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Synthesis and Transformation of Halochromones

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Abstract: Herein, an overview of the most important developments on the synthesis and reactivity of halogen-containing chromones, namely simple chromones, flavones, styrylchromones, thiochromones and furochromones are reviewed (since 2003).

Keywords: Chromones, cross-coupling reactions, halochromones, halogenation, reactivity, synthesis.

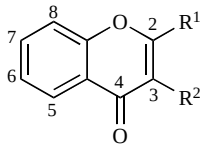
1. INTRODUCTION

Chromones (4*H*-1-benzopyran-4-ones) are one of the most abundant groups of naturally occurring oxygen containing heterocyclic compounds possessing a benzo-γ-pyrone framework, **1a**. The significance of these widely spread and highly diverse compounds is far beyond the important biological functions they assume in nature [1, 2].

Natural and synthetic chromone derivatives have been assigned as lead structures in drug development with some already being marketed [3]. The majority of the naturally occurring chromones are 2- and 3-aryl derivatives, called flavones **1b** and isoflavones **1c**, respectively. However, other types of chromones have also been found in the plant kingdom, such as 3-methylchromones **1d** and 2-styrylchromones **1e** (Fig. **1**).

Chromone-type compounds are well-known for their variety of biological properties, that include antitumor [4-15], hepatoprotective [16], antioxidant [17-21], anti-inflammatory [22-25], cardioprotective [26], antimicrobial [27, 28] and antiviral activities [29, 30]. The vast range of biological effects associated with these structural skeletons has led to substantial research devoted to the isolation from natural resources, synthesis and transformation of chromone derivatives and also to biological evaluation with emphasis on their potential medicinal applications.

Halogen-containing chromones **2** are scarce in nature [31] (Fig. **1**). All the naturally-occurring derivatives are mono- or dichlorinated compounds and were mainly isolated from bacteria and fungi [32-37]. Sordidone, 8-chloro-5,7-dihydroxy-2,6-dimethoxychromone, the first isolated halochromone, was found in *Lecanora* lichen [32, 33]. Some 6- and 8-mono- and 6,8-dichloro derivatives have been identified in *Streptomyces* strains [34-36] and recently three pestalochromones from *Pestalotiopsis* were isolated [37]. Halochromones also occur in higher plants, where 6-chloroapigenin was found in *Equisetum arvense* [38] and recently two 8-chloro-2-(2-phenylethyl)chromones were obtained from *Aquilaria sinensis* [39]. The versatility of halochromones as reactive organic intermediates allows the preparation of a whole series of other heterocyclic systems [40, 41]. Several biological activities have also been attributed to halochromones. Certain derivatives are known as potent anxiolytic and neuroleptic agents acting as stimulators of the central nervous system possessing high affinity for central benzodiazepine receptors [42-45]. Furthermore, halochromones are considered as antitumor agents [13, 46-48] possessing selective inhibitory activity of the breast cancer resistance protein [46] and DNA topoisomerases [13]. Cardioprotective [49] and antimicrobial [50] activities have also been associated with these compounds.



1a $R^1 = R^2 = H$
1b R^1= Ar, $R^2 = H$
1c $R^1 = H$, R^2 = Ar
1d $R^1 = H$, R^2 = Me
1e R^1 = Styryl, $R^2 = H$

2a R^1 = Hal, CH_2Hal;
$R^2 = R^3$ = any substituent
2b R^1 = any substituent;
R^2 = Hal, R^F, CCl_3, CH_2Hal;
R^3 = any substituent
2c $R^1 = R^2$ = any substituent;
R^3 = Hal, CH_2Hal, $COCH_2Hal$, COR^F

Fig. (1). General structure of chromones **1a-e** and of halogenated chromones **2a-c**.

The chemistry of halochromones was the subject of a book chapter [51] in 1977 and of a review article [52] describing the state of art of these compounds up to 2003. The increasing number of publications related to the study of the chemistry and the biological evaluation of halochromones led us to review recent work on the synthesis and transformation of halogen-containing chromones, flavones, styrylchromones, thiochromones (this particular group since its last review) [53] and furochromones, and also to cover sparse data not included in the 2003 review [52].

2. SYNTHESIS OF HALOCHROMONES

Among the methodologies developed over the years for the synthesis of chromones, the most efficient are the Claisen condensation, Baker-Venkataraman and Kostanecki-Robinson methods [54, 55]. The synthesis of halochromones can be carried out by applying the general methods for the synthesis of chromones using halogenated precursors or by halogenation of the chromone nucleus in a final stage. Recent developments in halochromones synthesis have been focused on 3-halochromones which allow the construction of more complex compounds from this base structure. The synthesis of mono- and polyhalobenzochromones (chromones in which an halogen or an halomethyl group is attached to the benzene ring) has also received considerable attention. Along with the synthesis of 2-halochromones (only a single recent publication was found), the synthesis of 2-(polyfluoroalkyl)chromones and 3-(polyhaloacyl) chromones are also considered. These two groups of derivatives are less documented in the literature, but interesting synthetically.

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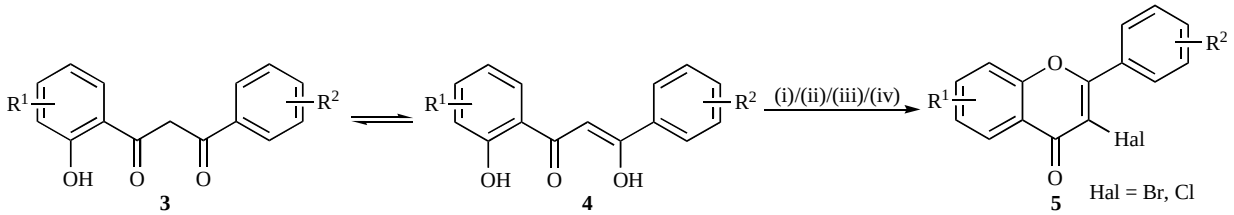
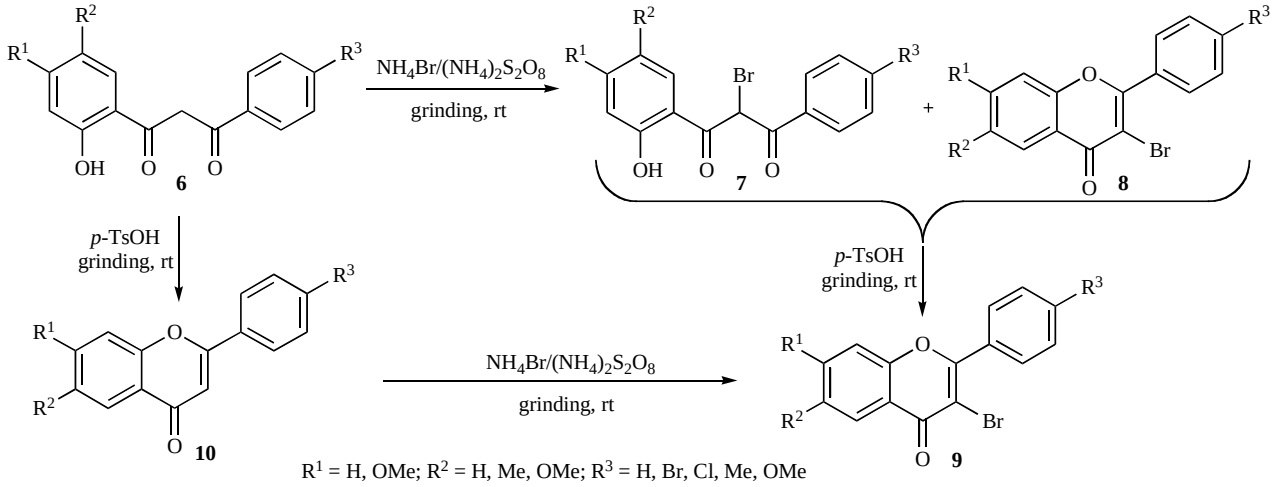


Scheme 1. One-pot synthesis of 3-haloflavones **5** from the 3-aryl-1-(2-hydroxyaryl)propane-1,3-diones **3**.



Scheme 2. Eco-friendly synthesis of 3-haloflavones **9** using the grinding technique.

2.1. Synthesis of 3-Halochromones

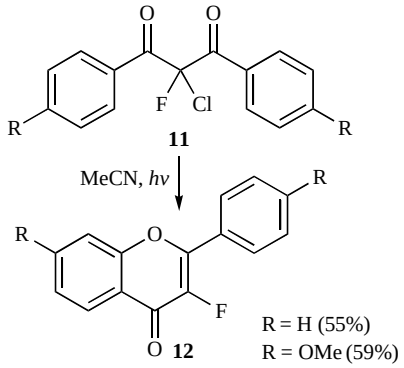
The synthesis of 3-halochromones can be achieved by two different methods: from acyclic compounds, or by direct halogenation of chromone-type compounds.

The selective chlorination or bromination of 3-aryl-1-(2-hydroxyaryl)propane-1,3-diones **3** (which exist in equilibrium with their enolic form **4**) [56] to give the corresponding 3-haloflavones **5** can be accomplished by reaction with ammonium halides and hydrogen peroxide in a biphasic media using phase-transfer catalysis [57] or by reaction with iodine monochloride or bromine in DMF (Scheme **1**) [58]. 3-Bromoflavones can also be prepared *via* bromination of 3-aryl-1-(2-hydroxyaryl)propane-1,3-diones with $CuBr_2$ (Scheme **1**) [59]. Under all these referred conditions the halogenation and cyclodehydration occur in a one-pot reaction procedure.

A similar and eco-friendly procedure for the preparation of 3-bromoflavones **9**, under free solvent conditions [60], consists of the selective bromination of 3-aryl-1-(2-hydroxyaryl)propane-1,3-dion-es **6** by grinding with ammonium bromide and ammonium persulfate at room temperature, followed by grinding the resulting mixture with *p*-toluenesulfonic acid (*p*-TsOH) (Scheme **2**). Flavones **10** can also be directly 3-brominated using the above conditions.

3-Bromoflavones [61] and 3-bromo-2-styrylchromones [62] can be obtained in moderate to good yields by the reaction of 3-aryl-1-(2-hydroxyaryl)propane-1,3-diones and of 5-aryl-1-(2-hydroxyaryl) pent-4-ene-1,3-diones with phenyltrimethylammonium tribromide (PTT) respectively, where the bromination and cyclodehydration occur in a one-pot reaction.

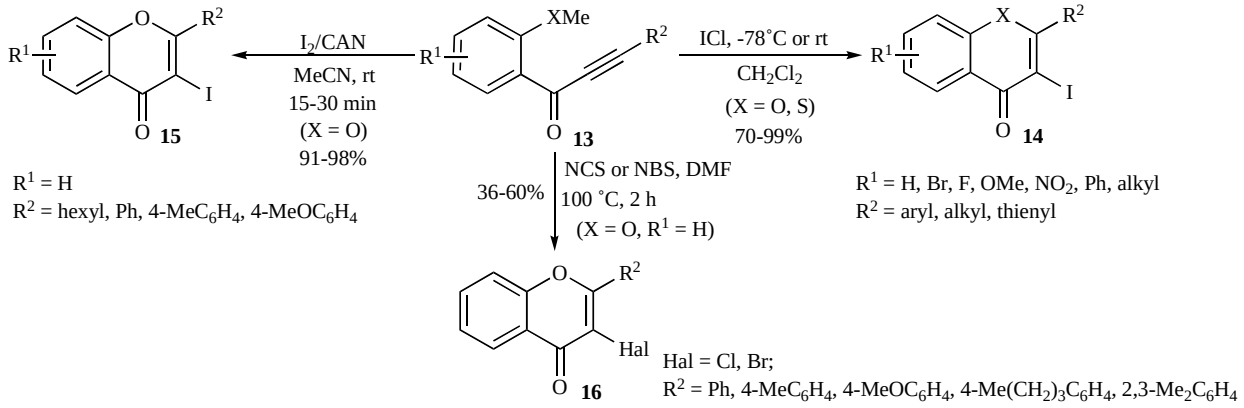
A new synthetic route for 3-fluoroflavones **12** in moderate yields consists of the photocyclization of substituted 1,3-diaryl-2-chloro-2-fluoropropane-1,3-diones **11** in MeCN (Scheme **3**) [63].



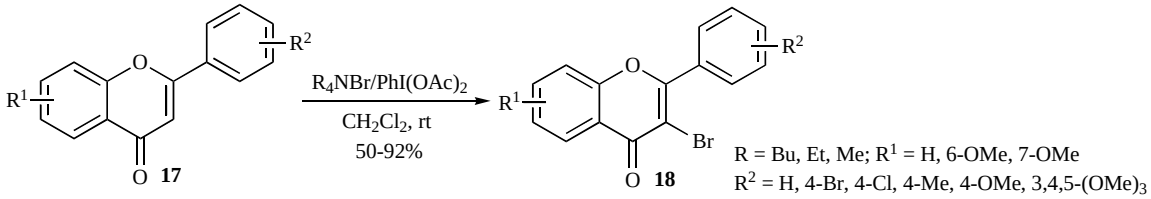
Scheme 3. Synthesis of 3-fluoroflavones **12** by a photochemical process.

3-Chloroflavone derivatives were not detected in the reaction mixture indicating that no cyclization products derived from C-F bond cleavage were formed. It is also important to notice that these reactions are very sensitive to the substituents in both aryl rings.

The cyclization of heteroatom-substituted (2-*O*/*S*-methylaryl) alkynones **13** provided a novel simple and highly efficient approach to prepare 3-iodo(chromones or thiochromones) **14** and **15**. This process can be induced by iodine monochloride, under mild conditions, and tolerates various functional groups giving good to excellent yields (Scheme **4**) [64]. The use of iodine-cerium(IV)ammonium nitrate (I_2/CAN) at room temperature gives 3-iodochromones **15** in excellent yield (Scheme **4**) [65]. This method was originally used to directly 3-iodinate flavones [66]. Electrophile-promoted cyclization with *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS) can also afford the corresponding 3-haloflavones **16** in moderate yields [67]. The latter cyclization reaction is quite sensi-



Scheme 4. Synthesis of 3-halo(chromones and thiochromones) **14-16** from (2-*O*/*S*-methylaryl)alkynones **13**.



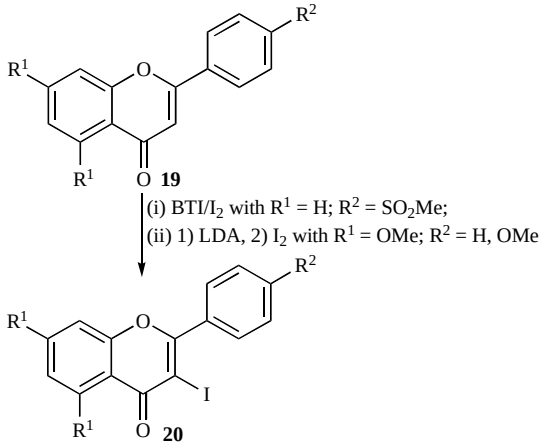
Scheme 5. Synthesis of 3-bromoflavones **18** by selective 3-bromination of flavones **17**.

tive to the solvent (other solvents than DMF were totally ineffective) and to the substituent on the alkyne moiety of **13**. In some cases the formation of addition side products were observed.

3-Halogenation of natural flavones glycosides have also been performed with NCS and NBS [68].

There are several new methods for the direct halogenation of chromones, using different halogen sources. Direct and selective 3-bromination of flavones **17** can be efficiently achieved with $R_4NBr/PhI(OAc)_2$ under mild conditions (Scheme **5**) [69]. This bromination reagent acts as a more environmental friendly alternative to molecular bromine. The presence of electron-donating substituents in the A or B rings leads to 3-bromoflavones **18** in high yields whereas with electron-withdrawing substituents lower yields are obtained.

The 3-iodination of chromone-type compounds, despite our focus on the recent advances on this field, is still carried out mainly using molecular iodine [70]. 3-Iodoflavones **20** can be synthesized by the reaction of flavones **19** with bis(trifluoroacetoxyiodo)benzene (BTI) and iodine [71] or by treatment with LDA, followed by the addition of molecular iodine (Scheme **6**) [72].

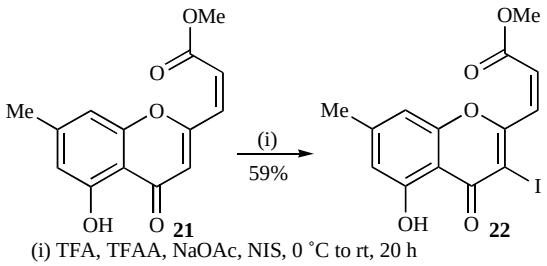


Scheme 6. Synthesis of 3-iodoflavones **20** by selective 3-iodination of flavones **19**.

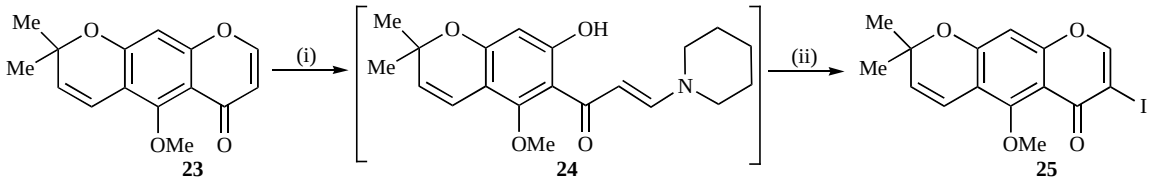
3-Chlorination of flavones can be successfully achieved with NCS in dichloromethane-pyridine [73]. Halogenation of substituted flavones with electrophilic reagents can be carried out easily than other chromone halogenations (*e.g.* 2-methylchromones), due to the stabilization of the 2-aryl group intermediate.

