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 (4H-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 compounds 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.

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.
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 (which exist in equilibrium with their enolic form) [56] to give the corresponding 3-haloflavones 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 CuBr₂ (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 [60], under free solvent conditions, consists of the selective bromination of 3-aryl-1-(2-hydroxyaryl)propane-1,3-diones 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 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 in moderate yields consists of the photocyclization of substituted 1,3-diaryl-2-chloro-2-fluoropropane-1,3-diones in MeCN (Scheme 3) [63].

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)alkynes provided a novel simple and highly efficient approach to prepare 3-iodochromones or thiocromones [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 (I₂/CAN) at room temperature gives 3-iodochromones 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 in moderate yields [67]. The latter cyclization reaction is quite sensi-
tive to the solvent (other solvents than DMF were totally ineffective) and to the substituent on the alkyne moiety of \( \text{13} \). 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 \( \text{17} \) can be efficiently achieved with \( \text{R}_4\text{NBr/PhI(OAc)}_2 \) 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 \( \text{18} \) 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 \( \text{19} \) can be synthesized by the reaction of flavones \( \text{19} \) with bis(trifluoracetoxoyiodo)benzene (BTI) and iodine [71] or by treatment with LDA, followed by the addition of molecular iodine (Scheme 6) [72].

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 \( \text{21} \) bearing an additional activated double bond, to give 5-hydroxy-3-iodochromone \( \text{22} \) 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 \( \text{CF}_3\text{CO}_2\text{Ag} \) as a catalyst [75].
3-Iodo-5-methoxy-8,8-dimethyl-8H-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 C=C 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.

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.
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'-hydroxycinnamaldehydeacetophenone 34 (R = styryl) to the corresponding 6-fluorohydroxyflavone 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](image)

**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'-hydroxycinnamaldehydeacetophenone 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 allyloxy-5'-chlorochalcones and 6-fluoroflavone 36 by oxidative cyclization of 5'-fluoro-2'-hydroxychalcone 34 (R = phenyl) with selenium dioxide in hot DMSO [91].

![Scheme 13](image)

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

One-pot synthesis of 6,8-diodoflavone 40 has been accomplished by diacetoxydibenzeno-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].

![Scheme 14](image)

**Scheme 14.** Synthesis of 6,8-diodoflavone 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] to prove a practical synthetic method for the synthesis of haloflavones.

The synthesis of haloflavones has also been successfully conducted by application of a protocol of Ca-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].

![Scheme 15](image)

**Scheme 15.** Synthesis of haloflavones 42 by 2-arylation 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].

![Scheme 16](image)

**Scheme 16.** Synthesis of halochromones 44 by a transition metal-free intramolecular Ullmann-type O-arylation.
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 (SAr) 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 alkyne and subsequent intramolecular SAr 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 was recently developed. It consists in a one-pot mixed-gas mild Sonogashira coupling reaction that affords o-alkynylphosphoryl 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 cumulonolate 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 (Hal1 = I, Hal2 = Cl) with butyl acrylate 57 followed by intramolecular cyclization (Scheme 21). The reaction is carried out at room temperature under balloon pressure of CO with NEt3 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 (Hal1 = F, Hal2 = Cl) and arylacetylenes 59 in the presence of PdCl2[PPh3]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-chloronaphthyl)-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)methylene-triphenylphosphorane, which undergo an intramolecular Wittig cyclization of the ester carbonate 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...
Phenylmethylthieno[2,3-b]quinoline underwent a 3,3-sigmatropic rearrangement affording 2-tetrafluoro-6-bromo-1-methylthieno[2,3-b]quinoline, which under reflux in 1,4-dioxane afforded the cyclized product 2-methylthieno[2,3-b]quinoline bromide (TBAB) or benzyltriethylammonium chloride (BTEAC) at room temperature.

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

Presumably 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/Me2S to form 6,8-dibromochrysin 76 and iodinated by molecular iodine in acetic acid to form 6,8-diodochrysin 77 (Scheme 27) [82].

