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Eric F. V. Scriven and Christopher A. Ramsden

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Editors

ERIC F.V. SCRIVEN

Department of Chemistry,
University of Florida,
Gainesville, FL, United States

CHRISTOPHER A. RAMSDEN

Lennard-Jones Laboratories,
Keele University, Staffordshire,
United Kingdom

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Contributors

Daniel T. Gryko
Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

Beata Koszarna
Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

Damian Kusy
Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

Timothy D. Lash
Department of Chemistry, Illinois State University, Normal, IL, United States

Justin M. Lopchuk
Drug Discovery Department, H. Lee Moffitt Cancer Center and Research Institute; Department of Oncologic Sciences, College of Medicine, University of South Florida, Tampa, FL, United States

Majid M. Heravi
Department of Chemistry, School of Physics and Chemistry, Alzahra University, Vanak, Tehran, Iran

Yevgen M. Poronik
Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

Gana Sanil
Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

Clementina M.M. Santos
Centro de Investigação de Montanha (CIMO), Instituto Politécnico de Bragança, Bragança, Portugal

Zachary P. Shultz
Drug Discovery Department, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, United States

Artur M.S. Silva
LAQV-REQUIMTE, Department of Chemistry, University of Aveiro, Aveiro, Portugal

Bartosz Szymański
Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

Olena Vakuliuk
Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

Vahideh Zadsirjan
Department of Chemistry, School of Physics and Chemistry, Alzahra University, Vanak, Tehran, Iran

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Preface

Chapter 1 in this volume, by Majid M. Heravi and Vahideh Zadsirjan (Alzahra University, Tehran, Iran), covers advances since 2015 in the Paal-Knorr reaction for the synthesis of furans, pyrroles, and thiophenes. Some applications in the synthesis of natural products are also discussed in the chapter. Justin M. Lopchuk and Zachary M. Schultz (Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, USA) in Chapter 2 review strategies for the synthesis of sulfoximine-containing heterocycles from their discovery in 1950 to the present. This chapter contains an extensive treatment of new methods of synthesis and the structural complexity of this very large group of heterocycles.

Chapter 3, by Clementina M.M. Santos (CIMO, Braganza Polytechnic Institute, Portugal) and Artur M.S. Silva (University of Aveiro, Portugal), presents a comprehensive survey of the methods available for the synthesis of 2,3-unsubstituted, 2- and 3-substituted 2,3-disubstituted 4*H*-chromen-4-ones-based literature coverage since 2012. Timothy D. Lash (Illinois State University, Normal, Illinois, USA), in Chapter 4, reviews advances, since 2001, in the chemistry of heteroporphyrins that contain O, S, Se, Te, or P replacing one or more core nitrogens, and heterocarbaporphyrins, with similar replacement of N by C. Reactivity of these compounds and the rearrangements they undergo are discussed.

Finally, Chapter 5 (Gana Sanil, Beata Koszarna, Yevgen M. Poronik, Olena Vakuliuk, Bartosz Szymanski, Damian Kusy, and Daniel T. Gryko, Polish Academy of Sciences, Warsaw, Poland) presents a comprehensive review of the chemistry of 1,4-dihydropyrrolo[3,2-*b*]pyrroles (DHPP). The chapter highlights the use of multicomponent synthetic reactions to afford previously unknown ladder-type heterocyclic skeletons. Photophysical properties of DHPP are critically reviewed.

Eric F.V. Scriven and Christopher A. Ramsden
April 2022

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CHAPTER THREE

Recent advances in the synthesis of 4*H*-chromen-4-ones (2012 – 2021)

Clementina M.M. Santos[a] **and Artur M.S. Silva**[b,*]

[a]Centro de Investigação de Montanha (CIMO), Instituto Politécnico de Bragança, Bragança, Portugal
[b]LAQV-REQUIMTE, Department of Chemistry, University of Aveiro, Aveiro, Portugal
*Corresponding author: e-mail address: artur.silva@ua.pt

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Abstract

Chromones is a family of oxygen heterocyclic compounds whose synthetic versatility and broad spectrum of bioactive properties has been widely reported over the past decade. The increasing number of publications related to the synthesis of this heterocyclic system highlights diverse synthetic approaches, using different starting materials, with novel and efficient synthetic details, applying alternative heating conditions, that provides a huge number of polyfunctionalized 4*H*-chromen-4-one derivatives. The purpose of this chapter is to present a comprehensive survey of the methodologies developed for the synthesis of 2,3-unsubstituted, 2- and 3-substituted and 2,3-disubstituted 4*H*-chromen-4-ones, focusing on the literature since 2012, in nearly 450 publications.

Keywords: Acetophenone, Aldol condensation, Baker-Venkataraman, Chalcone, Chromone, Cyclodehydration, Enaminone, Flavone, Isoflavone, Multicomponent reaction

Abbreviations

Ac	acetyl
AcOH	acetic acid
Bn	benzyl
Boc	*t*-butyloxycarbonyl
Bu	butyl
Cat	catalyst
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCC	*N*,*N*-dicyclohexylcarbodiimide
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	*N*,*N*-diisopropylethylamine
DMAc	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMF-DMA	*N*,*N*-dimethylformamide dimethyl acetal
DMSO	dimethyl sulfoxide
DPPB	1,4-bis(diphenylphosphino)butane

Et	ethyl
EtOH	ethanol
LED	light emitting diode
LiHMDS	lithium bis(trimethylsilyl)amide
Me	methyl
MW	microwave
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NHC	*N*-heterocyclic carbene
NIS	*N*-iodosuccinimide
NPs	nanoparticles
OTf	triflate
PEG	polyethylene glycol
Ph	phenyl
PIDA	phenyliodine(III) diacetate
PIFA	phenyliodonium bis(trifluoroacetate)
Pr	propyl
PTSA	*p*-toluenesulfonic acid
TBAB	tetrabutylammonium bromide
TBAI	tetrabutylammonium iodide
TBHP	*t*-butyl hydroperoxide
TBPB	*t*-butyl peroxybenzoate
TCT	2,4,6-trichloro-1,3,5-triazine
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
THF	tetrahydrofuran
TMSCl	trimethylsilyl chloride
TTA	thallium(III) acetate
TTS	thallium(III) *p*-tosylate

1. Introduction

4*H*-Chromen-4-one (Fig. 1), also known as chromone, is an important and versatile 6-*O*-membered heterocyclic system widespread in the plant kingdom.[1] The importance of this scaffold is highlighted by the huge number of publications dedicated to the synthesis of natural and synthetic derivatives over the past decade.

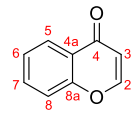


Fig. 1 Structure and numbering system of 4*H*-chromen-4-one core.

A large variety of reviews on the synthesis of chromone derivatives have been published, namely reviews on the synthesis of 2-aryl-4*H*-chromen-4-ones,[2–4] of 2- and 3-aminomethylchromone derivatives,[5] of 4*H*-chromen-4-ones annulated at C7—C8 bond with five-, six-, and seven-membered oxygen-containing heterocycles with two heteroatoms,[6] and on the catalytic one-pot synthesis of 2- and 3-substituted and 2,3-disubstituted 4*H*-chromen-4-ones.[7]

Reviews on the natural occurrence, synthesis and biological applications of simple 4*H*-chromen-4-ones[1]; on natural occurrence, structure elucidation and biological activities of 2-(2-phenylethyl)-4*H*-chromen-4-ones[8]; on natural occurrence and biosynthesis of methoxylated 2-aryl-4*H*-chromen-4-ones,[9] and on natural occurrence, synthesis, reactivity and biological properties of 2-styryl-4*H*-chromen-4-ones[10] have also appeared.

The synthesis and reactivity of 2-acyl-4*H*-chromen-4-ones,[11] of 2-aryl- and 2-aryl-3-substituted 4*H*-chromen-4-ones,[12] of halo-4*H*-chromen-4-ones,[13] of 4-oxo-4*H*-chromen-3-carbaldehydes,[14] of 4-oxo-4*H*-chromen-3-carbonitriles[15] of 2-methyl-4-oxo-4*H*-chromen-3-carboalkoxides,[16] of 4-oxo-4*H*-chromen-3-carboxylates and 4-oxo-4*H*-chromen-3-ylglyoxalates,[17] of electron-deficient 3-vinyl-4*H*-chromen-4-ones[18] and 4*H*-chromen-4-ones polyfluorinated in A-ring,[19] have been detailed in minireviews. The synthesis of furochromones, their transformation and biological activities has also reviewed.[20]

The synthesis and biological applications of 4*H*-chromen-4-ones,[21] of the subgroups 2-aryl-4*H*-chromen-4-ones[22]; 3-aryl-4*H*-chromen-4-ones, their glycosides and glycoconjugates[23]; fluorine-containing 2-aryl-5,7-dihydroxy-4*H*-chromen-4-ones,[24] 3-thienyl/3-benzothienyl-4*H*-chromen-4-ones,[25] and patented non-flavonoid chromones[26] have been overviewed.

Discussions of specific reactions such as application of palladium-catalyzed coupling reactions[27] and of Suzuki-Miyaura reaction[28] in the synthesis of 2-aryl- and 3-aryl-4*H*-chromen-4-ones, mechanism and application of Baker–Venkataraman O → C acyl migration reactions for the synthesis of 2-substituted and 2,3-disubstituted 4*H*-chromen-4-ones,[29] application of ring opening ring closure reactions with 3-substituted chromones under nucleophilic conditions to give a series of 2,3-disubstituted chromones[30] were accomplished.

The importance of specific reagents, namely, molecular iodine in the synthesis of 2-aryl-, 2-styryl- and 2-aryl-3-iodo- 4*H*-chromen-4-ones[31];

quinacetophenone as an easily accessible building block for the synthesis of various 2- and 3-substituted and 2,3-disubstituted 4*H*-chromen-4-ones;[32] the use of heteropolyacids as catalysts for the synthesis of 2-aryl-4*H*-chromen-4-ones;[33] 2-hydroxyaryl tertiary enaminones for the synthesis of C-3-functionalized chromones via tandem vinyl C—H bond elaboration and chromone annulation reactions;[34] acyclic 2-hydroxyaryl enaminones for the synthesis of 3-acyl-4*H*-chromen-4-ones;[35] 2-hydroxyaryl *N*,*N*-dimethylenaminones for the synthesis of 2,3-unsubstituted, 2- and 3-substituted 4*H*-chromen-4-ones;[36] and 2,3-unsubstituted 4*H*-chromen-4-ones for diversification of their chromone unit by direct C—H bond activation/functionalization at C-2 and C-3 sites[37] have been disclosed.

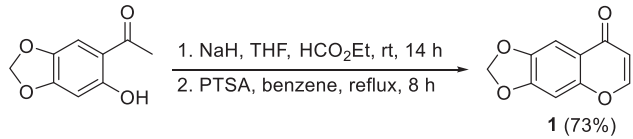
Overviews on the application of microwave irradiation for the synthesis and transformation of 4*H*-chromen-4-ones[38] and of six-membered *O*,*O*-heterocycles that includes the synthesis of some 4*H*-chromen-4-one derivatives have also been reported.[39]

The pharmacological importance of a huge variety of polyfunctionalized 4*H*-chromen-4-ones was also highlighted in several dedicated reviews.[40–45]

Herein, it is our intention to update readers on the tremendous potential of chromone synthetic chemistry, providing all the synthetic details, scope and yields of the most relevant transformations, for the synthesis of 2,3-unsubstituted, 2- and 3-substituted and 2,3-disubstituted 4*H*-chromen-4-ones, published from 2012 to 2021.

2. Synthesis of 2,3-unsubstituted 4*H*-chromen-4-ones

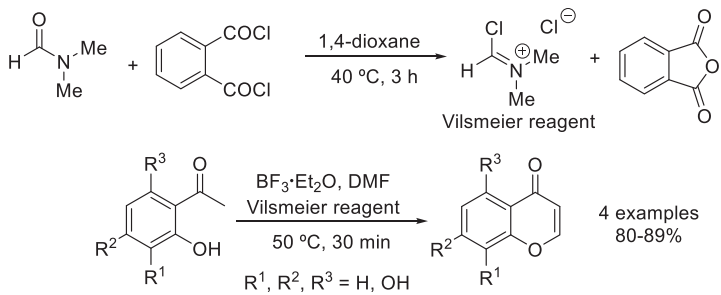
Chromone **1** was prepared by condensation of the 2′-hydroxyacetophenone with ethyl formate in the presence of sodium hydride in THF followed by dehydration of the resulting chroman-3-ol with *p*-toluenesulfonic acid (PTSA) in refluxing benzene (Scheme 1).[46] The condensation of 2′-hydroxy-4′-methoxyacetophenone with ethyl methanoate in the presence of sodium in diethyl ether followed by acidification in the presence of concentrated hydrochloric acid and acetic acid,



Scheme 1

in refluxing conditions, provided 7-methoxy-4*H*-chromen-4-one in good overall yield.[47] Similarly, condensation of the 2′,6′-dihydroxyacetophenone with ethyl formate in the presence of sodium ethoxide followed by acidification led to the synthesis of 5-hydroxychromone in excellent yield, on decagram scale.[48]

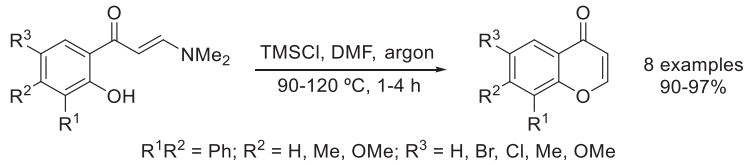
Basha et al. developed a methodology to prepare 2,3-unsubstituted chromones from 2′-hydroxyacetophenones, via one-carbon extension, using 2,4,6-trichloro-1,3,5-triazine (TCT)/DMF complex. Thus, 2′-hydroxyacetophenones and boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$) was cooled to 10 °C and DMF was added dropwise to the reaction mixture. Then, the in situ prepared TCT/DMF complex was added to the reaction mixture and heated to 60 °C for another 40 min. After acidification, the product was extracted with ethyl acetate and purified by column chromatography.[49] A year later, Yadav prepared 2,3-unsubstituted chromones from 2′-hydroxyacetophenones and Vilsmeier reagent, using $BF_3{\cdot}Et_2O$ and DMF at 50 °C for 30 min. For the preparation of Vilsmeier reagent, a mixture of DMF in 1,4-dioxane was added to phthaloyl dichloride at room temperature, and then the whole mixture was stirred at 40 °C for 3 h. The white precipitates formed were isolated by filtration under a nitrogen atmosphere (Scheme 2).[50]



Scheme 2

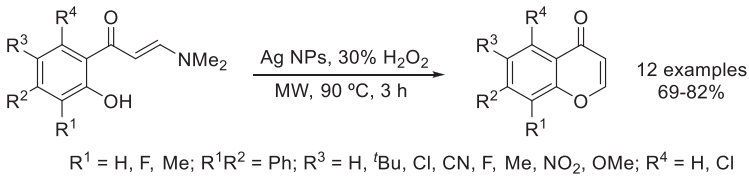
Enaminones can be used as versatile precursors for the preparation of 2,3-unsubstituted chromones, usually in two steps approaches, starting from 2′-hydroxyacetophenones. The first step is a synthesis of the (*E*)-3-(dimethylamino)-1-(2-hydroxyaryl)prop-2-en-1-ones by reaction of 2′-hydroxyacetophenones with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) in refluxing conditions. Subsequent treatment of the products with trimethylsilyl chloride (TMSCl) in hot DMF under argon

atmosphere afforded 2,3-unsubstituted chromones in nearly quantitative yield (Scheme 3).[51] Alternatively, cyclization can occur in refluxing acetic acid[52] and in the presence of concentrated hydrochloric acid in refluxing dichloromethane[53] or refluxing methanol.[54]



Scheme 3

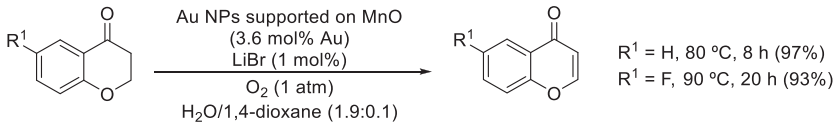
Balakrishna et al. developed an eco-friendlier strategy for the one-pot synthesis of 2,3-unsubstituted chromones through microwave-assisted propylphosphonic anhydride (T3P®)-promoted reaction of 2′-hydroxyacetophenones with DMA-DMF at 100 °C for 10 min followed by the addition of the catalyst at 90 °C an additional 10 min of reaction.[55] A greener protocol used enaminones and biologically capped silver nanoparticles as efficient catalyst, with high yields under mild reaction conditions. Thus, enaminones in aqueous solution of silver nanoparticles and 30% aqueous hydrogen peroxide underwent microwave irradiation at 90 °C for 3 h to give the desired product, without any side products (Scheme 4).[56]



Scheme 4

Ali et al. also reported the reaction of (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one with phosphorus tribromide, phosphorus oxychloride and phenylphosphonic dichloride in dry toluene containing triethylamine to furnish in all cases parent chromone. Unfortunately, the authors did not provide the yields obtained.[57] When the same enaminone underwent $Mn(OAc)_3$-promoted reaction with diethyl phosphite in a 1:2 mixture of acetic acid:1,4-dioxane at 80 °C for 12 h afforded mainly parent

chromone (52%) and a small amount of the phosphinative cyclization product, diethyl (4-oxo-4*H*-chromen-3-yl)phosphonate (20%).[58] A few 2,3-unsubstituted chromones were efficiently obtained from oxidation of chroman-4-ones under dual catalysis of *t*-butyl hydroperoxide (TBHP) and tetrabutylammonium iodide (TBAI) at 80 °C[59] and aerobic oxidative α,β-dehydrogenation of chroman-4-ones using an aqueous solution of gold nanoparticles supported on manganese oxide (Scheme 5).[60] The latest protocol was also applied to the oxidation of a couple of 2-aryl-4*H*-chroman-4-ones to give 2-aryl-4*H*-chromen-4-ones and of 3-methyl-4*H*-chroman-4-one to form 3-methyl-4*H*-chromen-4-one.[60]



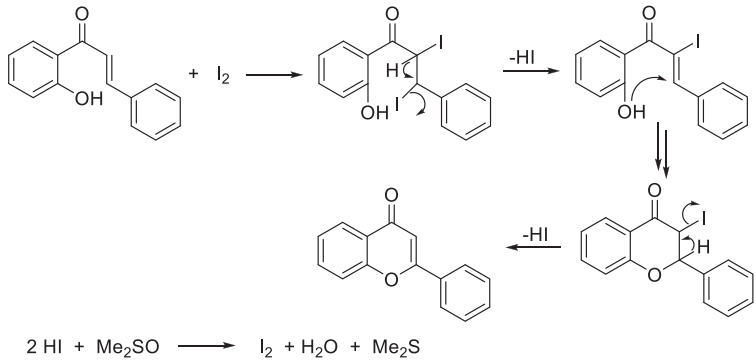
Scheme 5

3. Synthesis of 2-substituted 4*H*-chromen-4-ones

3.1 Through 2′-hydroxychalcones and related compounds

This is the one of most common and general approach for the preparation of a large variety of polyfunctionalized chromone derivatives, it involves the aldol condensation of 2′-hydroxyacetophenones with appropriate aldehydes leading to 2′-hydroxychalcones which underwent cyclodehydrogenation in different reaction conditions.

A wide range of 2-aryl-4*H*-chromen-4-ones, commonly known as flavones, was synthesized via cyclodehydrogenation reaction of (*E*)-2′-hydroxychalcones in the presence of a catalytic amount of molecular iodine in DMSO. The reaction proceeds in a short period of time (15 min to 8 h) and temperatures ranging from 100 °C,[61,62] 110 °C,[63,64] 120 °C,[65] 130 °C,[66,67] 140 °C,[68–70] 160 °C,[71,72] 180 °C[73] to reflux conditions.[74–85] The mechanism involves addition of iodine to the Cα—Cβ double bond; elimination of HI to form the α-iodinated chalcone; cyclization to chroman-4-one via attack of the hydroxyl group to the C-β position and finally elimination of a second HI to afford the desired

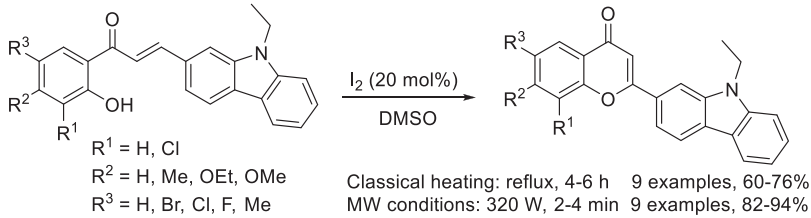


Scheme 6

4*H*-chromen-4-one. Iodine can be regenerated through oxidation of HI promoted by DMSO as oxidant (Scheme 6).