A study of the regioselective 3-bromination and 3-iodination of 5-hydroxy-2,7-dimethylchromone and related compounds with NBS and NIS, respectively, in specific acidic conditions, clearly demonstrated how slight changes in the reaction conditions or in the nature of a strategic positioned substituent can direct halogenation of the benzene ring instead of C-3 or contrariwise [74]. The reaction of chromones with halogens and other halogenating reagents usually gives halogen addition at the double bond of the pyrone ring [74]. The same study presented a highly efficient and selective method for the 3-iodination of a more elaborated 5-hydroxychromone **21** bearing an additional activated double bond, to give 5-hydroxy-3-iodochromone **22** in 59% yield (Scheme **7**). Even though this opens up the possibility of designing more complex molecular frameworks containing halochromone moieties, the reaction has a remarkable dependence on the stereochemistry of the exocyclic bond. Applying the same reaction conditions to the (*E*)-isomer results in a very low yield (5%).

3-Iodination of 8-isobutyl-5,6,7-trimethoxy-2-methylchromone was achieved in excellent yield (95%) by treatment with iodine in the presence CF_3CO_2Ag as a catalyst [75].



Scheme 7. Selective 3-iodination of 5-hydroxychromone **21** bearing activated double bonds.



(i) MeOH, piperidine, reflux; (ii) I_2, pyridine, $CHCl_3$, rt (89% overall yield)

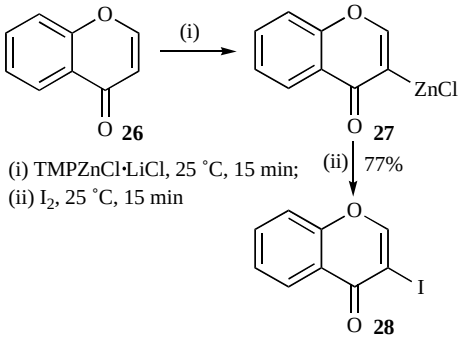
Scheme 8. Selective 3-iodination of 5-methoxychromone **23** bearing activated double bonds, *via* a ring opening – ring closure procedure.

3-Iodo-5-methoxy-8,8-dimethyl-8*H*-pyrano[3,2-*g*]chromone **25** can be efficiently prepared by C-ring opening of chromone **23** with piperidine in MeOH and subsequent treatment with iodine in the presence of pyridine (Scheme **8**) [76].

A recent publication on regioselective Lewis acid-triggered zincation [77] opened up the possibility of using the metallation of chromones for further functionalization [78]. Treatment of chromone **26** with TMPZnCl.LiCl (TMP = 2,2,6,6-tetramethylpiperidyl) resulted in selective 3-zincation to afford zinc reagent **27**. After iodolysis and flash-column chromatography 3-iodochromone **28** in 77% yield was obtained (Scheme **9**). The versatility of this method allows also the selective synthesis of 2-iodochromones (topic 2.3) by simply adding a Lewis acid, which completely inverts the zincation regioselectivity.

2-Unsubstituted 3-iodochromones were also obtained by treatment of the corresponding chromanones with iodine in DMSO, at 110 °C for 5 h [79].

The direct bromination of (*E*)-2-styrylchromones **29** with pyridinium tribromide (PTB) in acetic acid at room temperature revealed a mixture of brominated compounds, which included 3-bromo-2-(1,2-dibromo-2-phenylethyl)chromones **30** and (*E*)-3-bromo-2-styrylchromones **31** in low yields (15-42% and 0-16%, respectively) (Scheme **10**). These results are due to the similar reactivity of the C2=C3 and Cα=Cβ double bonds leading to a competitive bromination reaction [80]. In spite of not being a selective method, it represents an important approach for the direct 3-halogenation of 2-styrylchromones.



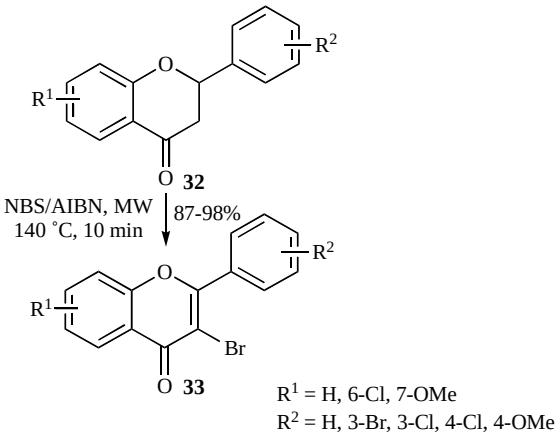
Scheme 9. Selective synthesis of 3-iodochromone **28** *via* 3-zincation of simple chromone.

The selective and fast transformation of flavanones **32** to 3-bromoflavones **33**, in good to excellent yields and short reaction time (10 min), with NBS as brominating agent, under solvent-free microwave irradiation, has been reported as an alternative synthetic route of 3-bromoflavones (Scheme **11**) [81].

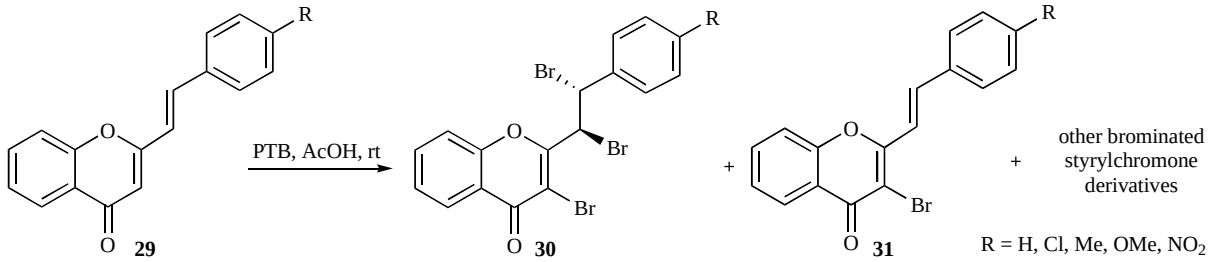
2.2. Synthesis of Ring A Mono- and Polyhalogenated Chromones

2.2.1. From Halogenated Precursors

Undoubtedly, the two main electrophilic centres of chromones that determine most of its chemistry are the C2 and C4 atoms in the α-pyrone ring. However to fully comprehend the chromone chemistry the whole nucleus cannot be ignored. The study of the synthesis of ring A halogenated chromones is of great importance. The higher level of functionality achieved by the introduction of halogen atoms in A ring allows more elaborated organic frameworks to be obtained. Furthermore, these halochromone derivatives have already been proven to be of biological importance and even possibly enhance the biological activity of chromones [45, 46, 82, 83]. The regioselectivity of the halogenation of chromones with different halogenating agents (considering also the strategic influence of the nature and position of substituents) demand a full study of the chromone core structure.



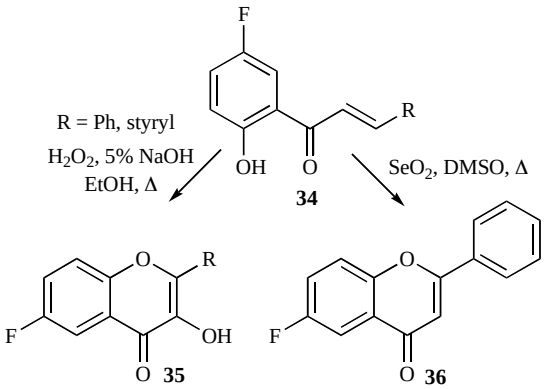
Scheme 11. Selective synthesis of 3-bromoflavones **33** from the corresponding flavanones **32**.



Scheme 10. 2-Styrylchromones **29** double bonds halogenation with PBT in acetic acid.

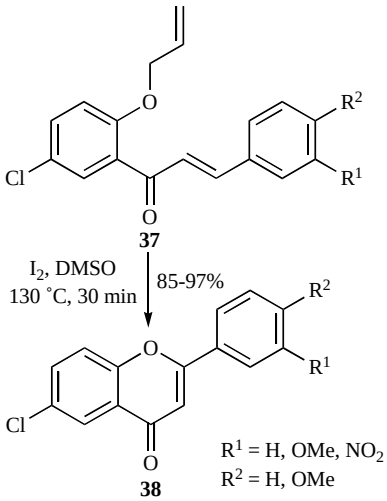
The synthesis of halochromones may be accomplished by the general synthetic methods using halogenated precursors.

Oxidative cyclization of 5'-fluoro-2'-hydroxychalcone **34** (R = phenyl) and 5'-fluoro-2'-hydroxycinnamylideneacetophenone **34** (R = styryl) to the corresponding 6-fluoro-3-hydroxyflavone **35** (R = phenyl) and 6-fluoro-3-hydroxy-2-styrylchromone **35** (R = styryl), respectively, can be achieved by reaction with alkaline hydrogen peroxide (Scheme **12**) [84]. Similar reaction conditions have been successfully used for the synthesis of other mono- and poly-halochromones [85-89]. 6-Fluoroflavone **36** can also be obtained through oxidative cyclization of 5'-fluoro-2'-hydroxychalcone **34** (R = phenyl) with selenium dioxide in hot DMSO (Scheme **12**) [84].



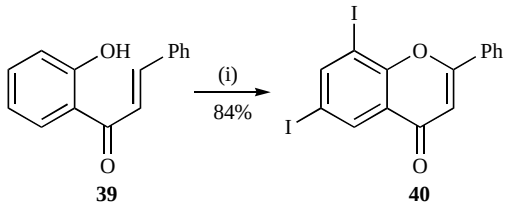
Scheme 12. Synthesis of 6-fluoro-2-(phenyl and styryl)chromones **35**, **36** by oxidative cyclization of 5'-fluoro-2'-hydroxychalcone **34** (R = phenyl) and 5'-fluoro-2'-hydroxycinnamylideneacetophenone **34** (R = styryl).

The usefulness of the DMSO–I_2 reagent system in the oxidative cyclization of 2'-hydroxychalcones to flavones and of flavanones to flavones is well-known [90]. Not surprisingly, this is not a protocol exception for the synthesis of halogen A ring containing chromones [91]. The versatility of this reagent was extended and explored in a new one-pot procedure that describes the efficient deprotection of 2'-allyloxychalcones **37** and subsequent oxidative cyclization to flavones **38** under mild conditions (Scheme **13**) [92]. Other novel synthetically interesting methodologies involve the use of salicylaldehydes as key substrates, instead of 2'-hydroxyacet-ophenones. Halogenated 2-hydroxychalcones, derived in high yield from the condensation of halogenated acetophenones and salicylaldehydes, underwent oxidative cyclization in the presence of iodine furnishing the corresponding haloflavones under solvent-free conditions [93].



Scheme 13. Synthesis of 6-chloroflavones **38** by oxidative cyclization of 2'-allyloxy-5'-chlorochalcones **37**.

One-pot synthesis of 6,8-diiodoflavone **40** has been accomplished by diacetoxyiodobenzene-catalyzed iodination of 2'-hydroxychalcone **39** with tetra-*n*-butylammonium iodide in acetic acid in the presence of sodium perborate (SPB) as a terminal oxidant (Scheme **14**) [94].

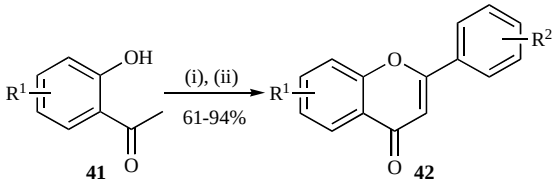


(i) $PhI(OAc)_2$, SPB, TBAI, AcOH, 60 ˚C, 8 h

Scheme 14. Synthesis of 6,8-diiodoflavone **40** from 2'-hydroxychalcone **39**.

The first synthesis of haloflavones by cyclodehydration of halogenated 3-aryl-1-(2-hydroxyaryl)propane-1,3-diones under Vilsmeier-Haack conditions with *bis*-(trichloromethyl)carbonate/DMF [95], or in the presence of $CuCl_2$ under microwave irradiation [96] proved to be a practical synthetic method for the synthesis of haloflavones.

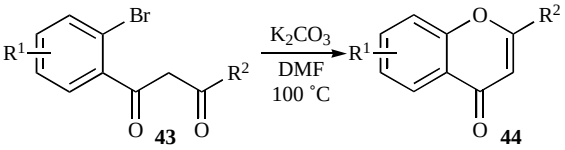
The synthesis of haloflavones has also been successfully conducted by application of a protocol of *Cα*-acylation originally described by Cushman [97] for the synthesis of hydroxylated flavones. A wide range of functionalized A and B ring halogenated flavones **42** were obtained in good to high yields (Scheme **15**) [98].



R^1 = H, Br, Me; R^2 = H, Br, Cl
(i) LiHMDS (4 equiv), THF, -78 ˚C to 20 ˚C
then R^2PhCOCl, THF, -78 ˚C to rt;
(ii) H_2SO_4, AcOH, 120 ˚C, 5 min

Scheme 15. Synthesis of haloflavones **42** by 2-aroylation of 2'-hydroxyacetophenones **41** followed by cyclodehydration.

A recent reported inexpensive and environmental friendly approach for the synthesis of (halo)chromone derivatives **44** involves a transition metal-free intramolecular Ullmann-type *O*-arylation of 3-alkyl/aryl-1-(2-bromoaryl)propane-1,3-diones **43** (Scheme **16**) [99].



R^1 = H, Cl, Me, OMe
R^2 = Me, Et, Ar (some of them bearing Cl or Br as substituents)

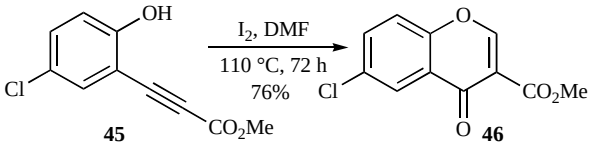
Scheme 16. Synthesis of halochromones **44** by a transition metal-free intramolecular Ullmann-type *O*-arylation.

A new method was developed for the synthesis of flavones almost in quantitative yields by oxidation of flavanones with manganese(III) acetate in the presence of perchloric acid and using acetic acid as solvent [100], which replaces toxic reagents such as thallium(III), selenium dioxide, and nickel peroxide usually used for this transformation [101]. Another pathway for the transformation of flavanones to flavones involves the microwave irradiation of the former with NBS in the presence of a catalytic amount of AIBN [69].

3-Carboxymethyl-6-chlorochromone **46** can be selectively prepared *via* reaction of 3-(5-chloro-2-hydroxyphenyl)propiolate **45** with iodine in DMF (Scheme **17**) [102]. Assisted by iodine, DMF participated in the reaction, implying that the combination of DMF and iodine act as an efficient formylating reagent. This method allowed the preparation of several other non-halogenated derivatives.

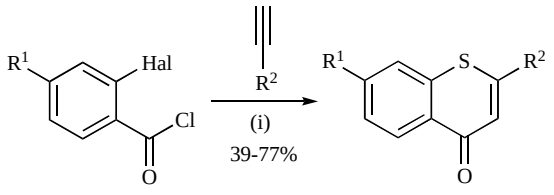
A novel consecutive one-pot three-component coupling-addition-substitution (S_NAr) sequence starting from *o*-haloaroyl chlorides **47**, alkynes and sodium sulfite monohydrate was reported for the synthesis of substituted halothiochromones **48** (Scheme **18**) [103]. This method involves an intramolecular Sonogashira coupling of 2-haloaroyl chlorides with terminal alkynes, followed by the Michael addition of the hydrosulfide ion to the formed alkynone and subsequent intramolecular S_NAr reaction, presumably assisted by Pd and/or Cu catalysis.

A similar novel stepwise, efficient protocol for the synthesis of chromones **52** bearing electron-donating groups such as halogens



45 **46**

Scheme 17. Synthesis of 3-carboxymethyl-6-chlorochromone **46** from methyl 3-(5-chloro-2-hydroxyphenyl)propiolate **45**.



47 **48**

Hal = F, Cl; R^1 = H, Cl;
R^2 = 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 3,4-$(OMe)_2C_6H_3$

(i) 1) $[PdCl_2(PPh_3)_2$ (0.02 equiv), CuI (0.04 equiv)], NEt_3 (1.05 equiv), THF, 1 h, rt;
2) $Na_2S.9H_2O$ (1.5 equiv), EtOH, 90 °C, 90 min, MW

Scheme 18. Synthesis of halothiochromones **48** from *o*-haloaroyl chlorides **47**, alkynes and sodium sulfite monohydrate.

was recently developed. It consists in a one-pot mixed-gas mild Sonogashira coupling reaction that affords *o*-alkynoylphenyl acetate intermediates **51**, followed by an 18-crown-6 ether mediated 6-*endo* cyclization (Scheme **19**) [104].