Synthesis of 6,8-diodo- and 6,8-dibromo-2-(phenyl or styrly)chromones 79 can be accomplished in a short reaction time and in good yields by oxidative cyclization of 2'-benzylxylo-6'-hydroxychalcone and 2'-benzoyloxy-6'-hydroxy-2'-cinnamylidenacetophenone 78 with DMSO/I2 or DMSO/Br2 or by halogenation of the corresponding 5-hydroxychromones 80 (Scheme 28) [115]. Using half equim of iodine or bromine the moniodo and monobromo derivatives have been obtained in low yields and not selectively although time consuming difficult chromato graphic separations are required. 6-Iodostyrlychromone derivatives were obtained by the reaction of 6-tributyltin derivatives with iodine in chloroform at room temperature. Novel radioiodinated styrlychromone derivatives were also synthesized by an iodode stannylation 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-iodoisoflavone 82 and (±)-trans-5-
iodination of 5,7-di-\(\text{O}-\)methylchrysin \(84\) with \(\text{ICl}\) in the presence of \(\text{AcOH}\) in \(\text{DMSO}\) afforded the 8-iodo derivative \(85\). Using the \(\text{I}_2/\text{CAN}\) 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-\(\text{O}-\)acetylchrysin \(90\) and 5,7-di-\(\text{O}-\)acetylchrysin \(91\) afforded 7-acetyl-6,8-diiodochrysin \(92\). However, the reaction of 5,7-di-\(\text{O}-\)methylchrysin \(84\) with \(\text{ICl}\) gave 6,8-diiodochrysin \(87\) and with \(\text{Br}_2/\text{H}_2\text{O}\) give the 6,8-dibromo derivative \(88\). Bromination of 5,7-di-\(\text{O}-\)methylchrysin \(84\) with \(\text{NBS}\) prompted the 8-bromo-7-\(\text{O}-\)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.

Iodination of 5,7-di-\(\text{O}-\)methylchrysin \(84\) with \(\text{ICl}\) in the presence of \(\text{AcOH}\) in \(\text{DMSO}\) afforded the 8-iodo derivative \(85\). Using the \(\text{I}_2/\text{CAN}\) 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-\(\text{O}-\)acetylchrysin \(90\) and 5,7-di-\(\text{O}-\)acetylchrysin \(91\) afforded 7-acetyl-6,8-diiodochrysin \(92\). However, the reaction of 5,7-di-\(\text{O}-\)methylchrysin \(84\) with \(\text{ICl}\) gave 6,8-diiodochrysin \(87\) and with \(\text{Br}_2/\text{H}_2\text{O}\) give the 6,8-dibromo derivative \(88\). Bromination of 5,7-di-\(\text{O}-\)methylchrysin \(84\) with \(\text{NBS}\) prompted the 8-bromo-7-\(\text{O}-\)methyl derivative \(89\) (Scheme 30) \[46\].

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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

\[\text{I}_2, \text{KOH/MeOH} \quad 3\,\text{h, rt} \quad 85\%\]

Scheme 29. Iodination of 7-\(\text{O}-\)methylbiochanin A \(81\) in alkaline medium.
by three different methodologies that have been described in the literature (Scheme 31). The first exploits the \( \omega \)-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\(_2\)Cl\(_2•\)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\(_2\)Zn\(_2•\)MgCl\(_2•\)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\(_2•\)OEt\(_2\) also provided, after iodolysis, 2-iodochromone \( 98 \).

It is known that the presence of a 2-polyfluoroalkyl group (\( RF \)) 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-

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

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

**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)-4H-thioxocromen-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 nitroazation 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 is clearly not an exception. Carbon-carbon bond-forming reaction in the presence of the palladium catalyst rationalized the formation of the coupled product. The catalytic process apparently involves heteroaryl-palladium formation, regioselective addition to the C-C triple bond of the terminal alkyne, and subsequent replacement of the 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.

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, allowing the first synthesis of 3-alkynyl substituted flavones 102 in moderate to good yields (Scheme 34) [155]. 3-Phenylethynyl-flavone can be prepared in good yield (80%) by the addition of phenylacetylene in triethylamine to 3-iodoflavone in DMF, followed by the addition of PdCl2(PPh3)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 PdCl2(PPh3)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 heteroaryl-palladium 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.