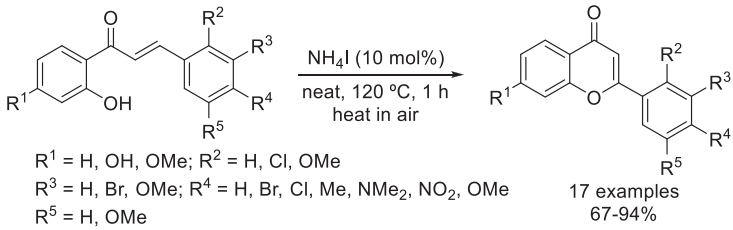
4-Oxo-4*H*-chromen-2-carboxylic acid arise in 70% yield from the cyclodehydrogenation reaction of (*E*)-4-(2-hydroxyphenyl)-4-oxobut-2-enoic acid using iodine in DMSO at 120 °C for 30 min.[86] The same catalytic system was used for the synthesis of 2-(pyrazol-4-yl)-4*H*-chromen-4-ones starting from 1-(2-hydroxyaryl)-3-(pyrazol-4-yl)prop-2-en-1-ones at 100–140 °C for 1.5–2.5 h[87–90] and for the synthesis of 2-(thiazol-4-yl)-4*H*-chromen-4-ones starting from 1-(2-hydroxyaryl)-3-(thiazol-4-yl) prop-2-en-1-ones at 160 °C for 3–4 h.[91] Oxidative cyclization reaction of 3-(furan-3-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one and of 1-(2-hydroxyphenyl)-3-(indol-3-yl)prop-2-en-1-one using a catalytic amount of iodine in DMSO led to, respectively, 2-(furan-3-yl)-4*H*-chromen-4-one and 2-(indol-3-yl)-4*H*-chromen-4-one.[92] Moreover, a series of ethyl l,1,2,3,6-tetrahydro-4-methyl-1-(6-methyl-4-oxo-4*H*-chromen-2-yl)-2-oxo/thioxo-6-phenyl pyrimidine-5-carboxylates were synthesized using molecular iodine in DMSO as catalytic system starting from the corresponding chalcone derivatives.[93]

Polysubstituted 2-(9-ethyl-9*H*-carbazol-3-yl)-4*H*-chromen-4-ones were prepared through oxidative cyclization of (*E*)-3-(9-ethyl-9*H*-carbazol-3-yl)-1-(2-hydroxyaryl)prop-2-en-1-ones in the presence of a catalytic amount of iodine in DMSO in conventional refluxing conditions for 4–6 h under microwave irradiation (320 W, 2–4 min). In these examples, microwave-assisted procedure proved to give better yields in shorter reaction times (Scheme 7).[94]



Scheme 7

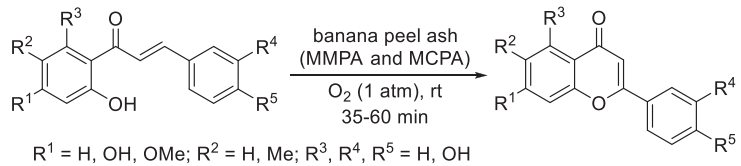
Different iodine systems can also be used as catalysts in the synthesis of a series of 4*H*-chromen-4-ones. Few examples of 2-aryl-4*H*-chromen-4-ones were obtained via deallylation of 2′-allyloxychalcones and oxidative cyclization promoted by molecular iodine in polyethylene glycol (PEG)-400 at 60 °C for 30–45 min[95] and oxidative cyclization of 2′-hydroxychalcones promoted by phenyliodine(III) diacetate (PIDA) and potassium hydroxide in methanol at room temperature.[96] Further derivatives arise from ultrasound-assisted oxidative cyclization of 2′-hydroxychalcones in the presence of iodine monochloride in DMSO at 50 °C for 30 min.[97] An eco-friendlier approach used equimolar amounts of potassium iodate, potassium iodide and sulfuric acid as in situ catalytic source for molecular iodine to convert 2′-hydroxychalcones into 2-aryl-4*H*-chromen-4-ones. It involves keeping the mixture in an ethanolic solution in the autoclave at 50 °C using 4–4.5 lb./ln^2 pressure for 20 min.[98] An alternative is to use ammonium iodide which, on exposure to air, decomposes to ammonia and iodine. The in situ generated iodine was used for the cyclization of 2′-hydroxychalcones to 2-aryl-4*H*-chromen-4-ones, under solvent-free conditions (Scheme 8).[99]



Scheme 8

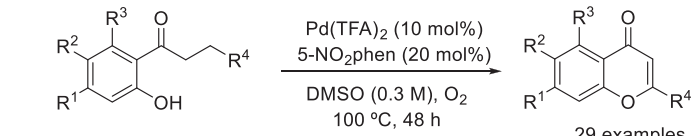
2-(2-Chloroquinolin-3-yl)-4*H*-chromen-4-ones were readily obtained from iodine-alumina catalyzed cyclization reaction of 1-(2-hydroxyaryl)-3-(2-chloroquinolin-3-yl)prop-2-en-1-ones under microwave irradiation (400 W) for 3 to 5 min, in excellent yields.[100]

Other catalytic systems have been used for the synthesis of 2-aryl-4*H*-chromen-4-ones involving oxidative cyclization reactions of a huge variety of 2′-hydroxychalcones in the presence of ferric chloride in refluxing methanol[101]; 3 equiv. of phosphoryl chloride/water in toluene at 90–95 °C[102]; cerium sulfate tetrahydrate in DMSO at 110°C,[103] silica-gel-supported cerium sulfate tetrahydrate, under solvent-free conditions[104]; freshly sublimed SeO_2 in refluxing dry isoamyl alcohol,[105] an excess of sodium perborate tetrahydrate in warm acetic acid[106] and two banana waste products, *Musa* sp. "Malbhog" peel ash (MMPA) and *Musa Champa* Hort. ex Hook. F. peel ash (MCPA), used as catalysts, under aerobic conditions at room temperature (Scheme 9).[107]



Scheme 9

Son et al. developed a different route for the selective synthesis of 2-methyl/2-(hetero)aryl-4*H*-chromen-4-ones starting from 2′-hydroxy-α,β-dihydrochalcone-type compounds. It involved a palladium(II)-catalyzed oxidative cyclization reaction in the presence 5-nitro-1,10-phenantroline in DMSO (0.3 M) at 100 °C under oxygen atmosphere for 48 h (Scheme 10).[108]



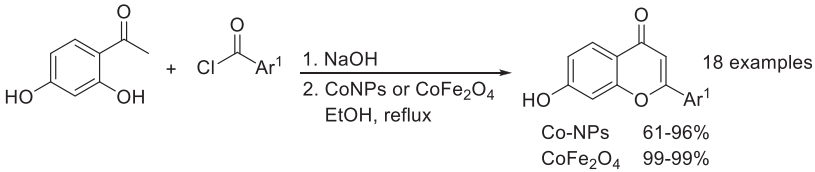
R^1 = H, Br, Cl, F, Me, OBn, OH, OMe, OPiv, OTf
R^2 = H, NO_2, OMe; R^3 = H, OMe
R^4 = Me, Ph, 2-OHC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-IC_6H_4, 4-OHC_6H_4, 4-$OMeC_6H_4$, 3,4-$(OMe)_2C_6H_3$, 3,5-$(OMe)_2C_6H_3$, 3,4,5-$(OMe)_3C_6H_2$, naphthalen-2-yl, furan-2-yl, thiophen-2-yl, 1-Meindol-3-yl

Scheme 10

Song *et al.* prepared six molybdate-based ionic liquids (ILs) to promote one-pot aerobic oxidative tandem reactions of 2′-hydroxyacetophenone

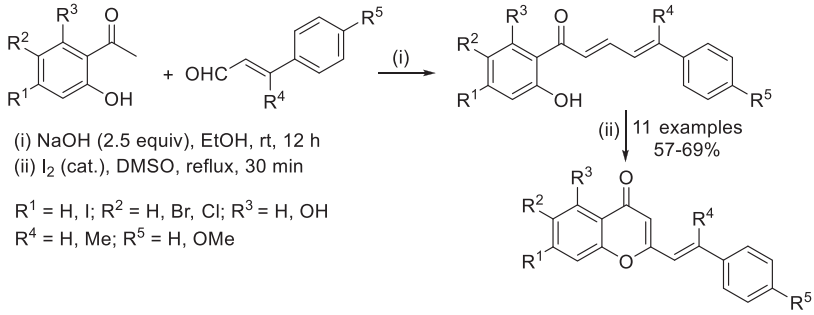
with benzaldehyde in *n*-hexanol at 140 °C for 3 h leading to synthesis of 2-phenyl-4*H*-chromen-4-one. This multi-step process involves base-catalyzed Claisen–Schmidt condensation, cyclization and further oxidative dehydrogenation.[109]

One-pot synthesis of 2-aryl-4*H*-chromen-4-ones arise from domino aldol-Michael-oxidation reaction of 2′-hydroxyacetophenones with substituted aromatic aldehydes using pyrrolidine and then iodine as oxidant in DMSO at 150 °C for the cyclodehydrogenation.[110] Further derivatives are prompted from an ecofriendly and large scale synthesis carried out in the presence of sodium hydroxide and Co-NPs or $CoFe_2O_4$ nanoparticles in refluxing ethanol (Scheme 11).[111] Gold nanoparticles supported on a Mg—Al layered double hydroxide catalyzed the reaction of 2′-hydroxyacetophenones with aliphatic or aromatic aldehydes in mesitylene at 130 °C to afford 2-substituted 4*H*-chromen-4-ones, in moderate to good yields.[112] This one-pot process consists of a Claisen–Schmidt condensation (base catalysis), an intramolecular oxa-Michael addition (base catalysis) on the formed 2′hydroxchalcones, and an aerobic oxidative dehydrogenation of chroman-4-ones (gold catalysis). Further examples of 2-(hetero)aryl-4*H*-chromen-4-ones arise 2-chloro-2′-hydroxyacetophenones with substituted aromatic aldehydes using a aqueous solution of sodium hydroxide (5%) in a 1:5 mixture of water:ethanol at room temperature.[113]



Scheme 11

Pawar et al. described a two-step approach for the synthesis of polysubstituted (*E*)-2-styryl-4*H*-chromen-4-ones involving aldol reaction of 2′-hydroxyacetophenones with cinnamaldehydes using sodium hydroxide as base and ethanol as solvent to afford the corresponding (*E*,*E*)-2′-hydroxycinnamylideneacetophenones followed by an oxidative cyclization reaction in the presence of a catalytic amount of iodine in refluxing DMSO (Scheme 12).[114] Other (*E*)-2-styryl-4*H*-chromen-4-ones were



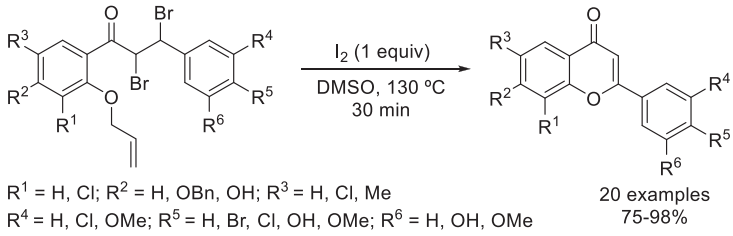
Scheme 12

prepared by one-pot reaction of 2′-hydroxyacetophenones with cinnamaldehydes in the presence of a catalytic amount of piperidine in PEG-400 at 40–50 °C for 30 min followed by addition of a catalytic amount of powdered iodine in PEG-400 and refluxed for 3–4 h.[115] 2-(1,2-Dihydroacenaphthylen-5-yl)-4*H*-chromen-4-one resulted from the reaction of 2′-hydroxyacetophenone with 5-acenaphthenecarboxaldehyde in the presence of an ethanolic solution of potassium hydroxide (60%) at room temperature for 48 h and subsequent addition of a catalytic amount of iodine in DMSO for 1 h at 140 °C.[116]

A wide range of 2-(hetero)aryl-4*H*-chromen-4-ones was synthesized via intermolecular *o*-acylation of substituted phenols with cinnamoyl chlorides mediated by $BiCl_3$ in refluxing carbon tetrachloride followed by intramolecular cyclodehydrogenation of the 2′-hydroxychalcones formed promoted by $RuCl_3{\cdot}3H_2O$ at reflux for additional 5 h.[117]

3.2 Through α,β-dihalochalcone derivatives

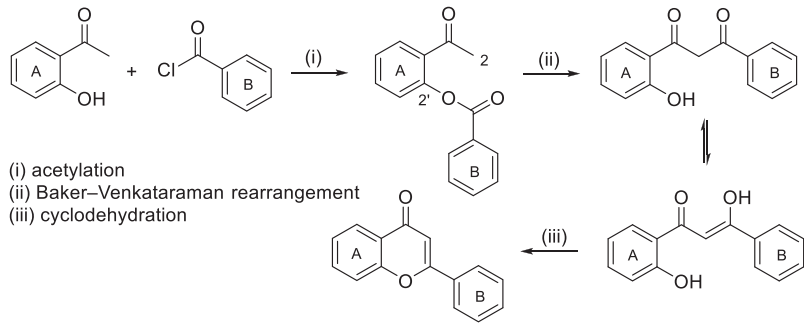
Few strategies have been reported for the synthesis of 2-aryl-4*H*-chromen-4-ones starting from α,β-dihalochalcone derivatives. Various 2-aryl-4*H*-chromen-4-ones were formed via cascade reaction of 2′-allyloxy-α,β-dibromochalcones in the presence of equimolar amounts of iodine in DMSO at 130 °C for 30 min. It involves deallylation, cyclization, debromination and dehydrobromination reactions in one step (Scheme 13).[118] Further derivatives were prepared in good yields from the cyclodehydrobromination of α,β-dibromo-2′-hydroxychalcones carried out in the presence of barium hydroxide moisture with 10 drops of ethanol at room temperature for 10 min, using grinding technique.[119] Treating α,β-diiodochalcone in the presence of potassium carbonate in dry DMF at 60 °C for 1 h led to 2-phenyl-4*H*-chromen-4-one.[120]



Scheme 13

3.3 Through Baker–Venkataraman rearrangement

This is one of the most popular strategies for the preparation of several 2-substituted chromone derivatives; most of the cases involve a three-step sequence (Scheme 14).



Scheme 14

The first step involves the condensation reaction of appropriate 2′-hydroxyacetophenones with acyl chlorides, under different reaction conditions, to afford the corresponding 2′-acyloxyacetophenones. Using commercially available acyl chlorides, the esterification occurs simply in dry pyridine[101,121–127] or in the presence of potassium carbonate as base and acetone as solvent.[128,129] Otherwise, acyl chlorides can be prepared in situ by treatment of the corresponding carboxylic acids with phosphoryl chloride in dry pyridine ranging from 0 °C[130–132] to room temperature[133–137] and even at 80 °C[138]; with thionyl chloride and pyridine in dichloromethane[139] or DMF[140]; with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) and 4-dimethylaminopyridine (DMAP) using DMSO,[141] triethylamine[142] or dichloromethane[143–145] as solvents; with *N*,*N*-dicyclohexylcarbodiimide (DCC) and DMAP in dichloromethane

at room temperature[139,146]; and with DCC in the presence of a catalytic amount of 4-pyrrolidinopyridine (4-PPy) in dichloromethane at room temperature.[136]

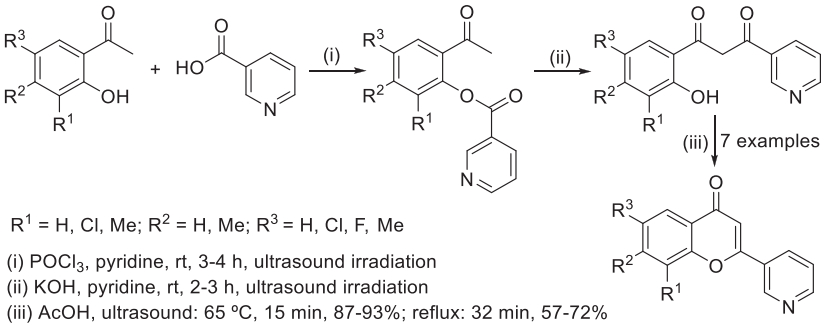
The second step, known as Baker–Venkataraman rearrangement, involves the transposition of the acyl group from the C-2′ to C-2 of the acetophenone moiety to give the corresponding 1-(2-hydroxyaryl)-propane-1,3-diones (in equilibrium with the respective enolic form). The reaction takes place in the presence of potassium hydroxide with pyridine[121–123,125–128,130–134,137,140–142,145,146] or DMSO[133,136,138] as solvent; or under less conventional conditions such as of sodium hydride in THF at reflux,[101,124] potassium *t*-butoxide in THF at room temperature,[139,143] sodium hydroxide in DMSO at 60 °C[143] or $MgBr_2{\cdot}Et_2O$ and *N*,*N*-diisopropylethylamine (DIPEA) in dichloromethane at room temperature.[127,147]

Finally, cyclodehydration of the 1,3-diketones formed provides the desired 2-substituted chromones. Generally, this catalytic reaction occurs in acidic medium such as in the presence of hydrobromic acid (48%) or sulfuric acid solution (20%),[141] under reflux conditions; concentrated sulfuric acid in refluxing ethanol[139,146] or acetic acid[78,121,122,126,128,129,140,142,145]; concentrated hydrochloric acid in refluxing ethanol[133,130] or acetic acid,[101,121,125,131–133,137] and PTSA in DMSO.[124,133,136] Milder reaction conditions, namely, using a catalytic amount of iodine in hot DMSO,[136,138] refluxing indium(III) bromide,[141] potassium carbonate in hot DMF,[148] potassium hydrogen sulfate at 120 °C under solvent-free conditions,[149] and trifluoromethanesulfinyl chloride in dichloromethane at room temperature,[150] have also been reported. Cyclization of 3-aryl-1-(2-hydroxyaryl)propane-1,3-diones by grinding with PTSA led to the corresponding flavones.[151] Various halogenated flavones have been prepared via microwave-assisted cyclization reaction of fluorine-containing 3-aryl-1-(2-hydroxphenyl)propane-1,3-diones promoted by acidic (H_2SO_4, EtOH, 50 W, 100 °C) or basic (DIPEA, toluene, 150 °C, 130 °C) conditions.[127]

Greener approaches used heteropolyacids as recyclable catalyst and glycerol as solvent[152] and a catalytic amount of mesoporous titania modified with tungstophosphoric acid catalyst in heterogeneous media (refluxing toluene) or in solvent-free conditions,[153] for the cyclodehydration step.

A single attempt to obtain 2-(pyridin-3-yl)-4*H*-chromen-4-ones used ultrasound irradiation to promote the three-step sequence starting from 2′-hydroxyacetophenones and nicotinic acid. In the last step, a comparative

study was performed using ultrasonic irradiation and classic heating conditions and the results showed that, in the former case, shorter reaction time and significantly improved yields were obtained (Scheme 15).[154] Similarly, a series of 2-[4-(1*H*-1,2,4-triazol-1-yl)styryl]-4*H*-chromen-4-ones has been synthesized via ultrasound and conventional heating conditions, for the three synthetic steps, employing 2′-hydroxyacetophenones and (*E*)-3-[4-(1*H*-1,2,4-triazol-1-yl)phenyl]acrylic acid as starting materials.[155]

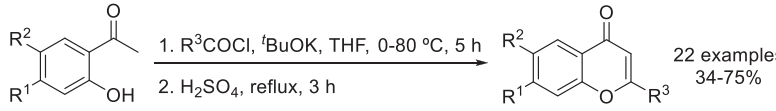


Scheme 15

A microwave-assisted protocol uses 2′-hydroxyacetophenones and benzoyl chloride in the presence of sodium hydroxide in chlorobenzene to afford the respective 1-(2-hydroxyaryl)-3-phenylpropane-1,3-diones which undergo cyclodehydration in the presence of copper(II) chloride in ethanol to provide some 2-aryl-4*H*-chromen-4-ones, in good yields, in a two-step route.[156]

Individual attempts to obtain the 1,3-diketone intermediates starting from 2′-hydroxyacetophenones used benzoyl chlorides[157] in the presence of lithium bis(trimethylsilyl)amide (LiHMDS) in dry THF at −78 °C, benzoyl chlorides in the presence of wet potassium carbonate (1% *w*/w water) in acetone[158,159]; and methyl succinyl chloride using potassium carbonate in acetonitrile.[160] Subsequent cyclization reactions occurred in acidic medium.[157–160]

Ghani et al. utilized a one-pot method for the synthesis of 2-substituted 4*H*-chromen-4-ones via condensation reaction and Baker–Venkataraman rearrangement of 2′-hydroxyacetophenones with aliphatic or aromatic acid chlorides promoted by potassium *t*-butoxide in THF followed by

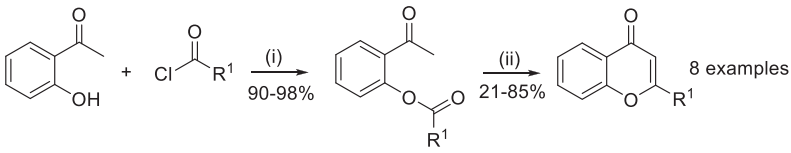


R^1 = H, F, OBn; R^2 = H, Br, OH, OMe
R^3 = cyclopropyl, cyclohexyl, CH_2cyclohexyl, Ph, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 4-FC_6H_4

Scheme 16

cyclization reaction mediated by concentrated sulfuric acid in refluxing conditions (Scheme 16).[161] Preparations of various 2-aryl-4*H*-chromen-4-ones were achieved by condensation of 2′-hydroxyacetophenones with benzoyl chlorides in the presence of potassium carbonate in refluxing acetone for 8 h, subsequent addition of a 1:1 mixture of methanol: water and refluxed for 2 h.[162] An improved methodology for the synthesis of other 2-aryl-4*H*-chromen-4-ones involved the reaction of 2′-hydroxyacetophenones with of benzoyl chlorides (2 equiv) in wet potassium carbonate (1% w/w water) in acetone medium, in the presence of pyridine (4 equiv) at reflux for 24–48 h. This one-pot synthesis (using pyridine as key reagent) provides the desired chromones in higher yields (>70%) than those obtained in the two-step procedure in the absence of pyridine (2–63% yield), previously described.[158,159]

A different protocol was reported to the synthesis of 2-substituted chromones having 2′-acyloxyacetophenones as intermediates. Thus, reacting 2′-hydroxyacetophenone with acyl chlorides in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and pyridine and using dichloromethane as solvent at 30 °C produces the corresponding phenolic esters which were cyclized with DBU (1 equiv) in refluxing pyridine to furnish the desired 4*H*-chromen-4-ones in moderate to good yields (Scheme 17).[163]



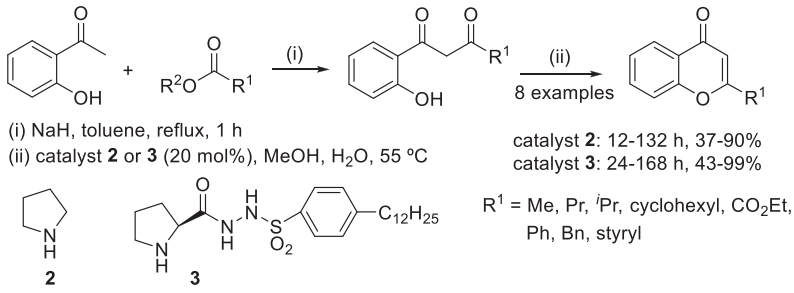
(i) DBU, pyridine, CH_2Cl_2, 30 ºC, 6 h; (ii) DBU, pyridine, reflux, 12 h
R^1 = Me, Bu, tBu, Pr, iPr, pentan-3-yl, *n*-hexyl, naphthalen-2-yl

Scheme 17

3.4 Other methods starting from 2′-hydroxyacetophenone derivatives

3.4.1 *Through condensation with carboxylic acid derivatives and cyclodehydration*

Efficient two-step's pathways have been designed for the synthesis of diversely 2-substituted chromones, having 1,3-diketones as key intermediates. The synthesis of 2-(2-arylethyl)-4*H*-chromen-4-ones was accomplished through Claisen condensation reaction of 2′-hydroxyacetophenones with several esters in the presence of sodium hydride in THF at reflux followed by treatment with acetic acid or catalytic hydrochloric acid in refluxing methanol.[164–166] Wen et al. developed an organocatalyzed synthesis of other 2-substituted chromones via condensation reaction of 2′-hydroxyacetophenones with several esters in the presence of sodium hydride in refluxing toluene followed by cyclodehydration, using commercially available pyrrolidine **2** or novel proline phenylsulfonylhydrazide **3** as catalysts, in a 0.05:2.5 mixture of water:methanol at 55 °C (Scheme 18).[167]



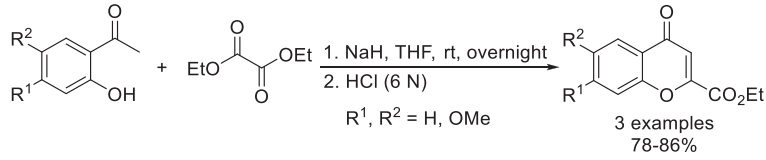
Scheme 18

Yang et al. synthesized 4′-bromo-7-methoxy-4*H*-chromen-4-one via Claisen condensation reaction of 2′,4′-dimethoxyacetophenone with methyl 4-bromobenzoate using sodium bis(trimethylsilyl)amide to produce the corresponding 1,3-diketone followed by demethylative cyclization reaction upon treatment with hydrobromic acid and sodium iodide in acetic acid.[168]

