Nian-Guang Li,[a,b] Zhi-Hao Shi,[c] Yu-Ping Tang,[a]* Hong-Yue Ma,[a]
Jian-Ping Yang,[a] Bao-Quan Li,[a] Zhen-Jiang Wang,[a] Shu-Lin Song,[a]
and Jin-Ao Duan[a]*

[a]Jiangsu Key Laboratory for TCM Formulae Research, Nanjing University of Chinese Medicine, Nanjing, Jiangsu 210046, China
[b]Department of Medicinal Chemistry, Nanjing University of Chinese Medicine, Nanjing, Jiangsu 210046, China
[c]Division of Organic Chemistry, China Pharmaceutical University, Nanjing, Jiangsu 211198, China
*E-mail: yupingtang@njutcm.edu.cn or dja@njutcm.edu.cn
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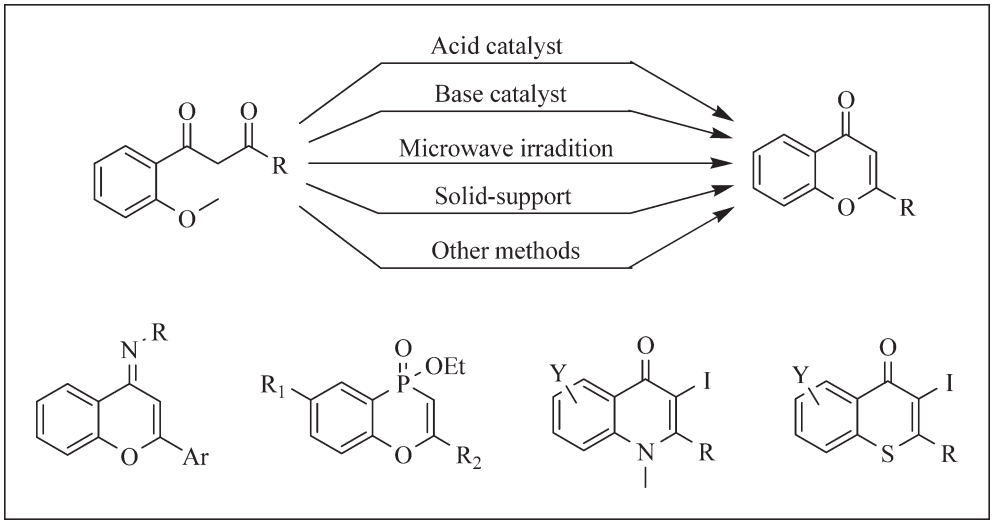

Because of important biological applications of chromones, some synthetic strategies leading to more complex derivatives have been widely explored in the past years. Thus, the purpose of this review is to report some recent improvements of the classical synthetic methods and of some nonclassical methods to obtain simple oxygenated chromones. The strategies for synthesis of heterocycle analogs containing phosphorus, nitrogen, and sulfur are also summarized.

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INTRODUCTION

Heterocycles play an important role in the design and discovery of new physiological/pharmacologically active compounds [1]. Chemically, chromones (4*H*-chromen-4-ones) are heterocyclic compounds with the benzo-γ-pyrone framework (Fig. 1). Molecules containing the chromone or benzopyranone ring have a wide range of biological activities. They have been shown to be tyrosine and protein kinase inhibitors [2–4], as well as anti-inflammatory [5], antiviral [6], antioxidant [7,8], and antihypertensive agents [6]. Chromone derivatives are also active at benzodiazepine receptors [9], and on lipoxygenase and cyclooxygenase [10]. In addition to this, they have been shown to be anticancer agents [11], possessing antimutagenic properties [12] and the ability to inhibit electron transport through inhibition at NADH: ubiquinone oxidoreductase and phorbol ester-inducedornithinedecarboxylase [13,14]. Chromones may also have application in cystic fibrosis treatment, as they activate the cystic fibrosis transmembrane conductance regulator [15]. Therefore, the vast range of biological effects associated with this scaffold has resulted in the chromone ring system being considered as a privileged structure [16]. The main objectives of chromones syntheses are not only for the development of more diverse and complex bioactive compounds for biological activity and structure-activity relationship (SAR) studies but also for other applications in Medicinal Chemistry, such as preparation of fluorescence probes, due to photochemical properties of chromones [17].

One of the first methods for the synthesis of chromones was introduced by Heywang and Kostanecki, which involved the decarboxylation of chromone-2-carboxylic acid [18]. Since then, several other routes with higher yields and less drastic experimental conditions have been developed.

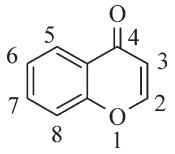


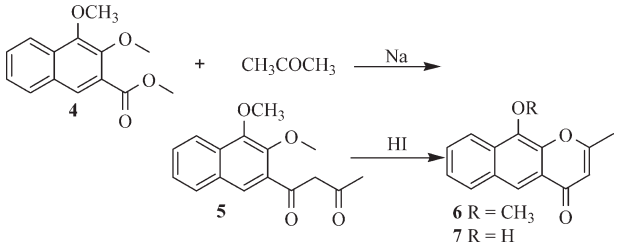
Figure 1. Chromone nucleus and numbering.

Chromones could be synthesized under either acidic or basic conditions. The classical 2,3-disubstituted benzopyranone (**3**) synthesis utilized acidic conditions (Scheme 1) and was by far the most common method [19]. It proceeded through an intramolecular condensation of molecules such as **2**, which were usually obtained through a Baker–Venkataraman rearrangement of compound **1**, or via a Claisen ester condensation (Scheme 1). Most synthesis required harsh acidic conditions as the final step. On the other hand, synthesis utilizing basic conditions typically consisted of piperidine in refluxing pyridine for several hours to affect ring closure. This was far less common [19]. Recently, microwave heating has also been used to affect ring cyclization [20]. In this review, our aim is to provide a comprehensive summary till the March 2009, with special emphasis on the synthesis of chromone ring based on different methods, and the same reactive condition in chromone ring closure will be cited along with the latest reported literature.

Acid as catalyst in chromone ring closure. Acid comprised a major catalyst in chromone ring closure, and many acids can be used including hydriodic acid, polyphosphoric acid (PPA), acetic acid, methanesulfonylchloride, hydrochloric acid, para toluene sulfonic acid (PTS), triflic anhydride, phosphorus oxychloride, perchloric acid, and sulfuric acid.

Hydriodic acid as a catalyst. In 1952, Wawzonek and Ready [21] reported the synthesis of chromone using hydriodic acid as a catalyst in the ring closure (Scheme 2). Methyl 1,2-dimethoxy-3-naphthoate (**4**), which was prepared from 1,2-dihydroxy-3-naphthoic acid by a two-step methylation process, was condensed with acetone in the desired fashion to afford **5**. Cyclization of the diketone (**5**) with hydriodic acid gave products which depended upon the time of refluxing. A period of 7 h gave a mixture of 2-methyl-8-hydroxy-6,7-benzochromon (**7**) and 2-methyl-8-methoxy-6,7-benzochromone (**6**). Complete demethylation was achieved only after 24 h of heating. This chromone ring closure using hydriodic acid as a catalyst was not common because it required high temperature and long reaction time, and sometimes the reactant might decompose under these conditions.

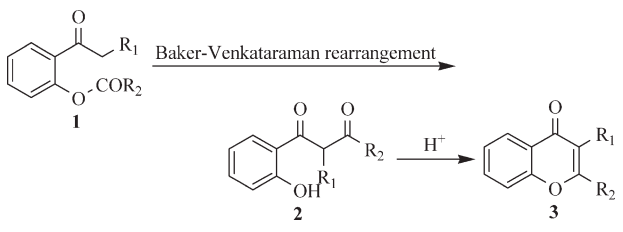
Scheme 2



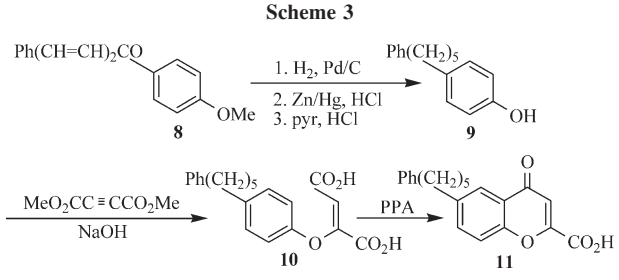
Polyphosphoric acid as a catalyst. In 1977, Lee and coworkers [22] took PPA as a catalyst in the chromone ring closure; in their synthetic route (Scheme 3), they firstly applied a two-step reduction procedure to the chalcone **8** with subsequent demethylation provided the aralkylphenol **9**, which, by modification [23] of the process described by Ruhemann and Stapleton [24] for the formation of chromone-2-carboxylic acids from phenols, was converted to the chromone **11** through PPA as the catalyst in the last step. This method was more suitable in the phenolic hydroxyl side chain in a carboxylic acid of the cyclization.

