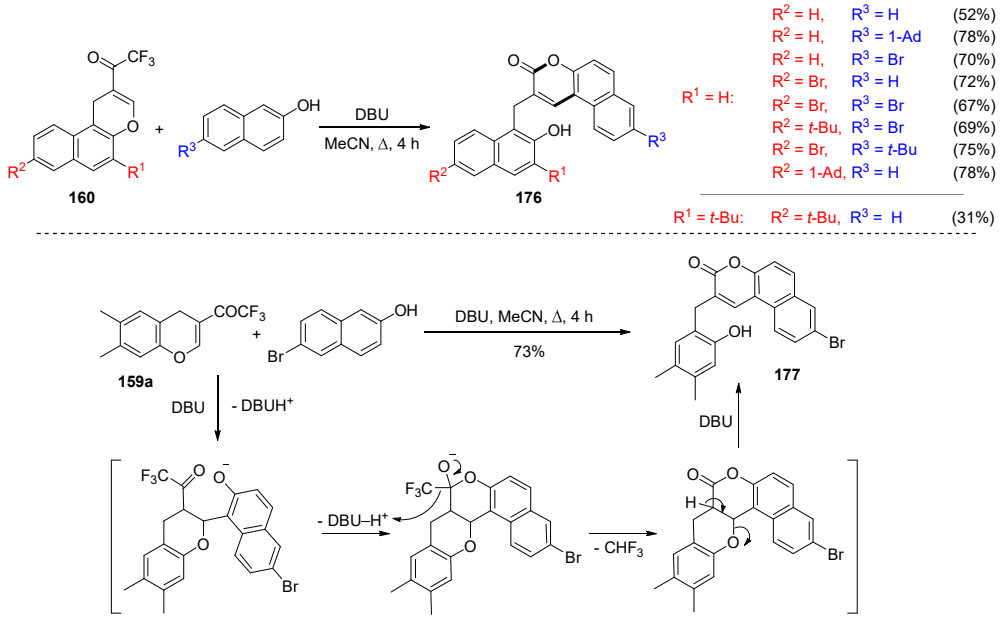
Another recently reported rearrangement was found in the reaction between equimolar amounts of benzo[*f*]chromens **160** and homopiperazine in methanol at room temperature or under short-term heating, which resulted in 3-(1,5-diazabicyclo[3.2.1]octan-8-yl)-3-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[*f*]chromen-3-ols **174** (Scheme 51).[82] Homopiperazine can also be considered as a 1,4-binucleophile, which produces two C–N bonds with the former α-carbon of benzo[*f*]chromen with the formation of a 1,5-diazabicyclo[3.2.1]octan skeleton due to the double aza-Michael addition; subsequent hemiketalization leads to the formation of the dihydropyran ring in the final product. The reaction of homopiperazine with 6-nitro-3-trifluoroacetyl-4*H*-chromene **159a** or 6,8-dibromo-3-trifluoroacetyl-4*H*-chromene **159b** in a ratio of 2:1 under similar conditions leads to 2-(2-1,5-diazabicyclo[3.2.1]octan-8-yl)ethyl)phenols **175**. Presumably, acid-type cleavage under the action of the second equivalent of homopiperazine occurs instead of intramolecular nucleophilic addition due to the reduced nucleophilicity of the hydroxyl group caused by the acceptor nature of the substituents. In the case of the use of mentioned 3-trifluoroacetyl-4*H*-chromenes and homopiperazine in an equimolar ratio, only the mixture of unreacted starting chromene and 1,5-diazabicyclo[3.2.1]octan derivative was isolated. Similar results were also obtained using 2,2,3,3,3-pentafluoro-1-(6-nitro-4*H*-chromen-3-yl)propan-1-one **159c**. To the best of our knowledge, these transformations are the first examples of 1,5-diazabicyclo[3.2.1]octan core construction using double Michael addition sequence.



Scheme 51. Reactions trifluoroacetylchromenes with homopiperazine.