Polymethoxy-4*H*-chromen-4-ones have been prepared by condensation of 2′-hydroxyacetophenone derivatives and acylbenzotriazoles in the presence of lithium bis(trimethylsilyl)amide (LiHMDS) in dry THF at −78 to 0 °C, followed by cyclodehydration promoted by p-PTSA in toluene at 80 °C.[169]

3.4.2 Through condensation with oxalates

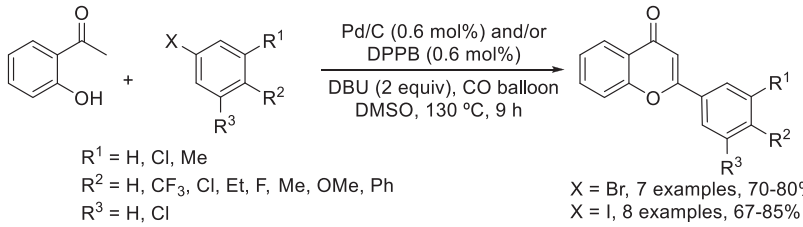
Diversely substituted ethyl 4-oxo-4*H*-chromene-2-carboxylates result from condensation reaction of 2′-hydroxyacetophenones with diethyl oxalate carried out in the presence of sodium ethoxide in ethanol at 60 °C for 16 h,[170] 100 °C for 10 h[145] or refluxing conditions during 1 h,[171,172] 2 h,[173] 10 h[174,175] or 12 h.[176] Subsequent intramolecular cyclization reaction in acidic medium completes the process to give the desired carboxylates. Further derivatives were obtained from the reaction of 2′-hydroxyacetophenones with diethyl oxalate in the presence of sodium hydride in THF at room temperature overnight followed by treatment with diluted hydrochloric acid (Scheme 19).[177]



Scheme 19

3.4.3 Through carbonylative reaction with aryl halides

Palladium catalysts have been used in carbonylation reactions of 2′-hydroxyacetophenones with aryl halides to produce 2-(hetero)aryl-4*H*-chromen-4-ones. Wu et al. used various 2′-hydroxyacetophenones and aryl bromides employing palladium(II) acetate as catalyst in the presence of 1,4-bis(diphenylphosphino)butane (DPPB) as ligand, DBU as base and DMSO as solvent to achieve this goal.[178] A similar strategy described by Lei et al. started from the reaction of 2′-hydroxyacetophenone with aryl halides involving palladium on carbon as an efficient and recyclable catalyst giving several 2-aryl-4*H*-chromen-4-ones in good yields (Scheme 20).[179]

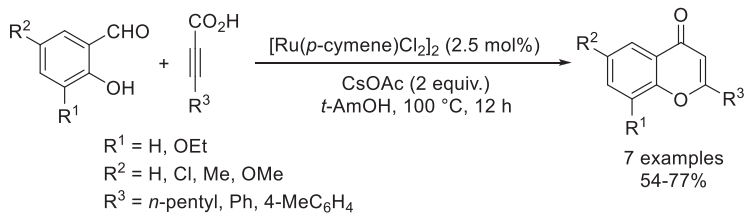


Scheme 20

3.5 Starting from salicylaldehydes

An alternative synthesis of 2-(hetero)aryl-4*H*-chromen-4-ones was designed using 2-hydroxychalcones instead of the previously described 2′-hydroxychalcones, as key intermediate. Thus, condensation reaction of acetophenones with various salicylaldehydes carried out in the presence of an aqueous solution of potassium hydroxide in refluxing ethanol provided the corresponding 2-hydroxychalcones that underwent oxidative cyclization reaction in the presence of catalytic iodine at 110–130 °C, under solvent-free conditions.[180] Recently, Tsai et al. revisited this synthesis and concluded that it is not a practicable strategy to use 2-hydroxychalcones as precursors of flavone derivatives.[70]

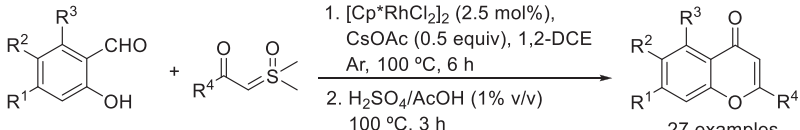
Palladium(II)-catalyzed regioselective intramolecular nucleophilic substitution reaction of salicylaldehydes with 1,1-dichloroalkenes using triphenylphosphine sulfide as ligand, benzyltriethylammonium chloride (TEBAC) as additive, sodium carbonate as base and NMP as solvent, at 110 °C for 24 h under a N_2 atmosphere provided a series of 2-(hetero) aryl-4*H*-chromen-4-ones.[181] Polysubstituted 2-alkyl/2-aryl-4*H*-chromen-4-ones were readily available through rhodium(I)-promoted aldehydic C—H bond alkynylation reaction of salicylaldehydes with 1-bromoalkynes, generated in situ from 1,1-dibromoalkenes, followed by annulation reaction using potassium carbonate in *N*,*N*-dimethylacetamide (DMAc) at 90 °C.[182] Further derivatives were obtained via ruthenium(II)-mediated C—H activation and annulation reaction of salicylaldehydes with terminal alkynes using cesium carbonate in *t*-amyl alcohol.[183] Using the same catalyst under the same reaction conditions, regioselective debrominative annulation reaction between salicylaldehydes and propargyl bromide afforded a series of 2-methyl-4*H*-chromen-4-ones[184] while C—H activation and decarboxylative coupling reaction of salicylaldehydes with alkynoic acids provided some 2-alkyl/2-aryl-4*H*-chromen-4-ones (Scheme 21).[185] 2-Butyl-4*H*-chromen-4-one was synthesized in 73% yield through condensation reaction of salicylaldehyde with hex-1-yne in the presence of butyl



Scheme 21

lithium in THF at −78 °C, oxidation with MnO_2 in dichloromethane at room temperature and finally treatment with potassium carbonate in refluxing acetone.[186]

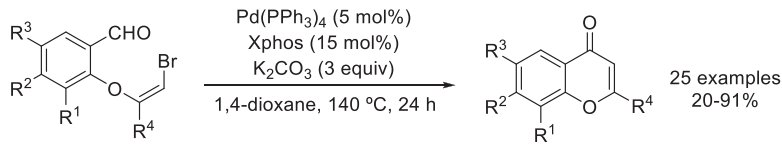
Various 2-methyl-4*H*-chromen-4-ones were produced via iridium(III)-mediated C—H activation and decarboxylative coupling reaction of salicylaldehydes with *t*-butyl diazoacetate using pivalic acid as additive and water as solvent, at 100 °C.[187] A rhodium(III) catalyst was used to promote C—H activation of salicylaldehydes followed by insertion reaction with sulfoxonium ylides and cyclization to furnish a variety of 2-alkyl/2-aryl-4*H*-chromen-4-ones carried out in the presence of silver triflate and pivalic acid in THF at 100 °C[188] or using cesium carbonate in 1,2-DCE at 100 °C followed by acidification (Scheme 22).[189]



R^1 = H, Br, Me, OMe; R^2 = H, Cl, Me
R^3 = H, Br, Cl, F, Me, NO_2, OMe
R^4 = ^{t}Bu, Ph, 2-ClC_6H_4, 2-MeC_6H_4, 2-$OMeC_6H_4$, 3-BrC_6H_4, 3-MeC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-$OMeC_6H_4$, naphthalen-2-yl, thiophen-2-yl, adamant-1-yl

Scheme 22

Further 2-alkyl/2-aryl-4*H*-chromen-4-ones were obtained through palladium(0)-catalyzed intramolecular acylation of 2-(1-bromoethen-2-yloxy)benzaldehydes, obtained from salicylaldehydes and 1-bromoalk-1-ynes, employing Xphos as ligand and potassium carbonate as base in 1,4-dioxane, in moderate to excellent yields (Scheme 23).[190]

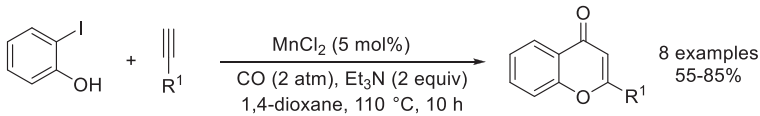


R^1 = H, Br, F, Me, OMe; R^2 = H, Br, F, Me; R^3 = H, Cl, F, Me, OMe
R^4 = Bu, hexyl, decyl, $(CH_2)_4OCOPh$, Ph, 3-MeC_6H_4, 3-$OMeC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-$OMeC_6H_4$

Scheme 23

3.6 Carbonylative coupling reaction of 2-halophenols with terminal alkynes

Various palladium catalysts have been used in the three-component reaction of 2-halophenols with terminal alkynes and carbon monoxide to give diversely 2-substituted 4*H*-chromen-4-ones. High catalytic activity has been observed using bis(triphenylphosphine)palladium(II) dichloride as catalyst in the presence of a benzimidazolium ligand in dipropylamine at 130 °C[191] or using triethylamine and PEG-2000 in water at room temperature.[192] Palladium(II) acetate,[193] palladium on carbon,[194] bridged-bis(*N*-heterocyclic carbene, NHC)palladium(II) complexes,[195] propylene-bridged bis(*NHC*)palladium(II) complexes covalently anchored on Merrifield's resin[196] and palladium-supported amine-functionalized montmorillonite as a heterogeneous catalyst[197] were also good catalytic systems for these regioselective syntheses. An alternative approach used $Mo(CO)_6$, as solid CO source, for the one-pot synthesis of 2-alkyl/2-aryl-4*H*-chromen-4-ones via carbonylative Sonogashira annulation reaction of 2-iodophenols with terminal alkynes promoted by a Pd-NHC catalyst and dimethylamine in DMF ate 95 °C.[198] More derivatives were obtained through carbonylative Sonogashira annulation reaction of 2-iodophenol with terminal alkynes promoted by nickel(II) acetate[199] or manganese chloride (Scheme 24)[200] using triethylamine as base and 1,4-dioxane as solvent.

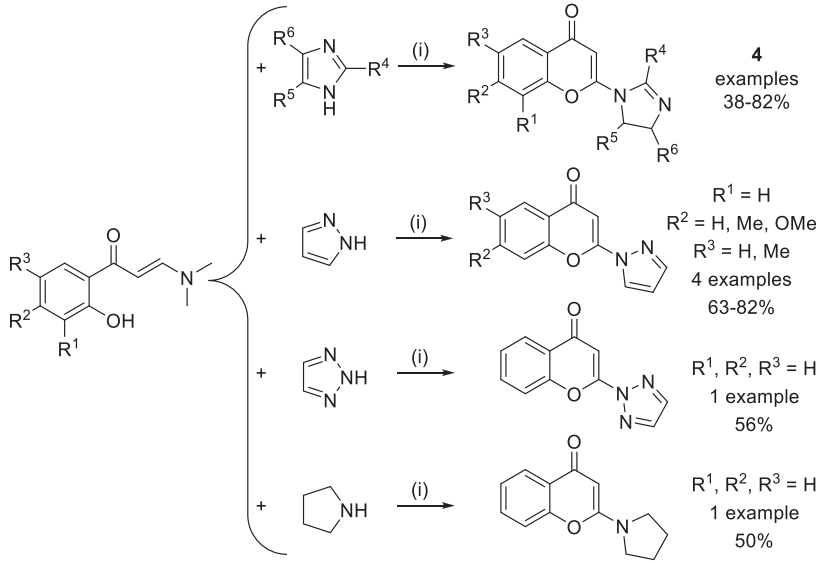


R^1 = *n*-Bu, Ph, 2-ClC_6H_4, 2-MeC_6H_4, 4-$NH_2C_6H_4$, 4-$NO_2C_6H_4$, 4-$OMeC_6H_4$, pyridin-3-yl

Scheme 24

3.7 Other two-component reactions

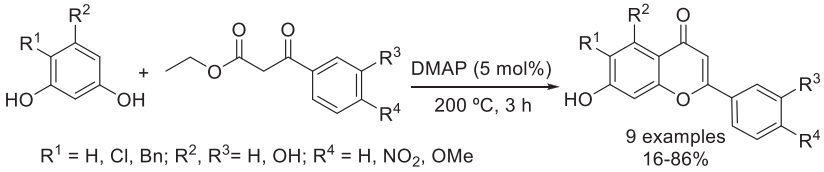
Intramolecular cyclization reaction of 1-(2-benzyloxyaryl)-3,-3-bismethylsulfanylprop-2-en-1-ones carried out in the presence of molecular iodine in 1,2-DCE at 80 °C delivered some 2-(methylthio)-4*H*-chromen-4-ones.[201] Unconventional selective synthesis of 2-nitrogenated 4*H*-chromen-4-ones was accomplished via copper(I)-catalyzed β-C(sp^2)-H functionalization tandem protocol using *o*-hydroxyphenyl enaminones and nitrogen nucleophiles (imidazoles, benzoimidazole, pyrazole, 1,2,3-triazole



Scheme 25

and pyrrolidine) carried out in the presence of PIDA as oxidant, molecular iodine as additive and sodium carbonate as base in DMF at 120 °C (Scheme 25).[202]

A couple of 2-substituted 4*H*-chromen-4-ones were prepared from intermolecular C—O addition of 2-alkynoic acids with the Kobayashi benzyne precursor *o*-(trimethylsilyl) phenyl triflate in the presence of tetrabutylammonium difluorotriphenylsilicate (TBAT) in hot toluene. Parent chromone was also prepared by this methodology in 71% yield.[203] Cyclocondensation reaction of benzene-1,3-diols with ethyl 3-aryl-3-oxopropanoates promoted by DMAP at 200 °C for 3 h afforded a series of 2-aryl-4*H*-chromen-4-ones (Scheme 26). It involves attack of the base on β-ketoester to yield an α-oxo ketene intermediate, addition of the phenol to form a phenol ester, base-promoted *o*-Fries rearrangement to give 1,3-diaryl diketone intermediate, followed by cyclization, proton transfer and dehydration reactions. This strategy was used for the synthesis of natural flavone acacetin.[204] Radiou et al. developed another approach for the one-step microwave-assisted synthesis of acacetin starting from ethyl



Scheme 26

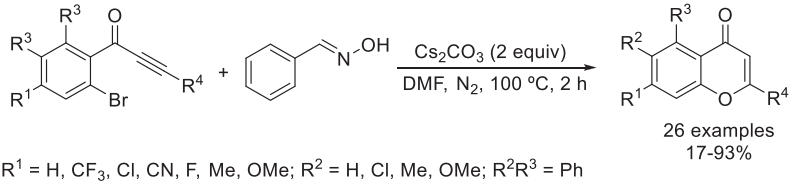
3-(4-methoxyphenyl)-3-oxopropionate and phloroglucinol using PEG-1000 as solvent at atmospheric pressure.[205] Thermal cyclocondensation reactions of phloroglucinol with ethyl 3-[4-(benzyloxy)-3-methoxyphenyl]-3--oxopropanoate at 240 °C for 5 min under neat conditions and microwave irradiation afforded 2-[4-(benzyloxy)-3-methoxyphenyl]-5,7-dihydroxy-4*H*-chromen-4-one[206] and with ethyl 3-(3,4-dimethoxyaryl)-3-oxopropanoates at 240 °C for 60–80 min, in a muffle furnace under neat conditions, provided a couple of 2-(3,4-dimethoxyaryl)-5,7-dihydroxy-4*H*-chromen-4-ones.[207]

One-pot Friedel – Crafts acylation of alkynes with 2-methoxybenzoyl chlorides to the synthesis of 2-substituted 4*H*-chromen-4-ones is conditions-controlled: applying 1-arylalk-1-ynes in the presence of an excess of aluminum chloride, (*Z*)-β-chlorovinyl ketone intermediates are formed to provide the corresponding 2-aryl-4*H*-chromen-4-ones in good yields; using 1-alkylalk-1-ynes, quenching treatment with aluminum chloride, triethylamine and potassium *t*-butoxide in dichloromethane was required to form *O*-demethylated (*E*)-β-chlorovinyl ketone intermediates before the formation of the desired 2-alkyl-4*H*-chromen-4-ones. The first protocol was extended to the synthesis of few 3-substituted-2-aryl-4*H*-chromen-4-ones.[208]

Under dual catalysis of silver nitrate and ammonium persulfate, decarboxylative annulation reaction of 2-(2-hydroxyaryl)-2-oxoacetic acids with (hetero)arylpropiolic acids in a 1:3 mixture of acetonitrile:water at 80 °C for 3 h prompted various 2-(hetero)aryl-4*H*-chromen-4-ones.[209]

3.8 Cyclization of arylpropargyl ketone/alcohol derivatives

A small library of diversely 2-substituted 4*H*-chromen-4-ones was obtained via Michael addition and Ullmann-type O-arylation reaction of 1-(2-bromoaryl)prop-2-yn-1-ones with benzaldehyde oxime carried out in the presence of cesium carbonate in DMF at 100 °C (Scheme 27).[210]

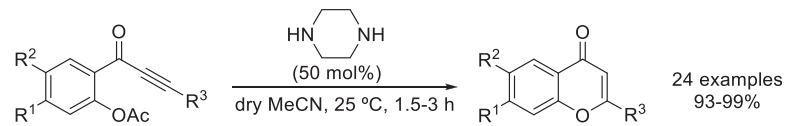


R^1 = H, CF_3, Cl, CN, F, Me, OMe; R^2 = H, Cl, Me, OMe; R^2R^3 = Ph
R^4 = *n*-Bu, $(CH_2)_2Ph$, Ph, 2-MeC_6H_4, 4-^{t}BuC_6H_4, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 4-EtC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-$OMeC_6H_4$, thiophen-2-yl

Scheme 27

A couple of 3-(2-benzoylaryl/2-benzyloxyaryl)prop-2-yn-1-one derivatives underwent hydration of the alkyne and cyclization reactions in the presence of concentrated sulfuric acid at 60 °C for 2 h to give 2-substituted 4*H*-chromen-4-ones.[211]

A wide range of 2-alkyl/2-aryl-4*H*-chromen-4-ones were synthesized via 6-*endo* cyclization reaction of 1-(2-acyloxyaryl)prop-2-yn-1-ones mediated by 18-crown-6 ether and potassium methoxide in THF at room temperature for 15 min[212] and promoted by piperazine in dry acetonitrile at room temperature for 1.5–3 h (Scheme 28).[213] Various 1-(2-allyloxy/2-prenyloxy)prop-2-yn-1-ones underwent microwave-assisted tandem Claisen rearrangement/6-*endo*-*dig* cyclization sequence in the presence of *N*,*N*-diethylaniline to furnish 8-allyl/8-prenyl-4*H*-chromen-4-ones. In some cases, for prenyl ethers, the tandem sequence can be extended by a Cope rearrangement to furnish 6-prenyl-4*H*-chromen-4-ones. 2-Unsubstituted 8-allylchromone was also prepared in a 26% yield.[214] Meanwhile, microwave irradiation of a couple of 3-aryl-1-(5-methoxy-2-prenyloxyphenyl)prop-2-yn-1-ones in *N*,*N*-diethylaniline resulted in deprenylation with concomitant 6-*endo*-*dig* cyclization to afford the corresponding 2-aryl-6-methoxy-4*H*-chromen-4-ones, in moderate yields.[215]

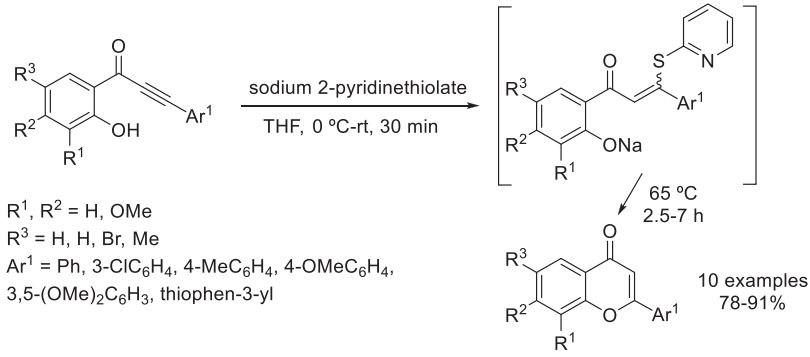


R^1 = H, Me; R^2 = H, Br, Cl, OMe; R^3 = *n*-Bu, *n*-pentyl, Ph, 3-FC_6H_4, 4-EtC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-*n*-pentylC_6H_4, thiophen-2-yl

Scheme 28

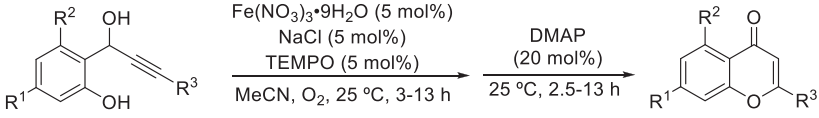
A series of 2-aryl-4*H*-chromen-4-ones was obtained from regioselective 6-*endo* cyclization reactions of 3-aryl-1-(2-hydroxyaryl)prop-2-yn-1-ones

promoted by trifluoromethanesulfonic acid in 1,2-DCE at 80 °C[216] and thallium(III) tosylate in methanol at 65 °C.[217] Further examples arise from one-pot 1,4-addition of sodium 2-pyridinethiolate to 3-aryl-1-(2-hydroxyaryl)prop-2-yn-1-ones in THF for 30 min from 0 °C to room temperature and the subsequent cyclization of the pyridin-2-ylthioenone intermediates at reflux conditions for 2.5–7 h (Scheme 29).[218]



Scheme 29

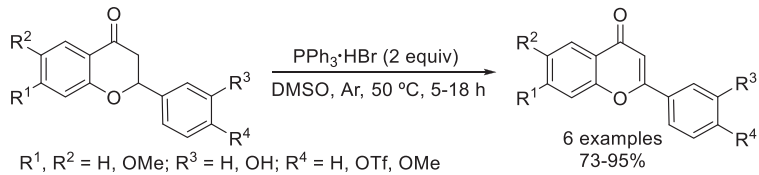
Cascade oxidative cyclization reactions of 1-(2-hydroxyaryl)prop-2-yn-1-ols mediated by lithium *t*-butoxide in DMF at 60 °C under air[219] and mediated by $Fe(NO_3)_3{\cdot}9H_2O$ in the presence of sodium chloride and 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) in acetonitrile with an oxygen balloon at 25 °C followed by addition of DMAP provide various 2-alkyl/2-aryl-4*H*-chromen-4-ones (Scheme 30).[220] Song *et al.* reported cascade oxidative cyclization reaction of 1-aryl-3-(2-hydroxyaryl)prop-2-yn-1-ols promoted by aqueous solution of HI in dichloromethane at 30 °C to afford 2-aryl-4*H*-chromen-4-ones, having 4-iodo-2*H*-chromenes as intermediates.[221]