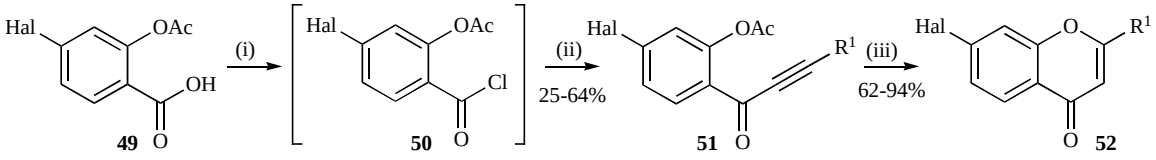
New general and regioselective synthesis of chromone-(3 and 8)-carboxamide derivatives **54** and **55** involving anionic carbamoyl translocation reactions have been developed (Scheme **20**). This synthetic route involves sequential intramolecular anionic *o*-Fries rearrangement and a Michael addition that proceed *via* a cumulenolate intermediate [105]. Depending on the amount of base LTMP (lithium 2,2,6,6-tetramethylpiperidide), chromone-3-carboxamides **54** (1.1-1.5 equiv) or chromone-8-carboxamides **55** (2.1-3.0 equiv) were obtained. This method allowed the preparation of several other non-halogenated derivatives.

Another synthetic approach to 6-chlorochromones **58** involved on a one-pot sequential Pd-catalyzed copper-free carbonylative Sonogashira reaction of 4-chloro-2-iodophenol **56** (Hal^1 = I, Hal^2 = Cl) with butyl acetylene **57** followed by intramolecular cyclization (Scheme **21**). The reaction is carried out at room temperature under balloon pressure of CO with NEt_3 as a base and water as solvent [106]. A similar methodology for 6-fluoroflavones **60** involved regioselective carbonylative annulation of 2-bromo-4-fluorophenol **56** (Hal^1 = Br, Hal^2 = F) and arylacetylenes **59** in the presence of $PdCl_2(PPh_3)_2$ as catalyst and a benzimidazole–triazole as ligand (Scheme **21**) [107].

The synthesis of 6-chlorohomoisoflavone **62** and 3-allyl-6-chlorochromones **63** were obtained from the reaction of (*E*)-1-(2-hydroxy-5-chlorophenyl)-3-(*N*,*N*-dimethylamino)prop-2-en-1-one **61** with respectively benzyl bromide and allyl bromides, in DMF (Scheme **22**) [108].

Halochromones **65** can also be obtained *via* an intramolecular Wittig reaction of acylphosphoranes. This one-pot reaction involves the formation of acylphosphoranes from the silyl ester of *O*-acyl(aroyl)salicylic acids **64** and (trimethylsilyl)methylenetriphenylphosphorane, which undergo an intramolecular Wittig cyclization of the ester carbonyl group (Scheme **23**) [109]. This method allowed the preparation of several other non-halogenated derivatives.

Sosnovskikh and co-workers described a novel synthesis of a variety of substituted 3-(polyhaloacyl)chromones **67** by the reaction of 2-hydroxy-2-(polyhaloalkyl)chromanones **66** with diethoxymethylacetate, which acts as formylating agent, and solvent (Scheme **24**) [110, 111]. Although in some cases this transformation results in low yields, the availability of the starting materials

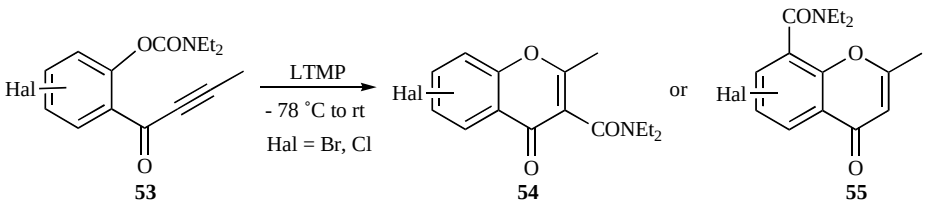


49 **50** **51** **52**

Hal = F, Cl, Br; R^1 = Ph, 3-$OMeC_6H_4$, 4-FC_6H_4

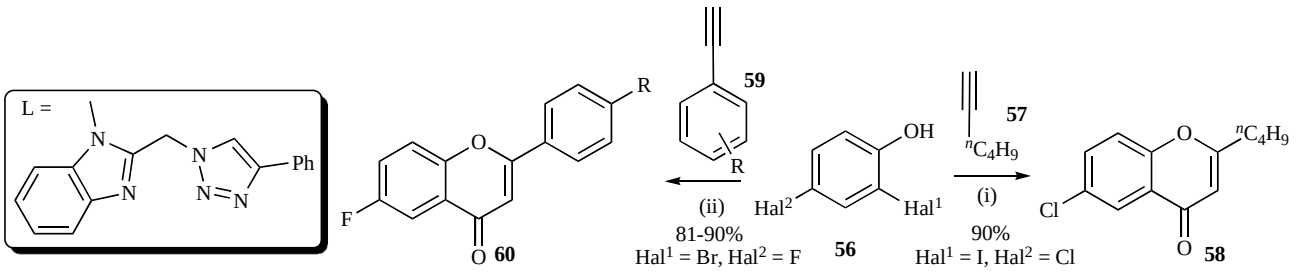
(i) oxalyl chloride, DMF (cat.)/THF, 0 ˚C to rt; (ii) $PdCl_2(PPh_3)_2$/CuI/NEt_3, THF, H_2/N_2, rt;
(iii) CH_3OK or ^tBuOK, 18-crown-6 ether, THF, rt, 15 min

Scheme 19. Synthesis of 7-halochromones **52** from 2-acetyloxy-4-halosalicylic acid derivatives **49**.

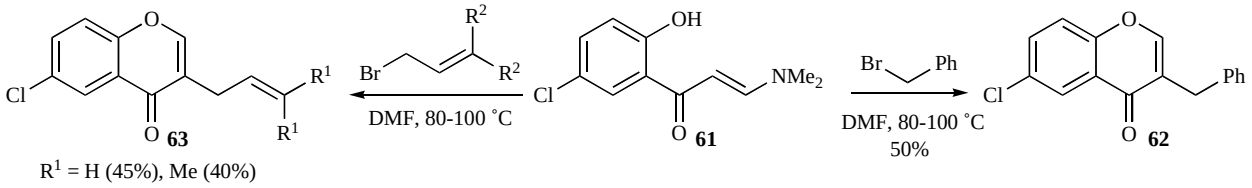


53 **54** **55**

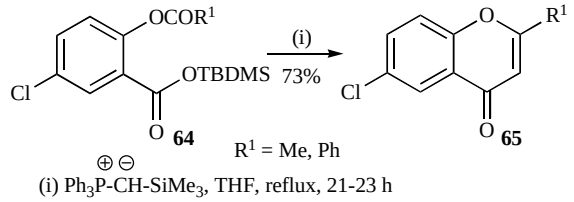
Scheme 20. Synthesis of chromone-(3 and 8)-carboxamides **54** and **55**.



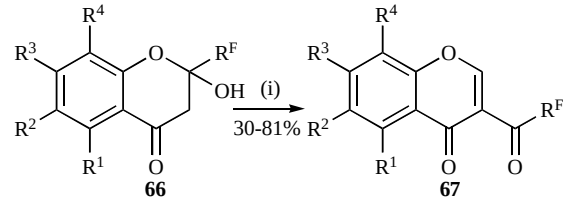
Scheme 21. Synthesis of 6-halochromones **58** and **60** by a carbonylative annulation of 4-halo-2-(iodo/bromo)phenol **56** and substituted acetylenes **57** and **59**.



Scheme 22. Synthesis of 6-chlorohomoisoflavone **62** and 3-allyl-6-chlorochromones **63**.



Scheme 23. Synthesis of 6-chlorochromones **65** by a Wittig reaction.



Scheme 24. Synthesis of 3-(polyhaloacyl)chromones **67**.

and the easy reaction and purification procedures are the great advantages of this approach. This general method was also extended to furanochromone derivatives [112].

Alkylation of 7-chloro-4-hydroxydithiocoumarin **68** with allyl halides allowed the synthesis of interesting thieno-fused thiochromenones **69** and **71**. The reaction with 2,3-dichloroprop-1-ene under phase transfer catalysis (chloroform/aqueous sodium hydroxide) in the presence of a catalytic amount of tetrabutylammonium bromide (TBAB) or benzyltriethylammonium chloride (BTEAC) at room temperature afforded the cyclized product 2-methylthieno [2,3-*b*]-4*H*-thiochromen-4-one **69** (Scheme **25**) [113]. However, the alkylation with 3-substituted allyl halides, under the same conditions, only gave the alkylated derivatives **70**, which under reflux in quinoline underwent a 3,3-sigmatropic rearrangement affording 2-methylthieno[2,3-*b*]-4*H*-thiochromen-4-ones **71**.

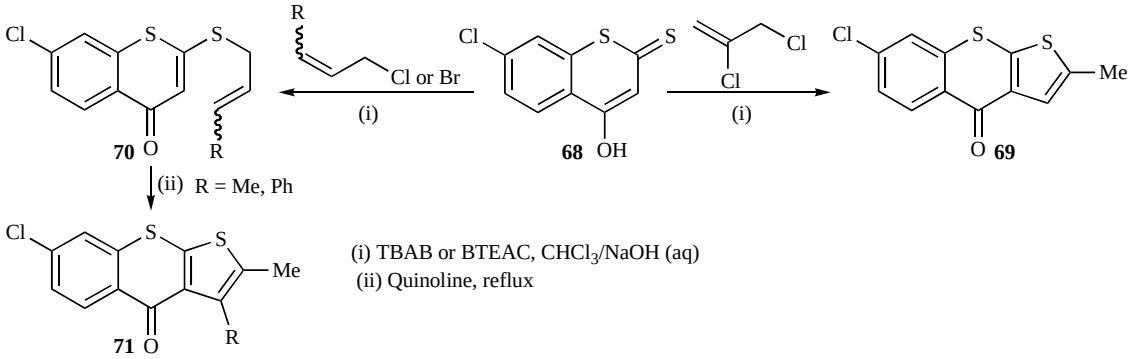
Aglycones **73** and **74** of pyralomicins, powerful natural antibiotics with an unusual chromone-fused pyrrole ring core, were obtained by an intramolecular base-promoted nucleophilic aromatic substitution with cleavage of the tosyl protecting group (Scheme **26**) [114]. A mixture of the possible regioisomers **73** and **74**, posteriorly separated by HPLC, were obtained by using different metal alkoxides which offered different regioselectivities (due to different associations of the metal ions between the carbonyl and one of the phenolic oxygens).

2.2.2. By Halogenation of Chromone Derivatives

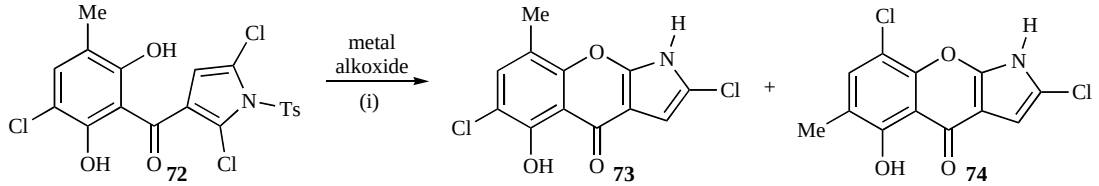
Overviewing the literature of the direct halogenation of chromone A ring it is almost exclusively based on iodination and bromination methods. To the best of our knowledge, there are three reports on A ring chlorination of chromones. One described the chlorination of quercetin by hypochlorous acid (unselective synthesis of 6-mono- and 6,8-dichloro derivatives) [83a]. A second reported the selective chlorination of genistein and biochanin A with thionyl chloride yielding 8-chlorogenistein, 6,8-dichlorogenistein and 6,8-dichlorobiochanin A in good yields (60-70%) [83b]. The third involved the synthesis of the naturally-occurring sordidone and was accomplished by 6-chlorination of 5,7-dihydroxy-2,6-dimethylchromone with sulfuryl chloride (60% yield) [83c]. The existence of activating substituents (*e.g.* hydroxyl and alkoxyl groups) in the A ring improve the halogenation by usual electrophiles. Chrysin **75** was directly brominated with bromine/Me_2S to form 6,8-dibromochrysin **76** and iodinated by molecular iodine in acetic acid to form 6,8-diiodochrysin **77** (Scheme **27**) [82].

Synthesis of 6,8-diiodo- and 6,8-dibromo-2-(phenyl or styryl)chromones **79** can be accomplished in a short reation time and in good yields by oxidative cyclization of 2'-benzyloxy-6'-hydroxychalcone and 2'-benzyloxy-6'-hydroxy-2-cinnamylideneacetophenone **78** with DMSO/I_2 or DMSO/Br_2 or by halogenation of the corresponding 5-hydroxychromones **80** (Scheme **28**) [115]. Using half equiv of iodine or bromine the monoiodo and monobromo derivatives have been obtained in low yields and not selectively although time consuming difficult chromatographic separations are required. 6-Iodostyrylchromone derivatives were obtained by the reaction of 6-tributyltin derivatives with iodine in chloroform at room temperature. Novel radioiodinated styrylchromone derivatives were also synthesized by an iododestannylation reaction using hydrogen peroxide as the oxidant [116].

The iodination of 3,3',4',7-tetra-*O*-methylquercetin with a slight excess of iodine in an alkaline methanol solution afforded a 3:1 mixture of 6- and 8-iodinated derivatives in satisfactory yield (74%). However, under the same conditions 7-*O*-methylbiochanin A **81** provided a racemic 58:41 mixture of (±)-*trans*-5-hydroxy-2,3,4',7-tetramethoxy-8-iodoisoflavanone **82** and (±)-*trans*-5-

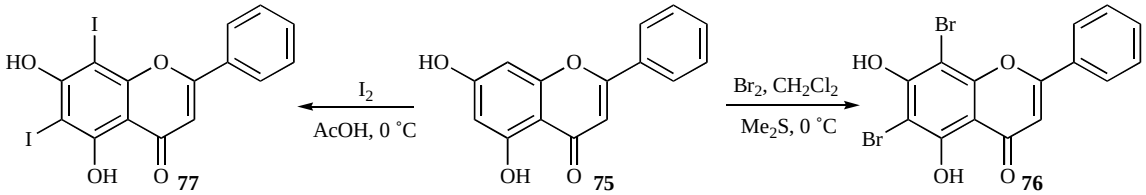


Scheme 25. Synthesis of 2-methylthieno[2,3-*b*]-4*H*-thiochromen-4-ones **69** and **71**.



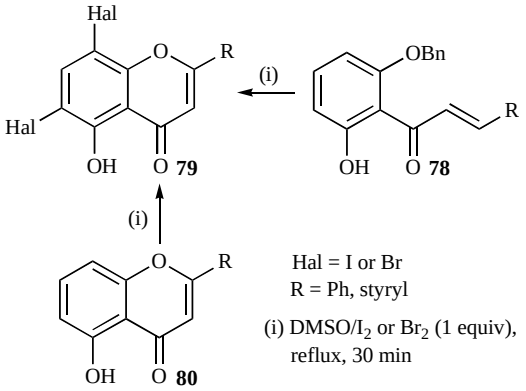
(i) Possible conditions: LiOMe, MeOH (1:1 ratio); NaOMe, MeOH (1:2.5 ratio); TlOEt, EtOH (1:2 ratio); $Mg(OMe)_2$, MeOH (3:1 ratio); $Sr(O^iPr)_2$, MeOH (1:1 ratio); $Ba(O^iPr)_2$, MeOH (1:2 ratio); $Al(O^iPr)_3$, MeOH (2:1 ratio); $Sm(O^iPr)_3$, MeOH (1:1 ratio)

Scheme 26. Synthesis of aglycones **73** and **74** of pyralomicins.



Scheme 27. Bromination and iodination of chrysin **75**.

hydroxy-2,3,4',7-tetramethoxy-6,8-diiodoisoflavanone **83** (Scheme **29**) [117].

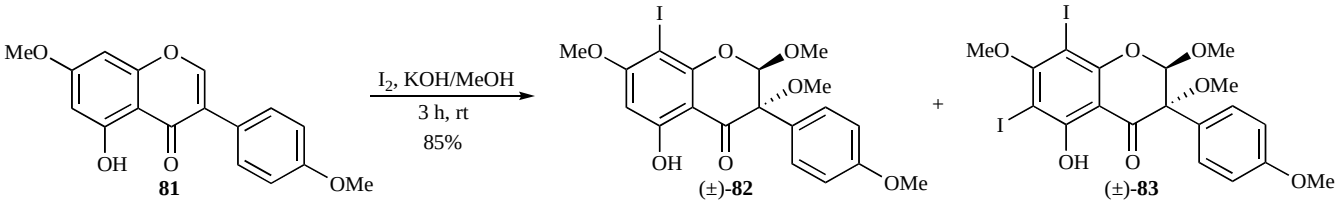


Scheme 28. Synthesis of 6,8-diiodo- and 6,8-dibromo-2-(phenyl or styryl)chromones **79**.