Acetic acid as a catalyst. In 1990, Harvey *et al*. [25] described a new synthesis of chromones and flavones based on the ortho-directed metalation of methoxymethyl aryl ethers with alkyllithium reagents (Scheme 4), and they applied acetic acid as a catalyst in the chromone ring closure. Their synthetic route entailed reaction of the ortho-lithiated intermediates **12** with a conjugated unsaturated aldehyde followed by oxidation of the allylic alcohol product **13** with ''periodinane'' to yield an ortho-allylic ketone **14**. The latter on heating in acetic acid undergoes loss of the methoxymethyl protecting group and cyclization to a chromanone (or flavanone, if a β-phenyl substitutent is present) **15**. Dehydrogenation by treatment with pyrrolidone hydrotribromide in dimethyl sulfoxide yielded the corresponding chromones

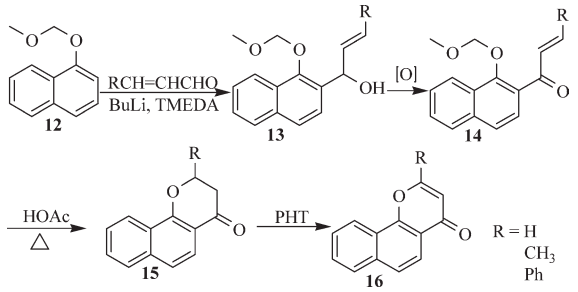
Scheme 1



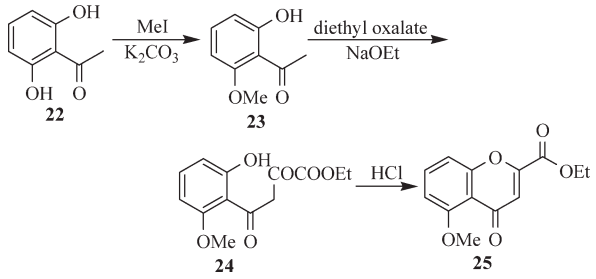
Scheme 3



Scheme 4



Scheme 6



(or flavones) **16**. This synthetic approach appeared general in its applicability. It has been applied to the synthesis of a series of polycyclic chromone and flavone compounds containing the naphthalene and pyrene ring systems that hold promise as agents for the chemoprevention of cancer.

Methanesulfonylchloride as a catalyst. In 2001, Ismail and Abd El Aziem [26] reported the synthesis of the new 3-substituted-7-methoxy-4*H*-1-benzopyran-4-ones (**21**) starting from 2-hydroxy-4-methoxyacetophenone (**17**) according to Scheme 5. The key step in this synthesis involved the alkylation with alkyl halide using potassium tertiary butoxide of 2-(*t*-butyldimethylsilyloxy)-4-methoxyacetophenone (**18**) which was prepared by the protection of the hydroxyl group of **17** using *t*-butyldimethylsilylchloride. The *O*-silyl protected alkylacetophenone derivatives (**19**) were, therefore, treated with tetra-*n*-butylammonium fluoride to produce the corresponding 2′-alkyl-2-hydroxy-4-methoxyacetophenone (**20**) in good yield. Cyclization of the alkyl derivatives **20** was achieved via methanesulfonylchloride using boron trifluoride diethyl etherate at 0°C [27] to give the desired 3-substituted-7-methoxy-4*H*-1-benzopyran-4-ones (**21**). This reaction conditions was relatively mild, and the reaction yield was also relatively high.

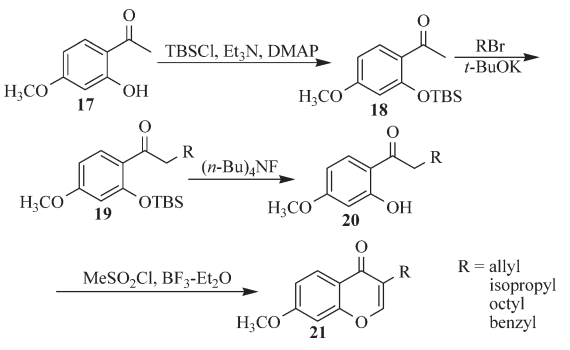
Hydrochloric acid as a catalyst. In 2003, Boumendjel and coworkers [28] obtained chromone **25** in three steps starting from 2,6-dihydroxyacetophenone (Scheme 6); this time they used concentrated hydrochloric acid as a catalyst in the ring closure. Treatment of the 2,6-dihydroxyacetophenone (**22**) with methyl iodide gave 2-hydroxy-6-methoxyacetophenone (**23**). Condensation of **23** with diethyl oxalate in the presence of sodium ethoxide in EtOH and then concentrated HCl catalysted cyclization afforded ester **25**, and a lot of reactions have adopted this approach [29–32].

Para toluene sulfonic acid as a catalyst. In 2004, Sabui and Venkateswaran [33] synthesized the chromone using PTS as a catalyst in the ring closure (Scheme 7). Condensation of the acetophenone **26** [34] with ethyl formate in the presence of sodium hydride followed by dehydration of the resulting chromanol furnished the 6-methoxy-7-methyl chromone **28** in an overall yield of 85%. This catalyst was especially suitable in the phenolic hydroxyl and aldehyde condensation cyclization.

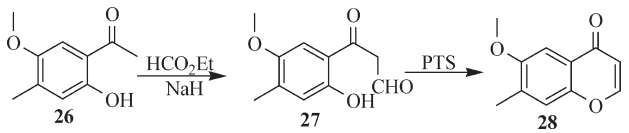
Triflic anhydride as a catalyst. In 2005, Griffin *et al*. [4] used triflic anhydride as a catalyst to construct the chromone ring (Scheme 8). Reaction of the appropriate 2-hydroxyarylcarboxylate esters **31**, which were prepared by carboxylation-esterification of the corresponding phenols **30** by standard methods, with *N*-acetylmorpholine, *N*-acetylthiomorpholine, or *N*-acetylpiperidine afforded the β-ketoamides **32**, and ring closure to the required chromones **33** was readily effected with triflic anhydride. Although the effect of this catalyst was better, but higher prices due to trifluoroacetic anhydride, making its practical application being limited.

Phosphorus oxychloride as a catalyst. This catalyst is most widely used in the chromone ring closure, and there are two ways in construction the chromone ring. One approach is that phenolic compounds and carbonyl compounds are refluxed in phosphorus oxychloride, another approach is that the phenolic compounds with the acyl side chain is refluxed in phosphorus oxychloride. In 2005, Balbi and coworkers [35] synthesized the

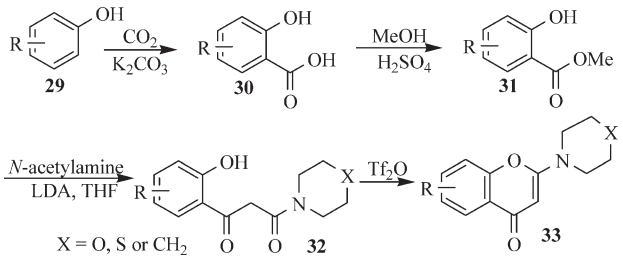
Scheme 5



Scheme 7



Scheme 8



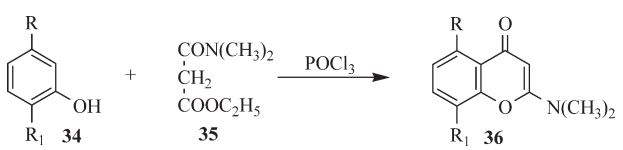
chromone ring via $POCl_3$ as a catalyst (Scheme 9). **36** was obtained by following their well-established method from substituted phenols and *N*,*N*′-(dimethyl)malonamide in the presence of phosphorus oxychloride [36,37].

In 2008, Yang and coworkers [38] prepared the 6-hydroxy-3-carbaldehyde chromone via a Vilsmeier reaction in another way (Scheme 10). 6-hydroxy-4-chromone-3-carbaldehydes **40** were easily prepared by the reaction of 2,5-dihydroxy-acetophenone **39** with DMF in $POCl_3$ solution [39–45].