Scheme 30

3.9 Starting from 6-*O*-membered heterocycles

Various protocols have been developed to the synthesis of 2-alkyl/2-aryl-4*H*-chromen-4-ones via oxidation of the corresponding chroman-4-ones. It includes the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing 1,4-dioxane,[222] molecular iodine in hot DMSO,[52,223] 2-iodobenzoic acid (IBX) in DMSO at 90 °C,[224,225] PPh_3·HBr in DMSO at 50 °C (Scheme 31),[226] pyridinium bromide perbromide in dichloromethane at room temperature followed by the addition of DBU in refluxing benzene[227] and under dual catalysis of TBHP and TBAI at 80 °C.[59] A series of 2-(hetero)aryl-4*H*-chroman-4-ones (naphthalen-2-yl, thiophen-1-yl, thiophen-2-yl, pyridine-3-yl, 2-methoxypyridin-4-yl) suffered oxidation in the presence of thallium(III) acetate (TTA) in refluxing acetic acid or acetonitrile to give the corresponding 2-(hetero)aryl-4*H*-chromen-4-ones, however, under the same conditions, 2-(naphthalen-1-yl)-4*H*-chroman-4-ones provided a mixture of the oxidized products, 2-(naphthalen-1-yl)-4*H*-chromen-4-ones, and of the oxidative rearranged products, 3-(naphthalen-1-yl)-4*H*-chromen-4-ones. In addition, the oxidation of the 2-pyridinylchroman-4-ones was also observed when using thallium(III) *p*-tosylate (TTS) in refluxing acetonitrile.[228]

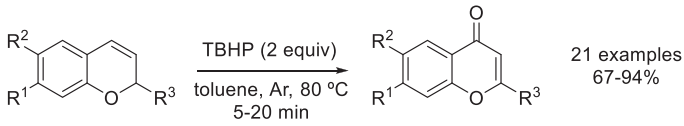


Scheme 31

2-{Diaryl[(trimethylsilyl)oxy]methyl}-4*H*-chroman-4-ones suffered dehydrosiloxylation promoted by a catalytic amount of PTSA in refluxing xylene to afford the corresponding 2-diarylmethyl-4*H*-chromen-4-ones. These products could also be prepared starting from the same precursors, which underwent desilylation by treatment with hydrochloric acid in 1,4-dioxane to obtain the alcohol intermediates and subsequent dehydration, mediated by a catalytic amount of PTSA in refluxing toluene.[229]

Moreover, 2,3-unsubstituted chroman-4-ones underwent one-pot palladium(II)-catalyzed dehydrogenation/oxidative boron-Heck coupling

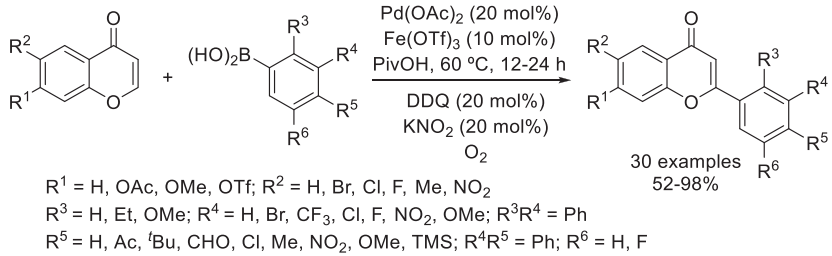
reaction with arylboronic acid pinacol esters using 5-nitrophenanthroline as ligand in DMSO at 100 °C under an O_2 atmosphere to achieved a variety of 2-aryl-4*H*-chromen-4-ones.[230,231] Further derivatives were efficiently obtained through oxidation of 2-aryl-2*H*-chromenes mediated by TBHP and copper(II) bromide in toluene at 80 °C, under argon atmosphere (Scheme 32) .[232] Few 4-hydroxy-2*H*-chromene-2-thiones suffered *S*-alkylation with ethyl iodide in the presence of potassium carbonate in refluxing acetone to afford 2-(ethylthio)-4*H*-chromen-4-ones.[233,234] The synthesis of 8-bromo-6-chloro-2-pentyl-4*H*-chromen-4-one was accomplished through microwave-promoted hydrobromide elimination reaction of 3,8-dibromo-6-chloro-2-pentylchroman-4-one using calcium carbonate in DMF at 100 °C for 20 min, in 84% yield.[121]



R^1 = H, OMe; R^2 = H, Cl, Me; R^3 = Ph, 2-BrC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-$OMeC_6H_4$, 3,4-$(OMe)_2C_6H_3$, 3-OMe-4-$OBnC_6H_3$, 3,4-OCH_2O-C_6H_3, 3,4,5-$(OMe)_3C_6H_2$, naphthalen-2-yl, pyridin-2-yl, pyridin-3-yl, furan-2-yl, thiophen-2-yl

Scheme 32

Interestingly, 2,3-unsubstituted 4*H*-chromen-4-ones are also alternative building blocks for the synthesis of 2-substituted 4*H*-chromen-4-ones. Thus, the synthesis of 2-alkyl-4*H*-chromen-4-ones was accomplished via regioselective oxidative C(sp^3)—H functionalization of 2,3-unsubstituted chromones with alkanes in the presence of $PhI(O_2CCF_3)_2$ and sodium azide in dichloromethane at room temperature[235] and with different ethers promoted by copper(II) oxide, TBHP and 1,4-diazabicyclo[2.2.2]octane (DABCO) at 120 °C for 36 h.[236] On the other hand, the synthesis of 2-aryl-4*H*-chromen-4-ones has been achieved through regioselective palladium(II) acetate-catalyzed oxidative arylation of 2,3-unsubstituted chromones with arenes carried out in the presence of silver acetate and cesium pivalate in pivalic acid[237] and with arylboronic acids using iron(III) triflate, DDQ and potassium nitrite in pivalic acid (Scheme 33)[238,239] or 1,10-phenanthroline in DMF,[240] under air atmosphere.



Scheme 33

A highly chemoselective 2,2,6,6-tetramethylpiperidyl (TMP) base, $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$, was prepared to allow C-2-selective zincation of parent chromone in THF at −30 °C and subsequent reaction with few electrophiles. Therefore, regiospecific metalation at C-2 and subsequent iodolysis provided 2-iodo-4*H*-chromen-4-one while copper(I)-mediated acylation with benzoyl chloride gave 2-benzoyl-4*H*-chromen-4-one and palladium(0)-catalyzed Negishi cross-coupling with aryl iodides furnished 2-aryl-4*H*-chromen-4-ones.[241]

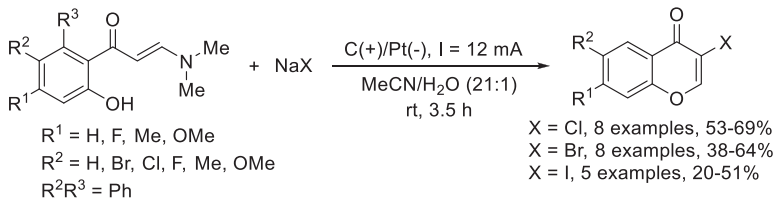
4. Synthesis of 3-substituted 4*H*-chromen-4-ones

4.1 Starting from 2-unsubstituted 2′-hydroxyacetophenones

4.1.1 Via O-hydroxyaryl enaminone formation

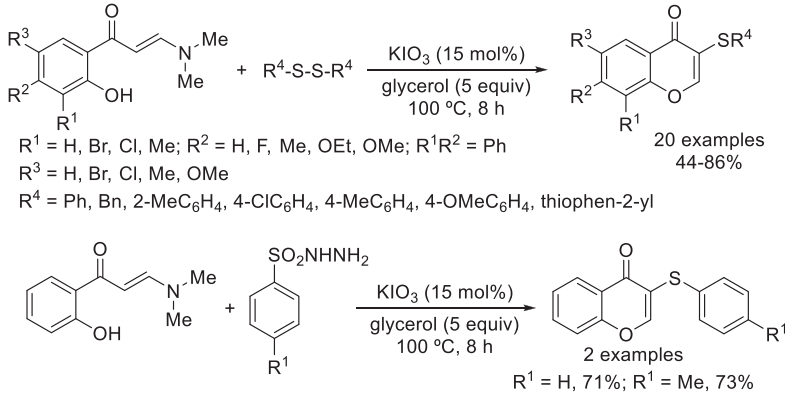
A common approach to obtain a wide variety of 3-substituted 4*H*-chromen-4-ones is using (*E*)-3-(dimethylamino)-1-(2-hydroxyaryl) prop-2-en-1-ones, commonly known as *o*-hydroxyaryl enaminones, as key intermediates, obtained mainly from the reaction of 2′-hydroxyacetophenones with DMF-DMA in DMF as solvent. Various 3-iodo-4*H*-chromen-4-ones arise from one-pot ring-closure and iodination sequence via addition of molecular iodine to *o*-hydroxyaryl enaminones employing methanol,[242–247] chloroform,[248,249] pyridine and chloroform,[250–254] pyridine and dichloromethane[47,255] as solvents, at room temperature. Examples of 3-fluoro-4*H*-chromen-4-ones were synthesized through the monofluorination of *o*-hydroxyaryl enaminones with Selectfluor® as fluorine source in 1,2-DCE at room temperature,[256] in the presence of sodium acetate and butylated hydroxytoluene (BHT)

in THF at room temperature,[257] and using potassium carbonate in acetonitrile at 100 °C.[258] Various 3-bromo/3-iodo-4*H*-chromen-4-ones were prompted via halogenation of *o*-hydroxyaryl enaminones using simple potassium halides (KBr/KI), respectively, in the presence of PIDA as oxidant and biomass-based available ethyl lactate as green medium at room temperature.[259] Another environmentally friendly synthesis of 3-halo-4*H*-chromen-4-ones resulted from electrochemical halogenation of *o*-hydroxyaryl enaminones using sodium halides (NaCl, NaBr, NaI) as halogen sources in a 21:1 mixture of acetonitrile:water at room temperature (Scheme 34).[260]



Scheme 34

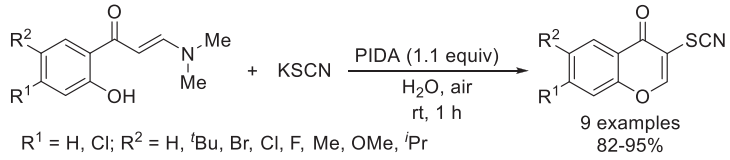
The synthesis of 3-hydroxy-4*H*-chromen-4-ones occurred through domino C(sp^2)–H hydroxylation/annulation reaction of *o*-hydroxyaryl enaminones using *m*-chloroperbenzoic acid (MCPBA) in dichloromethane.[261] Domino C(sp^2)–H sulfenylation/annulation reaction of *o*-hydroxyaryl enaminones with thiophenols promoted by aqueous HBr–DMSO system in chloroform at 100 °C,[262] and by KIO_3 in ethyl lactate at 60 °C[263] furnished a series of 3-sulfenylated 4*H*-chromen-4-ones. Further derivatives were readily achieved via domino reaction of *o*-hydroxyaryl enaminones with sulfonyl hydrazines mediated by KIO_3 in DMF at 130 °C,[264] with DMSO mediated by propylphosphonic anhydride (T3P®) in THF at 100 °C, with aryl methylsulfoxide promoted by T3P® in DMAc at 90 °C,[265] with diorganyl disulfides and arylsulfanyl hydrazides mediated by potassium iodate and glycerol at 100 °C (Scheme 35).[266] Some examples of sulfur-bridged 4*H*-chromen-4-ones were obtained through the reaction of *o*-hydroxyaryl enaminones with sulfur powder and molecular iodine in DMF at 90 °C for 12 h, under an air atmosphere.[267] Moreover, the synthesis of 3-sulfonyl-4*H*-chromen-4-ones occurred via molecular iodine-mediated domino C(sp^2)–H sulfonylation/annulation reaction of *o*-hydroxyaryl enaminones with sulfonyl hydrazines in DMAc at room temperature,[268] while several 3-dithiocarbamyl-4*H*-chromen-4-ones were prompted from annulation



Scheme 35

cascade reaction of *o*-hydroxyaryl enaminones with thiurams in the presence of potassium iodate and TEMPO in DMSO at 110 °C.[269]

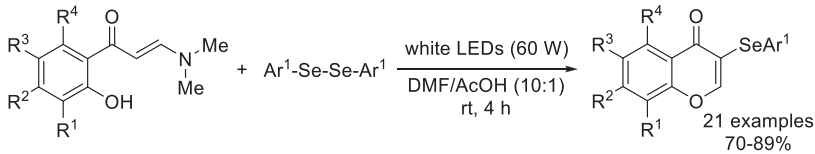
Various 3-thiocyanato-4*H*-chromen-4-ones were formed from thiocyanation and cyclization reactions of *o*-hydroxyaryl enaminones and commercially available potassium thiocyanate, as sulfur source, in the presence of potassium persulfate in 1,2-DCE,[270] using PIDA as oxidant in aqueous medium (Scheme 36)[271] and under undivided electrolytic conditions in acetonitrile,[272] at room temperature under an aerobic atmosphere. More derivatives arise from visible-light-induced thiocyanation of *o*-hydroxyaryl enaminones using ammonium thiocyanate as sulfur source in the presence of Rose Bengal in THF at room temperature[273] and through electrophilic thiocyanation of *o*-hydroxyaryl enaminones using *N*-thiocyanatophthalimide under grinding conditions.[274] The synthesis of 3-(*N*-arylthiocarbamoyl)-4*H*-chromen-4-ones was accomplished through the reaction *o*-hydroxyaryl enaminones with aryl isothiocyanates in hot DMF.[275]



Scheme 36

Diversely substituted *o*-hydroxyaryl enaminones underwent selenocyanation and cyclization reactions in the presence of potassium selenocyanate and potassium persulfate in 1,2-DCE at room temperature[276]

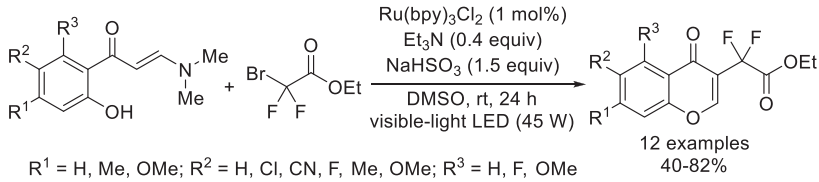
and using PIDA as oxidant in aqueous medium,[271] using *N*-selenocyanatophthalimide as selenocyanating reagent under grinding conditions,[274] or even using triselenodicyanide, generated in situ from the reaction of selenium dioxide and malononitrile, in DMSO at room temperature[277] to afford 3-selenocyanato-4*H*-chromen-4-ones. Some 3-phenylselenyl-4*H*-chromen-4-ones are prompted from the reaction of *o*-hydroxyaryl enaminones with phenylselenyl chloride mediated by silver triflate in dichloromethane[278] and through selenylation/cyclization reactions of *o*-hydroxyaryl enaminones with diorganyl diselenides promoted by visible-light LED in a 10:1 mixture of DMF:acetic acid at room temperature (Scheme 37)[279] and using a solvent-free protocol mediated by potassium iodate and glycerol at 100 °C,[266] a series of 3-(alkyl/aryl) selenyl-4*H*-chromen-4-ones were obtained.



R^1 = H, Br, NO_2; R^2 = H, Cl, F, Me, OMe; R^3 = H, Br, Cl, F, Me, NO_2, OMe; R^4 = H, OMe;
Ar^1 = Ph, 2-MeC_6H_4, 3-FC_6H_4, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 4-MeC_6H_4, 4-$OMeC_6H_4$, naphthalen-2-yl

Scheme 37

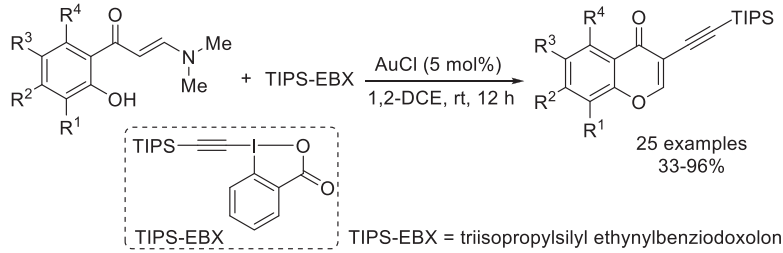
The synthesis of 3-trifluoromethyl-4*H*-chromen-4-ones can be accomplished through C—H trifluoromethylation/annulation reaction of *o*-hydroxyaryl enaminones and stable Langlois' reagent (CF_3SONa) as CF_3 source, in a metal-free approach using potassium persulfate as oxidant in DMSO at 80 °C,[280] promoted by copper(II) acetate, 1,10-phenantroline and TBHP in a 7:1 mixture of 1,1-dioxothiolan:water at 50 °C[281] and via visible-light photoredox catalysis promoted by an iridium(III) complex and using Ph_2SCF_3OTf as CF_3 source, in the presence of sodium acetate in acetone at room temperature.[282] The method developed by Xiang and Yang for the synthesis of 3-[(trifluoromethyl)thio]-4*H*-chromen-4-ones involved trifluoromethylthiolation and cyclization reactions of *o*-hydroxyaryl enaminones employing $AgSCF_3$ and trichloroisocyanuric acid in THF at room temperature.[283] One-pot photocatalytic radical cascade reactions of *o*-hydroxyaryl enaminones with ethyl



Scheme 38

bromodifluoroacetate promoted by an iridium(III) complex in the presence of sodium acetate in acetone at room temperature[282] or mediated by a ruthenium(II) catalyst in the presence of triethylamine and sodium hydrogen sulfite in DMSO at room temperature (Scheme 38)[284] provided several ethyl 2,2-difluoro-2-(4-oxo-4*H*-chromen-3-yl)acetates.

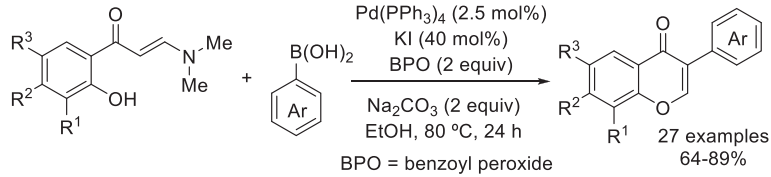
A wide variety of 3-CH_2substituted 4*H*-chromen-4-ones were synthesized via one-pot reaction of *o*-hydroxyaryl enaminones with alkyl iodides mediated by silver triflate in dichloromethane[278] and with benzyl bromides in the presence of sodium iodide in refluxing acetone.[285] More derivatives were obtained from oxa-Diels–Alder reaction of *o*-quinone methides, generated from *o*-(*N*,*N*-dimethylaminomethyl)phenols, with *o*-hydroxyaryl enaminones in diglyme, DMF or DMAc at temperatures above 150 °C, and subsequent cyclization reactions.[286] Gold(I)-catalyzed hydroxy group assisted C(sp^2)—H alkylation of *o*-hydroxyaryl enaminones with diazo compounds in dichloromethane at 60 °C gave 3-CH substituted 4*H*-chromen-4-ones, in good yields.[287] DDQ mediated tandem oxidative-coupling/annulation reactions of *o*-hydroxyaryl enaminones with 1,3-diarylpropenes to obtain 3-(1,3-diarylprop-2-en-1-yl)-4*H*-chromen-4-ones[288] and with cycloheptatriene to produce 3-(cycloheptatrienyl)-4*H*-chromen-4-ones,[289] in 1,2-DCE at room temperature. Several 3-vinyl-4*H*-chromen-4-ones were formed via domino C–H alkenylation and annulation reaction of *o*-hydroxyaryl enaminones with both terminal and internal alkenes promoted by palladium and iodide catalysts in the presence of TBHP and sodium bicarbonate in 1,2-DCE at 110 °C.[290] It is through gold(I)-catalyzed alkynylation/cyclization reaction that *o*-hydroxyaryl enaminones reacted with triisopropylsilyl ethynylbenziodoxolone (TIPS-EBX) in 1,2-DCE at room temperature to afford a series of 3-alkynyl-4*H*-chromen-4-ones (Scheme 39). The alkynylated products were also obtained when using TBDMS-EBX and TBDPS-EBX as alkynylation agents.[291]



R^1 = H, Cl, Me; R^2 = H, F, Me, OMe; R^1R^2 = Ph
R^3 = H, Br, Cl, CN, COPh, COMe, F, I, Me, NO_2, OH, OMe, Ph, CCH, CCTMS, CCC_5H_{11}, thiophen-2-yl; benzofuran-2-yl; R^3R^4 = Ph

Scheme 39

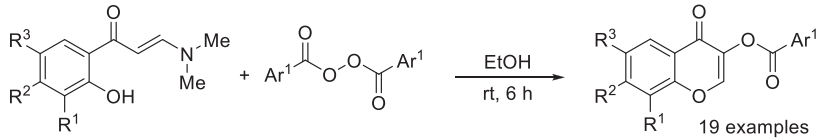
A diverse array of 3-aryl-4*H*-chromen-4-ones were readily available through arylation of *o*-hydroxyaryl enaminones with aryl diazonium tetrafluoroborates catalyzed by Eosin Y in DMSO under intensive irradiation with green LED light; with diaryliodonium triflates promoted by $Ru(bpy)_3Cl_2{\cdot}6H_2O$ in acetonitrile under green LED light irradiation[292]; with dimethyl(aryl)sulfonium salts in the presence of cesium carbonate in DMF under argon atmosphere; with triarylsulfonium salts mediated by $Ru(bpy)_3Cl_2{\cdot}6H_2O$ and sodium acetate in acetonitrile under blue LED light irradiation; with sulfonyl chlorides promoted by the same ruthenium catalyst and sodium carbonate in acetonitrile under blue LED light irradiation[293]; and with arylboronic acids mediated by $Pd(PPh_3)_4$ and KI in the presence of benzoyl peroxide (BPO) and sodium carbonate in ethanol (Scheme 40).[294] Qian et al. reported a copper(II)-carbene-triggered electrophilic cyclization of *o*-hydroxyaryl enaminones with 3-diazoindolin-2-imines using 1,2-DCE as solvent to afford 3-indolyl-4*H*-chromen-4-ones, in moderate to good yields.[295]



R^1R^2 = Ph; R^2 = H, Br, Cl, Me, OMe; R^3 = H, Br, Cl, F, Me;
Ar = Ph, 2-ClC_6H_4, 3-MeC_6H_4, 4-BrC_6H_4, 4-$^tBuC_6H_4$, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-$OMeC_6H_4$, thiophen-3-yl

Scheme 40

Under inert atmosphere, decarboxylative cross-coupling reaction of α-keto carboxylic acids bearing aromatic moieties with *o*-hydroxyaryl enaminones using silver nitrate and potassium persulfate in a 2:1 mixture of DMSO:water gave a range of 3-benzoyl-4*H*-chromen-4-ones.[296] Catalyst-free C–H acyloxylation of *o*-hydroxyaryl enaminones with aroyl peroxides in ethanol at room temperature provided 3-acyloxy-4*H*-chromen-4-ones (Scheme 41)[297] while 4-oxo-4*H*-chromen-3-carboxamides are prepared from the reaction of *o*-hydroxyaryl enaminones with various isocyanates in a minimal amount of DMF or toluene at 110 °C for 1–8 h.[298]

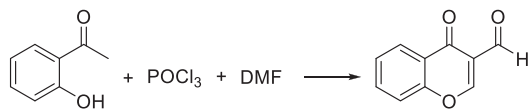


R^1R^2 = Ph; R^2 = H, Cl, OMe; R^3 = H, Cl, Me;
Ar^1 = Ph, 2-ClC_6H_4, 3-BrC_6H_4, 3-ClC_6H_4, 3-MeC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 4-$NO_2C_6H_4$

Scheme 41

4.1.2 Conversion into 4-oxo-chromen-3-carbaldehydes

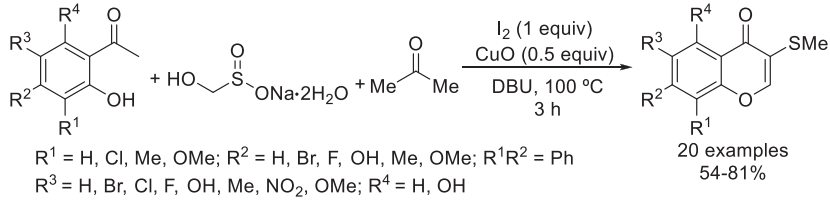
4-Oxo-4*H*-chromen-3-carbaldehyde and its derivatives are versatile building blocks for the synthesis of a huge number of heterocyclic compounds. In 2014, Sepay and Dey[299] reviewed the literature covering the previous 5 years on the synthesis and chemical reactivity of 4-oxo-4*H*-chromen-3-carbaldehyde and the synthetic strategies to prepare this moiety are quite similar to those described on the next decade. Thus, 2′-hydroxyacetophenones underwent Vilsmeier–Haack cyclization reaction in the presence of phosphorus(V) oxychloride ($POCl_3$) and DMF (Scheme 42) to afford an array of substituted 4-oxo-4*H*-chromen-3-carbaldehydes. The reaction occurs usually at room temperature[300–309] but warmer conditions, at 45–80 °C, can be applied.[255,310–313] More examples were obtained from the reaction of 2′-hydroxyacetophenones with oxalyl chloride in DMF at room temperature, in good yields.[170]



Scheme 42

Multicomponent reaction

Three-component reaction of 2′-hydroxyacetophenones with rongalite and dimethyl sulfoxide using an molecular iodine–DMSO reagent system in the presence of copper(II) oxide and DBU provided a series of 3-(methylthio)-4*H*-chromen-4-ones (Scheme 43).[314]

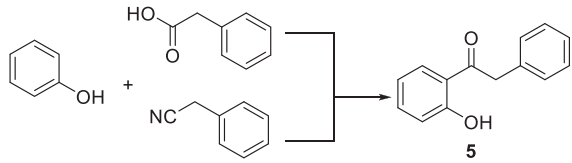


Scheme 43

4.2 Starting from 2-substituted 2′-hydroxyacetophenones

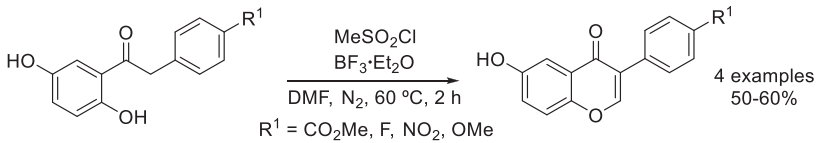
Another strategy to prepare a library of 3-substituted 4*H*-chromen-4-ones involves the use of 2-substituted 2′-hydroxyacetophenones as key intermediates.