The reaction of benzo[*f*]chromenes **160** with 2-naphthols as 1,3-binucleophiles in the presence of DBU leads to benzo[*f*]chromen-3-ones **176** that do not contain trifluoromethyl group (Scheme 52).[83] A similar transformation was also observed in the reaction of 6-bromonaphthalen-2-ol with

1-(6,7-dimethyl-4*H*-chromen-3-yl)-2,2,2-trifluoroethan-1-one **159a**, for which the reaction mechanism is presented below. Firts, the deprotonation of 2-naphthol by DBU takes place, the formed naphtholate then adding to trifluoroacetylchromene with ist α-carbon as a soft nucleophilic center in a Michael type reaction. Subsequent rearomatization of naphthol moiety, intramolecular ring closure followed by haloform-type elimination of trifluoromethyl group and dihydropyran ring opening lead to 3*H*-benzo[*f*]chromen-3-ones **177**.

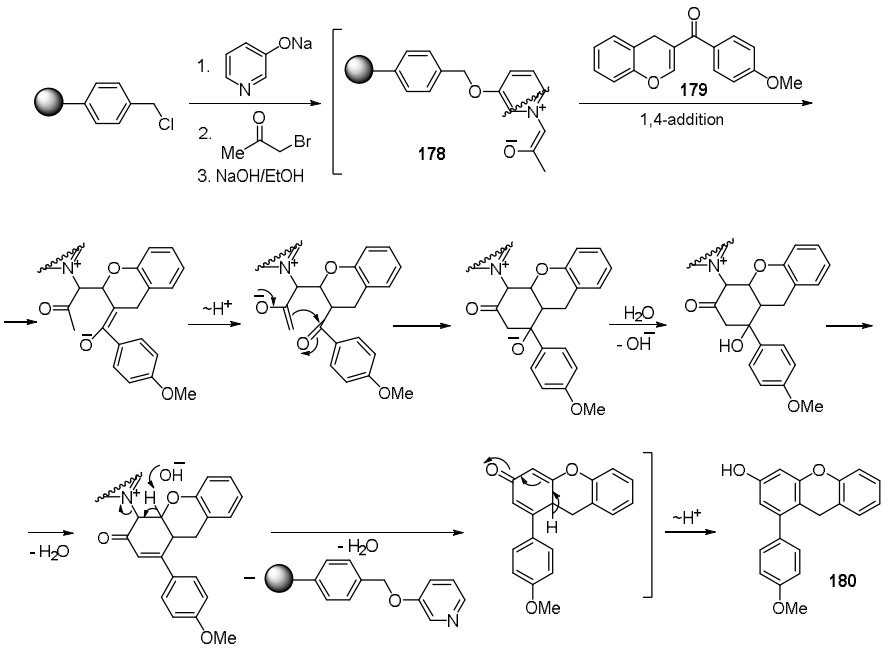


Scheme 52. Synthesis of benzo[*f*]coumarins from 2-trifluoroacetyl-1*H*-benzo[*f*]chromenes and 2-naphthols.

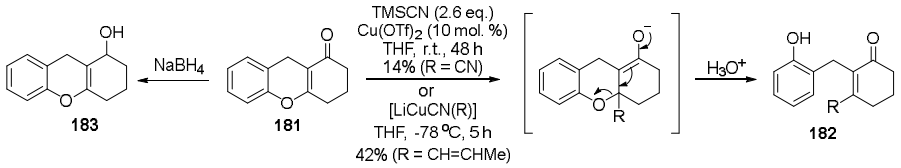
An interesting example is the solid-phase synthesis of 9*H*-xanthene **180** starting from the polymer-supported 3-hydroxypyridine which is further quaternized with bromoacetone. Under the action of base on the prepared pyridinium salt, ylide **178** is generated which underwent the Michael addition to give 3-(4-methoxybenzoyl)-4*H*-chromene **179** (Scheme 53). Subsequent intramolecular aldol condensation and cleavage of the hydroxypyridine fragment lead to 9*H*-xanthene **180**.[84]

Tetrahydroxantenones can be considered as condensed 3-acyl-4*H*-chromenes, however, as a rule, publications are devoted to their synthesis in various modifications without studying their synthetic potential in further transformations. It was described only a few examples of the reactions of tetrahydroxantenones as Michael acceptors. When treating tetrahydroxantenone **181** with trimethylsilyl cyanide (TMSCN) in the presence of $Cu(OTf)_2$, a 1,4-addition of cyanide ion occurs and then the opening of the oxygen-containing cycle. Under the action of cuprate reagent, it is possible to introduce the propenyl fragment preapare cyclohexenone **182** in moderate yield. At the same time, the reduction of tetrahydroxantenone with sodium borohydride proceeds as 1,2-addition with preservation of the xanthene system (compound **183**) (Scheme 54).[85]