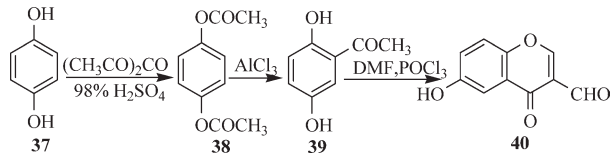
Perchloric acid as a catalyst. In 2006, Langer and coworkers [46] synthesized chromone using perchloric acid as a catalyst (Scheme 11). The reaction of 3-formylchromones **41** with Me_3SiOTf (**42**) and 1,3-bis(silyl enol ether) **43** afforded the 4-(2-hydroxybenzoyl)phenols **44**. The formation of the products could be explained by a domino ''Michael–retro-Michael–Aldol'' reaction. Compounds **44** were transformed into the novel chromones **45** by treatment with triethyl orthoformate and perchloric acid [47–49].

Sulfuric acid as a catalyst. In 2007, Cushman and coworkers [50] reported the synthesis of chromone using H_2SO_4 as a catalyst (Scheme 12). Commercially available 2-hydroxy-6-methoxyacetophenone (**23**) was subjected to Elbs oxidation using sodium persulfate and aqueous sodium hydroxide to yield the substituted acetophenone **46**, followed by regioselective methylation using anhydrous potassium carbonate and dimethyl sulfate in acetone to afford 6-hydroxy-2,3-dimethoxyacetophenone (**47**) in 53% yield in two steps. The generation of the dilithium dianion **48** of the acetophenone **47** was ensured by treatment with four equivalents of lithium hexamethyldisilylazide in THF. Treatment of dilithium dianion **48** with commercially available 2,6-dimethoxybenzoyl chloride, followed by acidification, afforded the

Scheme 9



Scheme 10



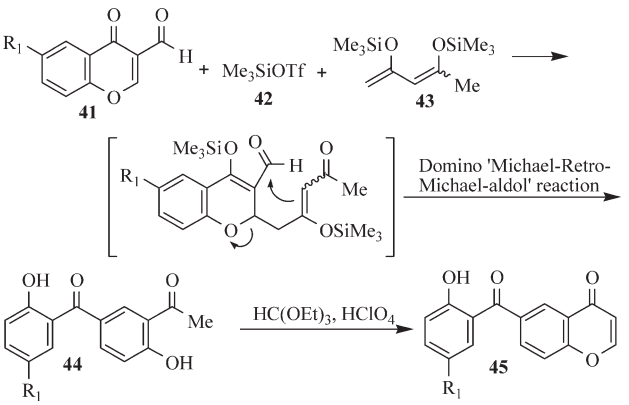
β-diketone intermediate **49**, which was used without purification for cyclization to zapotin (**50**) with the catalyst of H_2SO_4 [51–55]. This H_2SO_4 as catalyst and HCl as catalyst means were basically the same.

Base as catalyst in chromone ring closure. Although base as catalyst in the chromone ring closure is not common compared with acid, sometimes it can really bring some satisfactory results.

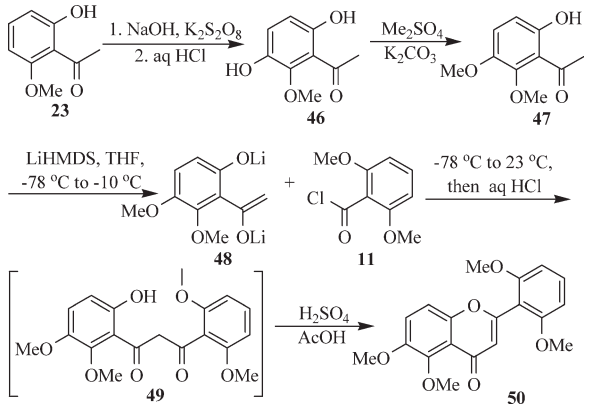
Sodium formate as a catalyst. In 2001, Wallace and coworkers [56] reported the synthesis of enantiomerically pure (*S*)-2-methylchroman-4-one **53** based on the following procedure (Scheme 13): Treating methyl 5-methyl-salicylate **51** with an excess of lithium diisopropylamide followed by the lithium derivative of (*R*)-(+)-methyl *p*-tolyl sulfoxide gave the desired ketosulfoxide (*R*)-**52** directly and in good yield. Then, the formation of the chromone **53** was achieved conventionally using acetic formic anhydride and sodium formate [57,58]. But this method is only applicable to compounds with ketosulfoxide.

Sodium methoxide as a catalyst. In 2001, Khan and coworkers [59] synthesized the chromone ring via cyclization on treating with 0.1*M* NaOMe solution (Scheme 14). The compounds **54** on bromination with the same reagent in CH_2Cl_2 gave the brominated products **55** in good yields. Various flavones (**57**) were obtained in good yields from the brominated products **55** by dehydrobromination followed by cyclization on treatment with 0.1*M* sodium methoxide solution. The main feature

Scheme 11



Scheme 12

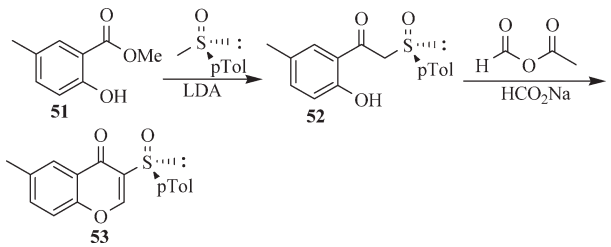


of this reaction was the bromination of the unsaturated olefinic bond.

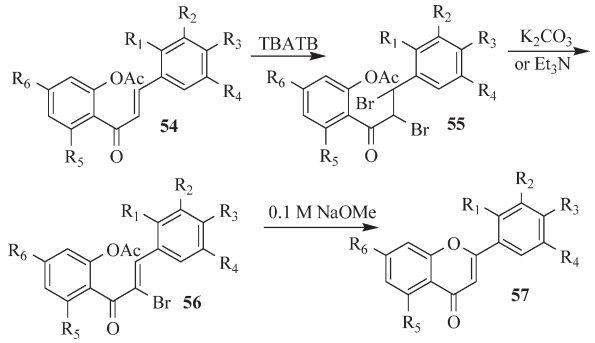
Sodium hydride as a catalyst. In 2003, Samat and coworkers [60] developed the synthesis of a series of new nine 3-benzoyl-2-benzylchromones through a classical and an optimized Kostanecki–Robinson method involving an *o*-hydroxyphenyl-β-diketone **59** and an acid anhydride **61** (Scheme 15). Most of the *o*-hydroxyphenyl-β-diketones **59** were obtained using a traditional method involving a reaction between *o*-hydroxy acetophenone **58** and acid chloride, followed by a Baker–Venkataraman rearrangement. The homoveratric anhydride **61** prepared from the reaction of dicyclohexylcarbodiimide with the corresponding acid **60** had been used to perform the Kostanecki–Robinson reaction. In this last reaction, Sodium hydride was used also as base to favor the formation of the expected chromone **62** instead of byproducts. However, this method had one drawback, the anhydride was not easy to prepare, especially for the aromatic acid anhydride.

Pyridine as a catalyst. In 2005, Lee *et al*. [61] synthesized the chromone using pyridine as a catalyst in the ring closure (Scheme 16). Dioxane-fused propiophenone (**64**) was prepared by Fries rearrangement of compound **63**, which was obtained from benzodioxane via two-step sequence, Friedel-Craft acylation with propionyl chloride and Bayer–Villiger oxidation. Chromone rings were

Scheme 13



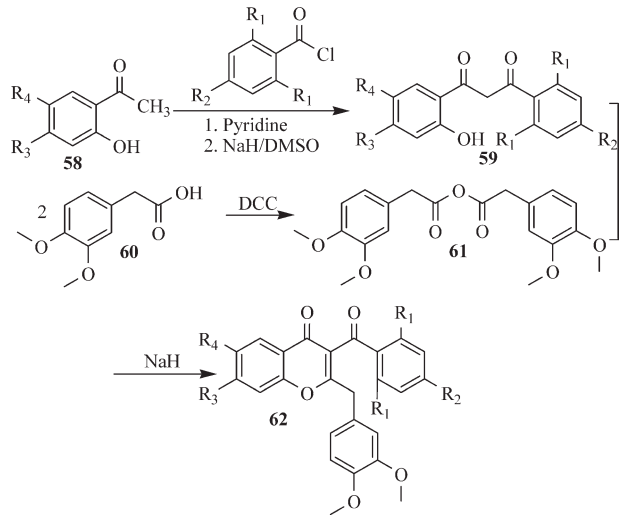
Scheme 14



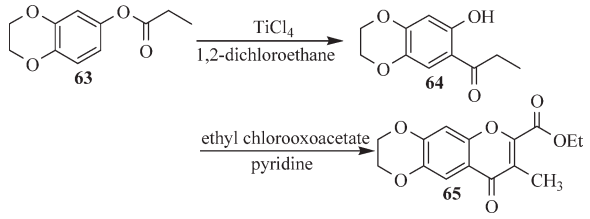
constructed by acylation of 2-hydroxyphenones **64** with ethyl chlorooxoacetate followed by *in situ* cyclization of the resulting esters in the presence of pyridine to provide compounds **65** [62]. This method of using pyridine as a catalyst was more suitable to acyl phenols and chloroacetyl carboxylic acid esters in the chromone ring closure.