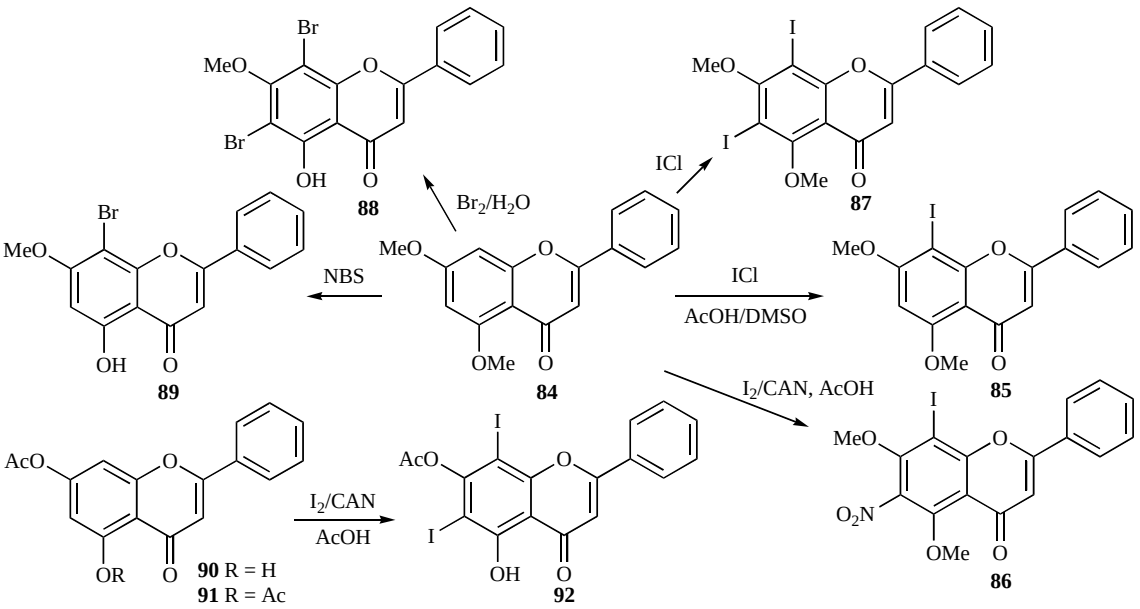
Iodination of 5,7-di-*O*-methylchrysin **84** with ICl in the presence of AcOH in DMSO afforded the 8-iodo derivative **85**. Using the I_2/CAN Li´s flavone 3-iodination conditions [66] a complicated mixture of compounds were obtained and only replacing anhydrous acetonitrile by acid acetic gave rise to a 8-iodo-6-nitro derivative **86** (Scheme **30**) [46]. Under the same conditions both 7-*O*-acetylchrysin **90** and 5,7-di-*O*-acetylchrysin **91** afforded 7-acetyl-6,8-diiodochrysin **92**. However, the reaction of 5,7-di-*O*-methylchrysin **84** with ICl gave 6,8-diiodochrysin **87** and with Br_2/H_2O give the 6,8-dibromo derivative **88**. Bromination of 5,7-di-*O*-methylchrysin **84** with NBS prompted the 8-bromo-7-*O*-methyl derivative **89** (Scheme **30**) [46].

The examples described above give an idea of how difficult and challenging is to control the regioselectivity of the chromone halogenation and how, even considering the same reaction conditions, different ring substituents can direct halogenation to different positions or simply preclude it.

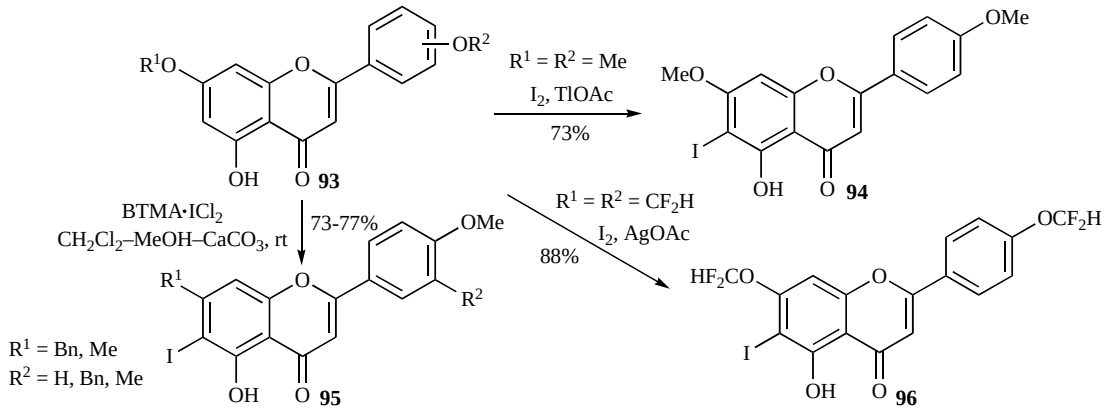
The direct iodination of 5,7-dioxygenated flavones (and generally electrophilic substitutions) are known to occur at C-8 [77, 118, 119]. The selective 6-iodination of flavones can be accomplished



Scheme 29. Iodination of 7-*O*-methylbiochanin A **81** in alkaline medium.



Scheme 30. Halogenation of chrysin derivatives **84**, **90** and **91**.



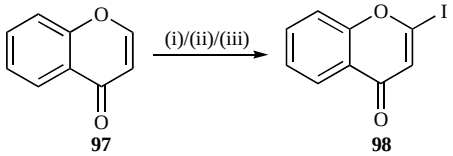
Scheme 31. Regioselective 6-iodination of 5,7-dioxygenated flavones **93**.

by three different methodologies that have been described in the literature (Scheme **31**). The first exploits the *o*-directing capabilities of thallium(I) salts in the iodination of phenols [120], and gives rise to the expected 6-iodo derivative **94** in good yield [121]. A greener alternative to regioselective 6-iodination of 5,7-dioxygenated flavones can be accomplished by using benzyltrimethylammonium dichloroiodate (BTMA•ICl_2) in a CH_2Cl_2-MeOH-$CaCO_3$ system at room temperature [122]. This method requires a free 5-hydroxyl group and an alkoxy chain at C-7, since the iodination of 5,7-dihydroxyflavones gave 6,8-diiodo derivatives. The third method to 6-iodinate 5,7-dioxygenated flavones involves the use of I_2/AgOAc under mild conditions (Scheme **31**) [123].

2.3. Synthesis of other Halochromones

Over the last 40-50 years [52] no significant advances in the synthesis of 2-halochromones have been achieved, since it is undeniably the most difficult position to introduce a halogen atom on a chromone ring. A paper on the Lewis acid-triggered zincation [77], not only suggests a novel methodology to synthesize 3-halochromones but also 2-halochromones with a metalation selectivity never accomplished before. In fact, this is the only new improvement in the synthesis of 2-halochromones since 1997 [124]. The reaction of unsubstituted chromone **97** with TMP_2Zn•$2MgCl_2$•2LiCl led to regioselective metalation at C-2 which, by subsequent iodolysis, gave 2-iodochromone **98** (Scheme **32**). The reversal of regioselective zincation by using TMPZnCl•LiCl (used in the lithiation of C-3 as already mentioned) upon addition of Lewis acids $MgCl_2$ or BF_3•OEt_2 also provided, after iodolysis, 2-iodochromone **98**.

It is known that the presence of a 2-polyfluoroalkyl group (R^F) in chromones enhances their reactivity (increases the electrophilicity of C-2 atom) compared to their nonfluorinated analogues and facilitates reactions with various nucleophilic reagents, and are highly reactive substrates for the synthesis of various heterocyclic derivatives [52, 125]. Perfluoroalkyl-containing organic compounds (particularly including the trifluoromethyl group) have been considered privileged targets as agrochemical and pharmaceutical agents due to their remarkable physical, chemical and biological proper-

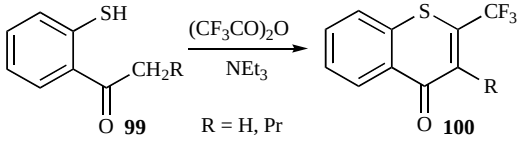


97 98

(i) 1) TMP_2Zn·$2MgCl_2$·2LiCl, THF, -30 ˚, 0.5 h, 2) I_2, 25 ˚C, 15 min (80%); (ii) 1) 0.5 M $MgCl_2$ in THF, 2) TMPZnCl·LiCl, -20 ˚C, 2 h, 3) I_2, 25 ˚C, 15 min (84%); (iii) 1) BF_3·OEt_2, 0 ˚C, 30 min, 2) TMPZnCl·LiCl, -20 ˚C, 1 h, 3) I_2, 25 ˚C, 15 min (76%)

Scheme 32. Regioselective synthesis of 2-iodochromone **98**.

ties, namely the altered electron density, acidity and increased lipophilicity [46, 126, 127]. The modified Baker-Venkataraman reaction of alkyl 2-mercaptophenyl ketones **99** with trifluoroacetic anhydride in the presence of triethylamine in refluxing THF gave 2-(trifluoromethyl)-4*H*-thiochromen-4-ones **100** (Scheme **33**) [128]. Castañeda used a similar procedure under solvent-free conditions to prepare 2-trifluoromethylchromones [129]. The pioneering recent synthesis of 3-hydroxy-2-(polyfluoroalkyl)chromones involved the nitrozation of the corresponding 2-(polyfluoroalkyl)chromanones [130].



Scheme 33. Synthesis of 2-(polyfluoroalkyl)chromones **100**.

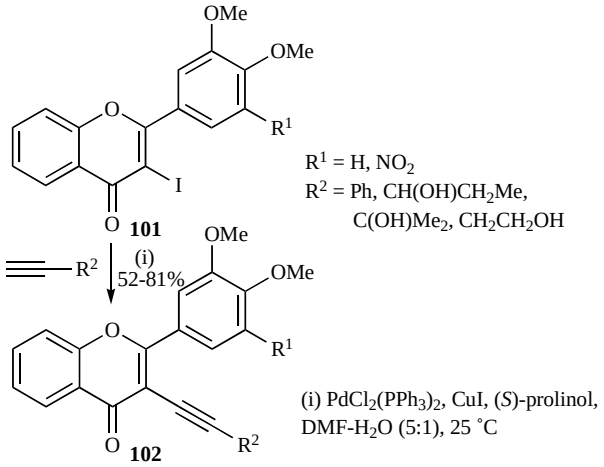
3. TRANSFORMATIONS OF HALOCHROMONES

Over the last decade, synthetic transformations assisted by transition metal catalysis have emerged [131-135] and halochromones chemistry is clearly not an exception. Carbon-carbon bond formation by an array of palladium-catalyzed cross-coupling reactions (namely Heck [136-139], Sonogashira [140-142], Suzuki [143-145] and Stille [146] reactions) are of great importance. The essence of these reactions lies in the serial introduction of two molecules (organic electrophiles as aryl halides and carbon nucleophiles) on palladium, *via* metal-carbon bonds. Subsequently, the proximity of the carbon atoms bound to the metal assists in their coupling with the formation of a new carbon-carbon single bond. This powerful synthetic methodology [147-151] is considered a golden strategic tool to build novel complex molecules, which have promising bioactive properties [152]. The awarding of the 2010 Nobel Prize in Chemistry to R. F. Heck, E. Negishi, and A. Suzuki, gave even more the attention to the development of these reactions [153, 154]. Here, the latest improvements in the reactivity of halochromones involving the palladium-catalyzed cross-coupling reactions will be described.

3.1. Reactivity of 3-Halochromones

The outstanding interest in transition metal-catalysis witnessed in modern organic synthesis prompted studies of the reactivity of 3-halochromones.

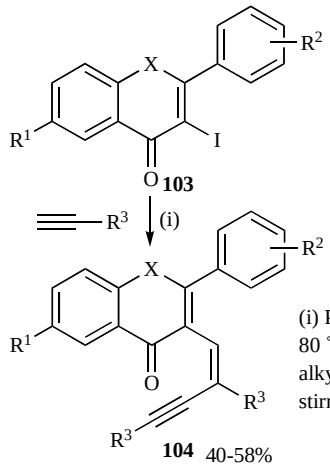
A palladium-copper catalyzed Sonogashira reaction of iodoflavones **101** in aqueous DMF and in the presence of (*S*)-prolinol facilitated the coupling with terminal alkynes under mild conditions,



Scheme 34. Synthesis of 3-alkynylated flavones **102**.

allowing the first synthesis of 3-alkynyl substituted flavones **102** in moderate to good yields (Scheme **34**) [155]. 3-Phenylethynylflavone can be prepared in good yield (80%) by the addition of phenylacetylene in triethylamine to 3-iodoflavone in DMF, followed by the addition of $PdCl_2(PPh_3)_2$ and CuI [156].

A mild and facile regio- and stereospecific synthesis of a variety of novel 3-enynyl-substituted flavones and thioflavones *via* a sequential one-pot copper-free Sonogashira procedure was studied [157, 158]. The cross-coupling reaction of 3-iodoflavones and 3-iodothioflavones **103** with an extensive range of terminal alkynes was carried out in the presence of $PdCl_2(PPh_3)_2$ and triethylamine affording the corresponding 3-enynyl derivatives **104** (Scheme **35**). The reaction is regioselective with the terminal alkyne substituent placed at the β-position of the double bond attached with the chromone nucleus. A tandem C−C bond-forming reaction in the presence of the palladium catalyst rationalized the formation of the coupled product. The catalytic process apparently involves heteroarylpalladium formation, regioselective addition to the C-C triple bond of the terminal alkyne, and subsequent displacement of palladium by another mole of alkyne. In the presence of CuI the expected Sonogashira reaction products 3-alkynyl(flavones and thioflavones) were obtained in moderate yields.

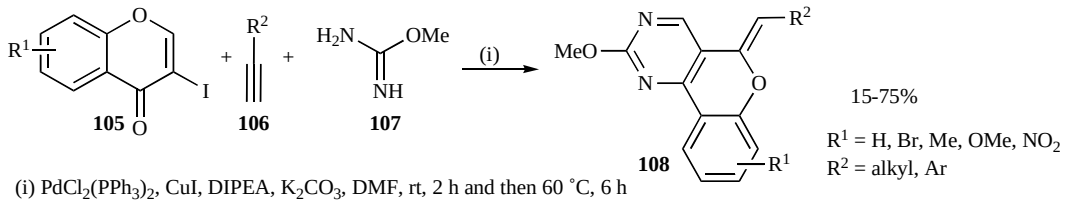


X = O, S; R^1 = H, Cl; R^2 = H, 3,4-$(OMe)_2$
R^3 = CH_2OH, CH(OH)Me, $C(OH)Me_2$, CH_2CH_2OH, $CH(OH)C_2H_5$, CH(OH)Ph, CH_2OPh-4-CHO, CH_2OPh-4-OMe, CH_2OPh-4-NO_2, CH_2OPh-2-Cl

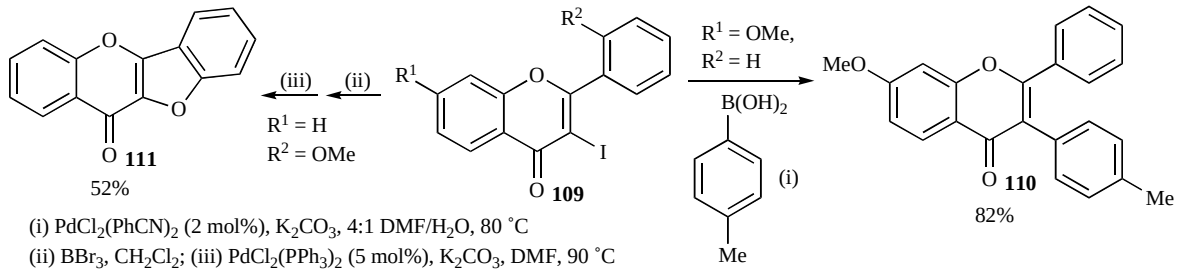
Scheme 35. Synthesis of 3-enynyl(flavones and thioflavones) **104** by a one-pot copper-free Sonogashira reaction.

A library of novel benzopyrano[4,3-*d*]pyrimidines **108**, an important pharmacophore that exhibits anti-inflammatory, antiplatelet, and antithrombotic activities [159], was generated by a one-pot three-component reaction of 3-iodochromones **105**, several substituted terminal alkynes **106** and methyl carbamidate **107** through a Sonogashira coupling, condensation, and cycloaddition reactions [160]. Using iodochromones bearing an electron-withdrawing group (NO_2 or Br) lead to the corresponding pyrimidines **108** in low yields. The reaction can also be performed in a sequential way, stirring the appropriate iodochromone, substituted alkyne, $PdCl_2(PPh_3)_2$, CuI, and DIPEA in DMF at room temperature for 2 h and then adding the substituted amidines and K_2CO_3 the resulting mixture was heated at 60 °C for 6 h (Scheme **36**). In some cases, this alternative approach gives slightly better reaction yields.

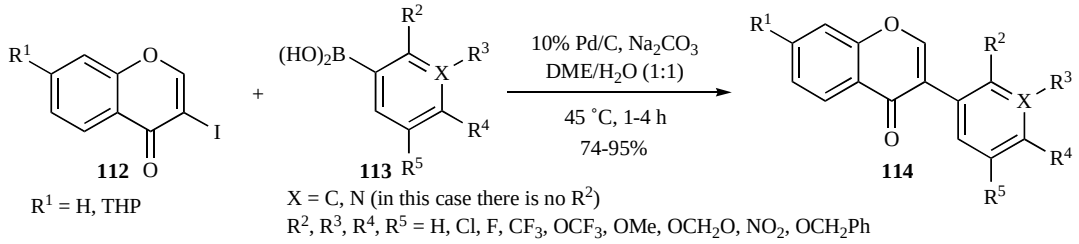
Suzuki cross-coupling reaction of 3-iodoflavone **109** with *p*-tolylboronic acid gave access to 2,3-diarylchromone **110** (Scheme **37**). Zhou and co-workers, also succeeded in the diversification of 3-iodoflavone derivatives **109** through demethylation of 2'-methoxyflavone and its subsequent Pd-catalyzed intramolecular C-



Scheme 36. Synthesis of benzopyrano[4,3-*d*]pyrimidines **108** through a one-pot three-component reaction of 3-iodochromones **105**, terminal alkynes **106** and methyl carbamidate **107**.



Scheme 37. Synthesis of a 2,3-diarylchromone **110** and 11*H*-benzofuro[3,2-*b*]chromen-11-one **111**.