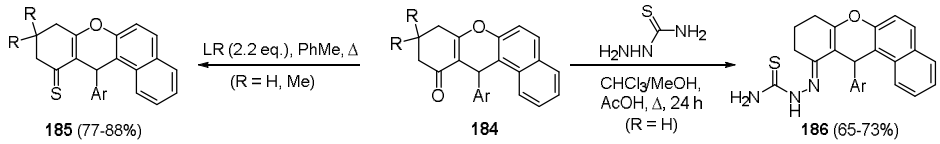
12-Aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-ones **184** react with Lawesson's reagent in boiling toluene to form the corresponding xanthen-11-thiones **185**.[86] It should be noted that this transformation failed under the action of P_2S_5. The reaction with thiosemicarbazide also proceeds as 1,2-addition with the formation of thiosemicarbazones **186** (Scheme 55).[87]



Scheme 53. Solid-phase synthesis of 1-(4-methoxyphenyl)-9*H*-xanthen-3-ol.



Scheme 54. Nucleophilic addition to tetrahydroxantenone.



Scheme 55. 1,2-Addition reactions of tetrahydrobenzo[*a*]xanthen-11-ones.

4. Conclusion

As summarized in this chapter, β-carbonyl-substituted dihydropyrans and 2-C-formyl/2-C-acyl glycals that are particulary significant for carbohydrate chemistry, are highly reactive electrophiles. The presence of the 1-oxabutadiene unit in their structure determines their ability to react with nucleophiles both by conjugate addition to the α-carbon atom of the pyran ring, and to the carbonyl group. The reaction pathway with nucleophiles primarily depends on the nature of the substituent at the carbonyl group. In the case of 3,4-dihydropyran-5-carbaldehydes, as a rule the 1,2-addition products are formed as main products, whereas for more polarized 5-trifluoroacetyl-3,4-dihydropyrans, the formation of conjugate addition products predominantly takes place. Moreover, these Michael adducts tend to reactions accompanied by the pyran ring opening. However, the formation of a mixture of isomers is often observed. Reactions involving 5-trichloroacetyl- and more rarely 5-trifluoroacetyl-3,4-dihydropyrans in some cases are accompanied by haloform-type cleavage. The important difference between trifluoroacetyldihydropyrans and their non-

fluorinated analogues is their ability to form products with stable hemiketal fragment [–C(CF_3)(OH)–O–] in their structure. Both nucleophilic centers can be involved in the reactions of dihydropyrans with binucleophiles, which lead to the formation of carbo- and heterocyclic compounds. In general, the steric factor favors the nucleophilic addition to the carbonyl group.

At the same time, 4*H*-chromenes and their benzo-fused analogues containing a carbonyl group in the β-position with respect to the oxygen atom remain poorly studied. In addition, known transformations are fragmentary and cover a rather narrow range of nucleophiles. This does not allow to have an overall picture of their reactivity and *a priori* predict the direction of the initial nucleophilic attack with sufficient accuracy. However, this also allows us to hope to see new works in the near future describing the unique reactions of this interesting class of compounds. This line of research, as well as the creation of new methods for obtaining and studying transformations of other six-membered heterocycles, are actively developing in our research group.[88]