In the case of 2-arylsubstituted intermediates **5** (Scheme 44), they can be obtained through Friedel–Crafts reaction of phenols with phenylacetic acids catalyzed by zinc chloride at 120 °C[315] and by $BF_3{\cdot}OEt_2$ at 70–110 °C, under an inert (argon or nitrogen) atmosphere,[49,50,316–321] and through acylation of phenols with substituted benzoacetonitriles, using HCl gas/anhydrous $ZnCl_2$ catalytic system in 1,4-dioxane[322] or dry diethyl ether.[323,324] Lee developed a versatile three-step protocol for the synthesis of 2-aryl-2′-hydroxyacetophenones starting from 2-methoxybenzoic acids.[325] The first step consists in the reaction of 2-methoxybenzoic acids with *N*-methoxy-*N*-methylcarbamoyl chloride in the presence of triethylamine and 4-(dimethylamino)pyridine (DMAP) in acetonitrile at room temperature to provide *N*-methoxy-*N*-methyl 2-methoxybenzamides. Subsequent acyl substitution with benzylmagnesium chlorides in THF at 0 °C afforded the respective 2-aryl-1-(2-methoxyaryl)ethan-1-ones. Finally, selective demethylation of the 2-methoxy group was performed using boron tribromide in dichloromethane to afford the desired 2-aryl-1-(2-hydroxyaryl)ethan-1-ones.[325]



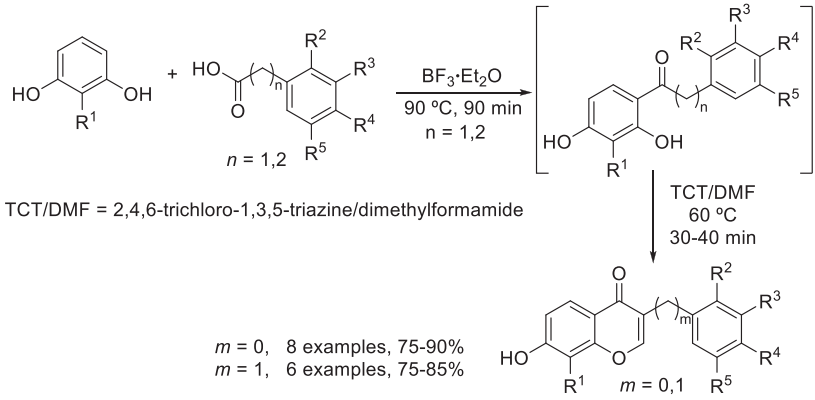
Scheme 44

To complete the sequence for the synthesis of 3-aryl-4*H*-chromen-4-ones, cyclization reaction of the formed 2-aryl-1-(2-hydroxyaryl)ethan-1-ones has to occur. The reaction can be accomplished upon treatment with DMF-DMA as carbon atom donor,[326,327] with methanosulfonyl chloride in DMF and $BF_3{\cdot}OEt_2$ as catalyst (Scheme 45),[315321,328] with DMF/$POCl_3$[50,329,330]and with DMF/$POCl_3$[323,325] or DMF/PCl_5[322,324] in the presence of $BF_3{\cdot}OEt_2$ to yield 3-aryl-4*H*-chromen-4-ones.



Scheme 45

Basha et al. reported a novel approach for the one-pot or two-step synthesis of 3-aryl- and 3-benzyl-4*H*-chromen-4-ones using 2-aryl-1-(2-hydroxyaryl)ethan-1-ones and 3-aryl-1-(2-hydroxyaryl)propan-1-ones, respectively, as intermediates.[49] These compounds were prepared in situ via Friedel–Crafts acylation reaction of substituted phenols with phenylacetic acids and phenylpropanoic acids, respectively, using $BF_3{\cdot}OEt_2$ as both Lewis acid and solvent at 90 °C for 90 min. In the next step, 2-aryl-1-(2-hydroxyaryl)ethan-1-ones and 3-aryl-1-(2-hydroxyaryl)propan-1-ones were treated with the TCT/DMF complex, generated in situ from TCT and DMF, to obtain 3-aryl- and 3-benzyl-4*H*-chromen-4-ones, respectively, in good yields (Scheme 46).[49]

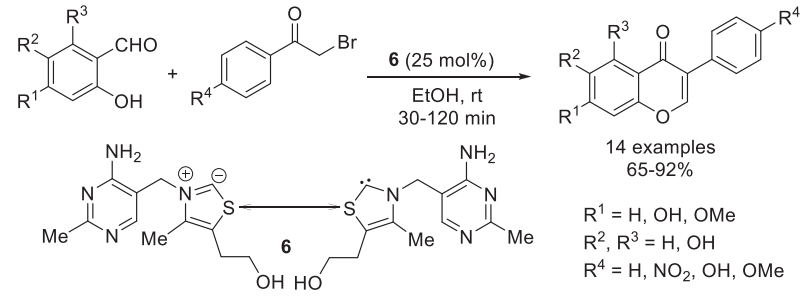


Scheme 46

The synthesis of 3-nitro-4*H*-chromen-4-one was achieved in 82% yield from the reaction of 2′-hydroxy-2-nitroacetophenone with triethyl orthoformate and concentrated sulfuric acid in refluxing conditions for 6 h.[331] The reaction of 2-alkyl-1-(2-hydroxyaryl)ethan-1-ones with DMF-DMA at reflux at 120 °C for 48 h led to formation of some 3-alkyl-4*H*-chromen-4-ones, in moderate to excellent yields.[332]

4.3 Starting from salicylaldehyde derivatives

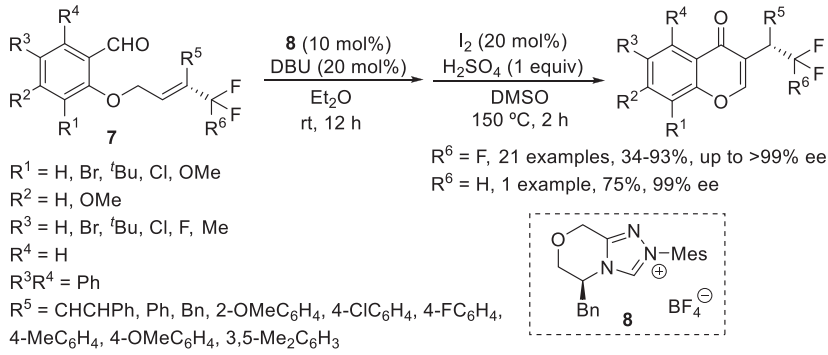
Various rhodium complexes bearing L-amino acid ligands (L-Pro, L-Phe or L-Val) were synthesized to catalyze oxidative coupling reaction of salicylaldehyde with phenylacetylene, via C—H bond activation, to give 3-phenyl-4*H*-chromen-4-one in good yields.[333] Further 3-aryl-4*H*-chromen-4-ones were readily available through one-pot domino reaction of salicylaldehydes with phenacyl bromides in the presence of catalytic amount of thiamine **6** in ethanol at room temperature (Scheme 47).



Scheme 47

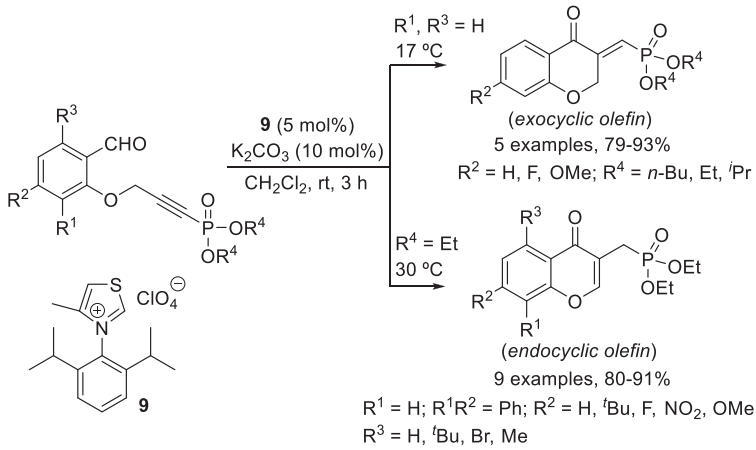
This NHC catalyst is a non-flammable, inexpensive, biodegradable, non-toxic and metal-ion-free reagent for an environmentally benign approach in the synthesis of 3-aryl-4*H*-chromen-4-ones.[334]

One-pot synthesis of 3-trifluoroethylated 4*H*-chromen-4-ones was prompted via radical cascade cyclization–coupling reaction of 2-(allyloxy) arylaldehydes using with Langlois' reagent (CF_3SO_2Na) employing potassium persulfate as oxidant in DMSO at 80 °C.[335] An enantioselective version for the synthesis of 3-trifluoroethylated/3-difluoroethylated 4*H*-chromen-4-ones used CF_3/CF_2Hsubstituted 2-(allyloxy)arylaldehydes **7** promoted by NHC catalyst **8** and DBU in diethyl ether at room temperature, which after removal of the solvent was treated with molecular iodine and sulfuric acid in DMSO at 150 °C (Scheme 48).[336]



Scheme 48

Intramolecular hydroacylation reaction of dialkyl 3-(2-formylaryloxy) prop-1-ynylphosphonates mediated by thiazolium salt **9** in the presence of potassium carbonate in dichloromethane was temperature-controlled: reaction at 17 °C for 3 h gave mainly exocyclic olefin products [(*E*)-dialkyl (4-oxo-2*H*-chromen-3(4*H*)-ylidene)methylphosphonates] while endocyclic olefin products [diethyl (4-oxo-4*H*-chromen-3-yl)methylphosphonates] were obtained at 30 °C for 3 h (Scheme 49). In addition, exocyclic olefins isomerized to the endocyclic derivatives when treated with thiazolium salt **9** and potassium carbonate for 3–5 h, in nearly quantitative yields.[337]

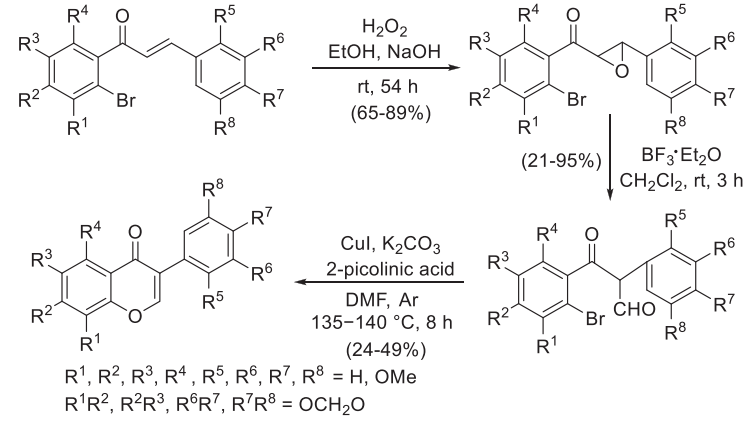


Scheme 49

Under microwave irradiation, NHC-catalyzed intramolecular hydroacylation reaction of 2-(2-formylaryloxy)acetonitriles employing 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride as catalyst, triethylamine as base and 1 equiv. of commercially available ionic liquid [bmim][BF_4] provided various 3-amino-4*H*-chromen-4-ones. A few 2-substituted 3-amino-4*H*-chromen-4-ones were also synthesized. Moreover, the protocol was extended to the synthesis of 4-oxo-4*H*-chromen-3-acetates using 4-(2-formylaryloxy)but-2-ynoates as starting materials.[338]

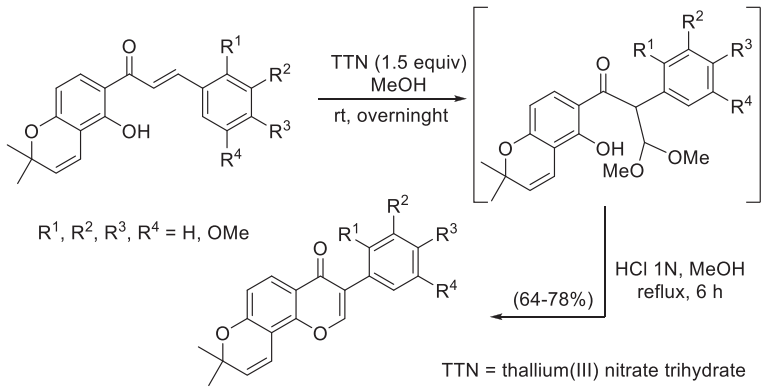
4.4 Starting from 2′-substituted chalcones

Semenov et al. reported the preparation of highly functionalized 3-aryl-4*H*-chromen-4-ones using 2′-bromochalcones as key building blocks. These chalcones underwent epoxidation in the presence of hydrogen peroxide in a mixture of sodium hydroxide and ethanol at room temperature. Subsequent epoxide rearrangement occurred in the presence of $BF_3{\cdot}OEt_2$ in dichloromethane to deliver the respective ketoaldehydes. The final step consists of a cyclization reaction of the ketoaldehydes in the presence of copper(I) iodide, potassium carbonate and 2-picolinic acid in dry DMF at 135–140 °C, under argon atmosphere (Scheme 50).[339]



Scheme 50

Another strategy involved oxidation and rearrangement reactions of 2′-hydroxychalcones in the presence of thallium(III) trinitrate trihydrate (TTN) and continuous stirring overnight at room temperature. After careful work-up and purification, the intermediates formed were treated with HCl in refluxing methanol to give the corresponding 3-aryl-4*H*-chromen-4-ones (Scheme 51).[54]

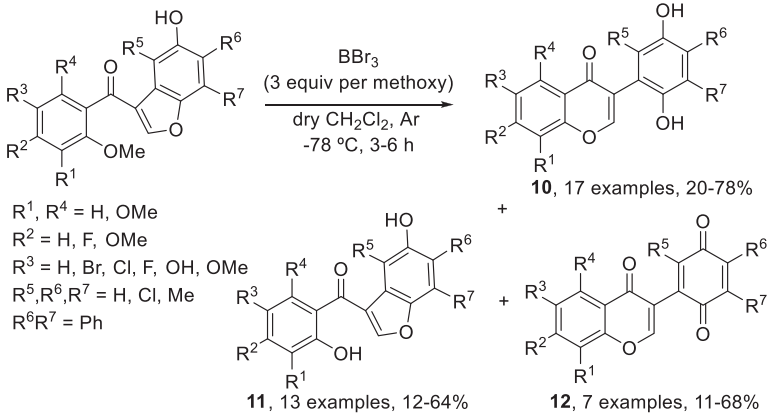


Scheme 51

4.5 Tandem reaction using methoxybenzoylbenzofurans

It is through tandem demethylation and ring-opening/cyclization reaction that a series of 5-hydroxy-3-(2-methoxybenzoyl)benzo[*b*]furans in the presence of boron tribromide in anhydrous dichloromethane under

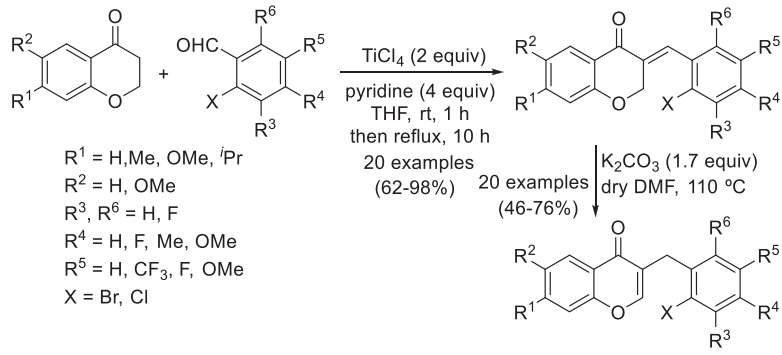
an argon atmosphere were converted into either of three products: 3-(2,5-dihydroxyaryl)-4*H*-chromen-4-ones **10**; the deprotection products, 5-hydroxy-3-(2-hydroxybenzoyl)benzo[*b*]furans **11**; and 4*H*-chromen-4-one-2′,5′-quinones **12** (Scheme 52), depending on the substituents and substitution patterns of the A- and B-rings of the 3-(2-methoxybenzoyl) benzo[*b*]furan precursors.[340]



Scheme 52

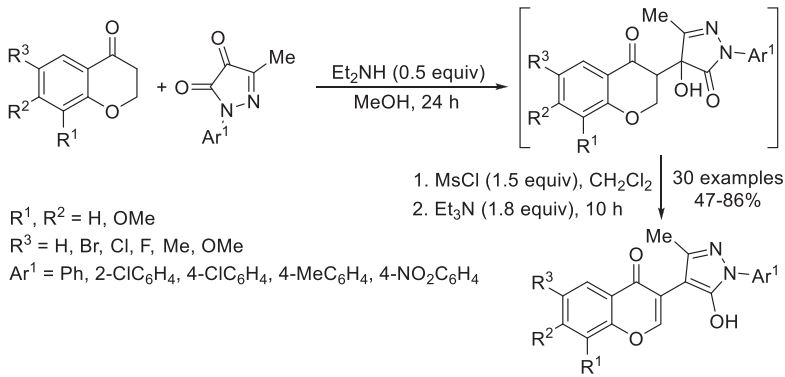
4.6 Starting from chroman-4-ones

The strategy proposed by Hou et al. for the synthesis of various substituted 3-(2-halobenzyl)-4*H*-chromen-4-ones involved an aldol condensation reaction between chroman-4-ones and 2-halobenzaldehydes promoted by titanium(IV) tetrachloride and pyridine in THF to afford substituted 3-(2-halobenzylidene)chroman-4-ones with subsequent double-bond migration in the presence of potassium carbonate in anhydrous DMF at 110 °C (Scheme 53).[341]



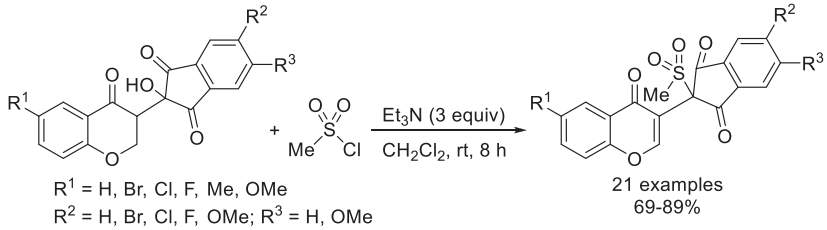
Scheme 53

Thermal-mediated [1,3]-hydrogen transfer from isatylidenylchroman-4-ones led to the synthesis of 3-oxindole-4*H*-chromen-4-one hybrids. The reaction occurs at 90 °C for 24 h, with catalyst- and solvent-free conditions and without column chromatography purification of the products obtained.[342] *N*-*t*-butyloxycarbonyl (Boc) oxindole-4*H*-chromen-4-ones were synthesized via a four-step sequence, all at room temperature: (i) aldol reaction of isatins with chroman-4-ones mediated by diethylamine in ethanol; (ii) O-protection with MsCl in the presence of triethylamine in dichloromethane; (iii) *N*-protection using DMAP and $(Boc)_2O$ in dichloromethane; and (iv) double-bond migration carried out in triethylamine in dichloromethane.[343] A series of N-arylated pyrazol-3-yl-4*H*-chromen-4-ones was prepared via aldol condensation of *N*-arylpyrazolones with chroman-4-ones catalyzed by diethylamine in methanol, subsequent O-protection of the intermediates with MsCl in dichloromethane and finally elimination and [1,5]-proton transfer in triethylamine to afford the desired products (Scheme 54).[344]



Scheme 54

The synthesis of sulfone-containing 3-(indane-1,3-dion-2-yl)-4*H*-chromen-4-ones were accomplished through methanesulfonylation reaction of indanedione-chroman-4-one hybrids with methanesulfonyl chloride and triethylamine in dichloromethane at room temperature (Scheme 55).[345] Kwesiga et al. studied the scope and limitations of the 2,3-oxidative aryl rearrangement of prenylated 2-arylchroman-4-ones mediated by PIDA, phenyliodonium bis(trifluoroacetate) (PIFA) and [hydroxy(tosyloxy)iodo] benzene (HTIB). From these reactions, prenylated 3-aryl-4*H*-chromen-4-ones were obtained as major 2,3-oxidative rearrangement products and