Sodium acetate as a catalyst. In 2005, Gabbutt and coworkers [63] synthesized 3-acylchromones by acylation of 2′-hydroxydibenzoylmethane with acid anhydrides in the presence of sodium acetate (Scheme 17). The requisite starting materials, 2′-hydroxydibenzoylmethanes **67**, were easily available by *O*-acylation of 2′-hydroxyacetophenone followed by Baker–Venkataraman (BV) rearrangement under standard conditions [64]. Acylation of the 1,3-diketones **67** with acetic anhydride gave the 2-alkyl-3-aroylchromones **68** in high yields [65]. This condensation reaction was not only applicable to acetic anhydride but also for other acid anhydride such as propionic anhydride and butyric anhydride.

Scheme 15



Scheme 16

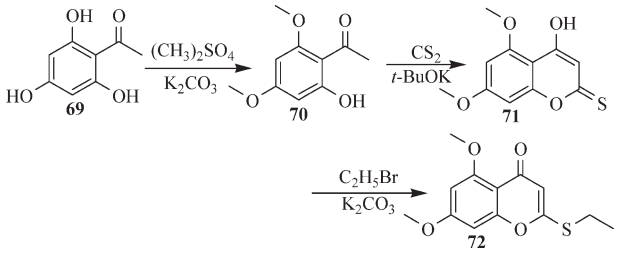


Potassium tert-butoxide as a catalyst. In 2007, Wu and coworkers [66] prepared the chromone ring using potassium *tert*-butoxide in the ring closure during their total synthesis 6-demethoxycapillarisin (Scheme 18). Methylation of **69** with dimethyl sulfate in the presence of K_2CO_3 in CH_3COCH_3 afforded **70**. The intermediate **70** was readily reacted with CS_2 in the presence of *t*-BuOK in toluene to provide **71**. Without purification, the lactone **71** reacted with C_2H_5Br and K_2CO_3 in CH_3COCH_3 to afford the key product **72** [67,68]. This reaction was very useful, which laid the foundation to expand the SAR of chromone ring with sulfur atom in the side chain.

Cs_2CO_3 as a catalyst. In 2008, Arai *et al*. [69] described a practical and useful synthesis of heterocyclic-substituted chromones (Scheme 19) and also developed a one-pot synthesis by Michael aldol reaction of chromone derivatives bearing heterocycle units. The 2,3-heterocyclic-substituted chromones **75** were obtained in one step, as shown in scheme 19, 4′-benzyloxy-2′-hydroxyacetophenone (**73**) reacted with heterocyclic aldehydes **74** to give 2,3-disubstituted chromone **75** in high yield under Cs_2CO_3 conditions.

Potassium carbonate as a catalyst. In 2009, Anwar and Hansen [70] used K_2CO_3 as a catalyst in the chromone ring closure during their first total synthesis of the marine natural product *all*-(*Z*)-5,7-dihydroxy-2-(4*Z*,7*Z*,10*Z*,13*Z*,16*Z*-nonadecapentaenyl)chromone (Scheme 20). In their synthetic route, aldehyde **76** was transformed to the terminal alkyne **77** in a Colvin rearrangement in 58% yield. Addition of aldehyde **78** in THF to the anion of **77** at −78°C yielded the secondary alcohol **79** in 60% yield. Oxidation of **79** with MnO_2 yielded MOM-protected ketone **80** in 88% yield. Mild deprotection of **80** with HCl in EtOH at ambient temperature, followed by intramolecular Michael addition under lenient basic conditions (K_2CO_3, acetone), afforded the natural product **81** in 49% yield for the latter two steps [71]. This reaction using phenol hydroxyl addition to the alkyne bond was relatively classical.

Scheme 18

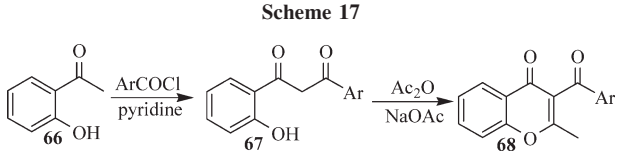


Chromone ring closure under the microwave irradiation. Recently, microwave irradiation [72,73] offers a considerable advantage over conventional heating because it results in substantial rate enhancements in a wide range of organic reactions. Cleaner reactions are also commonly achieved, together with improvements in yield and selectivity [74]. The increasing demand for clean and ''green'' chemical syntheses has resulted in increased use of microwave irradiation, so there have been several recent reports, describing the application of microwave irradiation to the synthesis of flavonoids.

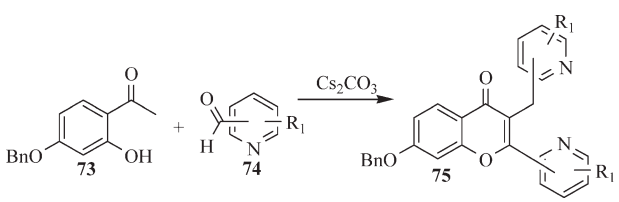
In 2005, Seijas *et al*. [75] reported an eco-friendly direct solvent-free synthesis of functionalized flavones **84** under microwave irradiation (Scheme 21). This method was valid for flavones with or without substitution in the B ring. Thus, the flavonoids were prepared from the corresponding ethyl benzoyl acetates **83** and phloroglucinol for 2–12 min of irradiation in 66–96% yields. The successful use of microwave irradiation in providing this rapid and direct route to flavones in comparison to classical procedures contributes to confirming the participation of specific effects in some microwave-assisted organic synthesis.

In 2005, Kabalka and Mereddy [76] reported a facile microwave synthesis of functionalized flavones and chromones via the cyclization of 1-(2-hydroxyaryl)-3-aryl-1,3-propanedione (Scheme 22). In their study, the intermediate 1,3-propanediones **85** were synthesized in 5 min via dehydrative cyclization to the corresponding flavones and chromones **86** in ethanol, in the presence of $CuCl_2$ under microwave irradiation.

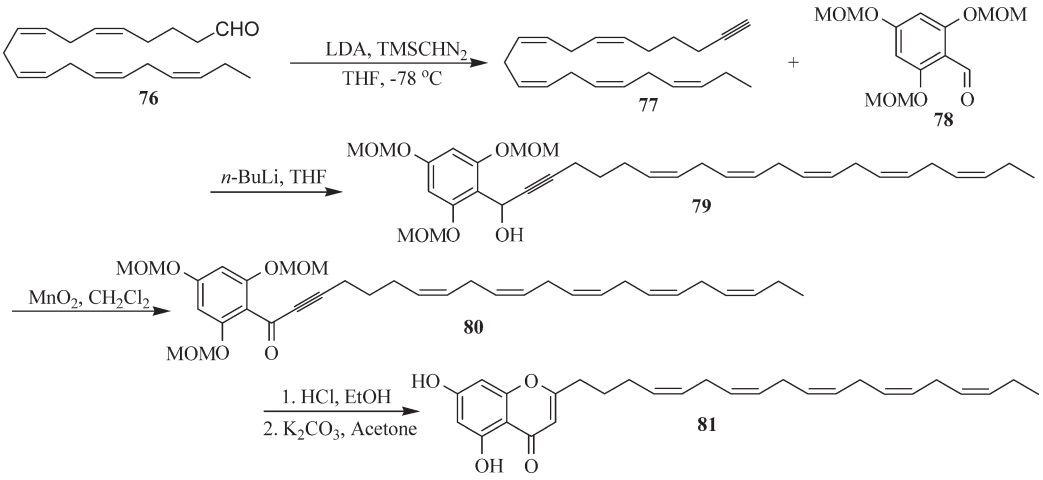
Scheme 17



Scheme 19



Scheme 20



In 2009, Luthman and coworkers. [77] reported a base-promoted condensation between 2-hydroxyacetophenones **87** and aliphatic aldehydes **88** (Scheme 23); they optimized the reaction to afford 2-alkyl-substituted 4-chromanones **89** in an efficient manner using microwave heating. Performing the reaction using diisopropylamine in EtOH at 170°C for 1 h gave high yield in 88%. The 4-chromanones could be further converted into highly functionalized 2,3,6,8-tetrasubstituted chromones in which a 3-substituent (acetate, amine, or bromine) was introduced via straightforward chemical transformations.