Acknowledgement

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References

1. Sun, Y.; Tian, L.; Huang, J.; Ma, H.-Y.; Zheng, Z.; Lv, A-L.; Yasukawa, K.; Pei, Y.-H. *Org. Lett.*, **2008**, *10*, 393-396.
2. Connolly, J. D.; Dagli, S.; Haque, M. E. *J. Indian Chem. Soc*., **2003**, *80*, 1169-1173.
3. Cheenpracha, S.; Ritthiwigrom, T.; Laphookhieo, S. *J. Nat. Prod*., **2013**, *76*, 723-726.
4. Tan, S.-J.; Lim, J.-L.; Low, Y.-Y.; Sim, K.-S.; Lim, S.-H.; Kam, T.-S. *J. Nat. Prod*., **2014**, *77*, 2068-2080.
5. Kam, T.-S.; Choo, Y.-M. *J. Nat. Prod*., **2004**, *67*, 547-552.
6. (a) Elderfield, R. C.; Gilman, R. E. *Phytochemistry*, **1972**, *11*, 339-343. (b) Yang, J.; Wearing, X. Z.; Le Quesne, P. W.; Deschamps, J. R.; Cook, J. M. *J. Nat. Prod*., **2008**, *71*, 1431-1440.
7. Zhu, S.; Xu, G.; Qin, C.; Chu, Q.; Xu, Y. *Monatsh. Chem.* **1999**, *130*, 671-680.
8. Desrosiers, J.-N.; Kelly, C. B.; Fandrick, D. R.; Nummy, L.; Campbell, S. J.; Wei, X.; Sarvestani, M.; Lee, H.; Sienkiewicz, A.; Sanyal, S.; Zeng, X.; Grinberg, N.; Ma, S.; Song, J. J.; Senanayake, C. H. *Org. Lett.* **2014**, *16*, 1724-1727.
9. Mamat, C.; Pundt, T.; Dang, T. H. T.; Klassen, R.; Reinke, H.; Köckerling, M.; Langer, P. *Eur. J. Org. Chem.* **2008**, 492-502.
10. Kondratov, I. S.; Dolovanyuk, V. G.; Tolmachova, N. A.; Gerus, I. I.; Bergander, K.; Fröhlich, R.; Haufe, G. *Org. Biomol. Chem*. **2012**, *10*, 8778-8785.
11. Bari, A.; Milicevic, S.; Feist, H.; Michalik, D.; Michalik, M.; Peseke, K. *Synthesis* **2005**, *2005*, 2758-2764.
12. Rudloff, I.; Peseke, K.; Reinke, H. *J. Prakt. Chem.* **1998**, *340*, 334-340.
13. Bari, A. *Z. Naturforsch, B: J. Chem. Sci.* **2014**, *69b*, 98-102.
14. Rudloff, I.; Michalik, M.; Montero, A.; Peseke, K. *Synthesis* **2001**, *2001*, 1686-1692.
15. Appendino, G.; Cravotto, G.; Tagliapietra, S.; Nano, G. M.; Palmisano, G. *Helv. Chim. Acta.* **1990**, *73*, 1865-1878.
16. (a) Sagar, R.; Park, J.; Koh, M.; Park, S. B. *J. Org. Chem.* **2009**, *74*, 2171-2174. (b) Kumari, P.; Gupta, S.; Narayana, C.; Ahmad, S.; Vishnoi, N.; Singh, S. Sagar, R. *New J. Chem.* **2018**, *42*, 13985-13997.
17. Kumari, P.; Narayana, C.; Dubey, S.; Gupta, A.; Sagar, R. *Org. Biomol. Chem.* **2018**, *16*, 2049-2059.
18. Zhu, S.; Jin, G.; Jiang, H. *Can. J. Chem.* **2005**, *83*, 2127-2131.
19. Zhu, S.; Qin, C.; Xu, G.; Chu, Q.; Huang, Q. *J. Fluorine Chem.* **1999**, *99*, 141-144.
20. Mellor, J. M.; Reid, G.; El-Sagheer, A. H.; El-Tamany, El-S. H. *Tetrahedron* **2000**, *56*, 10039-10055.