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 (NO2 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, PdCl2(PPh3)2, CuI, and DIPEA in DMF at room temperature for 2 h and then adding the substituted amidines and K2CO3, 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-diarylcromone 110 (Scheme 37). Zhou and co-workers, also succeeded in the diversification of 3-iodoflavone derivatives 109 through demethylation of 2'-methoxylflavone and its subsequent Pd-catalyzed intramolecular C-


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 PdCl2(PPh3)2, K2CO3 and DMF/H2O, 90 °C 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(PPh3)4 and Na2CO3 in benzene afforded the correspond-15-75%

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-(8H)-one 120 allowed to obtain a substituted isoflava-

3-Iodoflavone 122 was easily transformed to the fused polycyclic aromatic product 124 through a Pd-catalyzed carboamination 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].
3-Iodochromones 125 are sufficiently converted to the air-stable and crystallisable 3-(trimethylstannyl)chromones 126 and crystallisable 3-(trimethylstannyl)chromones 127 with 4-iodonitrobenzene afforded ring A substituted 4′-nitroisoflavones 127 (Scheme 42) [165]. Stille reaction of 3-bromo-5,7-di-methoxy-2-styrylchromones 128 with 4-iodonitrobenzene and an aryne. The reaction mechanism indicating the initial formation of the 2,3-distyrylchromones 126 followed by an aryne. The reaction mechanism indicating the initial formation of the 2,3-distyrylchromones 126 followed by an aryne.

The first palladium cross-coupling reaction of 3-iodochromones 125 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(PPh3)4 and triphenylphosphine as catalyst and using triethylamine as base, mainly leading to the initially unexpected formation of 2,3-diarylxanthone derivatives 134-136. The structural assignment of the minor products, 2,3-dialy-3,4-dihydroxanthones 135, demystified the reaction mechanism indicating the initial formation of the expected 2,3-distyrylxanthones 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 (R2 = 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, K2CO3, (Bu)4NBr, DMF], several 3-bromoflavones react with styrene derivatives leading to (E)-3-styrylfлавones with total diasteoselectivity. 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 NEt3 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
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 ethanol 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].

An efficient entry to functionalized 2-(2-hydroxy-benzoyl)-4H-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(PPh₃)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 PdCl₂(PPh₃)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 (BBr₃ demethylation conditions) the obtained chrysin analogues towards possible biological activity against cyclooxygenase (COX)-2 catalyzed prostaglandin E₂ 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 arylation products.
heating afforded a range of functionalized flavones in moderate to good yields (Scheme 50) [98].

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

Vinyl and allyl groups were introduced to 8-iodo-5,7-di-O-methylchrysin through Stille coupling, by reacting with vinylbutyltin 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 were synthesized using Heck coupling reaction of 7-bromo-3-hydroxychromones 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$_2$CO$_3$, KCl, Bu$_4$NBr, DMF] were found to give higher yields in shorter reaction periods [182].

Dahlén and co-workers 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 were possible resulting in the corresponding products and in good yields and regioselectivity. The functionalization of flavones with methyl acrylate (Scheme 50) [98].

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Functionalization of the 6-position of \( \text{162} \) and \( \text{164} \) was possible with the use of electron-rich and sterically hindered phosphine \( \text{P(\text{tBu})_3} \) (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 \( \text{169} \), potential topoisomerase inhibitor anticancer agents, were prepared by the nucleophilic substitution of both 7-chlorine atom and \( \text{N}-\text{methylanilino} \) moiety of 7-chloro-6-fluoro-3-formyl-2-(\( \text{N}-\text{methyl-N-phenylamino} \))chromone \( \text{167} \) (Scheme 55) [13].

The nucleophilic substitution of the 7-fluorine atom of 5,6,7,8-tetrafluoro-2-ethoxycarbonylchromone \( \text{170} \) by the action of primary amines was carried out in good yields (Scheme 56) [185, 186]. The same type of reaction occurred when 6,7,8-trifluoro-3-methyl-

\[ \text{MeO}_2\text{C} \]

\[ \text{Ar} \]  

\[ \text{Br} \]

\[ \text{Ar} \]

\[ \text{O} \]

\[ \text{CO}_2\text{Me} \]

\[ \text{Pd(OAc)}_2, \text{P(o-tolyl) }_3, \text{NEt/Pr}_2, \text{DMF} \]

\[ \text{MeO}_2\text{C} \]

\[ \text{Ar} \]  

\[ \text{OH} \]

\[ \text{O} \]

\[ \text{Ar} \]

\[ \text{OH} \]

\[ \text{O} \]

\[ \text{Ar} \]

\[ \text{159} \]

\[ \text{160} \]

Scheme 53. Heck reaction functionalization of 3-hydroxyflavone-type compounds \( \text{159} \).