Scheme 55

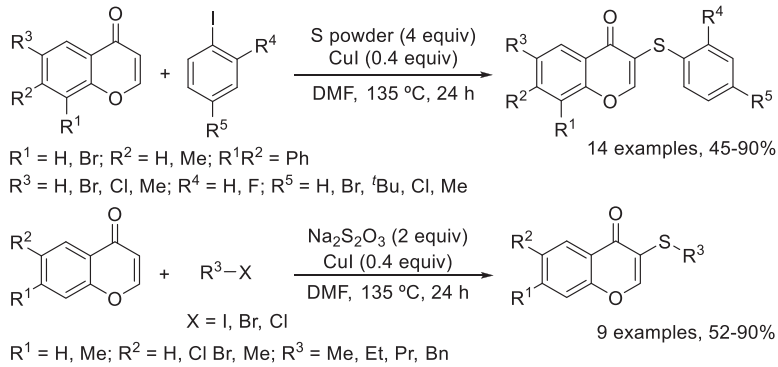
prenylated 2-aryl-4*H*-chromen-4-ones were isolated as minor oxidation products.[346] A more selective protocol was reported by Kurapati et al. for the oxidative rearrangement of various 2-(hetero)aryl-4*H*-chroman-4-ones (naphthalen-1-yl, naphthalen-2-yl, thiophen-1-yl, thiophen-2-yl), carried out in the presence of TTS in refluxing acetonitrile to produce the corresponding 3-(hetero)aryl-4*H*-chromen-4-ones.[228]

4.7 Starting from 2,3-unsubstituted 4*H*-chromen-4-ones

Vints and Rozen published a two-steps protocol for the synthesis of some 3-fluoro-4*H*-chromen-4-ones starting from the reaction of 2,3-unsubstituted chromones with diluted fluorine in nitrogen at −78 °C in a mixture of chloroform/trichlorofluromethane/ethanol (usually in 5:4:1 ratio) to provide *cis*-2,3-difluoro-4*H*-chroman-4-ones, which underwent easily dehydrofluorination by adsorption on a silica gel column and eluting with petroleum ether/ethyl acetate.[347]

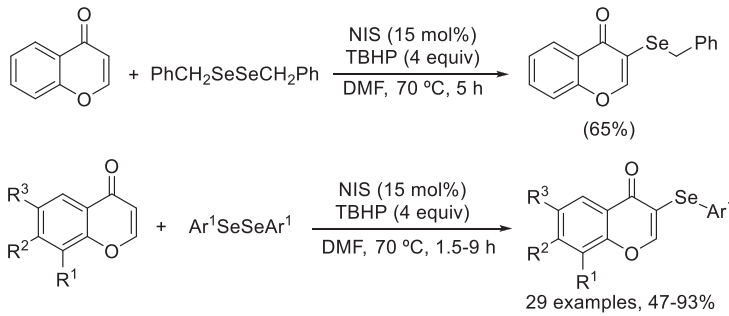
Various metal-free sulfenylation methods (C—S bond construction) have emerged in the past recent years, via direct C—H functionalization of 2,3-unsubstituted chromen-4-ones, to prepare a series of 3-*S*-substituted 4*H*-chromen-4-ones. Thus, regioselective sulfenylation reaction of 2,3-unsubstituted chromen-4-ones mediated by ammonium iodide can be performed by several sulfenylation agents/conditions such as DMSO in acetonitrile,[348] sulfonyl hydrazides in DMAc,[348] and alkyl/arylsulfonyl chlorides,[349] aryl thiols,[350] sodium benzenesulfinates[351] and diaryl dissulfides,[352] in DMF. These sulfenylation approaches allowed the synthesis of 3-methylthio- and a wide variety of 3-arylthio-4*H*-chromen-4-ones, in good yields without using any oxidants in the reaction medium. However, some of these methods still required the use of pre-functionalized sulfur agents which were expensive or not easy to make and were not economical for large scale production. Meanwhile, Tang *et al.* published a simple and environmentally friendly methodology for the regioselective synthesis of 3-*S*-alkyl- or 3-*S*-aryl-4*H*-chromen-4-ones

employing easily available alkyl or aryl halides and using, respectively sulfur powder or sodium thiosulfate as sulfenylation reagents, catalyzed by copper(I) iodide in DMF at 135 °C (Scheme 56).[353] A different sulfenylation agent, potassium thiocyanate, was used in the synthesis of 3-*S*-(alkyl/aryl)-4*H*-chromen-4-ones starting from 2,3-unsubstituted chromen-4-ones and alkyl/aryl halides mediated by copper(I) cyanide in DMF.[354]



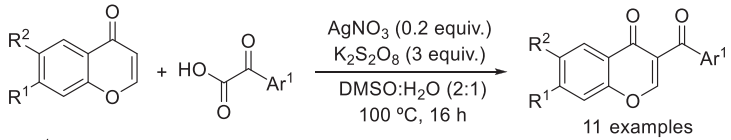
Scheme 56

Polysubstituted 3-arylseleno-4*H*-chromen-4-ones were prepared via direct C—H functionalization of 2,3-unsubstituted chromones with aryl halides, using potassium selenocyanate[354] and selenium powder[355] as selenation agents promoted respectively by copper(I) iodide and copper(I) cyanide, in DMF. An alternative regioselective selenation reaction employs dialkyl/diaryl diselenides promoted by *N*-iodosuccinimide (NIS) and TBHP in DMF to obtain 3-alkyl/arylseleno-4*H*-chromen-4-ones (Scheme 57).[356]



Scheme 57

Another TMP base, $TMP_2ZnCl{\cdot}LiCl$, similar to the one previously described in Section 3, was applied to the selective C-3-selective zincation of parent chromen-4-one in THF at 25 °C and subsequent reaction with various electrophiles to provide a series of 3-alkyl/aryl-4*H*-chromen-4-ones.[241] Decarboxylative acylation reaction of 2,3-unsubstituted chromones with α-keto acids bearing (hetero)aromatic moieties promoted by silver nitrate and potassium persulfate in a 2:1 mixture of DMSO:water delivered a range of 3-benzoyl-4*H*-chromen-4-ones, in moderate to good yields (Scheme 58).[296]



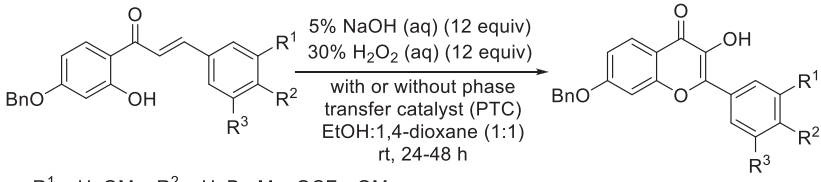
R^1 = H, Me, OMe
R^2 = H, Cl, Me
Ar^1 = 2-FC_6H_4, 3-BrC_6H_4, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, pyridin-3-yl, thiophen-2-yl

Scheme 58

5. Synthesis of 2,3-disubstituted 4*H*-chromen-4-ones

5.1 Cyclization of 2′-hydroxychalcones

A well-established strategy for the synthesis of 2-(hetero)aryl-3-hydroxy-4*H*-chromen-4-ones consists of the cyclization of 1-(2-hydroxyaryl)-3-[(hetero)aryl]prop-2-en-1-ones in alkaline hydrogen peroxide, known as Algar–Flynn–Oyamada (AFO) protocol. Sodium and potassium hydroxides are the most common bases applied and the reaction usually proceeds at ice cold conditions, using methanol[83,357–363] or ethanol[77,82,364–367] as solvents. The resulting suspensions had to be treated under acidic conditions to recover the desired 2-aryl-3-hydroxy-4*H*-chromen-4-ones. Nhu et al. reported a variation of the conventional AFO reaction using phase transfer catalysis to expand the scope and compared the yields obtained from both methodologies, starting from a series of 4′-benzyloxy-2′-hydroxychalcones. Both ammonium and phosphonium salts were used as phase transfer catalysts, varying according to the substitution pattern of the B-ring of 2-aryl-3-hydroxy-4*H*-chromen-4-one core (Scheme 59).[368]



R^1 = H, OMe; R^2 = H, Br, Me, OCF_3, OMe
R^1R^2 = OCH_2O; R^3 = H, OMe

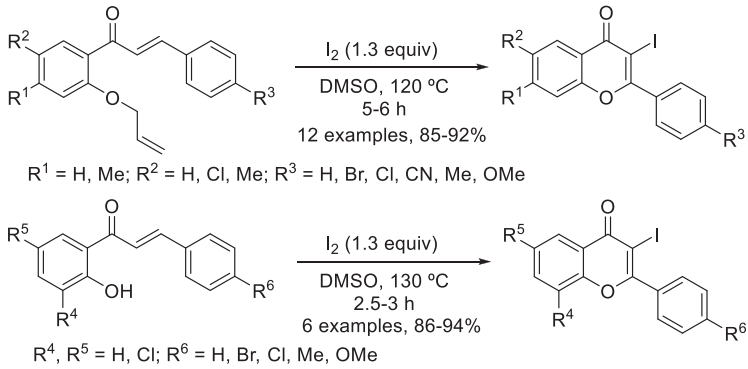
without PTC 4 examples, 19-45%
with PTC 7 examples, 16-82%

PTC: benzyltriphenylphosphonium chloride, propyltriphenylphosphonium bromide, ethyltriphenylphosphonium iodide, isopropyltriphenylphosphonium iodide, tetrabutylammonium bromide/iodide/hydrogenosulfate

Scheme 59

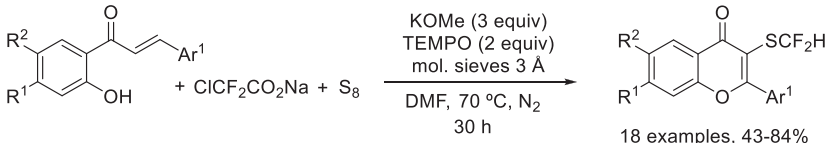
3-Fluoro-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-4-one was synthesized from fluorination reaction of 2′-hydroxy-3,4,5-trimethoxychalcones with 2 equiv. of *N*-fluorobenzenesulfonimide in pyridine at room temperature for 12 h followed by heating the mixture to 80 °C for 12 h.[125] A wide variety of 2-aryl-3-chloro-4*H*-chromen-4-ones has been prepared in good yields through oxidative cyclization reaction of polysubstituted 2′-hydroxychalcones using copper(II) chloride in DMSO at reflux conditions.[75] A couple of α,β-dibromochalcones underwent cyclization reaction in the presence of sodium acetate in refluxing ethanol to provide the respective 3-bromo-2-phenyl-4*H*-chromen-4-ones.[120]

Molecular iodine has been applied in chromone chemistry in several chemical transformations as a versatile, economic, and easily available reagent. Thus, polysubstituted 2-aryl-3-methyl-4*H*-chromen-4-ones have been synthesized through oxidative cyclization reaction of 2′-hydroxy-α-methylchalcones in the presence of a catalytic amount of iodine in DMSO.[369] Treating allyloxy-2′-hydroxy-α-methylchalcones with equimolar amounts of molecular iodine in DMSO induced oxidative cyclization reaction to afford allyloxy-2-aryl-3-methyl-4*H*-chromen-4-ones. Interestingly, using 1.1 equiv. of molecular iodine in DMSO, smoothly deallylating occurred to provide the corresponding hydroxylated 3-methyl-4*H*-chromen-4-ones, in good yields.[370] Direct synthesis of 2-aryl-3-iodo-4*H*-chromen-4-ones can be accomplished employing 2′-allyloxychalcones and deactivated 2′-hydroxychalcones as starting materials, in presence of an excess of molecular iodine in hot DMSO (Scheme 60).[371]



Scheme 60

A series of 2-aryl-3-benzyl-4*H*-chromen-4-ones has been prepared via ruthenium(I)-catalyzed coupling reaction of 2′-hydroxychalcones with aromatic aldehydes in the presence of cesium carbonate in DMSO at 120 °C, in good yields.[185] Three-component reaction of 2′-hydroxychalcones with sodium 2-chloro-2,2-difluoroacetate as difluoromethylthiolating agent and elemental sulfur, under basic conditions using TEMPO as the oxidant delivered a series of 3-HCF_2S-containing 2-aryl-4*H*-chromen-4-ones (Scheme 61). It involves tandem oxa-Michael addition and oxidative difluoromethylthiolation reactions.[372]



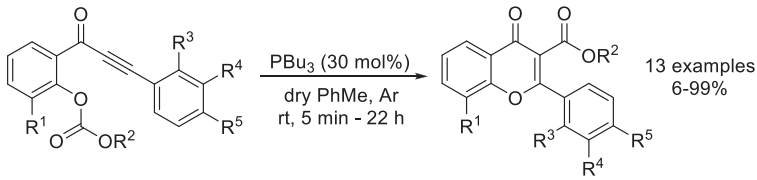
R^1 = H, Br, OMe; R^2 = H, Cl
Ar^1 = Ph, 3-$OMeC_6H_4$, 3-$CF_3C_6H_4$, 3-$OMeC_6H_4$, 4-BrC_6H_4, 4-$^tBuC_6H_4$, 4-$CF_3C_6H_4$, 4-CNC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-PhC_6H_4, naphthalen-2-yl, furan-2-yl, benzofuran-2-yl, thiophen-2-yl

Scheme 61

5.2 Cyclization of 1-(2-acyloxyaryl)prop-2-yn-1-one derivatives

One-pot synthesis of 3-aroyl-2-aryl-4*H*-chromen-4-ones has been accomplished via tandem acyl transfer and regioselective cyclization reactions of 1-(2-acyloxyaryl)-3-arylprop-2-yn-1-ones promoted by 9-azajulolidine as catalyst in DMF at 30 °C. Small amounts of the corresponding 2-aryl-4*H*-chromen-4-ones were also isolated, in some cases.[373] Using the same

tandem acyl transfer-cyclization mechanism, various 1-[2-(3-aryl-1-oxoprop-2-yn-1-yl)aryl]carbonates were converted into 3-alkoxycarbonyl-2-aryl-4*H*-chromen-4-ones after treatment with tributylphosphine in dry toluene at room temperature, under argon atmosphere (Scheme 62).[374]

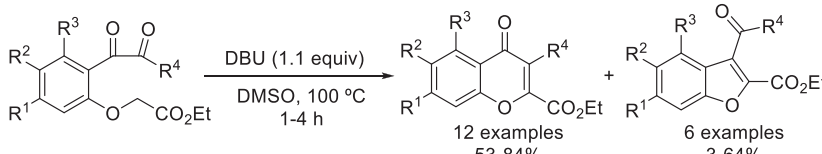


R^1 = H, OTHP; R^2 = H, allyl, ^{t}Bu, CH_2Cl_3, Et, Me, ^{i}Pr, Ph, Bn, 4-$OMeC_6H_4$
R^3 = H, OMOM; R^4 = H, OMe; R^5 = H, F, OMe

Scheme 62

5.3 Cyclization of *O*-diketo phenoxyacetates

Regioselective 6-*exo*-*trig* cyclization/dehydration sequence of *o*-diketo phenoxyacetates mediated by DBU in DMSO at 100 °C led mainly to the synthesis of 3-substituted 4-oxo-4*H*-chromen-2-carboxylates. In some cases, it was also possible to isolate minor amounts of the corresponding 3-carbonylated benzofuran-2-carboxylates, obtained via 5-*exo*-trig cyclization reaction (Scheme 63). The diketo precursors were prepared in a three-step sequence starting from *o*-halophenols: (i) alkylation with ethyl 2-bromoacetate in alkaline conditions to furnish the *o*-halo phenoxyacetates; (ii) Sonogashira cross-coupling reaction with a variety of terminal alkynes to afford *o*-alkynyl phenoxyacetates and (iii) oxidation of the alkyne moiety to give dicarbonyl phenoxyacetates.[375,376]



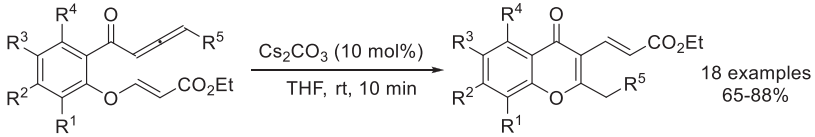
R^1 = H, CO_2Et, OMe, OTs; R^2 , R^3 = H, OMe
R^4 = *n*-Bu, ^{t}Bu, CH_2OTHP, Ph, 2-$OMeC_6H_4$, 4-$OMeC_6H_4$, 3,4-$(OMe)_2C_6H_3$

Scheme 63

5.4 Cyclization of *O*-keto phenoxyacrylates

A new method was developed for the synthesis of (*E*)-ethyl 3-(2-alkyl-4-oxo-4*H*-chromen-3-yl)acrylates in good yields by tandem reaction

of (*E*)-ethyl 3-[2-(1-oxobuta-2,3-dien-1-yl)phenoxy]acrylates in the presence of cesium carbonate in THF at room temperature for 10 min (Scheme 64).[377]



R^1 = H, Br, Cl; R^2 = H, OMe; R^3 = H, Br, Cl, Me; R^3R^4 = Ph

R^5 = H, Me, Ph, 2-CNC_6H_4, 4-MeC_6H_4, 2-Me-5-ClC_6H_3, 3,5-$(OMe)_2C_6H_3$

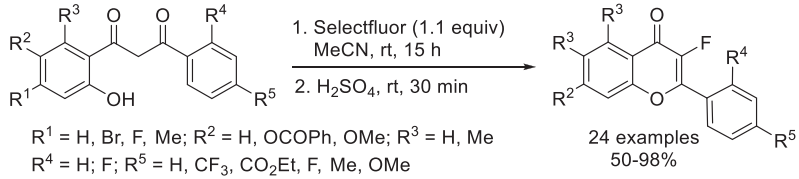
Scheme 64

5.5 Starting from 2′-hydroxyacetophenone derivatives

5.5.1 Cyclization 1-(2-hydroxyaryl)propane-1,3-dione derivatives

Not surprisingly, cyclization of substituted propane-1,3-diones obtained from Baker–Venkataraman rearrangement is not a protocol exception on the synthesis of 2,3-disubstituted 4*H*-chromen-4-ones. Thus, the first step involved esterification of 2′-hydroxyacetophenones with acyl chlorides (see Section 3.3) followed by Baker–Venkataraman rearrangement to afford the expected 1-(2-hydroxyaryl)propane-1,3-diones using potassium hydroxide in pyridine[378]; potassium[379] or sodium[380] *t*-butoxide in DMF; $MgBr_2{\cdot}OEt_2$ and DIPEA in dichloromethane at room temperature.[147] In the final step, cyclodehydration reaction of the propane-1,3-diones formed can occur in the presence of hydrochloric acid in methanol,[147] promoted by *N*-triflyl phosphoramide in methanol at 40 °C,[380] mediated by commercial available pyrrolidine or proline phenylsulfonylhydrazide in a 0.05:2.5 mixture of water:methanol at 55 °C[167] and using a microwave-assisted protocol in the presence of potassium carbonate in water[136] to afford the desired 2,3-disubstituted 4*H*-chromen-4-ones.

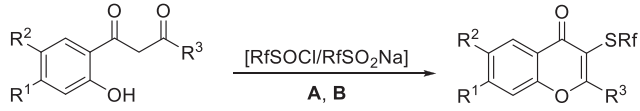
A concise and efficient one-pot synthesis of 2-aryl-3-fluoro-4*H*-chromen-4-ones developed by Wang et al. consisted of the fluorination of 3-aryl-1-(2-hydroxaryl)propane-1,3-diones using Selectfluor® as fluorination agent in the presence of a small amount of acetonitrile at room temperature, followed by cyclodehydration in the presence of a trace amount of concentrated sulfuric acid, at room temperature (Scheme 65).[381]



Scheme 65

Under solvent-free conditions, various 2-aryl-3-bromo-4*H*-chromen-4-ones have been prepared via selective bromination of 3-aryl-1-(2-hydroxyaryl)propane-1,3-diones using ammonium bromide and ammonium persulfate at room temperature under grinding conditions, followed by cyclodehydration in the presence of PTSA at room temperature, also under grinding conditions.[151] An environmental friendly approach for the synthesis of (*E*)-3-bromo-2-styryl-4*H*-chromen-4-ones was accomplished via selective C-2 bromination of 5-aryl-1-(2-hydroxyphenyl)pent-4-ene-1,3-diones followed by the in situ cyclization reaction mediated by *N*-bromosuccinimide (NBS), under microwave irradiation and solvent-free conditions. Using the same precursors, regioselective C-2 iodination promoted by NIS in the presence of the catalytic system trifluoroacetic acid/trifluoroacetic anhydride and sodium acetate furnished mainly (*E*)-3-iodo-2-styryl-4*H*-chromen-4-ones. In both cases, small amounts of the corresponding 2-styrylchromones non-halogenated at C-3 were also recovered.[382]

A wide variety of 2-alkyl/(hetero)aryl-3-(trifluoromethylthio)-4*H*-chromen-4-ones was synthesized via intramolecular trifluorome thylthiolation/cyclization reactions of 3-alkyl/(hetero)aryl-1-(2-hydroxyaryl) propane-1,3-diones with trifluoromethanesulfinyl chloride (CF_3SOCl) in the presence of pyridine in dichloromethane, for 10 min at room temperature. Under similar conditions, the reaction with $ClCF_2CF_2SO_2Na$, *n*-$C_4F_9SO_2Na$ and *n*-$C_6F_{13}SO_2Na$ in the presence of phosphorus oxychloride gave the corresponding 2-aryl-3-(perfluoroalkylthio)-4*H*-chromen-4-ones, in modest yields (Scheme 66).[383]



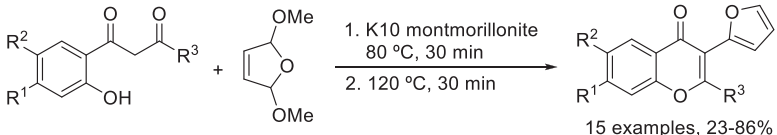
A: Rf = CF_3 (3 equiv), pyridine (3 equiv), CH_2Cl_2, N_2, rt, 10 min
B: $RfSO_2Na$ (1.5 equiv), $POCl_3$ (3 equiv), pyridine (3 equiv), CH_2Cl_2, N_2, rt, 10 min

Conditions **A**
R^1, R^2 = H, Me;
R^3 = Me, Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-$OMeC_6H_4$, furan-2-yl
Rf = CF_3, 13 examples, 54-75%

Conditions **B**
R^1, R^2 = H, R^3 = Ph, Rf = CF_2CF_2Cl, 61%
R^1, R^2 = H, R^3 = Ph, Rf = C_4F_9, 47%
R^1, R^2 = H, R^3 = Ph, Rf = C_6F_{13}, 50%