21. Coles, S. J.; Mellor, J. M.; El-Sagheer, A. H.; Salem, E. El-D. M.; Metwally, R. N. *Tetrahedron* **2000**, *56*, 10057-10066.
22. Mellor, J. M.; El-Sagheer, A. H.; Salem, E. El-D. M. *Tetrahedron Lett.* **2000**, *41*, 7383-7386.
23. Denmark, S. E.; Habermas, K. L.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 168-194.
24. Harrington, P. E.; Li, L.; Tius, M. A. *J. Org. Chem.* **1999**, *64*, 4025-4029.
25. Posner, G. H.; Babiak, K. A.; Loomis, G. L.; Frazee, W. J.; Mittal, R. D.; Karle, I. L. *J. Am. Chem. Soc.* **1980**, *102*, 7498-7505.
26. Weinges, K.; Iatridou, H.; Dietz, U. *Liebigs Ann. Chem.* **1991**, 893-902.
27. Bharate, S.; Mahajan, T.; Gole, Y.; Nambiar, M.; Matan, T.; Kulkarni-Almeida, A.; Balachandran, S.; Junjappa, H.; Balakrishnan, A.; Vishwakarma, R. *Bioorg. Med. Chem.* **2008**, *16*, 7167-7176.
28. Montero, A.; Feist, H.; Michalik, M.; Quincoces, J.; Peseke, K. *Synthesis* **2002**, *2002*, 664-668.
29. Potthoff, B.; Breitmaier, E. *Chem. Ber.* **1986**, *119*, 3204-3207.
30. Zanatta, N.; Lopes, E.; Fantinel, L.; Bonacorso, H.; Martins, M. *Synthesis* **2002**, *2002*, 2404-2408.
31. Zanatta, N.; da Silva, F. M.; da Rosa, L. S.; Jank, L.; Bonacorso, H. G.; Martins, M. A. P. *Tetrahedron Lett.* **2007**, *48*, 6531-6534.
32. Li, M.; Tang, C.; Yang, J.; Gu, Y. *Chem. Commun.* **2011**, *47*, 4529-4531.
33. Liu, C.; Taheri, A.; Lai, B.; Gu, Y. *Catal. Sci. Technol.* **2015**, *5*, 234-245.
34. Hanke, R.; Breitmaier, E. *Chem. Ber.* **1982**, *115*, 1657-1661.
35. Walizei, G. H.; Breitmaier, E. *Synthesis* **1989**, *1989*, 337-340.
36. Lin, Z.-P.; Wong, F. F.; Chen, Y.-B.; Lin, C.-H.; Hsieh, M.-T.; Lien, J.-C.; Chou, Y.-H.; Lin, H.-C. *Tetrahedron* **2013**, *69*, 3991-3999.
37. Chu, Q.; Song, L.; Jin, G.; Zhu, S. *J. Fluorine Chem.* **2001**, *108*, 51-56.
38. Chu, Q.; Wang, Y.; Zhu, S. *Synth. Commun.* **2000**, *30*, 677-687.
39. Mamat, C.; Hein, M.; Miethchen, R. *Carbohydr. Res.* **2006**, *341*, 1758-1763.
40. Kaźmierska, A.; Gryl, M.; Stadnicka, K.; Sieroń, L.; Eilmes, A.; Nowak, J.; Matković, M.; Radic-Stojković, M.; Piantanida, I.; Eilmes, J. *Tetrahedron* **2015**, *71*, 4163-4173.
41. Maiti, D. K.; Halder, S.; Pandit, P.; Chatterjee, N.; Joarder, D. D.; Pramanik, N.; Saima, Y.; Patra, A.; Maiti, P. K. *J. Org. Chem.* **2009**, *74*, 8086-8097.
42. Pramanik, N.; Sarkar, S.; Roy, D.; Debnath, S.; Ghosh, S.; Khamarui, S.; Maiti, D. K. *RSC Adv.* **2015**, *5*, 101959-101964.
43. Jones, B. G.; Branch, S. K.; Thompson, A. S.; Threadgill, M. D. *J. Chem. Soc., Perkin Trans.* **1996**, 2685-2691.
44. Song, L.; Chu, Q.; Zhu, S. *J. Fluorine Chem.* **2001**, *107*, 107-112.
45. Flores, A. F. C.; Zanatta, N.; Rosa, A.; Brondani, S.; Martins, M. A. P. *Tetrahedron Lett.* **2002**, *43*, 5005-5008.
46. Chambers, R. D. *Fluorine in Organic Chemistry*, Blackwell Publishing Ltd., **2004**.
47. Kim, Y.; Oh, K .; Song, H .; Lee, D.-S .; Park, S. B. *J. Med. Chem.* **2013**, *56*, 7100-7109.
48. Bari, A .; Feist, H .; Michalik, D .; Michalik, M .; Peseke, K. *Synthesis* **2004**, *2004*, 2863-2868.
49. Lim, D.; Park, S. B. *Chem. Eur. J.* **2013**, *19*, 7100-7108.
50. Yadav, J. S.; Reddy, V. V. S.; Satheesh, G.; Lakshmi, P. N.; Kumar, S. K.; Kunwar, A. C. *Tetrahedron Lett.* **2004**, *45*, 8587-8590.
51. Sagar, R.; Kim, M.-J.; Park, S. B. *Tetrahedron Lett.* **2008**, *49*, 5080-5083.
52. Kotha, S.; Ali, R.; Saifuddin, M. *Tetrahedron* **2015**, *71*, 9003-9011.
53. Xiang, D.; Bi, X.; Liao, P.; Fang, G.; Wang, Z.; Xin, X.; Dong, D. *RSC Adv.* **2013**, *3*, 386-389.
54. Martins, M. A. P.; Zoch, A. N.; Flores, A. F. C.; Clar, G.; Zanatta, N. *J. Heterocycl. Chem.* **1995**, *32*, 739-741.
55. Colla, A.; Martins, M. A. P.; Clar, G.; Krimmer, S.; Fischer, P. *Synthesis* **1991**, *1991*, 483-486.
56. Xiang, D.; Xin, X.; Liu, X.; Zhang, R.; Yang, J.; Dong, D. *Org. Lett.* **2012**, *14*, 644-647.
57. Zanatta, N.; Amaral, S. S.; Esteves-Souza, A.; Echevarria, A.; Brondani, P. B.; Flores, D. C.; Bonacorso, H. G.; Flores, A. F. C.; Martins, M. A. P. *Synthesis* **2006**, *2006*, 2305-2312.
58. Bari, A.; Feist, H.; Michalik, M.; Peseke, K. *Molecules* **2005**, 837-842.