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 (\( \text{R}^3 \)) group, due to its strong electron-withdrawing capacity, gives the chromone’s core a huge diversity of possible transformations.

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

Ghosh and Karak also studied the bromine replacement of 2-bromomethylchromone \( \text{174} \) 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 \( \text{178} \) (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.
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-RF-chromones) 185, particularly 2-(polyfluoromethyl)chromones (2-CF₃-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-RF-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 synthesized 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 acetaldehyde 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-arylo-2-(bromo or dibromo)chromones 174 and 175 with nucleophiles.


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-RFCO-chromones). The presence of a 3-RFCO on a chromone nucleus dramatically changes the reactivity of the pyrone ring especially towards nucleophiles, and it is an extremely interesting build-
Scheme 61. Detrifluorocetylation of 3-cyano-2-trifluoromethylchromones 192.

Scheme 62. Reaction of 3-RFCO-chromones 197 with amines.

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 or electron-withdrawing groups) generally proceed via a nucleophilic 1,4-addition with concomitant opening of the pyrone ring and subsequent intramolecular cyclization of the intermediate at the CORF group leading to aminomethylene-2-pyrone 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 RCO group. Treatment of chromeno[3,4-d]isoxazoles 207 with trifluoroacetic acid gave 3-cyano-2-RF-chromones 208 (Scheme 64).

The synthesis of R-f-containing pyrazoles 213 and 214 were readily achieved by the reaction of 3-RFCO-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 RCO group to give 4-(2-hydroxyaryl)-3-RF-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-
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\(^F\)CO-chromones 216 with indole and \( N \)-methylindole in refluxing pyridine, and \( N \)-methylpyrrole under solvent-free conditions gave an isomeric mixture of 3-(azolylmethylene)
The synthesis of 4-R F-pyrimidines of 3-R FCO-chromones compounds be readily converted to depolyfluoroacylation.

The reaction of 3-R FCO-chromones in the formation of hemiketals methylene compound) and ammonium acetate by a one-pot three-component reaction to afford novel R F-containing nicotinamide compounds. The reaction mechanism proceeded at the C-2 of the component reaction. The reactions presented high stereoselective character with major or total formation (in some cases) of endo products (Scheme 67).

The reaction of 3-R FCO-chromones with alkyl orthoformates in the corresponding alcohol resulted in a regioselective manner (Scheme 66). The reaction with di- or tri-picolinic acid gave 5-ethyl-5-hydroxy-2-methyl-5 H -chromeno[4,3-b]pyridine-3-carbonitrile (Scheme 67). Despite the moderate yields obtained, the operational simplicity and the use of accessible starting materials and cheap reagents make this approach convenient.

3-R FCO-chromones suffered heterodiene cycloaddition with cyclic vinyl ethers (3,4-dihydro-2H-pyran and 2,3-dihydrofuran) and vinyl vinyl ether to give rise novel R F-containing nicotinamide derivatives (Scheme 66) (202). Reaction of 3-R FCO-chromones with cyclic vinyl ethers (3,4-dihydro-2H-pyran and 2,3-dihydrofuran) and ethyl vinyl ether to give rise novel R F-containing nicotinamide derivatives.

The reaction of 3-R FCO-chromones 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. 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 chromone with pyrone ring-opening and subsequent cyclization. In

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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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>AcOH</td>
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<tr>
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<td>Azobisisobutyronitrile</td>
</tr>
<tr>
<td>aq</td>
<td>Aqueous</td>
</tr>
<tr>
<td>BTEAC</td>
<td>Benzyltriethylammonium chloride</td>
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<td>Benzyltrimethylammonium dichloroiodate</td>
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<td>Catalyst</td>
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<td>NCS</td>
<td>N-chlorosuccinimide</td>
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<td>NMP</td>
<td>N-methyl-2-pyridonide</td>
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<td>Trifluromethanesulfonate</td>
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<tr>
<td>PMB</td>
<td>p-Methoxybenzyl</td>
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<td>p-TsOH</td>
<td>p-Toluensulfonic acid</td>
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<td>PTB</td>
<td>Pyridinium tribromide</td>
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<td>TMS</td>
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REFERENCES


Synthesis and Transformation of Halochromones


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Current Organic Synthesis, 2014, Vol. 11, No. 3 341