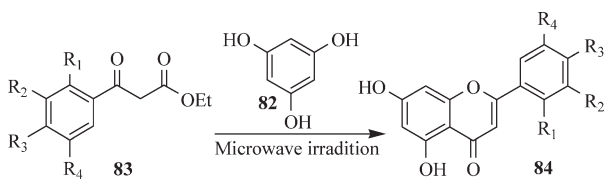
Chromone ring closure via solid-support. In recent years, solid-phase chemical reaction has appeared many advantages including good selectivity, high yield, simple operation, and no pollution, and some researcher has applied this method in chromone synthesis.

Via solid-support catalysts. In 2002, Blanco and coworkers [78] studied the catalytic performance of MPA ($(H_3PMo_{12}O_{40}\cdot nH_2O)$ and TPA ($H_3PW_{12}O_{40}\cdot nH_2O$) (Scheme 24), both bulk or supported on silica (S), to obtain flavones and substituted chromones **96** from 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones **95**, using glacial acetic acid as solvent at 90°C. The result showed that the conversion to flavones and substituted chromones was in general higher in homogeneous phase than that observed for the supported catalysts. Nevertheless, the use of the supported catalysts enabled an easy separation and recovery of the catalyst for its immediate reuse without any important decrease of the catalytic activity. In addition, the unchanged starting material may be recycled to the reactor because it was almost quantitatively recovered and secondary products were not practically formed.

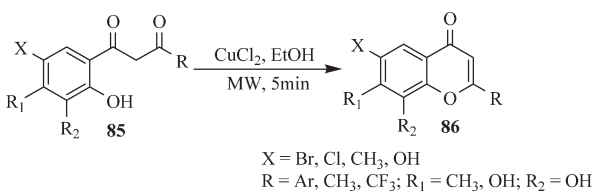
In 2005, van Lier and coworkers [79] explored silica gel-supported $InBr_3$ or $InCl_3$ (15–20 mol %) as a new solid-support catalysts for the facile and efficient oxidation, under solvent free conditions (Scheme 25), of 2′-hydroxychalcones **97** to yield the corresponding flavones **98** in >80% yield. The catalysts were easily prepared, stable, and efficient under mild reaction conditions.

Trifluoromethanesulfonic acid (TFMS) is known to be a strong acid, and it is used in many organic reactions such as Friedel Crafts reactions, polymerization, Koch carbonylation, among others [80]. However, the recovery of the triflic acid from the reaction mixture results in the formation of large amounts of waste [80]. So, in 2007, Romanelli and coworkers described the synthesis and characterization of TFMS supported on mesoporous titania [81] using urea as a low-cost, pore-forming agent (Scheme 26), via HCl catalyzed sol–gel reactions. The acidic characteristics of the solids were determined by potentiometric titration with *n*-butylamine. The use of these solid catalysts provided interesting yields in the cyclization reaction of 1-(2-hydroxyphenyl)-3-aryl-1,3-

Scheme 21

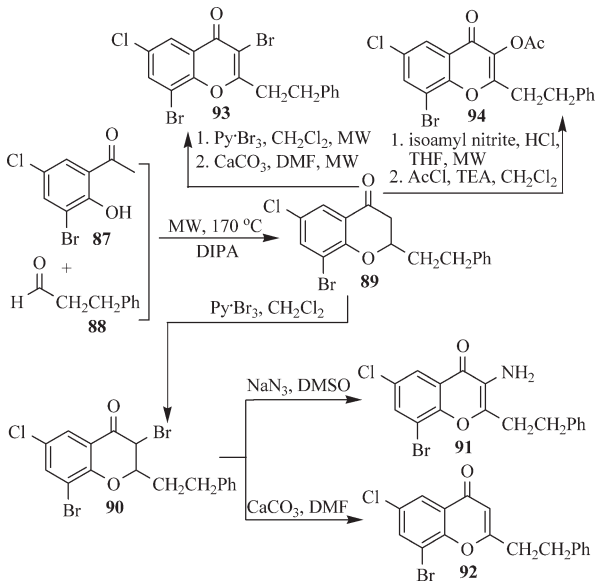


Scheme 22



X = Br, Cl, CH_3, OH
R = Ar, CH_3, CF_3; $R_1 = CH_3$, OH; R_2 = OH

Scheme 23

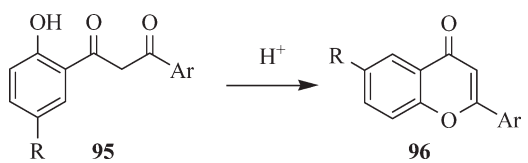


propanediones **99** to flavone **100**, also leading to an easy separation and recovering of the catalysts for further use.

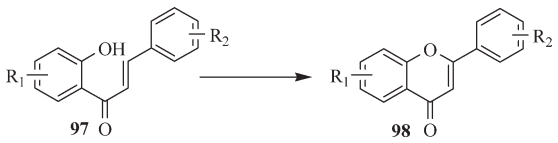
In 2009, Romanelli and coworkers [82] also prepared the $TFMSC_1$ and $TFMSC_2$ catalysts by adsorption of TFMS on two activated carbons with different textural properties used as supports (Scheme 27). The $TFMSC_2$ catalyst used as solid catalyst provided interesting yields in the cyclization reaction of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones **101** to flavones and chromones **102**, also leading to an easy separation and recovery of the catalysts for further use. Moreover, as a significant decrease of the catalytic activity was not observed, they can be recycled without any activity loss.

Solid-supported synthesis. In 2001, Borrell *et al*. [83] developed procedures for the synthesis of the solid-supported synthetic equivalents of chromones (Scheme 28). Treatment of the Wang chloro resin in DMA with 3 equiv of *o*-hydroxyacetophenone **103** and 3 equiv of NaOMe at 80°C overnight quantitatively afforded **104**. Compound **104** was then treated with DMF and $POCl_3$ under Vilsmeier–Haack reaction conditions affording chromone **105** as the major product. In this way, heterocyclic libraries could be effectively and rapidly synthesized.

Scheme 24

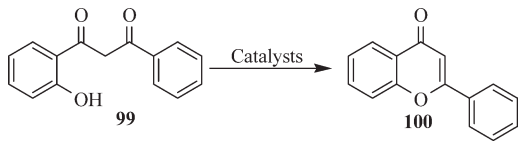


Scheme 25

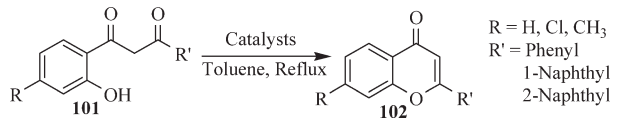


In 2004, Albericio and coworkers [84] described an effective solid-phase preparation of the pharmaceutically interesting 4*H*-2-(3-hydroxy-4-methoxyphenyl)-naphtho [1,2-*b*]pyran-1-one system from an anchored bisarylacetylene (Scheme 29). The coupling reaction between the resin **107** and acetylene **106** with $PdCl_2(PPh_3)_2$, CuI as catalyst, Et_3N as base, and THF as solvent cleanly afforded the resin **108**. Then *O*-silylation of the MOM methoxy group with Me_3SiBr followed by demethylation via nucleophilic attack of bromide gave the *O*-trimethylsilyl derivative. This compound was susceptible to further electrophilic addition by the triple bond and trapping of the resulting carbocation intermediate by atmospheric H_2O then generated the keto group. Further oxidation gave the anchored compound **109**. Final cleavage with $AlCl_3$ rendered **110**. Through this solid-phase strategy, the quite rare 2-(aryl)naphtho[1,2-*b*]pyran-1-one was effectively synthesized. These compounds, like other polycondensed heterocyclic systems bearing electrondonating substituents, are of undoubted pharmaceutical interest. This solid-phase synthetic strategy will facilitate the preparation of libraries with applications in drug discovery.