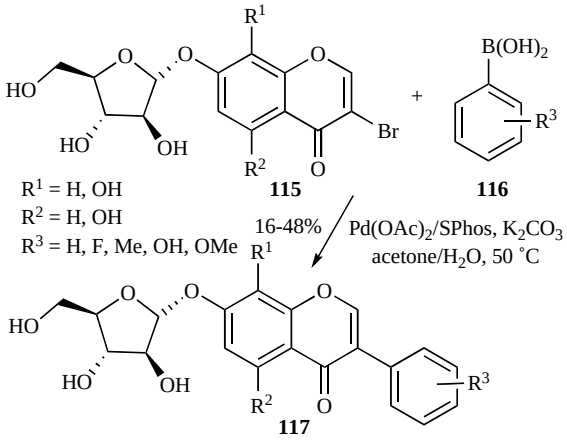


Scheme 38. Synthesis of isoflavones **114**.

O bond formation leading to tetracyclic furan-containing product **111**, offering an increase in molecular complexity by transformation into polycyclic aromatic compounds (Scheme **37**) [64].

Bearing in mind the construction of the isoflavone core by a possible scalable synthesis, Felpin and co-workers [161] bed on a solution-phase Suzuki reaction using Pd(0)/C as heterogenous practical and inexpensive catalyst under ligand-free conditions, which was then used by other authors (Scheme **38**) [162, 163]. Beyond the excellent yields of cross-coupled products **114**, the heterogeneous nature of the catalyst is extremely well suited for large-scale applications. Suzuki coupling of 3-iodo-2-methylthiochromone with phenylboronic acid under $PdCl_2(PPh_3)_2$, K_2CO_3 and DMF/H_2O reaction conditions afforded 3-iodo-2-methylthioisoflavone in an excellent yield (94%) [164]. The cross-coupling of halogenated 3-iodochromones with substituted phenylboronic acids in the presence of $Pd(PPh_3)_4$ and Na_2CO_3 in benzene afforded the corresponding halogenated isoflavones in moderate to high yields [75, 165]. The reaction of 3-bromoflavone with phenylboronic acid in the presence of $Pd(PPh_3)_4$ and K_3PO_4 under microwave irradiation conditions afforded the 2,3-diphenylchromone in good yield (86%) [98].

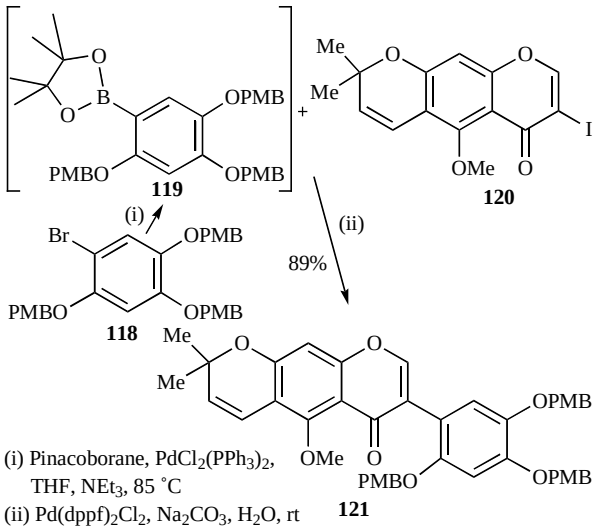
A Suzuki-Miyaura cross-coupling reaction of glycosylated 3-bromochromones **115** with an array of different commercially available aryl boronic acids **116** under $Pd(OAc)_2$/SPhos conditions led to the synthesis of 7-glycosylisoflavones **117** (Scheme **39**) [166]. This coupling reaction offers a quick and divergent path to this class of natural compounds, which are difficult to acess by other methods although the low yields. The isoflavone skeleton in the convergent total synthesis of kwakhurin was constructed by Suzuki-Miyaura coupling of the appropriate 3-bromochromone and arylboronic acid in the presence of tetrabutylammonium bromide as additive [167].



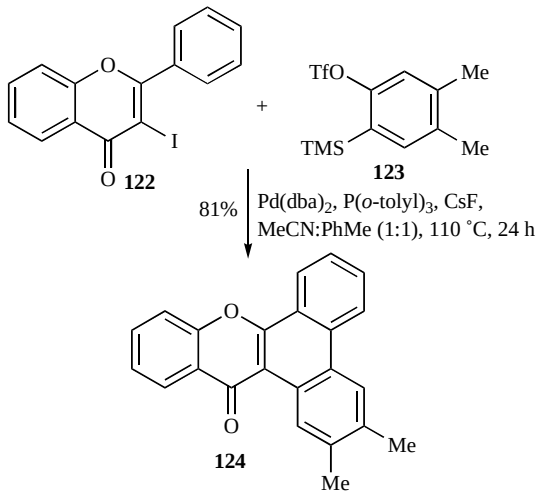
Scheme 39. Synthesis of isoflavones **117**.

A one-pot sequential boronation and Suzuki-Miyaura cross-coupling protocol of 3-iodo-5-methoxy-8,8-dimethylpyrano[3,2-*g*]chromen-4(8*H*)-one **120** allowed to obtain a substituted isoflavone-type compound **121** in an excellent overall yield avoiding the stability issue of borate ester (Scheme **40**) [76]. In the total synthesis of glaziovianin A, a powerful antitumor isoflavone, and various of their pharmacological active analogues a similar procedure was used in the Suzuki-Miyaura cross-coupling reaction of iodochromones and stable arylboronates [168, 169].

3-Iodoflavone **122** was easily transformed to the fused polycyclic aromatic product **124** through a Pd-catalyzed carboannulation reaction with an aryne, formed *in situ* from the reaction of fluoride anion with 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **123** (Scheme **41**) [170].



Scheme 40. A tandem boronation and Suzuki cross-coupling protocol of 3-iodo-5-methoxy-8,8-dimethylpyrano[3,2-*g*]chromen-4(8*H*)-one **121**.

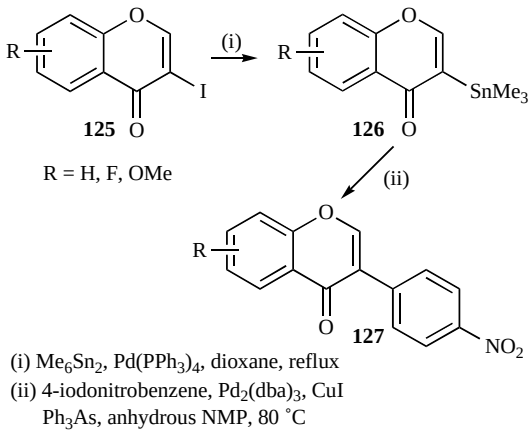


Scheme 41. Synthesis of fused polycyclic aromatic product **124** through a Pd-catalyzed carboannulation reaction of 3-iodoflavone **122** and an aryne.

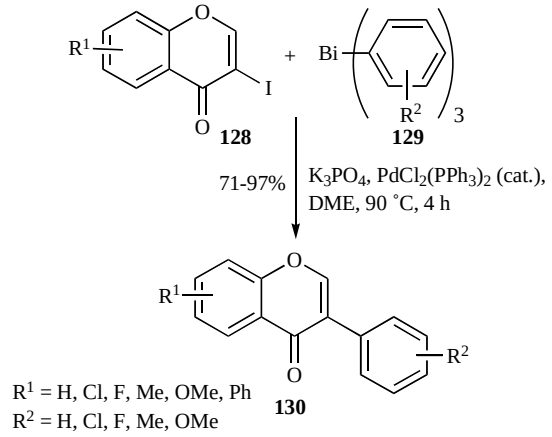
3-Iodochromones **125** are efficiently converted to the air-stable and crystallisable 3-(trimethylstannyl)chromones **126** by using $Pd(PPh_3)_4$ and hexamethylditin in dioxane. The Stille reaction of 3-(trimethylstannyl)chromones **126** with 4-iodonitrobenzene afforded ring A substituted 4'-nitroisoflavones **127** (Scheme **42**) [165]. Stille reaction of 3-bromo-5,7-di-*O*-methylchrysin with allyltributyltin in the presence of a catalytic amount of $Pd(PPh_3)_4$ in anhydrous DMF prompted the synthesis of 3-allyl-5,7-di-*O*-methylchrysin [171].

The first palladium cross-coupling reaction of 3-iodochromones with various triarylbismuths, used as substoichiometric multicoupling nucleophiles, gave access to the synthesis of a variety of functionalized isoflavones. Reaction conditions were studied and optimized with different bases and solvents at different temperatures to establish the optimum combinations for this novel transformation: 3.3 equiv of iodochromone derivatives **128**; 1 equiv of triarylbismuths **129**, 0.09 equiv of palladium(II) catalyst and 6 equiv of base (Scheme **43**) [172].

Under Heck conditions, 3-bromo-2-styrylchromones **131** were coupled with styrenes **132** in the presence of $Pd(PPh_3)_4$ and triphenylphosphine as catalyst and using triethylamine as base, mainly leading to the initially unexpected formation of 2,3-



Scheme 42. Synthesis of ring A substituted 4'-nitroisoflavones **127** from 3-iodochromones **125**.



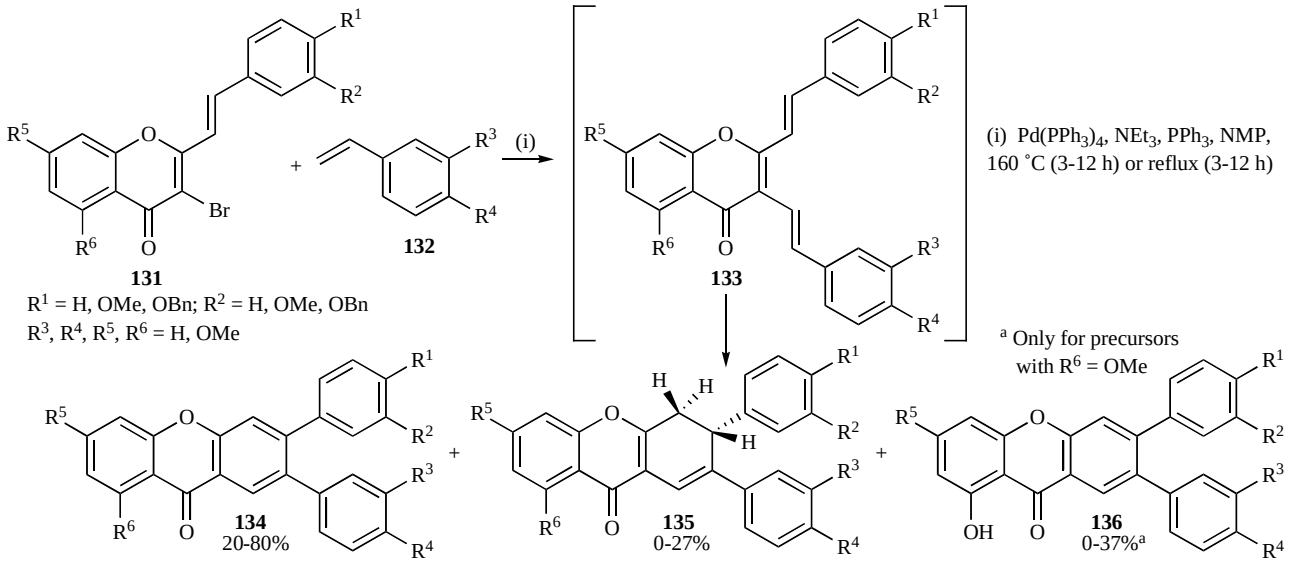
Scheme 43. Synthesis of isoflavones **130** from 3-iodochromones **128** and triarylbismuths **129**.

diarylxanthone derivatives **134-136**. The structural assignment of the minor products, 2,3-diaryl-3,4-dihydroxanthones **135**, demystified the reaction mechanism indicating the initial formation of the expected 2,3-distyrylchromones **133** products, which suffer thermal electrocyclization, due to the high temperature conditions, and oxidation leading to the final obtained compounds. Starting from 5-methoxy-2-styrylchromones **131** (R^6 = OMe), 8-hydroxy-2,3-diarylxanthones **136** were also obtained (Scheme **44**) [62, 173, 174].

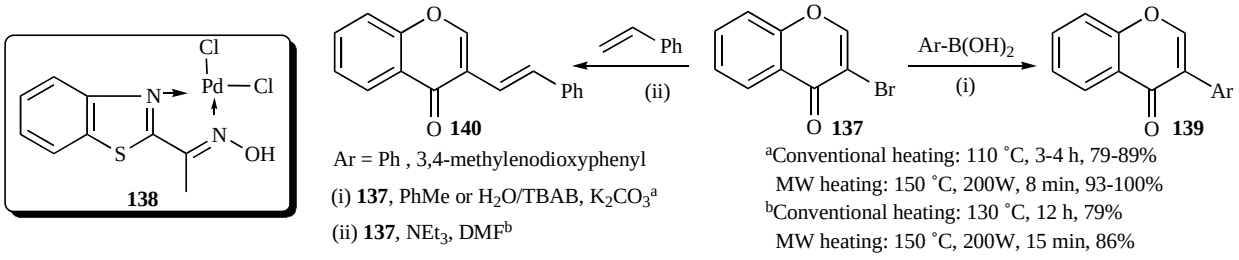
Also taking advantage of Heck-Jeffery reaction conditions [$Pd(OAc)_2$, K_2CO_3, $(Bu)_4NBr$, DMF], several 3-bromoflavones react with styrene derivatives leading to (*E*)-3-styrylflavones with total diastereoselectivity. The use of microwave irradiation was found to be the key to greatly improve this transformation (300 W, 5-10 min) [61].

One of the key-steps in the total synthesis of vinaxanthone, a fungus metabolite, was the cross-coupling reaction of 6,7-dimethoxy-3-iodochromone-5-carboxylate with methyl vinyl ketone in the presence of $Pd(OAc)_2$, using NEt_3 as base and MeCN as solvent at 50 °C, for 7.5 h [79].

Suzuki and Heck cross-coupling reactions of 3-bromochromone **137** using a stable new homogenous benzothiazole-based palladium(II) pre-catalyst **138** were studied by Dawood [175], both under thermal and microwave heating conditions (Scheme **45**). The reaction of phenylboronic acid with 3-bromochromone **137** in the presence of the pre-catalyst **138** in toluene and potassium carbonate under thermal heating for 4 h afforded isoflavone **139** (Ar = Ph) in



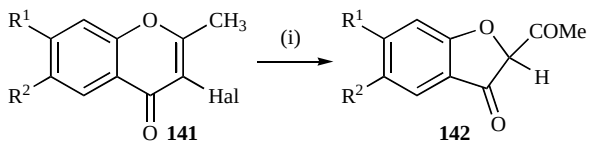
Scheme 44. Synthesis of 2,3-diarylxanthones **134-136**.



Scheme 45. Synthesis of isoflavones **139** and 3-styrylchromone **140** from 3-bromochromone **137**.

an excellent yield (89%). Optimum conversion (93% isolated yield) was achieved within 8 min when the same coupling was carried out under microwave irradiation. When water was used as solvent, in the reaction with 3,4-methylenedioxyphenylboronic acid, full conversion into 3-(3,4-methylenedioxyphenyl)chromone **139** (Ar = 3,4-methylenedioxyphenyl) was achieved after 8 min under microwave irradiation. 3-Styrylchromone **140** was obtained through Heck cross-coupling reaction of 3-bromochromone with styrene using pre-catalyst **138** in DMF and triethylamine (Scheme **45**). Under microwave irradiation the 3-styrylchromone **140** is obtained in 86% yield.

Since 2003 there are only two new transformations of 3-halochromones, both in 2012, that were not based on metal cross-coupling reactions. Treatment of an ethanolic solution of substituted 3-halo-2-methylchromones **141** with aqueous KOH solution under microwaves for 1 min resulted in the formation of 2-acetylcoumaran-3-ones **142** (Scheme **46**) [176].



Scheme 46. Synthesis of 2-acetylcoumaran-3-ones **142** from 3-halochromones **141**.

An efficient entry to functionalized 2-(2-hydroxy-benzoyl)-4*H*-furo[3,2-*c*]chromones **145** performed by reaction of 2-aminochromones **144** with 3-bromochromones **143** was established (Scheme **47**) [177]. In this reaction, 2-aminochromone acts as a masked 4-hydroxycoumarin.

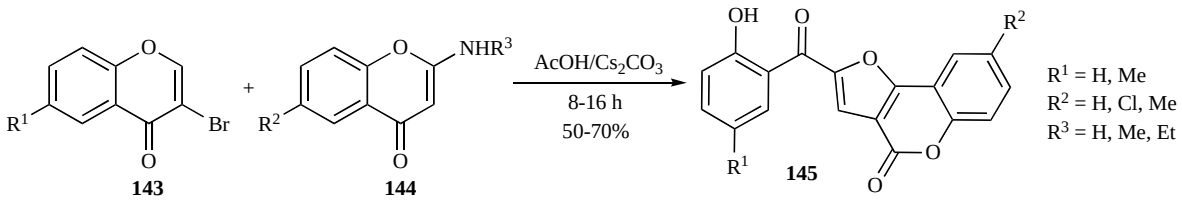
3.2. Reactivity of other Mono- and Polyhalogenated Chromones

Along with 3-halochromones, other mono- and polyhalogenated chromones were also described in the literature as exceptional frameworks for the construction of more complex compounds, namely by metal-catalyzed reactions.