59. Zanatta, N.; Fagundes, M. B.; Ellensohn, R.; Marques, M.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **1998**, *35*, 451-455.
60. Zanatta, N.; Fantinel, L.; Lourega, R. V.; Bonacorso, H. G.; Martins, M. A. P. *Synthesis* **2008**, *2008*, 358-362.
61. Zanatta, N.; Madruga, C. C.; Marisco, P. C.; da Rosa, L. S.; da Silva, F. M.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **2010**, *47*, 1234-1239.
62. Zanatta, N.; Lopes, E. C. S.; Fantinel, L.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **2002**, *39*, 943-947.
63. Zanatta, N.; Cortelini, M. de F. M.; Carpes, M. J. S.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **1997**, *34*, 509-513.
64. Effenberger, F.; Barthelmess, I. *J. Heterocycl. Chem.* **1995**, *32*, 599-602.
65. Lee, S.; Lim, D.; Lee, E.; Lee, N.; Lee, H.-G.; Cechetto, J.; Liuzzi, M.; Freitas Jr., L. H.; Song, J. S.; Bae, M. A.; Oh, S.; Ayong, L.; Park, S. B. *J. Med. Chem.* **2014**, *57*, 7425-7434.
66. Rossi, E.; Abbiati, G.; Pini, E. *Synlett* **1999**, 1265-1267.
67. Tarasenko, K. V.; Gerus, I. I.; Kukhar, V. P. *J. Fluorine Chem.* **2007**, *128*, 1264-1270.
68. Weinges, K.; Eltz, H. v. d.; Hartz, G. *Liebigs Ann. Chem.* **1982**, 872-883.
69. Fang, X.; Chen, Y.; He, D.; Yang, X.; Wu, F. *J. Fluorine Chem.* **2008**, *129*, 1167-1172.
70. Hojo, M.; Masuda, R.; Sakaguchi, S.; Takagawa, M. *Synthesis* **1986**, *1986*, 1016-1017.
71. (a) Trost, B. M.; Balkovec, J. M.; Mao, M. K.-T. *J. Am. Chem. Soc.* **1986**, *108*, 4974-4983. (b) Madruga, C. da C.; Clerici, E.; Martins, M. A. P.; Zanatta, N. *J. Heterocycl. Chem.* **1995**, *32*, 735-738.
72. (a) Kam, T.-S.; Iek, I.-H.; Choo, Y.-M. *Phytochemistry* **1999**, *51*, 839-844. (b) Kumaran, E.; Santhi, M.; Balasubramanian, K. K.; Bhagavathy, S. *Carbohydr. Res.* **2011**, *346*, 1654-1661. (c) Reddy, Y. S.; Kancharla, P. K.; Roy, R.; Vankar, Y. D. *Org. Biomol. Chem.* **2012**, *10*, 2760-2773.
73. Ramesh, N. G. *Eur. J. Org. Chem.* **2014**, 689-707.
74. For recent reviews on 3-formylchromone chemistry, see: (a) Ibrahim, M. A.; Ali, T. El-S.; El-Gohary, N. M.; El-Kazak, A. M. *Eur. J. Chem.* **2013**, *4*, 311-328; (b) Ghosh, C. K.; Patra, A. *J. Heterocycl. Chem.* **2008**, *45*, 1529-1547; (c) Plaskon, A. S.; Grygorenko, O. O.; Ryabukhin, S. V. *Tetrahedron* **2012**, *68*, 2743-2757.