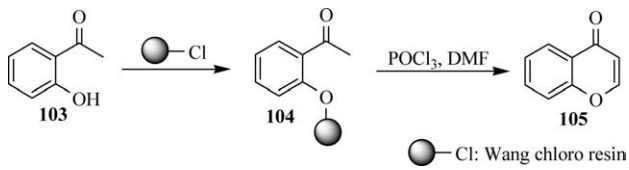
Scheme 26



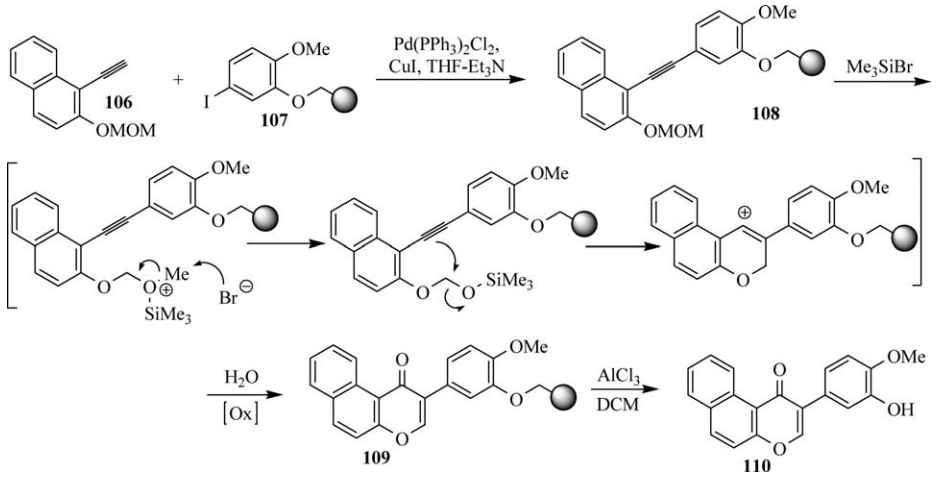
Scheme 27



Scheme 28



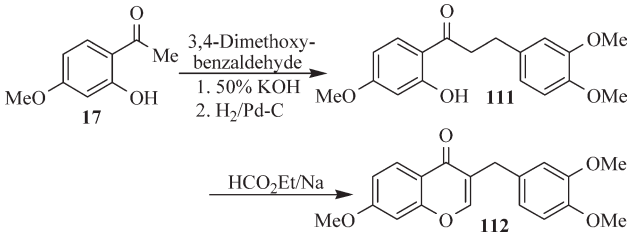
Scheme 29



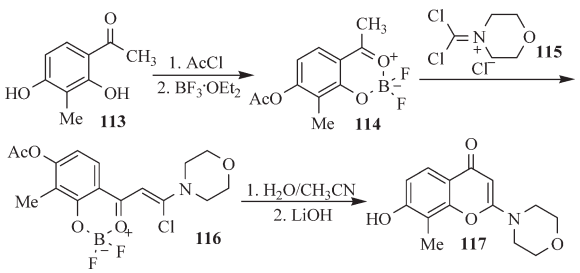
Chromone ring closure through other methods. Besides the above acid catalyst, base catalyst, microwave irradiation, and solid-supported synthesis in ring closure, there are many other catalysts and reaction conditions in this chromone construction.

Sodium as a catalyst. In 1993, Davis and Chen [85] synthesized the chromone through a highly efficient procedure catalysted by sodium sand (Scheme 30). Heating 2-hydroxy-4-methoxyacetophenone (**17**) with 3,4-dimethoxybenzaldehyde in methanol using 50% aqueous KOH followed by hydrogenation over 10% palladium on activated carbon gave 2′-hydroxy-4′,3,4-trimethoxydihydrochalcone (**111**) in 89% overall yield. Treatment of **111** in ethyl formate with sodium sand at 0°C afforded chromone **112** in high yield. However, this reaction was not practical because the hot sodium sand was very dangerous during the reaction.

Scheme 30



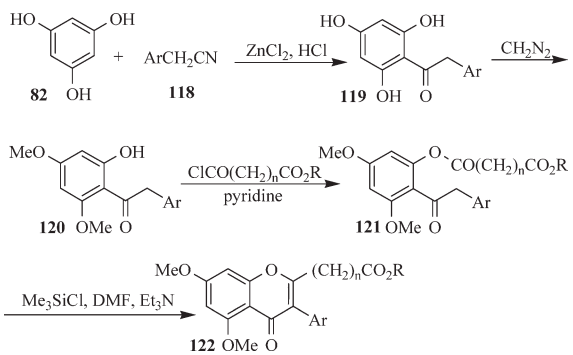
Scheme 31



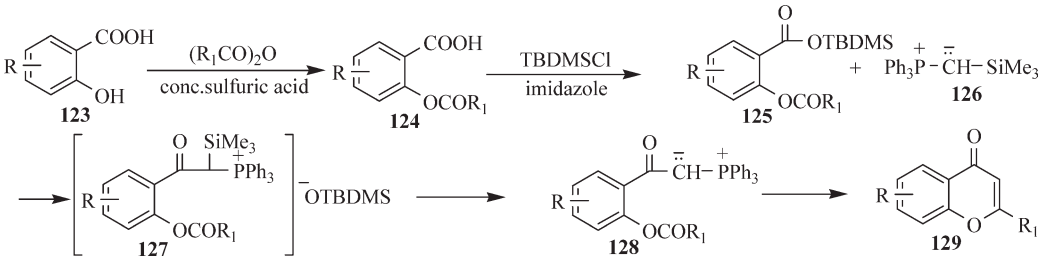
Through basic hydrolysis. In 1993, Morris *et al*. [86] accomplished the preparation of chromone utilizing a novel synthesis of 2-aminochromones **117** via the condensation of BF_2 complexes of 2'-hydroxyacetophenones with phosgeniminium salts [87] (Scheme 31). Acetylation of **113** followed by treatment with $BF_3{\cdot}OEt_2$ afforded the BF_2 complex **114** in 76% overall yield. Reaction of **114** with 4-(dichloromethylene)morpholinium chloride (**115**) (65°C, 24 h) produced **116**. Liberation of the BF_2 complex (H_2O, CH_3CN) promoted cyclization to afford chromone **117** upon basic hydrolysis of the acetate protecting group (67% from **114**). Through this method, a side chain containing nitrogen atoms could be introduced into the chromone ring.

Me_3SiCl as a catalyst. In 1999, Pelter *et al*. [88] reported the synthesis of chromone ring via Me_3SiCl/DMF/Et_3N (Scheme 32). Phloroglucinol **82** was reacted with 4-methoxybenzyl cyanide **118** by a modified procedure using catalytic $ZnCl_2$ to give **119** in 91% yield. Methylation of **119** with diazomethane in methanol readily gave **120** in which only the 2-hydroxyl group

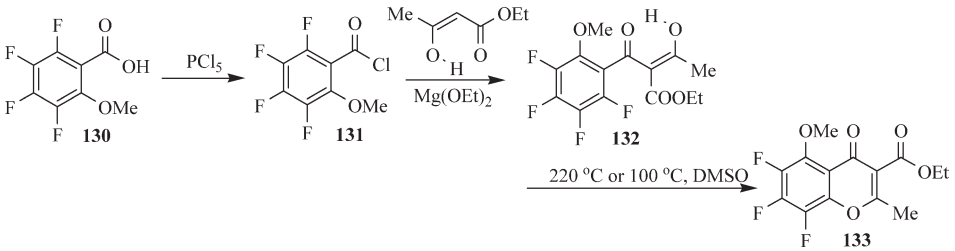
Scheme 32



Scheme 33



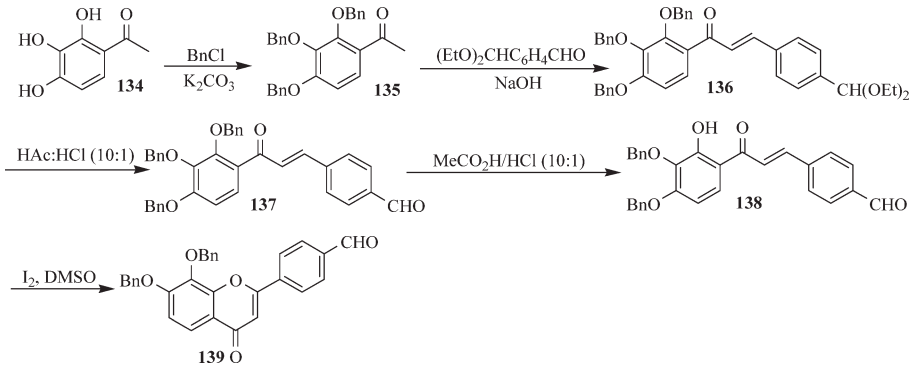
Scheme 34



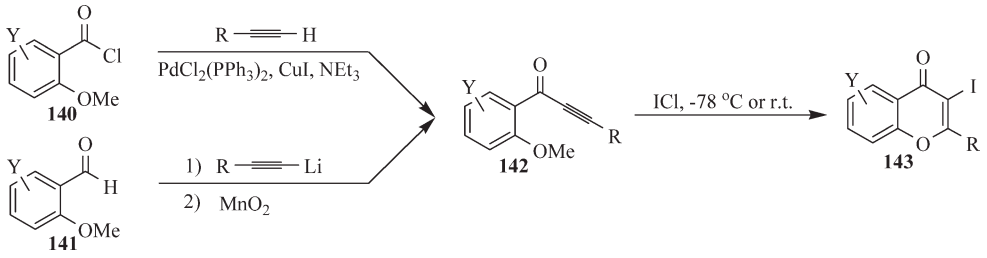
was free. Acylation of **120** gave the required esters **121**. A simple modification using $Me_3SiCl/DMF/Et_3N$ converted **121** to **122** in high yield.