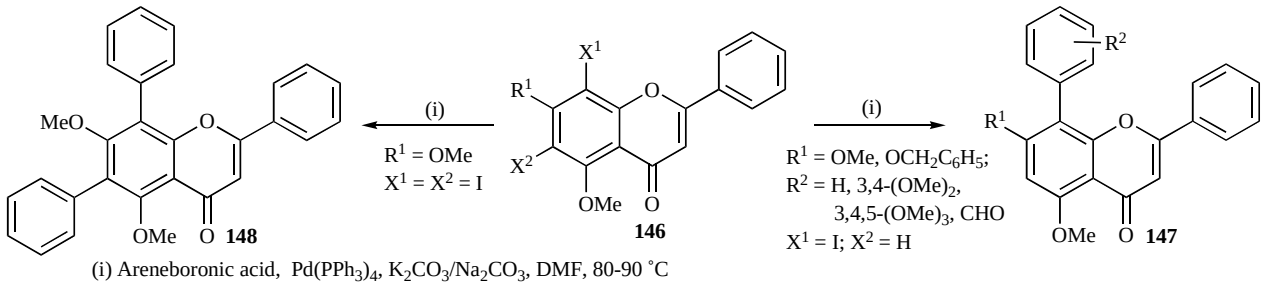
Suzuki-Miyaura cross-coupling reaction of 8-iodo- and 6,8-diiodoflavones **146** with areneboronic acids in DMF with a catalytic amount of $Pd(PPh_3)_4$ and a base afforded 8-aryl- **147** and 6,8-diarylflavones **148**, respectively (Scheme **48**) [82, 118]. This is a convenient method to increase molecular complexity in a predictable and controlled way. Other polysubstituted 8-iodoflavones were transformed into a range of 8-aryl derivatives by Suzuki arylation reactions using $PdCl_2(PPh_3)_2$ as a catalyst [178].

Via similar Suzuki-Miyaura reaction conditions as applied to the reaction of 8-iodo-5,7-di-*O*-methoxychrysin **149** with alkyl and areneboronic acids various 8-(alkyl- and aryl)chrysin derivatives **150** were prepared in satisfactory yields (50-79%) (Scheme **49**) [179]. After methyl groups cleavage (BBr_3 demethylation conditions) the obtained chrysin analogues towards possible biological activity against cyclooxygenase (COX)-2 catalyzed prostaglandin E_2 and iNOS-mediated NO production. Among these analogues, 5,7-dihydroxy-8-(pyridin-4-yl)flavone exhibited impressive inhibitory activity compared to those of chrysin.

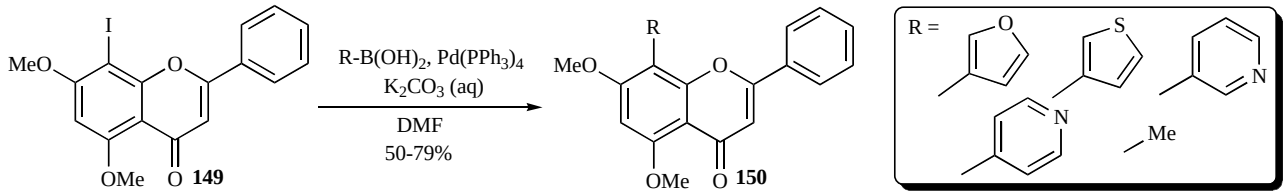
Suzuki-Miyaura reaction of several monobrominated flavones using Li's POPd with CsF [180] furnished the corresponding arylated flavones in good yields (53-84%). Efforts to selectively monoarylate 7-bromo-4'-chloroflavone using this protocol were unsuccessful and provided inseparable mixtures of monoarylated and bisarylated products. Application of Buchwald-Hartwig amination reaction conditions $Pd_2(dba)_3$-BINAP-NaO^{t}Bu with microwave



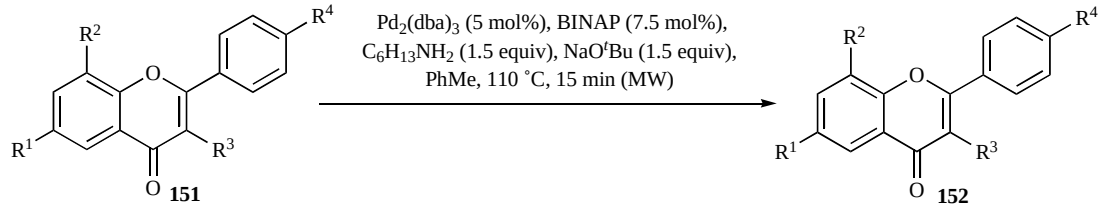
Scheme 47. Synthesis of 2-(2-hydroxybenzoyl)-4*H*-furo[3,2-*c*]chromones **145**.



Scheme 48. Synthesis of 8-aryl- **147** and 6,8-diarylflavones **148** by Suzuki-Miyaura cross-coupling reaction.



Scheme 49. Synthesis of 8-substituted 5,7-di-*O*-methylcrysin **150** by Suzuki-Miyaura cross-coupling reaction.



R1 = H, R2 = H; R3 = Br; R4 = H
R1 = Br, R2 = R3 = R4 = H
R1 = H, R2 = Br, R3 = R4 = H
R1 = Br, R2 = H, R3 = R4 = Cl

[a]Pd(OAc)2 instead of Pd(dba)3
[b]1 equiv C6H13NH2, 80 °C, 1 h (MW)

R1 = H, R2 = H; R3 = NHC6H13; R4 = H (33%)[a]
R1 = NHC6H13, R2 = R3 = R4 = H (42%)
R1 = H, R2 = NHC6H13, R3 = R4 = H (77%)
R1 = NHC6H13, R2 = H, R3 = R4 = Cl (37%)[b]

Scheme 50. Buchwald-Hartwig aminations on bromoflavones **151**.

heating afforded a range of functionalized flavones **152** in moderate to good yields (Scheme **50**) [98].

The fluorinated biflavone **156** was synthesized *via* the standard Suzuki-Miyaura coupling reaction of 4',7-bis(difluoromethoxy)-6-iodo-5-methoxyflavone **155** with 4',7-dimethoxyflavone 3'-boronate **154** that was prepared through boronation of iodoflavone **153** and purified through column chromatography prior to the coupling with 6-iodoflavone **155** (Scheme **51**) [123].

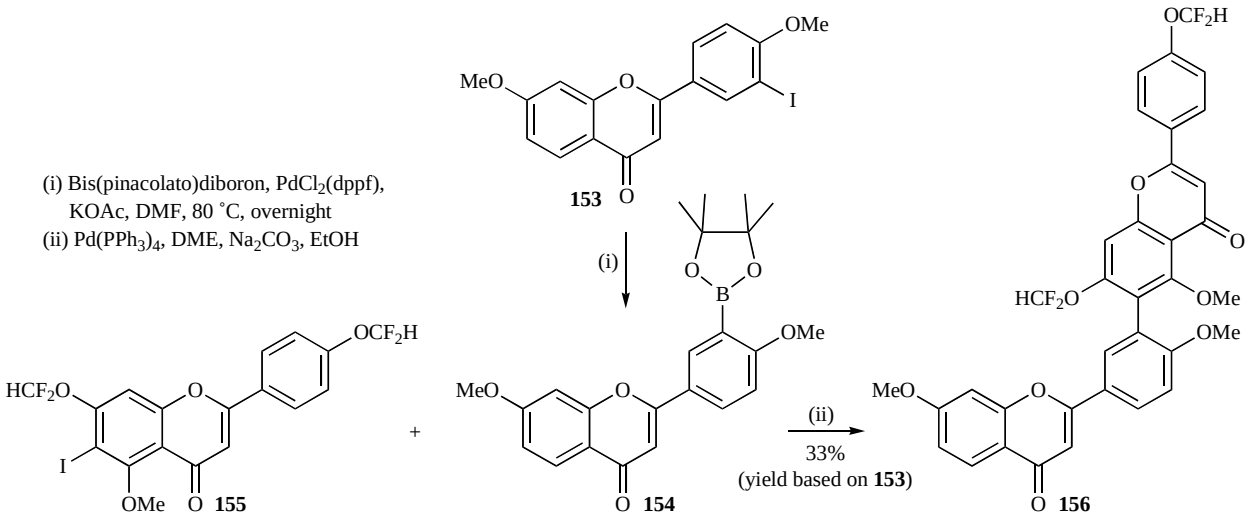
Vinyl and allyl groups were introduced to 8-iodo-5,7-di-*O*-methylchrysin **157** through Stille coupling, by reacting with vinyl-butyltin or allylbutyltin in the presence of a catalytic amount of $Pd(PPh_3)_4$ in DMF as solvent (Scheme **52**) [171].

In the synthesis of radioiodinated 2-styrylchromones as potential binders for amyloid plaques, some 6-tributyltin 2-styrylchromones were synthesized from the corresponding bromo derivatives using a Pd(0)-catalyzed bromo to tributyltin exchange reaction [116].

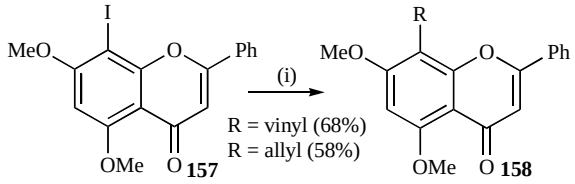
7-(2-Methoxycarbonylvinyl)-3-hydroxychromones **160** were synthesized using Heck coupling reaction of 7-bromo-3-hydroxychromones **159** with methyl acrylate (Scheme **53**) [181]. These compounds, bearing an electron acceptor group at 7-position, were revealed as good dyes with red shifted dual emission, which may be important for the development of new fluorescent probes in biological research.

Chromones bearing bromo substituents at their A and C rings were reacted with various terminal alkenes by the Heck reaction affording alkenyl-substituted chromones. In the presence of a phosphine ligand [$Pd(PPh_3)_4$ or $Pd(OAc)_2$, PPh_3, NEt_3, NMP], the reactivity of substrates with bromine in their A ring showed a marked difference; higher reactivity was found in the case of 7-bromochromone compared to 6-bromochromone. Modified Jeffery's conditions [$Pd(OAc)_2$, K_2CO_3, KCl, Bu_4NBr, DMF] were found to give higher yields in shorter reaction periods [182].

Dahlén and co-workers [183, 184] envisaged and established a program to introduce substituents at 6- and 8-positions of flavone-type compounds using palladium-mediated reactions. Thus, both Heck and Stille coupling reactions in the 8-position of 8-bromo-6-chloroflavone **161** were possible resulting in the corresponding products **162** and **164** in good yields and regioselectivity. The func-



Scheme 51. Synthesis of a fluorinated biflavone **156** through a Suzuki-Miyaura coupling reaction.



(i) Vinyltributyltin or allyltributyltin, $Pd(PPh_3)_4$, DMF, 100 ˚C

Scheme 52. Synthesis of 8-(allyl and vinyl)-5,7-di-*O*-methylchrysin **158** through a Stille coupling reaction.

tionalization of the 6-position of **162** and **164** was possible with the use of electron-rich and sterically hindered phosphine $P(^tBu)_3$ (Scheme **54**). In these studies, the Heck and Stille coupling reactions were used to functionalize flavones at 3-, 6- and 8- positions.

The same research group [87] used an identical synthetic strategy for 2,3,6,8-tetrasubstituted chromones from 2-(aryl or styryl)-8-bromo-6-chloro-3-hydroxychromones. This scaffold allowed the regioselective introduction of different substituents in the 3-, 6-, and 8-positions using palladium-mediated reactions (Stille, Heck, Sonogashira, and Suzuki reactions). In general, these reactions gave high yields and microwave fast heating to high temperatures in sealed vessels was more effective compared to traditional thermal heating.

6-Fluoro-3-formyl-2,7-di(morpholino or piperidino)chromones **169**, potential topoisomerase inhibitor anticancer agents, were prepared by the nucleophilic substitution of both 7-chlorine atom and *N*-methylanilino moiety of 7-chloro-6-fluoro-3-formyl-2-(*N*-methyl-*N*-phenylamino)chromone **167** (Scheme **55**) [13].

The nucleophilic substitution of the 7-fluorine atom of 5,6,7,8-tetrafluoro-2-ethoxycarbonylchromone **170** by the action of primary amines was carried out in good yields (Scheme **56**) [185, 186]. The same type of reaction occured when 6,7,8-trifluoro-3-methylchromone-3-benzocarboxamide was reacted with secondary amines, in acetonitrile [187].

4',6-Dicyanoflavone **173** was obtained from the reaction of 4',6-dibromoflavone **172** with copper(I) cyanide in NMP under heating conditions and isolated over neutral Al_2O_3 (Scheme **57**) [188]. 8-Iodo- and 6,8-diiodochrysin derivatives were converted to 8-trifluoromethyl and 6,8-ditrifluoromethyl analogues by the reaction with $FSO_2CF_2CO_2Me$ in the presence of CuI in DMF [46].

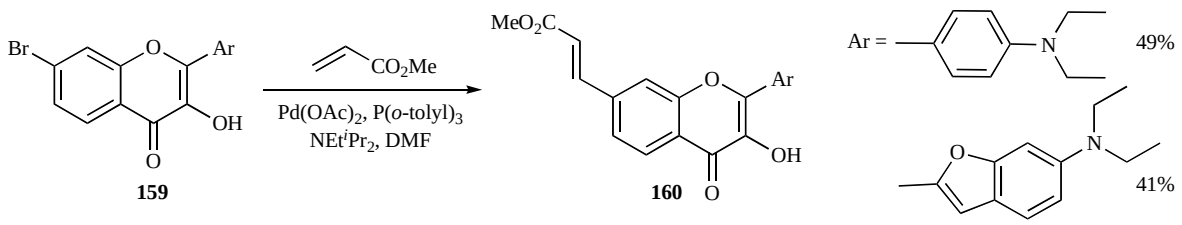
3.3. Reactivity of Halomethylchromones

The main focus of the reactivity of halomethylchromones is based on their three electropositive centres, namely the carbon bonded to the halogen, and the C-2 and C-4 carbons of their pyran ring. The presence of a polyhaloalkyl (R^F) group, due to its strong electron-withdrawing capacity, gives the chromone´s core a huge diversity of possible transformations.

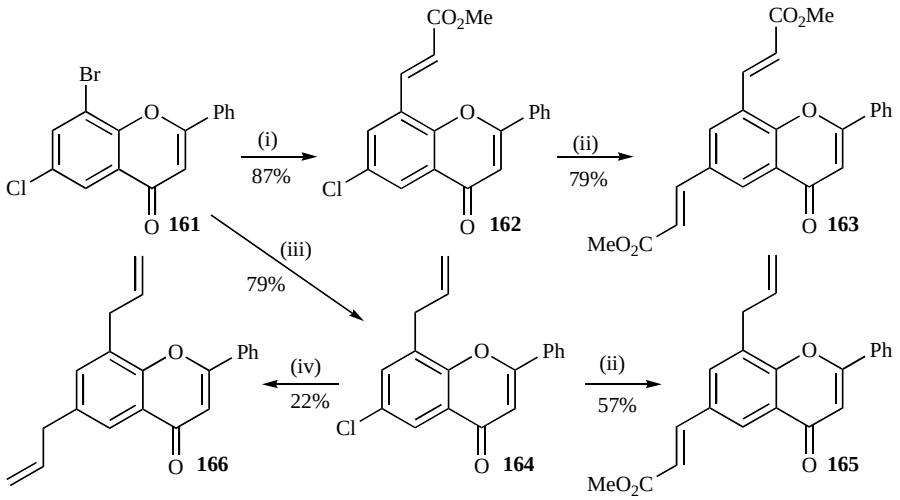
Thieno[3,4-*b*]chromones **176**, compounds displaying interesting fluorescence properties, were obtained from the reaction of 3-aroyl-2-(bromo- and dibromomethyl)chromones **174** and **175** with thioacetamide in DMF (Scheme **58**) [189]. In the same paper, the behaviour of 2-bromomethylchromone **174** towards sodium acetate in refluxing ethanol or cooling DMF was also studied, resulting in the replacement of bromine by acetate anion to give compound **177** (Scheme **58**).

Ghosh and Karak also studied the bromine replacement of 2-bromomethylchromone **174** by other nucleophiles, but the most relevant aspect of their study was the reaction with bisnucleophiles and the formation of chromone-fused oxazine and pyridazines **178** (Scheme **58**) [190].

The potential antibacterial agents 2-(arylthiomethyl)chromones were accessed by the nucleophilic displacement of bromine of 2-(bromomethyl)chromones with thiophenol in refluxing dry DMF

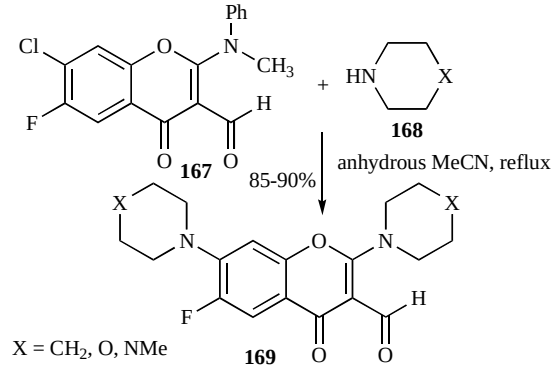


Scheme 53. Heck reaction functionalization of 3-hydroxyflavone-type compounds **159**.