75. For some important examples, see: (a) Kotjarov, A.; Igrashev, R. A.; Iaroshenko, V. O.; Sevenard, D. V.; Sosnovskikh, V. Ya. *Synthesis* **2009**, *2009*, 3233-3242. (b) Sosnovskikh, V. Ya.; Moshkin, V. S.; Kodess, I. M. *Tetrahedron* **2008**, *64*, 7877-7889. (c) Iaroshenko, V. O.; Savych, I.; Villinger, A.; Sosnovskikh, V. Ya.; Langer, P. *Org. Biomol. Chem.* **2012**, *10*, 9344-9348. (d) Savych, I.; Ejaz, S. A.; Shah, S. J. A.; Iaroshenko, V. O.; Villinger, A.; Sosnovskikh, V. Ya.; Iqbal, J.; Abbasi, A.; Langer, P. *Eur. J. Org. Chem.* **2017**, 186-202.
76. (a) Lukashenko, A. V.; Osyanin, V. A.; Osipov, D. V.; Klimochkin, Yu. N. *J. Org. Chem.* **2017**, *82*, 1517-1528. (b) Lukashenko, A. V.; Osyanin, V. A.; Osipov, D. V.; Klimochkin, Yu. N. *Chem. Heterocycl. Compd.* **2016**, *52*, 711-715. (c) Lukashenko, A. V.; Osipov, D. V.; Osyanin, V. A.; Klimochkin, Yu. N. *Russ. J. Org. Chem.* **2016**, *52*, 1817-1821. (d) Korzhenko, K. S.; Osipov, D.V.; Osyanin, V. A.; Krasnikov, P. E.; Klimochkin, Yu. N. *Chem. Heterocycl. Compd.* **2018**, *54*, 940-945.
77. Osipov, D. V.; Osyanin, V. A.; Klimochkin, Yu. N. *Russ. Chem. Rev.* **2017**, *86*, 625-687.
78. Osyanin, V. A.; Popova, Yu. V.; Osipov, D. V.; Klimochkin, Yu. N. *Chem. Heterocycl. Compd.* **2016**, *52*, 809-813.
79. Popova, Yu. V.; Sakhnenko, D. V.; Arbuzova, I. V.; Osyanin, V. A.; Osipov, D. V.; Klimochkin, Yu. N. *Chem. Heterocycl. Compd.* **2016**, *52*, 803-808.
80. Popova, Yu. V.; Osipov, D. V.; Osyanin, V. A.; Klimochkin, Yu. N. *Russ. J. Org. Chem.* **2017**, *53*, 599-603.
81. Osyanin, V. A.; Popova, Yu. V.; Sakhnenko, D. V.; Osipov, D. V.; Klimochkin, Yu. N. *Chem. Heterocycl. Compd.* **2016**, *52*, 559-563.
82. Osipov, D. V.; Osyanin, V. A.; Klimochkin, Yu. N. *J. Fluorine Chem.* **2017**, *202*, 71-75.
83. Osyanin, V. A.; Osipov, D. V.; Popova, Yu. V.; Semenova, I. A.; Klimochkin, Yu. N. *Chem. Heterocycl. Compd.* **2016**, *52*, 1012-1016.
84. Katritzky, A. R.; Belyakov, S. A.; Fang, Y.; Kiely, J. S. *Tetrahedron Lett.* **1998**, *39*, 8051-8054.