Via intramolecular ester carbonyl olefination. In 2000, Kumar and Bodas [89] reported a new and simple route to 4*H*-chromen-4-ones via intramolecular ester carbonyl olefination using (trimethylsilyl)methylenetriphenylphosphorane (Scheme 33). Salicylic acid or its substituted derivative **123** was converted into its *O*-acyl(aroyl) derivatives **124** by reaction with the corresponding anhydride. Compound **124** was then treated with *tert*-butyldimethylsilyl chloride in the presence of imidazole to furnish the corresponding silyl ester **125** in excellent yields. When a mixture of compound **125** and

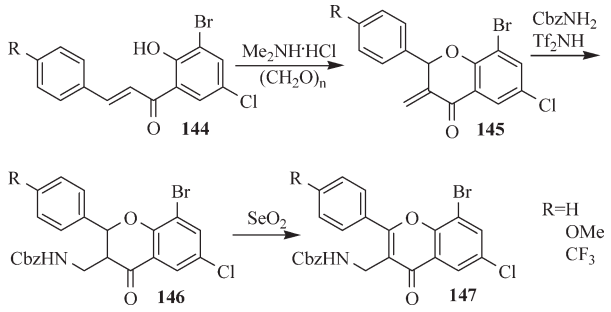
Scheme 35



Scheme 36



Scheme 37



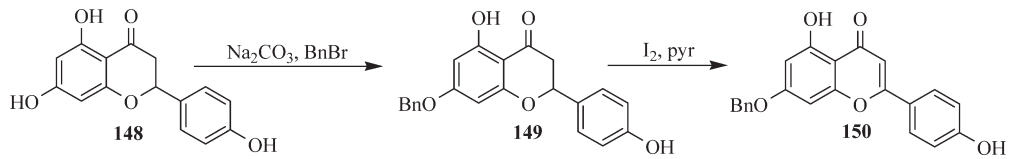
(trimethylsilyl)methylenetriphenylphosphorane **126** was heated in refluxing THF, the desired chromones **129** was obtained in 55–80% yields. This is the first report of chromone synthesis via intramolecular Wittig ester carbonyl olefination using (trimethylsilyl) methylenetriphenyl-phosphorane.

Via heating. In 2001, Saloutin and coworkers [90] described the acylation of ethyl acetoacetate by the fluorobenzoyl chloride and synthesis of novel flurobenzopyran-2(4)-one (Scheme 34). 2-Dimethoxy-3,4,5,6-tetrafluorobenzoyl chloride **131** was obtained by heating the corresponding acid **130** with an excess of phosphorus pentachloride. Then, the interaction of fluorobenzoyl chloride **131** with ethyl acetoacetate in the presence of magnesium ethoxide resulted in β,β′-dioxaester **132**, which readily cyclized into chromone **133** on heating in the absence of solvents or in DMSO. The cyclization proceeded through intramolecular substitution of the *o*-fluorine atom in the fluorophenyl substituent.

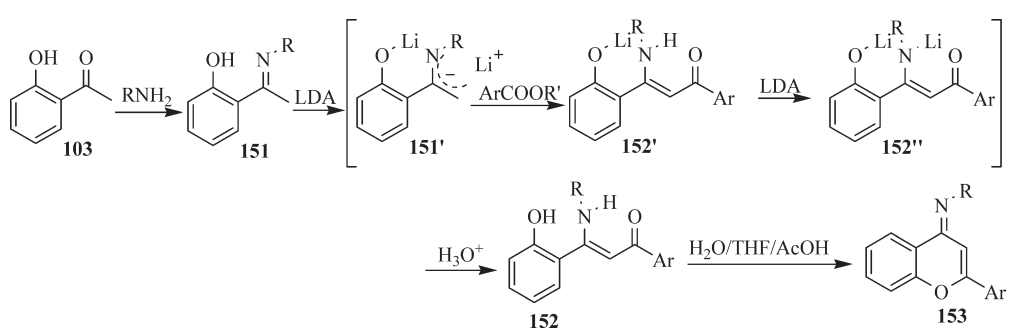
Iodine as a catalyst. In 2004, Tomé and coworkers [91] reported the synthesis of chromone through iodine as a catalyst (Scheme 35). Benzylation of 2′,3′,4′-trihydroxyacetophenone **134** with benzyl chloride in the presence of potassium carbonate afforded the corresponding 2′,3′,4′-tribenzyloxy-acetophenone **135** in 90% yield. This compound was condensed with terephthalaldehyde mono(diethyl acetal) to give chalcone **136**. Hydrolysis of the acetal group furnished the formylchalcone **137**. Selective debenzylation of the 2-benzyloxy group was achieved by the treatment of **137** with a mixture of acetic acid and concentrated hydrochloric acid (10:1) for 1 h at 40°C. Finally, formylflavone **139** was obtained by oxidative cyclization of **138** in refluxing dimethylsulfoxide with a catalytic amount of iodine. This approach was widely used in chromone ring closure, and many synthesis have adopted this approach [92–95].

Via ICl-induced cyclization. In 2006, Larock and coworkers [96] described the ICl-induced cyclization of heteroatom-substituted alkynones **142** (Scheme 36); this method provided a simple, highly efficient approach to various 3-iodochromones **143**. The 2-methoxyaryl-containing alkynones required were readily prepared in one or two steps by two complementary methods: (1) the palladium/copper-catalyzed Sonogashira coupling of an acid chloride **140** with a terminal acetylene at room temperature or 50°C [97] or (2) the addition of a lithium acetylide to an aldehyde **141**, followed by oxidation of the resulted secondary alcohol by activated MnO_2 [98]. This process was run under mild conditions, tolerated various functional groups, and generally provided chromones in good to excellent yields.

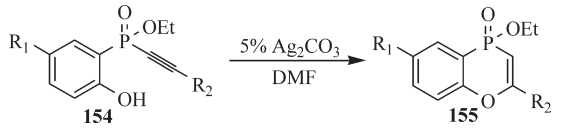
Scheme 38



Scheme 39



Scheme 40



Under Mannich conditions. In 2007, Luthman and coworkers [99] developed an efficient synthetic route to Cbz-protected 3-aminomethyl-2-aryl-8-bromo-6-chlorochromones **147** (Scheme 37). In their synthetic route, 3-Aryl-1-(3-bromo-5-chloro-2-hydroxyphenyl)-2-propen-1-one **144** was reacted under Mannich conditions yielding 2-aryl-8-bromo-6-chloro-3-methylenechroman-4-one **145**, which was further converted to the target compound **147** via an aza-Michael reaction followed by an SeO_2 oxidation [100–103]. This procedure represented a new method to introduce a primary aminomethyl group at the 3-position of a 2-arylchromone scaffold.

Through base-induced elimination. In 2009, Rizzacasa and coworkers [104] described the synthesis of chromone through Iodination of naringenin followed by base-induced elimination (Scheme 38). This began with selective benzylation of naringenin (**148**) on the more acidic C7 phenol to afford benzyl ether **149**. Iodination followed by base-induced elimination gave the flavone **150** in a reasonable yield for the two steps.

Synthesis of heterocycle analog of chromone. The chromones have gained considerable synthetic and pharmacological interest for a long time because of their diverse biological activities, and recent studies have indicated that a lot of natural heterocycle analog containing phosphorus, sulphur, and nitrogen also show the expected bioactivity, so many synthesis of heterocycle analog of chromone have been reported with high regioselectivity and good yields.