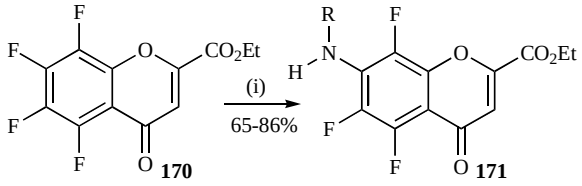


(i) methyl acrylate, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, NEt_3, DMF, 160 ˚C, 30 min, MW
(ii) methyl acrylate, $Pd_2(dba)_3$, $[P(^tBu)_3H]BF_4$, NEt_3, dioxane, 160 ˚C, 30 min, MW
(iii) allylSnBu$_3$, $Pd(PPh_3)_4$, dioxane, 80 ˚C, 14 h; (iv) allylSnBu$_3$, $Pd_2(dba)_3$, $P(^tBu)_3$, dioxane, 80 ˚C, 14 h

Scheme 54. Heck and Stille reactions for the functionalization of 8-bromo-6-chloroflavone **161**.



Scheme 55. Nucleophilic reaction of 7-chloro-6-fluoro-3-formyl-2-(*N*-methyl-*N*-phenylamino)chromone **167**.



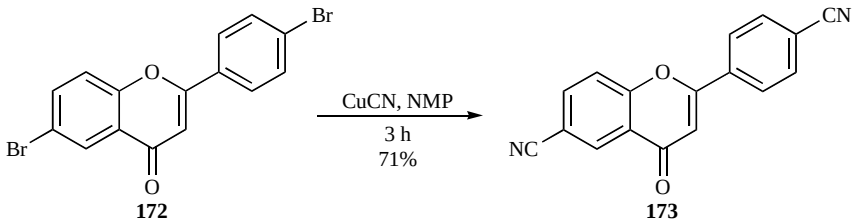
Scheme 56. Nucleophilic reaction of 5,6,7,8-tetrafluoro-2-ethoxycarbonylchromone **170**.

[191]. Treatment of 6-(bromomethyl)chromone with hexamethylenetetramine in refluxing acetic acid and further addition of HCl afforded chromone-6-carboxyaldehyde in good yield [188].

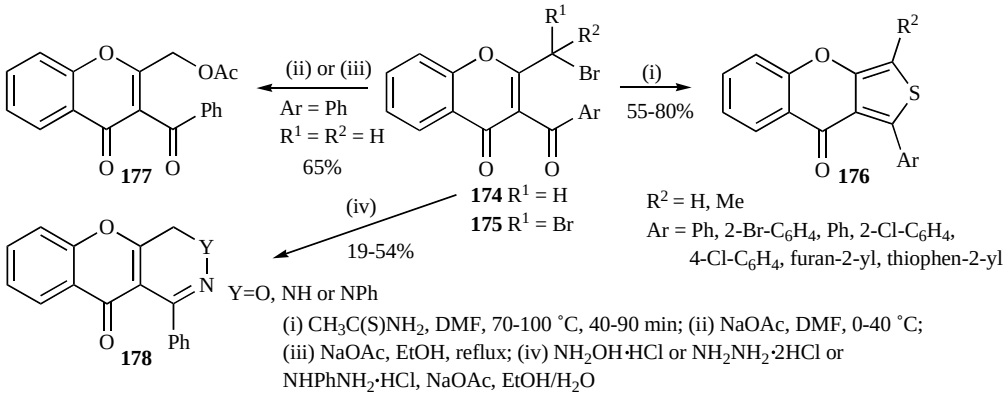
Novel dithiocarbamate substituted chromones **182-184**, some of them with potent broad-spectrum antitumor activity, were recently prepared by a three-component reaction protocol starting from halochromones **179-181**, an amine and carbon disulphide (Scheme **59**) [192], and potassium phosphate [193].

During the last decade Sosnovskikh [128, 194-201] and his group continued to devote great attention to the chemistry of 2-(polyhaloalkyl)chromones (2-R^F-chromones) **185**, particularly 2-(polyfluoromethyl)chromones (2-CF_3-chromones) [52]. Some of their possible reactions are depicted in (Scheme **60**): the reaction with ketimines leading to compounds **186-189** [194, 196, 198]; with acetophenones in the presence of lithium diisopropylamide to give 2-aroylmethyl-2-R^F-chromanones **190** [197]; and a novel annulation reaction with salicylaldehydes in the presence of piperidine that constituted a direct route to chromeno[2,3-*b*]chromen-11-ones **191** by a tandem intermolecular oxa-Michael addition and subsequent intramolecular Mannich condensation [195].

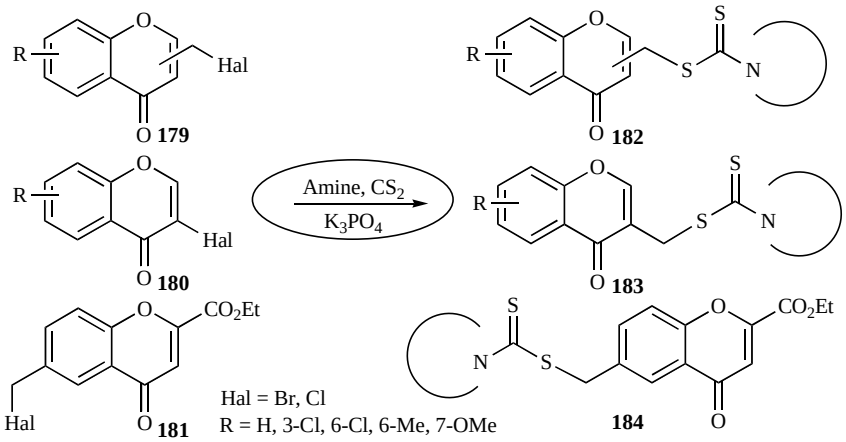
3-Cyano-2-(trifluoromethyl)chromones **192** undergo detrifluoroacetylation when reacted with morpholine, in a mixture of DMF and water affording 2-aminochromones **193** (Scheme **61**). These compounds can also be synthezised through salicyloylacetonitriles **194**, which were obtained by the treatment of **192** with aqueous alkaline medium or with a mixture of DMSO-water. Reaction of 3-cyano-2-(trifluoromethyl)chromones **192** with acetamidine hydrochloride under weak acidic conditions (NaOAc) in refluxing DMF afforded a 73:27 mixture of pyrimidin-5-one **195** and the corresponding imine derivative **196**, indicating that partial hydrolysis had occurred. This reaction comprises two intramolecular cyclizations at the keto and cyano groups to form a tricyclic imino intermediate **196**, which hydrolyzed to **195** (Scheme **61**) [194].



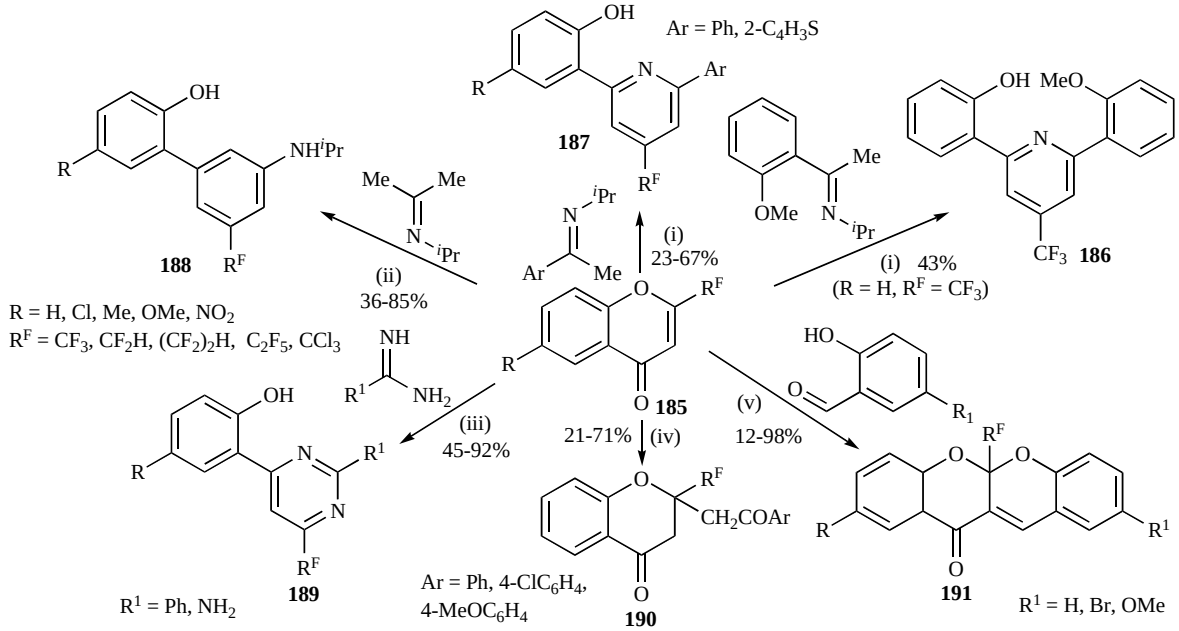
Scheme 57. Synthesis of 4',6-dicyanoflavone **173**.



Scheme 58. Reaction of 3-aroyl-2-(bromo or dibromo)chromones **174** and **175** with nucleophiles.



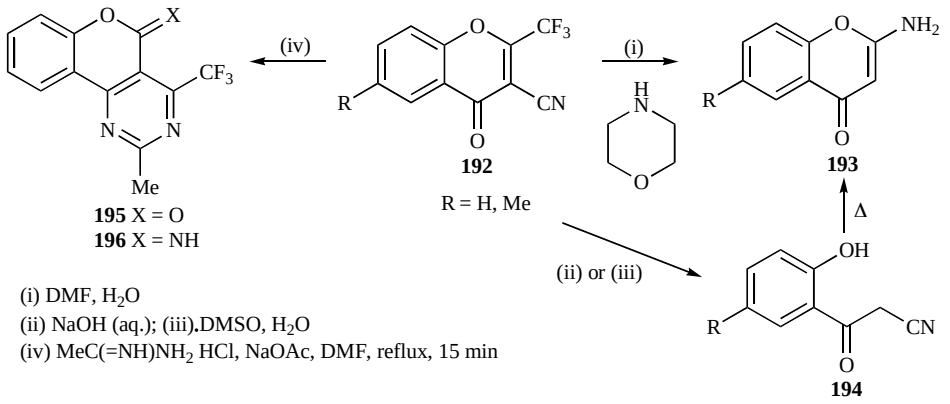
Scheme 59. Synthesis of dithiocarbamate substituted chromones **182-184**.



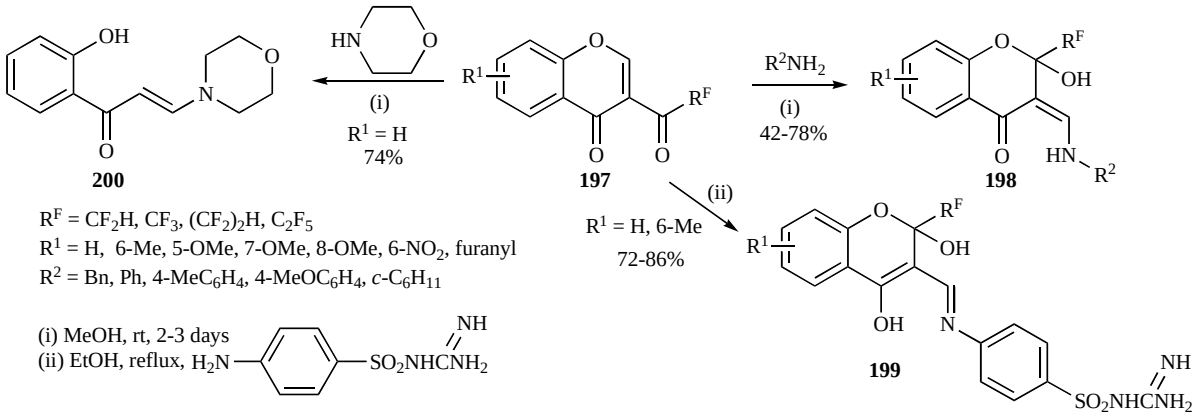
Scheme 60. Some of the reported transformations of 2-(polyhaloalkyl)chromones **185**.

3.4. Reactivity of 3-(Polyhaloacyl)chromones

Over the last few years Sosnovskikh and his group started to explore and develop the chemistry of 3-(polyfluoroacyl)chromones (3-R^FCO-chromones). The presence of a 3-R^FCO on a chromone nucleus dramatically changes the reactivity of the pyrone ring especially towards nucleophiles, and it is an extremely interesting build-



Scheme 61. Detrifluoroacetylation of 3-cyano-2-trifluoromethylchromones **192**.



Scheme 62. Reaction of 3-R^FCO-chromones **197** with amines.

ing block for the construction of more complex R^F-containing heterocycles.

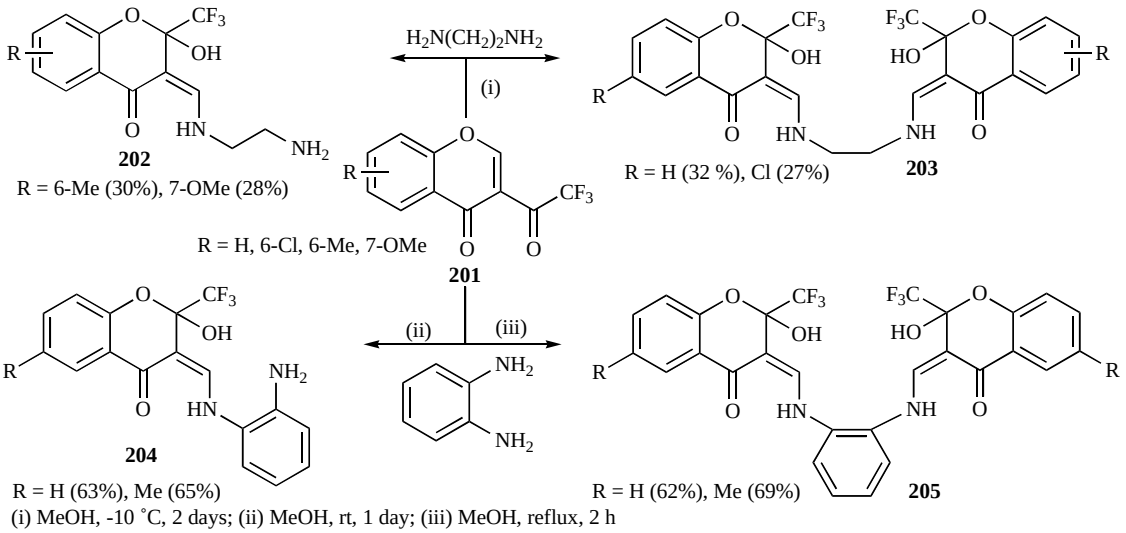
Reaction of 3-R^FCO-chromones **197** with amines [110, 112, 202, 203] (aliphatic and aromatic amines, the latter bearing electron-donating or electron-withdrawing groups) generally proceed *via* a nucleophilic 1,4-addition mechanism with concomitant opening of the pyrone ring and subsequent intramolecular cyclization of the intermediate at the COR^F group leading to aminomethylene-2-hydroxy-2-R^F-chromanones **198** (Scheme **62**). The hydrogen bond between the pyranone carbonyl oxygen and the hydrogen of the NH group of chromanones **198** is an effective driving force to explain their formation, but the presence of the R^F group which also stabilizes the cyclic hemiketal form and makes the dehydration step difficult must also be considered. Reaction with sulfaguanidine (4-amino-*N*-carbamimidoylbenzenesulfonamide) in refluxing ethanol gave the same type of chromanone derivatives **199** (Scheme **62**). Under the same conditions, morpholine react in a divergent manner to give a 1:1 mixture of aminoenone **200** and morpholinium trifluoracetate (a detrifluoromethylacetylation took place) [202].

The reactivity of 3-(trifluoroacetyl)chromones **201** with diamines was also studied (Scheme **63**) [204]. Reaction with the more basic ethylenediamine was carried out under mild conditions and proved to be influenced by the substituents of the benzene ring of chromones: electron-donating groups gave only mono-adducts **202**, while the unsubstituted and 6-chlorochromone gave bis-adducts **203**. The reaction with the less basic *o*-phenylenediamine can be controlled by the experimental conditions, affording mono-adducts **204** with an excess of *o*-phenylenediamine in methanol at ~20 °C or bis-adducts **205** in refluxing methanol with an excess of chromone (Scheme **63**). All the products were obtained by precipitation from the reaction mixture.