Scheme 66

The reaction of 3-aryl-1-(2-hydroxyaryl)propane-1,3-diones with acetic anhydride and sodium acetate at reflux provided various 3-aroyl-2-methyl-4*H*-chromen-4-ones.[131,378] Various 3-aroyl-2-(hetero)aryl-4*H*-chromen-4-ones have been obtained via aldol condensation of 3-(hetero)aryl-1-(2-hydroxyaryl)propane-1,3-diones with aromatic aldehydes in ethanol and subsequent oxidation with selenium dioxide, at reflux for 6–8 h in 1,4-dioxane.[379] K10 montmorillonite clay was applied as an heterogenous green catalyst in the one-pot synthesis of 2-substituted 3-(furan-2-yl)-4*H*-chromen-4-ones starting from a mixture of 3-substituted 1-(2-hydroxyaryl)propane-1,3-diones with 2,5-dimethoxy-2,5-dihydrofuran at 80 °C for 30 min and subsequent heating conditions at 120 °C for further 30 min (Scheme 67). This protocol was extended to the synthesis of few 2-unsubstituted 3-(furan-2-yl)-4*H*-chromen-4-ones.[384]



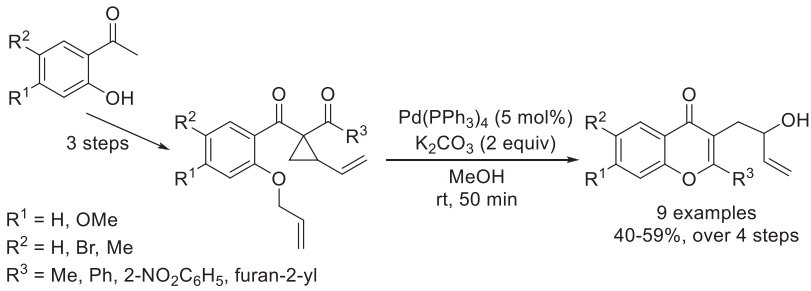
15 examples, 23-86%

R^1 = H, OH, OMe; R^2 = H, Br, F, Me, NO_2; R^1R^2 = Ph
R^3 = Me, ^{i}Pr, Ph, furan-2-yl, thiophen-2-yl

Scheme 67

Huang et al. described a novel synthesis of 3-geranyl- and 3-isopentenyl 2-aryl-4*H*-chromen-4-ones through the alkylation reaction of 1-(2-hydroxphenyl)-3-phenylpropane-1,3-dione with geranyl and isopentyl bromide, respectively, in the presence of potassium carbonate in acetone. The alkylation occurred in both hydroxy groups and at C-2. Subsequent

cyclizations were performed and optimal conditions for 3-isopentenyl derivative was using concentrated hydrochloric acid in 10% acetic acid solution, while for 3-geranyl-4*H*-chromen-4-one was employing concentrated sulfuric acid in methanol.[385] It is through tandem deprotection–cyclization reactions that 1-alkyl/ary-3-[2-(prop-2-en-1-yloxy)aryl]-2-vinylcyclopropylpropane-1,3-diones in the presence of tetrakis(triphenylphosphine)palladium(0) and potassium carbonate in methanol were converted into 2-alkyl/aryl-3-(2-hydroxybut-3-en-1-yl)-4*H*-chromen-4-ones (Scheme 68).[386,387] Under the same reaction conditions, 1-alkyl/aryl-3-[2-(prop-2-en-1-yloxy)aryl] propane-1,3-diones were transformed into 2-alkyl/aryl-3-(prop-2-en-1-yl)-4*H*-chromen-4-ones, after final acidic treatment.[388,389]

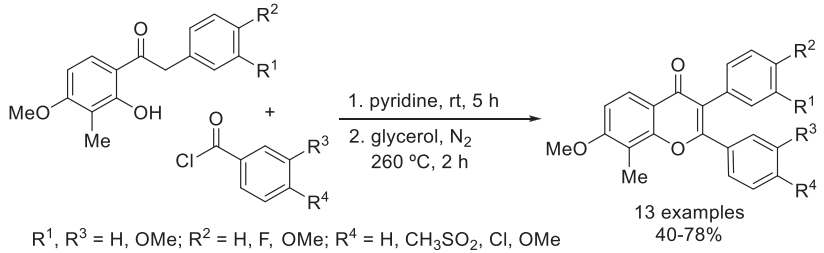


Scheme 68

5.5.2 Through condensation with carbonyl compounds

Modified AFO reaction for the synthesis of 2-(hetero)aryl-3-hydroxy-4*H*-chromen-4-ones has been developed using 2′-hydroxyacetophenones as substrates. Thus, condensation reaction with aromatic aldehydes under basic conditions followed by oxidative cyclization in the presence of alkaline hydrogen peroxide afforded the desired products in moderate to good yields. This improved one-pot protocol provides higher yields in shorter reaction times, with a simple purification procedure since no intermediates or side products were isolated.[390–392]

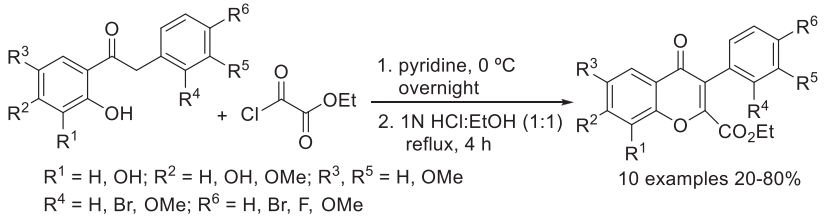
Various 2,3-diaryl-7-methoxy-8-methyl-4*H*-chromen-4-ones were prepared by esterification reaction of 2-aryl-2′-hydroxy-3′-methoxy-4′-methylacetophenones with aroyl chlorides in pyridine at room temperature for 5 h and subsequent heating in freshly distilled anhydrous glycerol at 260 °C for 2 h, under nitrogen atmosphere (Scheme 69).[393,394] One-pot Knoevenagel condensation reaction of 2′-hydroxyacetophenones with aroyl chlorides in the presence of LiHMDS in THF followed by oxidation



Scheme 69

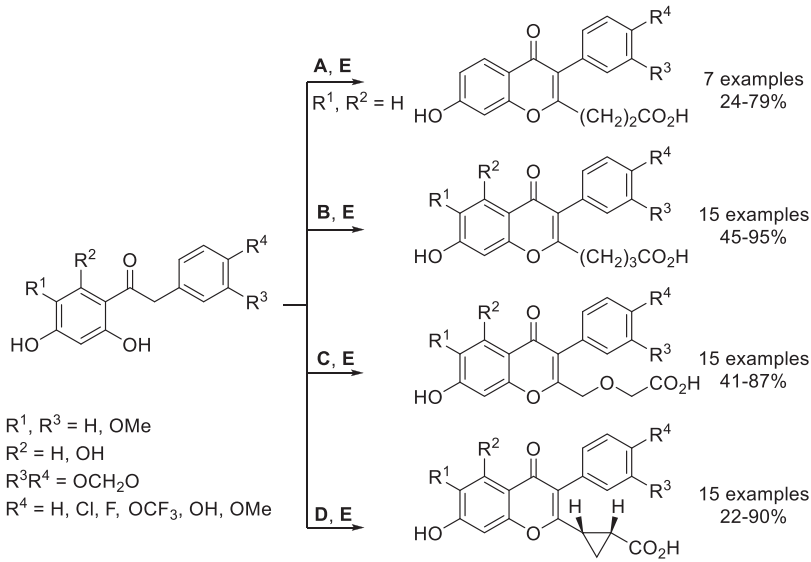
promoted by hydrochloric acid furnished a series of 3-aroyl-2-aryl-4*H*-chromen-4-ones.[395] Some more derivatives arose from condensation of 2′,4′-dihydroxyacetophenone with 2 equiv. of aroyl chlorides in the presence of potassium carbonate in acetone at room temperature to yield the intermediates 2,4-bis(aryloxy)acetophenones, subsequent Baker-Venkataraman rearrangement in refluxing conditions for 24 h and final treatment with diluted hydrochloric acid.[396]

Various 2,3-dimethyl-4*H*-chromen-4-ones were readily available through one-pot Kostanecki–Robinson cyclization protocol, reacting 2′-hydroxypropiophenones as starting materials with acetic anhydride and sodium acetate under reflux, subsequent treatment with anhydrous triethylamine and the mixture was heated overnight at 115 °C and finally acidification with hydrochloric acid at 40 °C.[397–400] Ethyl 8-methoxy-3-methyl-4-oxo-4*H*-chromen-2-carboxylate was prepared by microwave-assisted condensation reaction of 2′-hydroxy-3′-methoxypropiophenone with ethyl chlorooxoacetate in the presence of triethylamine in dichloromethane at 100 °C in a reproducible but rather moderate yield.[400] Moreover, ethyl 3-aryl-4-oxo-4*H*-chromen-2-carboxylates were prepared from the reaction of 2-aryl-1-(2-hydroxaryl)ethan-1-ones with ethyl chlorooxoacetate in pyridine at 0 °C and subsequent acidification with a 1:1 mixture of 1 N hydrochloric acid:ethanol, under refluxing conditions (Scheme 70).[376]



Scheme 70

A couple of 3-aryl-2-methyl-4*H*-chromen-4-ones have been prepared in good yields via condensation reaction of 2-aryl-1-(2-hydroxyaryl) ethan-1-ones with acetic anhydride and fused sodium acetate in refluxing conditions.[401] The reaction of 1-(2,4-dihydroxyphenyl)-2-(4-chlorophenyl) ethan-1-one with acetic anhydride in triethylamine at 140 °C followed by hydrolysis gave the corresponding 7-acetoxy-3-(4-chlorophenyl)-2-methyl-4*H*-chromen-4-one.[402] Other 2-(ω-carboxyalkyl)-3-(hetero)aryl-4*H*-chromen-4-ones were synthesized via condensation reaction of 2-[(hetero)aryl]-1-(2-hydroxyaryl)ethan-1-ones with cyclic carboxylic anhydrides (succinic, glutaric and diglycolic) in dry pyridine at room temperature for 24 h[403] and with succinic, glutaric, diglycolic and 1,2-cyclopropanedicarboxylic acid anhydrides in the presence of triethylamine and DBU in 1,4-dioxane, followed by acidification (Scheme 71).[404,405]



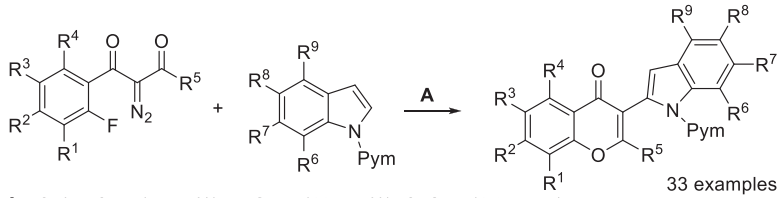
A: succinic anhydride, Et_3N, DBU, 1,4-dioxane, 100 ºC, 6-8 h
B: glutaric anhydride, Et_3N, DBU, 1,4-dioxane, 100 ºC, 6-8 h
C: diglycolic anhydride, Et_3N, DBU, 1,4-dioxane, 100 ºC, 6-8 h
D:1,2-cyclopropanedicaboxylic acid anhydride, Et_3N, DBU, 1,4-dioxane, 100ºC, 6-8 h
E: H_2SO_4, H_2O, 80 ºC, 10-20 min

Scheme 71

5.6 Starting from α-diazo 1,3-diketones

Rhodium(II)-catalyzed coupling reaction of 2-diazo-1-(2-fluoroaryl) propano-1,3-diones with *N*-pyrimidylindoles in the presence of $AgSbF_6$,

cesium acetate and sodium carbonate in *m*-xylene at 140 °C under air atmosphere delivered a small library of 2-substituted 3-(*N*-pyrimidylindolin-2-yl)-4*H*-chromen-4-ones (Scheme 72). The reaction proceeded via C—H activation and C—F cleavage with high functional group compatibility, in moderate to excellent yields. The authors extended the protocol to other *N*-substituted heteroarenes (e.g., isoquinolinones, 2-phenylpyridines), by changing the solvent to THF.[406]



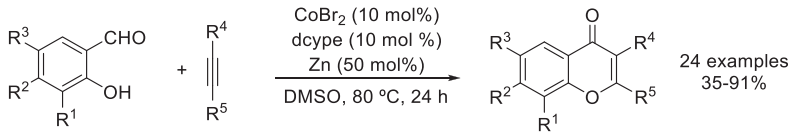
A: $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (16 mol%), CsOAc (1.0 equiv), Na_2CO_3 (1.0 equiv), *m*-xylene, air, 140 ºC,12 h

R^1 = H, Br, CF_3, R^2 = H, Cl, Me, OMe; R^3 = H, Br, Me; R^4 = H, Cl, F
R^5 = Et, Me, Ph; R^6 = H, CO_2Me, Et, F, OMe; R^7 = H, CHO, CO_2Me, F, Me, OMe
R^8 = H, Cl, CO_2Me, Me; R^9 = H, Br, CF_3, F, Me, OMe

Scheme 72

5.7 Starting from salicylaldehyde/salicylic acid derivatives

Synthesis of a wide variety of 2,3-disubstituted 4*H*-chromen-4-ones has been accomplished via coupling reaction of salicylaldehydes with activated internal alkynes, in a metal-free approach using $PhNMe_3I$ as catalyst, TBHP as oxidant and acetonitrile as solvent,[407] using a ruthenium(II)-catalyst and cesium carbonate in *t*-amyl alcohol[183] and using a metal-catalyzed system generated by cobalt(II) bromide, dcype [1,2-bis(dicyclohexylphosphino) ethane] and zinc, in DMSO at 80 °C (Scheme 73).[408] Polysubstituted 2-aryl-3-benzyl-4*H*-chromen-4-ones were obtained through ruthenium(I)-catalyzed C—H activation and decarboxylate coupling reaction of salicyaldehydes with arylproioynic acids carried out in the presence of cesium carbonate in DMSO at 120 °C for 12 h.[185]

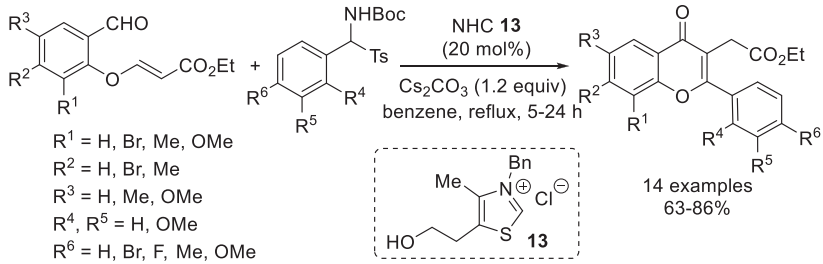


dcype = 1,2-bis(dicyclohexylphosphino)ethane

R^1 = H, Me, OMe; R^2 = H, F, Me, OMe; R^3 = H, Me, OMe, $SiMe_3$; R^4 = Bu, $SiMe_3$, $SiMe_2Ph$
R^5 = Bu, *n*-hexyl, cyclohex-1-en-1-yl, CH_2OBn, Ph, 3-$CF_3C_6H_4$, 3-FC_6H_4, 3-MeC_6H_4, 3-$OMeC_6H_4$, 4-$(COPh)C_6H_4$, 4-$(CO_2Et)C_6H_4$, 4-FC_6H_4, 4-OHC_6H_4, 4-$OMeC_6H_4$, 4-$(SiMe_3)C_6H_4$

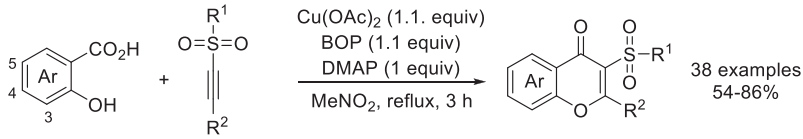
Scheme 73

Tandem C—H activation/decarbonylation/annulation process between salicylaldehydes and 2-diazo-3-oxobutanoate derivatives promoted by a rhodium(III) catalyst in the presence of 2 equiv. of acetic acid in 1,2-DCE at 80 °C[409] and mediated by a iridium(III) complex and PivOH in methanol at room temperature[410] or water at 80 °C[187] furnished a series of functionalized 2-substituted 4-oxo-4*H*-chromen-3-carboxylate derivatives. Zhao et al. developed a controllable chemoselective synthesis of ethyl 2-aryl-4-oxo-4*H*-chromen-3-acetates via NHC-catalyzed cascade reaction of 3-(2-formylaryloxy)acrylates with *t*-butyl aryl (tosyl)methylcarbamates using cesium carbonate as base in refluxing benzene (Scheme 74).[411]



Scheme 74

A small library of 2-substituted 3-sulfonyl-4*H*-chromen-4-ones have been achieved in the copper(II) acetate-mediated [4 + 2] annulation reaction of sulfonylacetylenes with salicylic acids in the presence of benzotriazol-1-yloxy tri-(dimethylamino)phosphonium hexafluorophosphate (BOP) and DMAP in refluxing nitromethane (Scheme 75).[412]



BOP = benzotriazol-1-yloxy tri-(dimethylamino)phosphonium hexafluorophosphate

Ar = Ph, 3,5-$F_2C_6H_2$, 4-$OMeC_6H_3$, 5-ClC_6H_3, 5-FC_6H_3, naphthalen-1-yl, 5-Br-naphthalen-1-yl

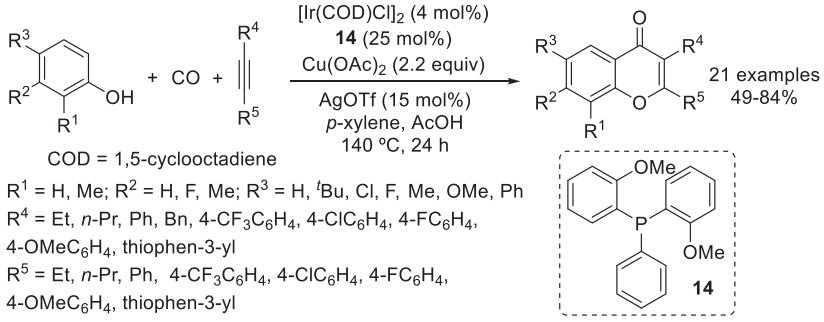
R^1 = *n*-Bu, Me, Ph, 3-MeC_6H_4, 4-*n*-BuC_6H_4, 4-^{t}BuMeC_6H_4, 4-EtC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-^{i}PrC_6H_4

R^2 = CF_3, Et, Me, Bn, CH_2-3,4-$(OMe)_2C_6H_3$, CH_2-4-FC_6H_4, CH_2-4-MeC_6H_4, CH_2-4-$OMeC_6H_4$, CH_2-naphthalen-1-yl, CH_2-thiophen-2-yl

Scheme 75

5.8 Starting from phenols

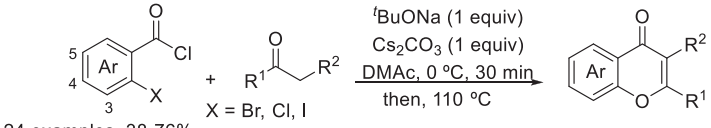
Regio- and chemoselective domino Friedel–Crafts acylation/Allan–Robinson reaction of polysubstituted phenols with a large excess of α-substituted acetic acids mediated by titanium tetrachloride at 100 °C under argon atmosphere provided a series of 2,3-disubstituted 4*H*-chromen-4-ones.[413] More derivatives were obtained from carbonylative coupling reaction of simple phenols with internal alkynes using $[Ir(COD)Cl]_2$ as catalyst (COD = 1,5-cyclooctadiene), bis(2-methoxyphenyl)(phenyl)phosphane **14** as ligand, copper(II) acetate as oxidant, silver triflate as additive in the presence of a small amount of acetic acid in *p*-xylene at 140 °C (Scheme 76).[414]



Scheme 76

5.9 Starting from aroyl chlorides

A transition-metal-free protocol for the synthesis of 2-substituted 4-oxo-4*H*-chromen-3-carboxylates used *o*-non-substituted acyl chlorides and 3-aryl-3-oxopropanoates as building blocks, potassium carbonate and DIPEA as base and DMF as solvent.[415] Another transition-metal-free approach, for the synthesis of functionalized 2,3-disubstituted 4*H*-chromen-4-ones occurred via sequential C-acylation and O-arylation reaction of 2-haloaroyl chlorides with readily available ketone derivatives (e.g., aroylacetates, acylacetates, benzoylacetonitriles) promoted by sodium *t*-butoxide and cesium carbonate in DMAc at 110 °C (Scheme 77). In some cases, only sodium *t*-butoxide was needed to isolate the desired products.[416]

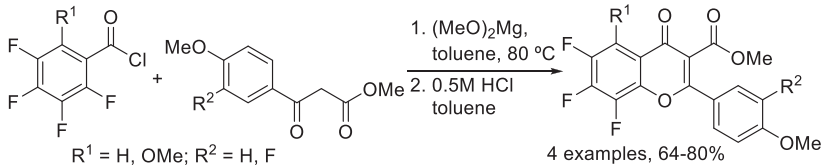


24 examples, 38-76%
R^2 = CO_2Et, COPh, CO-4-$OMeC_6H_4$
Ar = Ph, 3-ClC_6H_3, 4-ClC_6H_3, 4-FC_6H_3, 4-MeC_6H_3, 5-ClC_6H_3, 5-MeC_6H_3, 5-$OMeC_6H_3$, 5-$NO_2C_6H_3$, pyridine, thiophene, benzothiophene
R^1 = Ph, 2-MeC_6H_4, 2-$OMeC_6H_4$, 4-$CF_3C_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-$OMeC_6H_4$, 3,4-$(OMe)_2C_6H_3$, pyridin-2-yl, furan-2-yl, furan-3-yl

2 examples, 58-71%
R^2 = CN; Ar = Ph, R^1 = Ph, 4-$OMeC_6H_4$

Scheme 77

Shcherbakov et al. published the reaction of 2-fluoroaroyl chlorides with 3-oxopropanoates or penta-1,3-dione in the presence of magnesium methoxide in refluxing toluene, which after treatment with a 10% solution of sulfuric acid provided a few 2-substituted 4-oxo-4*H*-chromen-3-carboxylates[417] or 3-acetyl-2-methyl-4*H*-chromen-4-ones[418], respectively. Years later the author's group extended this protocol also to reaction with 1,3-diphenylpropan-1,3-dione. It was found that, for more efficient synthesis of the corresponding 3-acyl-4*H*-chromen-4-ones, the neutralization step should occur in the presence of a diluted solution of hydrochloric acid followed by treatment with DIPEA in refluxing toluene.[419] When using 3-aryl-3-oxopropanoates as starting materials, after activation of 2-fluoroaroyl chlorides with magnesium methoxide and acidic treatment with diluted hydrochloric acid, the desired methyl 2-aryl-4-oxo-4*H*-chromen-3-carboxylates were obtained in good yields (Scheme 78).[420]



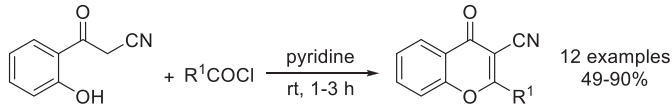
R^1 = H, OMe; R^2 = H, F

4 examples, 64-80%

Scheme 78

One-pot domino Friedel–Crafts acylation/annulation reaction of internal alkynes with 2-methoxyaroyl chlorides in the presence of stoichiometric amount of aluminum bromide in dichloromethane prompted a wide variety of 2,3-disubstituted 4*H*-chromen-4-ones.[421] Other 2-methoxyaroyl

chlorides underwent annulation reaction with ynamides promoted by tin tetrachloride in dichloromethane at 30 °C to give 3-substituted 2-amino-4*H*-chromen-4-ones.[422] Various 2-substituted 4-oxo-4*H*-chromen-3-carbonitriles were readily available through condensation reaction of 3-(2-hydroxyaryl)-3-oxopropionitrile with acyl chlorides in pyridine at room temperature (Scheme 79).[423]