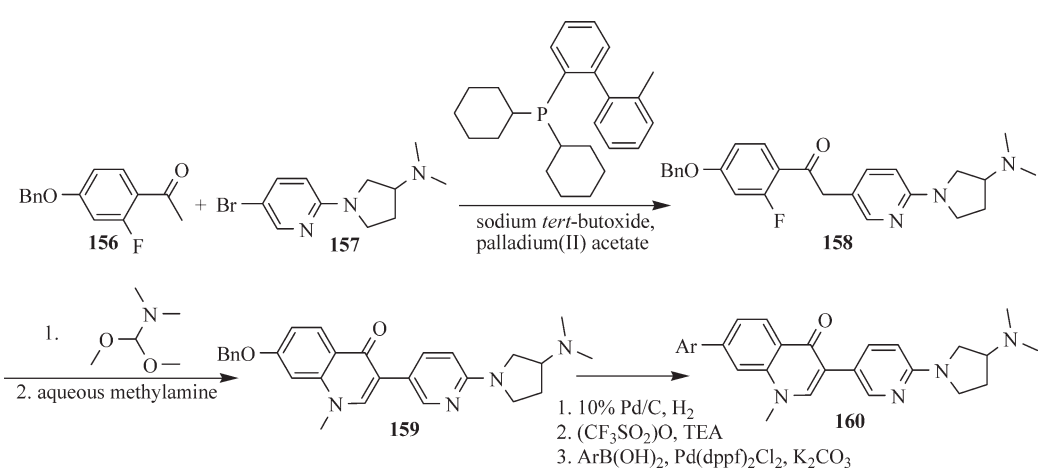
Synthesis of 4H-Chromen-4-ylidenamines. 4*H*-Chromen-4-ylidenamines **153** were derivatives of chromones, that have awakened new interest because the simplest of them (2-phenyl-*4H*-chromen-4-imine), has been used [105] for treatment of cell proliferative diseases and for its antihypoxic, hypotensive, and antiallergic properties. So, in 2000, Palmieri's group [106] described a method to obtain 4*H*-chromen-4-ylidenamines **153** (Scheme 39). The reaction of *o*-imidoyl phenol dianions **151′** with aromatic esters and subsequent acid cyclization of the 3-(2-hydroxyphenyl)-3-(amino)-1-phenylprop-2-en-1-ones **152** afforded *4H*-chromen-4-ylidenamines **153** in satisfactory yields, a class of compounds of renewed interest.

Synthesis of phosphachromones. Because there was a remarkable similarity in reactivity and bioactivities between the carbon species and their phosphorus counterparts [107,108], one can anticipate that the phosphachromone analog of chromone would have potential bioactivities similar to those of chromones, so in 2008, Ding and coworkers [109] reported a novel Ag_2CO_3-catalyzed cyclization reaction of *O*-hydroxyphenylethynylphosphinates **154** to phosphachromones **155** with high regioselectivity and good yields (Scheme 40), which provided an effective approach to synthesize the new kind of phosphorus heterocycles.

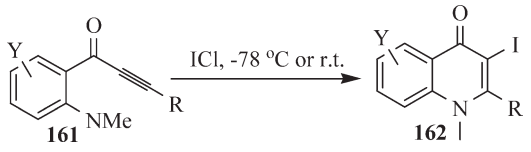
Synthesis of quinolones. In 2006, Dyck and coworkers [110] reported the synthesis of the quinolone derivatives (Scheme 41). Bromopyridine **157** was coupled to 4′-benzyloxy-2′-fluoroacetophenone **156** to provide **158**. Aminomethylenation with dimethylformamide dimethyl acetal provided the precyclization intermediate which, upon reaction with methylamine, provided the quinolone core (**159**). Removal of the benzyl protecting group gave the phenol, which was converted to the triflate and coupled with aryl boronic acids to provide the target quinolones **160**.

In 2006, Larock and coworkers [96] described the ICl-induced cyclization of nitrogen-substituted alkynones **161** to afford the quinolones **162** in good to excellent yields (Scheme 42).

Scheme 41



Scheme 42



In 2008, Nam and coworkers [111] reported the synthesis of quinolinone as they designed and synthesized the 4-quinolinone 2-carboxamides as calpain inhibitors (Scheme 43). Diethyl oxalpropionate (**163**) was condensed with aniline in acetic acid to give anilino-maleate **164**. Compound **164** was heated at 250°C in mineral oil to form the cyclized product, quinolinone **165**.

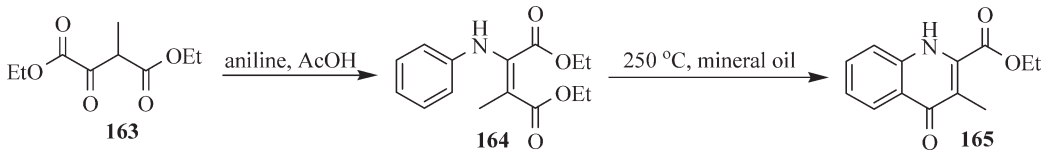
Synthesis of thioflavones. In 2004, Kataoka *et al*. [112] reported the synthesis of thioflavones as they studied the SARs of thioflavone derivatives as specific inhibitors of the ERK-MAP kinase signaling pathway (Scheme 44). Condensation of benzaldehydes **166** with α-benzoyl sulfoxide **167** gave α-sulfinyl enones **168** in good yields. Cyclization of **168** followed by debenzylation was performed by the treatment with formic acid at 5°C to give 3-(methylsulfinyl)-2,3-dihydro-4*H*-1-benzothiopyran-4-ones **169** as a mixture of diastereoisomers. Refluxing the diastereomer mixtures of **169** in benzene caused the elimination of methanesulfenic acid to form thioflavones **170**.

In 2006, Larock and coworkers [96] described the ICl-induced cyclization of sulphur-substituted alkynones **171** to give various 3-iodo-thiochromones **172** in good to excellent yields (Scheme 45).

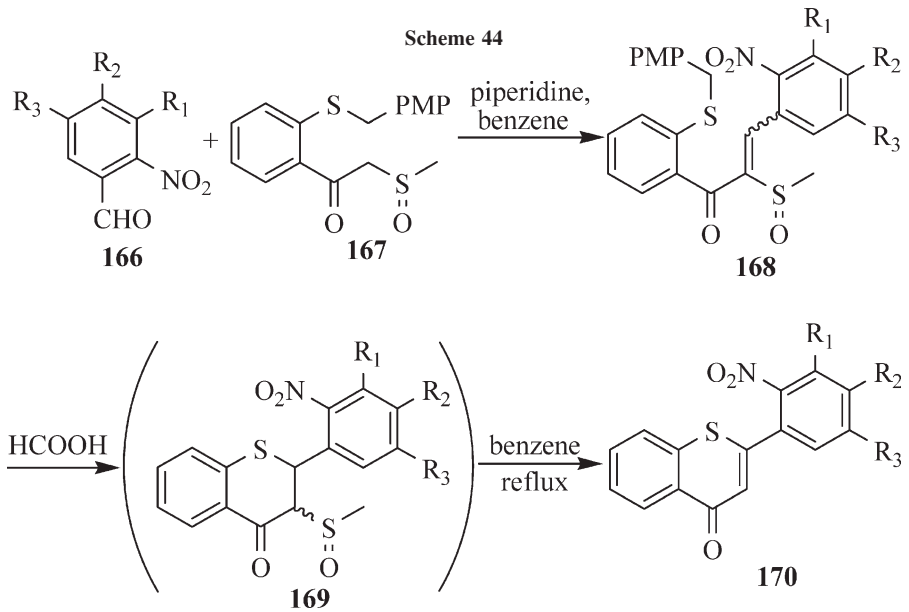
CONCLUSIONS

Chromone derivatives have high potential in drug discovery. Synthesis of large compound libraries is a general trend in a modern drug discovery process. Furthermore, computer-aided drug design can be used to perform virtual screening before the compounds are synthesized. Both methodologies require rapid synthesis of the compounds preferably from a limited number of starting materials. So, in recent years, a lot of synthetic method to construct the chromone ring appeared. In this review, some recent improvements of the classical synthetic methods and of some nonclassical methods to obtain simple oxygenated chromones have been reported, which includes acid as catalyst, base as catalyst, microwave irradiation assisted synthesis, solid-supported synthesis, and other methods. Furthermore, recent studies have indicated that a lot of natural heterocycle analog containing phosphorus, sulphur, and nitrogen also show the expected bioactivity, so many synthesis of heterocycle analog of chromone have been reported with high regioselectivity

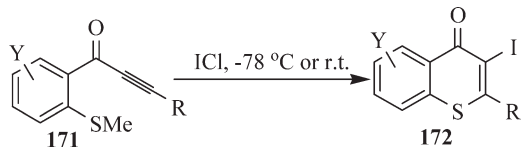
Scheme 43



Scheme 44



Scheme 45



and good yields. So, the strategies for synthesis of heterocycle analog containing phosphorus, nitrogen, and sulfur are also summarized in this review. We hope this review will stimulate interest in the synthesis of chromone with biological activities in the near future.

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