85. Linsenmeier, A. M.; Bräse, S. *Eur. J. Org. Chem.* **2012**, 6455-6459.
86. Khurana, J. M.; Magoo, D.; Aggarwal, K.; Aggarwal, N.; Kumar, R.; Srivastava, C. *Eur. J. Med. Chem.* **2012**, *58*, 470-477
87. Sethukumar, A.; Vithya, V.; Kumar, C. U.; Prakasam, B. A. *J. Mol. Struct.* **2012**, *1008*, 8-16.
88. For more recent selected examples of our researches, see: (a) Osipov, D. V.; Osyanin, V. A.; Khaysanova, G. D.; Masterova, E. R.; Krasnikov, P. E.; Klimochkin, Yu. N. *J. Org. Chem.* **2018**, *83*, 4775-4785. (b) Osipov, D. V.; Osyanin, V. A.; Voskressensky, L. G.; Klimochkin, Yu. N. *Synthesis* **2017**, *49*, 2286-2296. (c) Shiryaev, V. A.; Radchenko, E. V.; Palyulin, V. A.; Zefirov, N. S.; Bormotov, N. I.; Serova, O. A.; Shishkina, L. N.; Baimuratov, M. R.; Bormasheva, K. M.; Gruzd, Yu. A.; Ivleva, E. A.; Leonova, M. V.; Lukashenko, A. V.; Osipov, D. V.; Osyanin, V. A.; Reznikov, A. N.; Shadrikova, V. A.; Sibiryakova, A. E.; Tkachenko, I. M.; Klimochkin, Yu. N. *Eur. J. Med. Chem.* **2018**, *158*, 214-235. (d) Spasov, A. A.; Babkov, D. A.; Osipov, D. V.; Klochkov, V. G.; Prilepskaya, D. R.; Demidov, M. R.; Osyanin, V. A.; Klimochkin, Yu. N. *Bioorg. Med. Chem. Lett.* **2018**, *29*, 119-123. (e) Konovalov, A. I.; Antipin, I. S.; Burilov, V. A.; Madzhidov, T. I.; Kurbangalieva, A. R.; Nemtarev, A. V.; Solovieva, S. E.; Stoikov, I. I.; Mamedov, V. A.; Zakharova, L. Ya.; Gavrilova, E. L.; Sinyashin, O. G.; Balova, I. A.; Vasilyev, A. V.; Zenkevich, I. G.; Krasavin, M. Yu.; Kuznetsov, M. A.; Molchanov, A. P.; Novikov, M. S.; Nikolaev, V. A.; Rodina, L. L.; Khlebnikov, A. F.; Beletskaya, I. P.; Vatsadze, S. Z.; Gromov, S. P.; Zyk, N. V.; Lebedev, A. T.; Lemenovskii, D. A.; Petrosyan, V. S.; Nenaidenko, V. G.; Negrebetskii, V. V.; Baukov, Yu. I.; Shmigol', T. A.; Korlyukov, A. A.; Tikhomirov, A. S.; Shchekotikhin, A. E.; Traven', V. F.; Voskresenskii, L. G.; Zubkov, F. I.; Golubchikov, O. A.; Semeikin, A. S.; Berezin, D. B.; Stuzhin, P. A.; Filimonov, V. D.; Krasnokutskaya, E. A.; Fedorov, A. Yu.; Nyuchev, A. V.; Orlov, V. Yu.; Begunov, R. S.; Rusakov, A. I.; Kolobov, A. V.; Kofanov, E. R.; Fedotova, O. V.; Egorova, A. Yu.; Charushin, V. N.; Chupakhin, O. N.; Klimochkin, Yu. N.; Osyanin, V. A.; Reznikov, A. N.; Fisyuk, A. S.; Sagitullina, G. P.; Aksenov, A. V.; Aksenov, N. A.; Grachev, M. K.; Maslennikova, V. I.; Koroteev, M. P.; Brel', A. K.; Lisina, S. V.; Medvedeva, S. M.; Shikhaliev, Kh. S.; Suboch, G. A.; Tovbis, M. S.; Mironovich, L. M.; Ivanov, S. M.; Kurbatov, S. V.; Kletskii, M. E.; Burov, O. N.; Kobrakov, K. I.; Kuznetsov, D. N. *Russ. J. Org. Chem.* **2018**, *54*, 157-371.