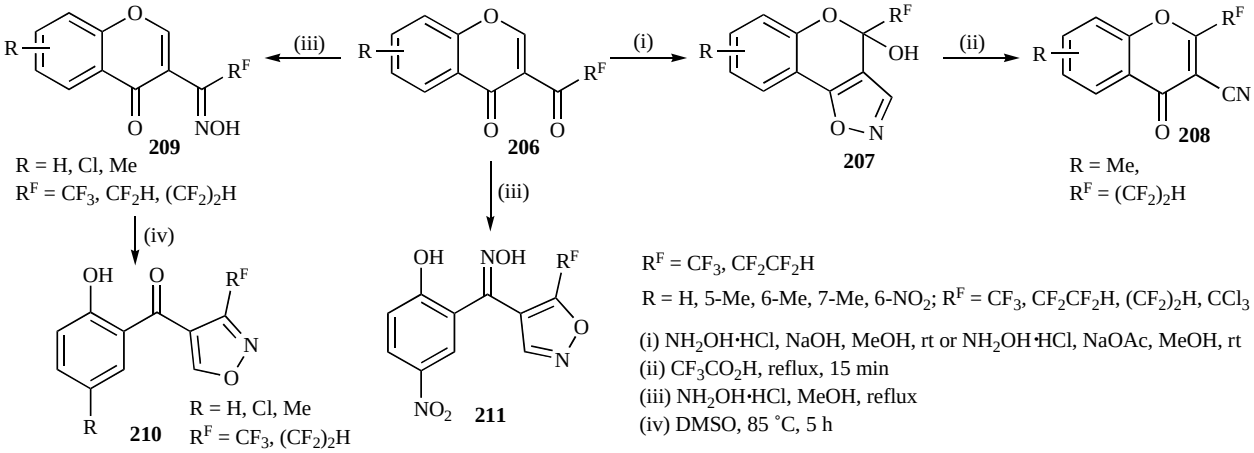
The reaction of 3-(polyfluoroacetyl)chromones **206** with hydroxylamine gave novel R^F-containing isoxazole and chromone derivatives, depending on reaction conditions (Scheme **64**) [194, 205]. The reaction with two molar equiv of hydroxylamine, obtained *in situ* from hydroxylamine hydrochloride in basic medium, in methanol at room temperature yielded chromeno[3,4-*d*]isoxazoles **207** (Scheme **64**). The reaction proceeded by attack at the C-2 atom (nucleophilic 1,4-addition), with posterior pyrone ring opening, heterocyclization between the hydroxylamine and the carbonyl group and finally formation of the cyclic hemiketal due to the presence of the R^FCO group. Treatment of chromeno[3,4-*d*]isoxazoles **207** with trifluoroacetic acid gave 3-cyano-2-R^F-chromones **208** (Scheme **64**).

The reaction of 3-R^FCO-chromones **206** with hydroxylamine hydrochloride in the presence of a catalytic amount of concentrated HCl in methanol afforded the corresponding oximes **209** formed by nucleophilic 1,2-addition of hydroxylamine to the R^FCO group. These oximes were transformed into salicyloylisoxazoles **210** by heating them in DMSO for 5 h. However, refluxing chromones bearing the electron-withdrawing 6-nitro group with hydroxylamine hydrochloride in methanol for 5 h led to the formation of 5-R^F-4-salicyloylisoxazole oximes **211** (Scheme **64**).

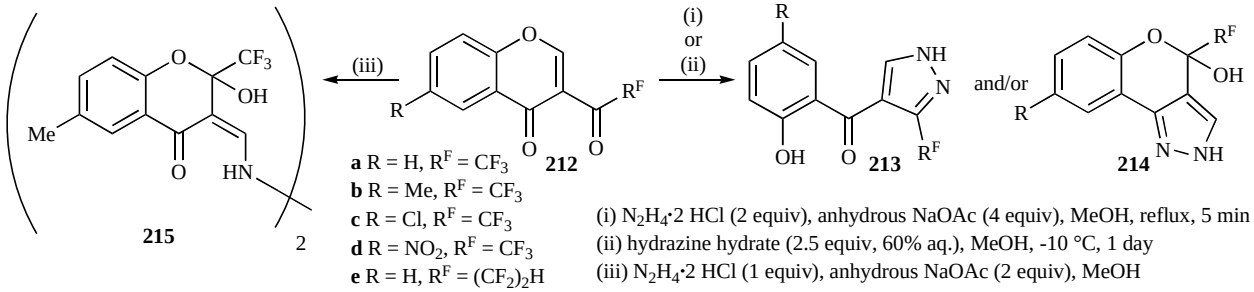
The synthesis of R^F-containing pyrazoles **213** and **214** were readily achieved by the reaction of 3-R^FCO-chromones **212** with hydrazine derivatives (Scheme **65**) [206]. The mechanism involves a nucleophilic 1,4-addition with subsequent pyrone ring opening and heterocyclization at the R^FCO group to give 4-(2-hydroxyaroyl)-3-R^F-alkylpyrazoles **213** or at the aroyl group to give 4-polyfluoroalkyl-2,4-dihydrochromeno[4,3-*c*]pyrazol-4-ols **214** after hemiketal formation. The regioselectivity inherent to these reactions is far from generic. The observed ratio of these products which, in some cases, is very satisfactory, strongly depends on fac-



Scheme 63. Reaction of 3-(trifluoroacetyl)chromones **201** with diamines.



Scheme 64. Reaction of 3-(polyfluoroacetyl)chromones **206** with hydroxylamine.

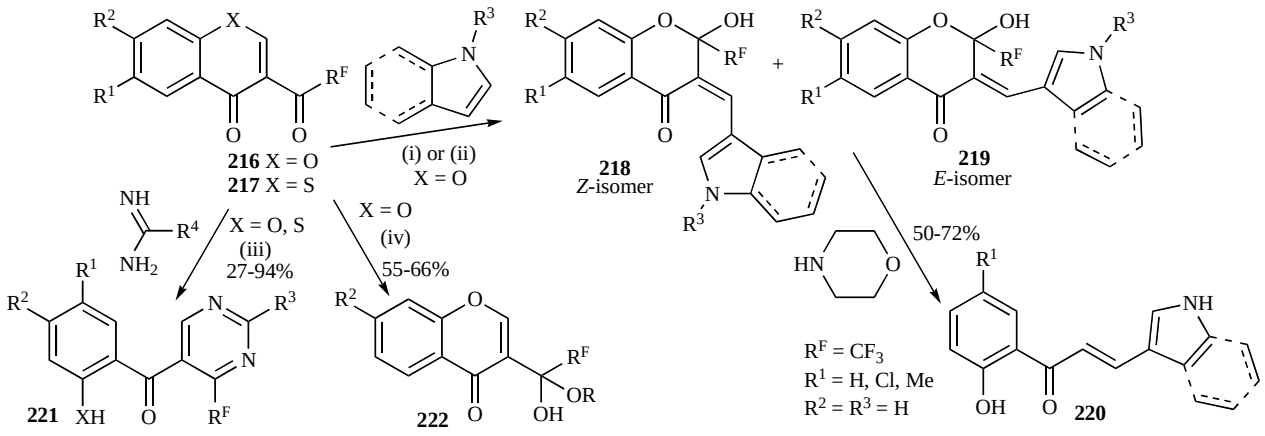


Scheme 65. Reaction of 3-(polyfluoroacetyl)chromones **212** with hydrazine.

tors such as the length of the R^F group, the nature of the chromone substituents and basic or acidic reaction conditions (Scheme **65**).

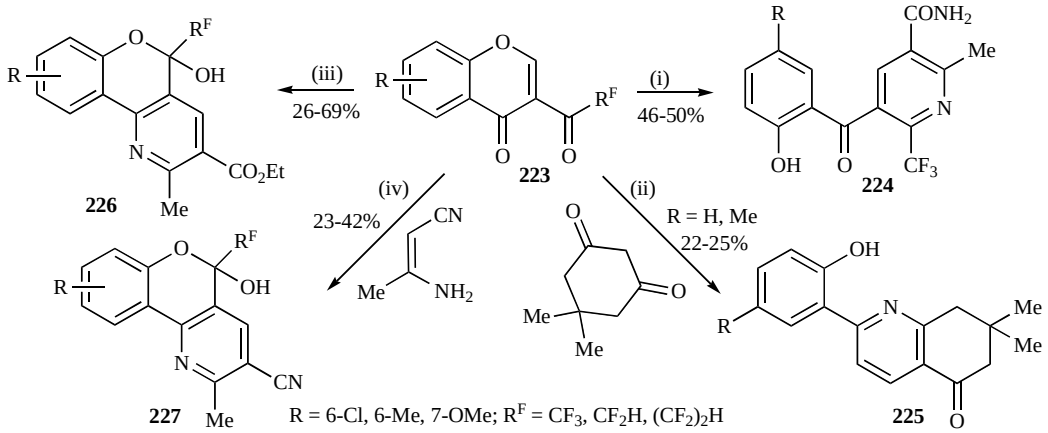
The reaction of unsubstituted 3-(trifluoromethyl)chromone **212a** or their 6-methyl derivative **212b** with hydrazine dihydrochloride in the presence of anhydrous sodium acetate (in the molar ratio of 1:2:4, respectively) gave only 3-(trifluoromethyl)pyrazoles **213a,b**; the 6-chloro derivative **212c** gave a mixture of pyrazoles **213c** and **214c**, while the 6-nitro derivative **212d** gave only 4-(trifluoromethyl)-2,4-dihydrochromeno[4,3-*c*]pyrazol-4-ol **214d**. The reaction of **212a,b** with an excess of hydrazine hydrate (2.5 equiv) decomposes the chromones into the corresponding 2'-hydroxyacetophenones, while that of **212c** still gave the mixture of **213c** and **214c**. Replacing the CF_3 group by a $(CF_2)_2H$ group, chromone **212e** led to a mixture of pyrazoles with the composition and yield dependent on the reaction conditions. Under acidic conditions (procedure i), a 65:35 mixture in the ratio of **213e**:**214e** was obtained from chromone **212e** (57% yield), whereas under basic conditions (procedure ii), a ratio of 28:72 was obtained (Scheme **65**). The reaction of chromone **212b** with hydrazine dihydrochloride in the presence of anhydrous sodium acetate (in the molar ratio of 1:1:2, respectively) led to the bis-adduct **215** (Scheme 65). The same type of reactions and pyrazoles has been described for the reaction of **212** with methyl and phenyl hydrazines.

Reaction of 3-R^FCO-chromones **216** with indole and *N*-methylindole in refluxing pyridine, and *N*-methylpyrrole under solvent-free conditions gave an isomeric mixture of 3-(azolylmethylene)



R = Et, Me; R^1 = H, Cl, Me; R^2 = H, OMe; R^3 = H, Me; R^4= H, Me, Ph, 4-HOC_6H_4, NH_2, NMe_2, morpholine;
R^F = CF_3, CF_2CF_3, CF_2H, $(CF_2)_2H$, $(CF_2)_2CF_3$;
(i) Anhydrous pyridine, reflux, 3 h; (ii) heated at 85 ˚C, 1 h; (iii) DMF, 80 - 100 ˚C, 12 h; (iv) $HC(R_2O)_3$, ROH, HCl/*p*-TsOH

Scheme 66. Transformation of 3-(polyfluoroacetyl)chromones **216** and **217** into other heterocyclic compounds.



R = 6-Cl, 6-Me, 7-OMe; R^F = CF_3, CF_2H, $(CF_2)_2H$
(i) $AcCH_2CONH_2$, $AcONH_4$, EtOH, reflux, 4 h; (ii) $AcONH_4$, EtOH, reflux, 4 h;
(iii) $AcCH_2CO_2Et$, $AcONH_4$, EtOH, reflux, 30 min-4 h; (iv) AcOH, EtOH, reflux, 30 min-4 h

Scheme 67. Transformation of 3-(polyfluoroacetyl)chromones **223** into other heterocyclic compounds.

chromanones **218** and **219** (mixture of *Z*- and *E*-isomers) which can be readily converted to *trans*-(indolyl/pyrrolyl)chalcone-type compounds **220** by treatment with morpholine (Scheme 66) [207, 208]. The synthesis of 4-R^F-pyrimidines **221** were achieved by reaction of 3-R^FCO-chromones **216** and sulfur-analogs **217** with 1,3-*NCN*-dinucleophiles (Scheme **66**) [202]. Reaction of 3-R^FCO-chromones **216** with alkyl orthoformates in the corresponding alcohol resulted in the formation of hemiketals **222** (Scheme **66**) [202].

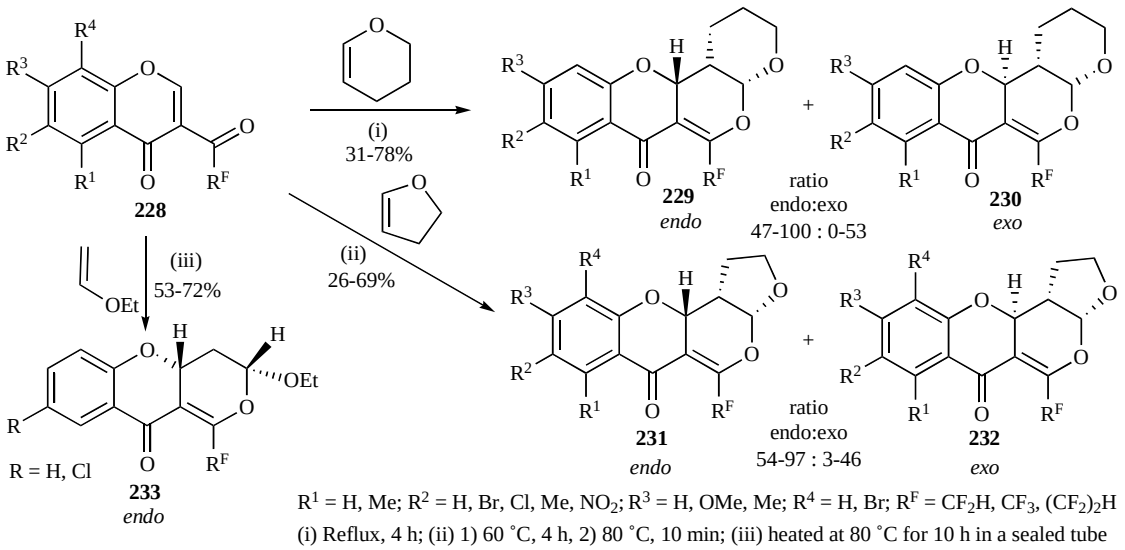
3-R^FCO-chromones **223** reacted with acetoacetamide (an active methylene compound) and ammonium acetate by a one-pot three-component reaction to afford novel R^F-containing nicotinamide derivatives **224** in a regioselective manner (Scheme **67**) [209]. These chromones were isolated as pure compounds after precipitation and filtration from the reaction mixture. The reaction with dimedone enamine, arising from dimedone and ammonium acetate, gave 2-(2-hydroxyaryl)-7,7-dimethyl-7,8-dihydroquinolin-5(6*H*)-ones **225**. The reaction mechanism proceeded at the C-2 of the chromone with pyrone ring-opening and subsequent cyclization. In the case of the dimedone derivative, the intramolecular cyclization involved the participation of the NH_2 and ArCO groups followed by depolyfluoroacylation.

The reaction of 3-R^FCO-chromones **223** with ethyl acetoacetate under the same reaction conditions afforded chromeno[4,3-*b*]pyridine-3-carboxylates **226**, while the reaction with β-aminocrotononitrile in refluxing ethanol in the presence of acetic acid gave 5-ethyl-5-hydroxy-2-methyl-5*H*-chromeno[4,3-*b*]pyridine-3-carbonitrile **227** (Scheme **67**). Despite the moderate yields obtained, the operational simplicity and the use of acessible starting materials and cheap reagents make this approach convienient.

3-R^FCO-chromones **228** suffered heterodiene cycloaddition with cyclic vinyl ethers (3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran) and ethyl vinyl ether to give rise novel R^F-containing fused pyrans **229-233** in moderate to good yields, after filtration from the reaction mixture (Scheme **68**) [210, 211]. The electron-withdrawing force of the R^F group in the heterodienes **228** allowed these hetero-Diels-Alder reactions to run under mild conditions. These reactions presented high stereoselective character with major or total formation (in some cases) of *endo* products **229**, **231** and **233** (Scheme **68**).

4. CLOSING REMARKS

Over the last decade, the chemistry of halochromones has undergone a flourishing development not only in relation to synthetic methods but also to subsequent transformations into biologically important compounds. Important efforts have been made to improve synthetic methods in terms of practicability and efficiency to allow the enlargement of a library of synthetic analogues. Neverthe-



Scheme 68. Heterodiene cycloaddition reactions of 3-(polyfluoroacetyl)chromones **228**.

less, the recent advances in halochromones chemistry has been driven by their potential to be converted into other more elaborate compounds. Due to their perfectly suited framework they can be involved in metal organic catalytic synthesis. Halochromones will therefore continue to be at the centre of future synthetic advances and new molecules with important biological activity will be produced.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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LIST OF ABBREVIATIONS

AcOH	=	Acetic acid
AIBN	=	Azobisisobutyronitrile
aq	=	Aqueous
BTEAC	=	Benzyltriethylammonium chloride
BTI	=	Bis(trifluoroacetoxyiodo)benzene
BTMA	=	Benzyltrimethylammonium dichloroiodate
CAN	=	Cerium(IV) ammonium nitrate
Cat	=	Catalyst
DIPEA	=	*N*,*N*-diisopropylethylamine
DMF	=	Dimethylformamide
DMSO	=	Dimethylsulfoxide
Hal	=	Halogen atom
iNOS	=	Inducible nitric oxide synthase
LDA	=	Lithium diisopropylamide
LiHMDS	=	Lithium bis(trimethylsilyl)amide
LTMP	=	Lithium 2,2,6,6-tetramethylpiperidide
MW	=	Microwave
NBS	=	*N*-bromosuccinimide
NCS	=	*N*-chlorosuccinimide
NIS	=	*N*-iodosuccinimide
NMP	=	*N*-methyl-2-pyrrolidone
OTf	=	Trifluoromethanesulfonate
PMB	=	*p*-Methoxybenzyl
p-TsOH	=	*p*-Toluenesulfonic acid
PTB	=	Pyridinium tribromide
PTT	=	Phenyltrimethylammonium tribromide
R^F	=	Polyhaloalkyl
R^FCO	=	Polyfluoroacyl
TBAB	=	Tetrabutylammonium bromide
TBAI	=	Tetrabutylammonium iodide
TBDMS	=	*t*-Butyldimethylsilyl
TFA	=	Trifluoroacetic acid
TFAA	=	Trifluoroacetic anhydride
THF	=	Tetrahydrofuran
TMS	=	Trimethylsilyl

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