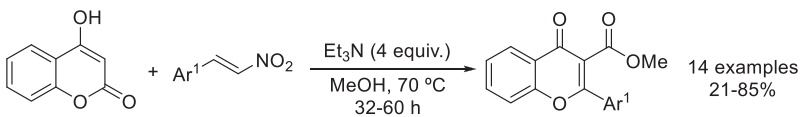


R^1 = Et, Me, Ph, Bn, 2-ClC_6H_4, 2-FC_6H_4, 2-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, furan-2-yl, thiophen-2-yl, 5-Me-thiophen-2-yl

Scheme 79

5.10 Starting from 2*H*-chromen-2-ones

The synthesis of 2-aryl-4-oxo-4*H*-chromen-3-carboxylates has been accomplished through three-component reaction of 4-hydroxy-2*H*-chromen-2-ones with β-nitroalkenes and different alcohols in the presence of triethylamine (Scheme 80)[424] or DMAP,[425] at 70–80 °C. Further derivatives were formed via multicomponent reaction of 4-hydroxy-2*H*-chromen-2-one with benzaldehydes, nitromethane and methanol in the presence of triethylamine.[424] Reacting 4-hydroxy-2*H*-chromen-2-one with β-nitroalkenes and different amines in the presence of DMAP at 70–80 °C prompted few 2-aryl-4-oxo-4*H*-chromen-3-carboxamides, in 65–69% yield.[425]



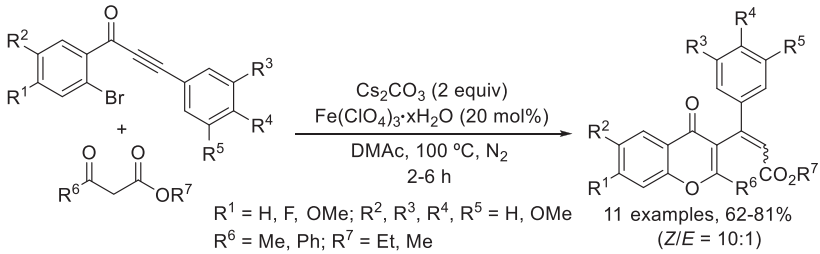
Ar^1 = Ph, 2-BrC_6H_4, 2-$OMeC_6H_4$, 3-$OMeC_6H_4$, 3-$NO_2C_6H_4$, 4-FC_6H_4, 4-MeC_6H_4, 4-$NEt_2C_6H_4$, 4-$OMeC_6H_4$, 3-OMe-4-MeC_6H_3, 3,4-$OCH_2OC_6H_3$, 3,5-$(OMe)_2$-4-EtC_6H_2, naphthalen-1-yl, thiophen-2-yl

Scheme 80

5.11 Starting from 1-(2-halo/2-methoxyaryl)prop-2-yn-1-ones

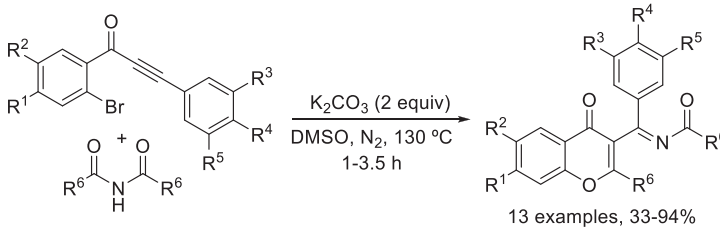
Wang *et al.* reported a highly efficient, regiospecific and environmental friendly approach to produce 2-substituted 3-allyl-4*H*-chromen-4-ones

starting from 1-(2-halo/2-methoxyaryl)prop-2-yn-1-ones and allylic alcohols, using tributylphosphine as catalyst, potassium carbonate as base and DMF as solvent, under a nitrogen atmosphere at 100 °C. It involved a tandem Michael addition–Claisen rearrangement–O-arylation reaction sequence.[426] Diversely 3-vinylsubstituted 2-aryl-4*H*-chromen-4-ones were obtained from the reaction of 3-aryl-1-(2-haloaryl)prop-2-yn-1-ones with 1-aryl-2-phenylethan-1-ones carried out in the presence of cesium carbonate in DMF at 80 °C.[427] Examples of (*Z*/*E*)-3-vinylsubstituted 2-alkyl/aryl-4*H*-chromen-4-ones were prompted via tandem reaction of 1-(2-bromoaryl) prop-2-yn-1-ones with 3-oxobutanoates promoted by $Fe(ClO_4)_3{\cdot}xH_2O$ and cesium carbonate in DMAc at 100 °C (Scheme 81)[428] and of 1-(2-haloaryl) prop-2-yn-1-ones with 3-oxopropanenitriles promoted by cesium carbonate in DMAc at 110 °C.[429]



Scheme 81

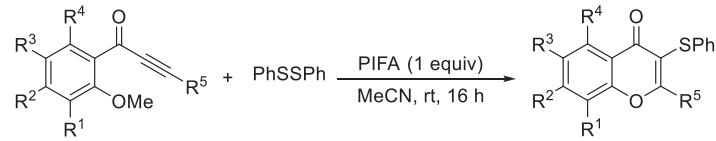
Cyclization reaction of 3-aryl-1-(2-methoxyphenyl)prop-2-yn-1-ones in the presence of cyclic and acyclic aromatic acetals and boron trifluoride etherate in acetonitrile at room temperature resulted in regioselective formation of 3-alkoxy(aryl)methyl-2-aryl-4*H*-chromen-4-ones.[430] Various 2-aryl-4*H*-chromen-4-ones bearing enamides at C-3 were synthesized in moderate to excellent yields from tandem reaction of 1-(2-bromoaryl) prop-2-yn-1-ones with acyclic imides employing potassium carbonate as base in DMSO at 130 °C (Scheme 82).[431] It is through a regioselective tandem [3 + 2] cycloaddition/ring-opening/*O*-arylation protocol that 1-(2-haloaryl)prop-2-yn-1-ones reacted with quinoline *N*-oxides in DMF at 120 °C, under air for 12 h, to afford 2-alkyl/aryl-3-(quinolin-2-yl)-4*H*-chromen-4-ones. The reaction was extended to other heteroarene (isoquinolin-1-yl and pyridin-2-yl) *N*-oxides and better yields were obtained when the reaction was conducted in basic conditions (sodium phosphate in DMF at 100 °C).[432]



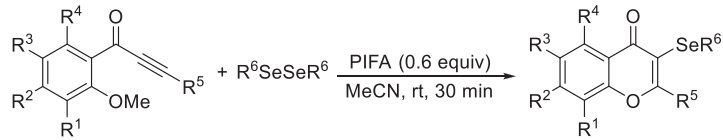
R^1 = H, F, OMe; R^2 = H, Cl, OMe; R^3 = H, Me, OMe; R^3R^4 = Ph;
R^4, R^5 = H, OMe; R^6 = Ph, 4-ClC_6H_4, 4-MeC_6H_4

Scheme 82

The synthesis of 2-aryl-3-sulfenyl-4*H*-chromen-4-ones was accomplished via iron(III) chloride-mediated regioselective cyclization reaction of 1-(2-methoxyphenyl)prop-2-yn-1-ones with *N*-arylthiobenzamides in dichloromethane at room temperature for 20 h.[433] Other 1-(2-methoxyaryl) prop-2-yn-1-ones underwent metal-free cyclization reaction with diorganyl disulfides promoted by PIFA in acetonitrile at room temperature to provide 2-alkyl/aryl-3-sulfenyl-4*H*-chromen-4-ones, in good yields. The scope of the reaction was efficiently extended to diorganyl diselenides to afford several 2-alkyl/aryl-3-selenyl-4*H*-chromen-4-ones (Scheme 83).[434]



R^1, R^2 = H, Me; R^3 = H, Br; R^4 = H, F; R^5 = Ph, 4-ClC_6H_4, 4-$OMeC_6H_4$,cyclopropyl



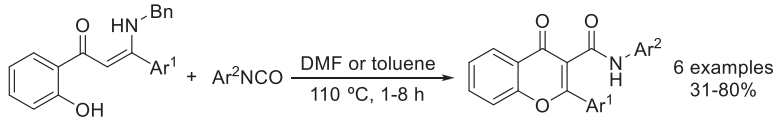
R^1 = H, Me; R^2 = H, Br, Cl, Me; R^3 = H, Br, Cl; R^4 = H, CF_3;
R^5 = Ph, 2-FC_6H_4, 2-MeC_6H_4, 3-BrC_6H_4, 3-MeC_6H_4, 4-ClC_6H_4, 4-$OMeC_6H_4$, cyclopropyl, thiophen-3-yl
R^6 = Me, Ph, 4-ClC_6H_4, 4-MeC_6H_4

Scheme 83

5.12 Other methods

Few examples of 2-aryl-3-iodo-4*H*-chromen-4-ones arose from heterocyclization reaction of (*E*)-3-aryl-3-benzylamino-1-(2-hydroxyaryl) prop-2-en-1-ones in presence of molecular iodine in methanol at room

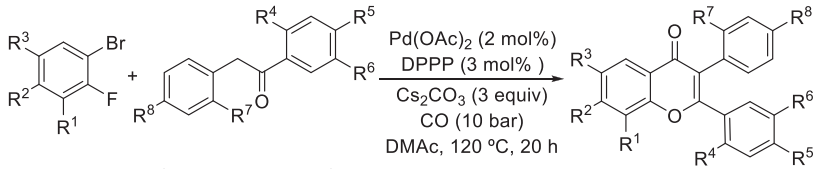
temperature for 16 h.[435] Treating the same precursors with various isocyanates in a minimal amount of DMF or toluene at 110 °C delivered 2-aryl-4-oxo-4*H*-chromen-3-carboxamides (Scheme 84)[298] and with aryl isothiocyanates in hot DMF yielded 2-aryl-4-oxo-4*H*-chromen-3-thiocarboxamides.[275]



Ar^1 = Ph, 4-MeC_6H_4, furan-2-yl, thiophen-2-yl; Ar^2 = Ph, 4-$CF_3C_6H_4$, 2,4-$Cl_2C_6H_3$

Scheme 84

Chen et al. established a protocol for the synthesis of 2,3-diphenyl-4*H*-chromen-4-ones involving palladium(II)-catalyzed carbonylative reaction of 1-bromo-2-fluorobenzenes with 2-arylacetophenone in the presence of DPPB and cesium carbonate in DMAc at 140 °C for 40 h, in modest yields.[436] Years later, the same research group improved this transformation using several 1-bromo-2-fluorobenzenes and 1,2-diarylethan-1-ones in the presence of other palladium(II) catalyst, DPPP [1,3-bis (diphenylphosphino)propane] and cesium carbonate in DMAc at 120 °C for 20 h for the synthesis of diversely substituted 2,3-diaryl-4*H*-chromen-4-ones (Scheme 85).[437]



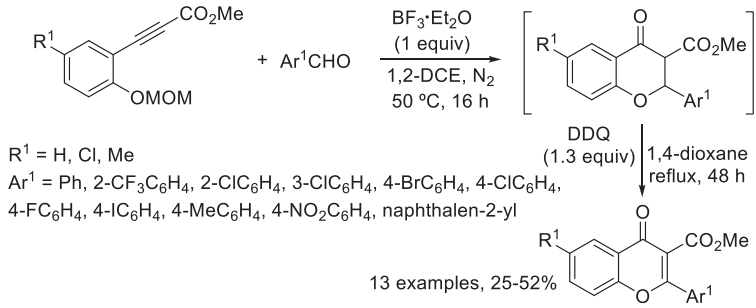
DPPP = 1,3-bis(diphenylphosphino)propane

R^1, R^2 = H, F, Me; R^3 = H, CHF_2, Cl, F, Me; R^4, R^7 = H, Cl, Me
R^5 = H, Cl, Me, OMe, cyclohexyl; R^6 = H, Me; R^8 = H, Cl, OMe

Scheme 85

Various 1-(2-benzyloxyaryl)-3,3-bismethylsulfanylprop-2-en-1-ones underwent iodination and intramolecular cyclization reactions, performed in the presence of molecular iodine in 1,2-DCE at 80 °C and subsequent treatment with molecular iodine and a solution of *N*-chlorosuccinimide (NCS) in 1,2-DCE at 80 °C for 30 min to deliver 3-iodo-2-(methylthio)-4*H*-chromen-4-ones.[201] 2-Aryl-4-oxo-4*H*-chromen-3-carboxylates were prepared via one-pot cascade reaction of methyl 3-[2-(methoxymethoxy)

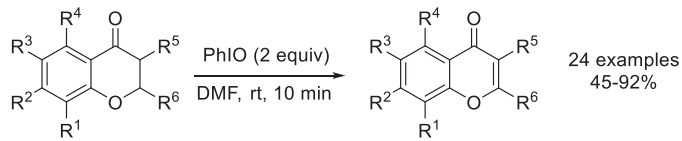
aryl]prop-2-yn-1-carboxylates with aromatic aldehydes using $BF_3{\cdot}Et_2O$ in 1,2-DCE and subsequent oxidation with DDQ in refluxing 1,4-dioxane (Scheme 86). It involved a four-step sequence: Lewis acid catalyzed phenol ether deprotection, aldehyde olefination, intramolecular oxa-Michael addition reaction, and a sequential oxidation.[438]



Scheme 86

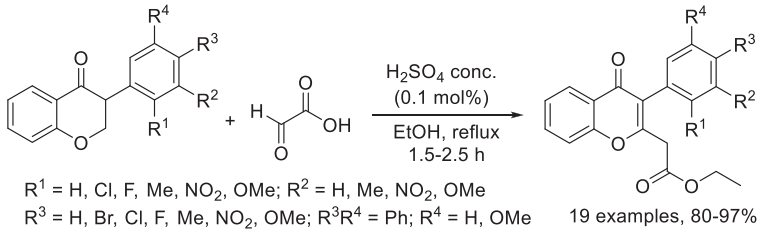
5.13 Oxidation of chroman-4-ones

Excellent yields of 2-aryl-3-methyl-4*H*-chromen-4-ones were obtained through selective aromatization reaction of 2-aryl-3-methyl-4*H*-chroman-4-ones using copper(II) chloride in DMSO at 110 °C as catalytic system.[439] 3-Benzoyl-2-methyl-4*H*-chroman-4-one underwent oxidation with Rose Bengal under visible light irradiation to produce 3-benzoyl-2-methyl-4*H*-chromen-4-one.[440] An alternative approach for the synthesis of 2,3-disubstituted 4*H*-chromen-4-ones starting from the corresponding chroman-4-ones is through dehydrogenative oxidation reaction conducted in the presence of the "green" oxidant iodosobenzene in DMF at room temperature. This protocol was applied to a series of chroman-4-ones activated at C-3 with electron-withdrawing substituents (ethoxycarbonyl, methoxycarbonyl, acetyl and carbonitrile), in moderate to excellent yields (Scheme 87).[441]



Scheme 87

Various 3-substituted 2-diarylmethyl-4*H*-chromen-4-ones can be synthesized via dehydrosiloxylation reaction of 3-substituted 2-{diaryl[(trimethylsilyl)oxy]methyl}-4*H*-chroman-4-ones mediated by a catalytic amount of PTSA in refluxing xylene and via desilylation of the same precursors by treatment with hydrochloric acid in 1,4-dioxane and subsequent dehydration carried out in the presence of a catalytic amount of PTSA in refluxing toluene.[229] A couple of methoxylated 2-aryl-3-hydroxy-4*H*-chromen-4-ones were prepared via oxidation of the respective 2-aryl-4*H*-chroman-4-ones with isoamyl nitrite under acidic conditions to give ketoxime intermediates which were further hydrolyzed with sulfuric acid in acetic acid at reflux temperature.[442] Kondhare et al. developed an efficient access to ethyl 2-(3-aryl-4-oxo-4*H*-chromen-2-yl)acetates employing Claisen–Schmidt condensation of 2-aryl-4*H*-chroman-4-ones with glyoxylic acid in the presence of a catalytic amount of sulfuric acid in refluxing ethanol (Scheme 88).[443]

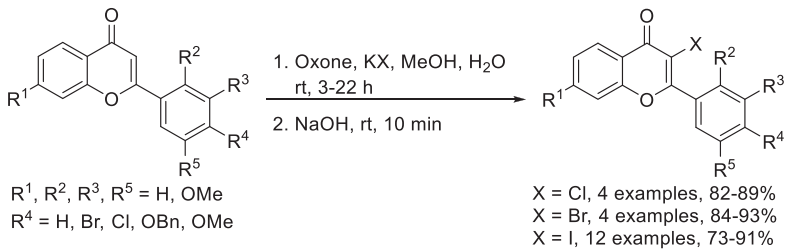


Scheme 88

5.14 Functionalization at C-2/C-3 of 4*H*-chromen-4-ones

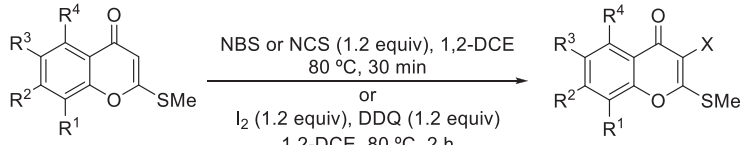
A series of 2-aryl-4*H*-chromen-4-ones reacted with diluted fluorine in nitrogen at −78 °C in a mixture of chloroform/trichlorofluromethane/ethanol to afford *cis*-2-aryl-2,3-difluoro-4*H*-chroman-4-ones, which underwent facile dehydrofluorination by adsorbing it on a silica gel column to produce 2-aryl-3-fluoro-4*H*-chromen-4-ones.[347] Using the same starting materials, bromination with NBS in acetic anhydride followed by addition of methanol under reflux conditions,[126] with an excess of NBS and pyridine in dry carbon tetrachloride[74] and with ammonium bromide and ammonium persulfate at room temperature under grinding and solvent-free conditions[151] afforded 2-aryl-3-bromo-4*H*-chromen-4-ones while iodination with equimolar amounts of molecular iodine in DMSO at 130 °C gave access to 2-aryl-3-iodo-4*H*-chromen-4-ones in 87–92% yield.[371] The synthesis of

3-chloro-2-phenyl-4*H*-chromen-4-one occurred through the reaction of 2-phenyl-4*H*-chromen-4-one with iodosobenzene diacetate and TMSCl in dichloromethane at 0 °C[188] and of 3-bromo-2-(3,4-dimethoxyphenyl)-7-methoxy-4*H*-chromen-4-one has been accomplished in from the reaction of 2-(3,4-dimethoxyphenyl)-7-methoxy-4*H*-chromen-4-one with iodosobenzene diacetate and tetrabutylammonium bromide (TBAB) in anhydrous dichloromethane at room temperature.[79] Selective iodination of methyl 3-(5-hydroxy-7-methyl-4-oxo-4*H*-chromen-2-yl)propanoate with NIS in the presence of sodium acetate, trifluoroacetic acid and trifluoroacetic anhydride at room temperature prompted methyl 3-(5-hydroxy-3-iodo-7-methyl-4-oxo-4*H*-chromen-2-yl)propanoate.[160] A more general and safer work-up strategy for synthesis of 2-aryl-3-halo-4*H*-chromen-4-ones involved one-pot two-step reaction of 2-aryl-4*H*-chromen-4-ones with active molecular halogen, prepared in situ from potassium halide and Oxone®, in methanol to afford 2-aryl-3-halo-2-methoxy-4*H*-chroman-4-ones as isolable intermediates followed by addition of sodium hydroxide to promote the elimination of one methanol molecule. This protocol provides an efficient synthesis of 3-chloro-, 3-bromo- and 3-iodo 2-aryl-4*H*-chromen-4-ones starting from the same 2-aryl-4*H*-chromen-4-one building blocks (Scheme 89).[444]



Scheme 89

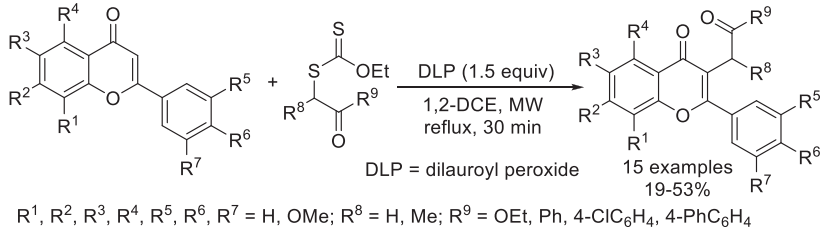
Various 2-(methylthio)-4*H*-chromen-4-ones underwent bromination and chlorination reactions, respectively with NBS or NCS in 1,2-DCE (1 mL) at 80 °C for 30 min to provide 3-bromo/chloro-2-(methylthio)-4*H*-chromen-4-ones while iodination occurred in the presence of molecular iodine and DDQ in 1,2-DCE at 80 °C for 2 h to afford 3-iodo-2-(methylthio)-4*H*-chromen-4-ones (Scheme 90).[201] The synthesis of 2-aryl-3-trifluoromethyl-4*H*-chromen-4-one was accomplished through regioselective C—H α-trifluoromethylation of 2-aryl-4*H*-chromen-4-one with Togni's reagent promoted by copper(I) iodide



Scheme 90

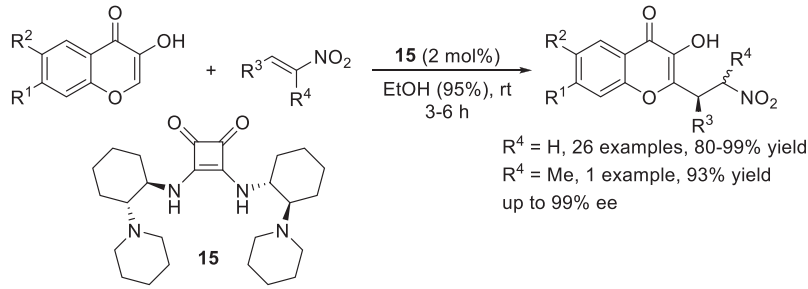
in DMF at 80 °C.[188,445] Some 2-aryl-4*H*-chromen-4-ones suffered lithiation with lithium diisopropylamide (LDA) in THF, quenching with trimethylborate, subsequent oxidation and hydrolysis of the intermediate boronate with hydrogen peroxide in glacial acetic acid to deliver 2-aryl-3-hydroxy-4*H*-chromen-4-ones.[446]

A wide variety of 2-aryl-4*H*-chromen-4-ones has been involved in iron(III)-catalyzed reaction with cycloalkanes and with *N*,*N*-dialkylformamides using *t*-butyl peroxybenzoate (TBPB), DABCO and potassium persulfate at 115 °C to afford, respectively, 2-aryl-3-cycloalkyl-4*H*-chromen-4-ones and 3-amidated 2-aryl-4*H*-chromen-4-ones. In addition, the reaction of 2-aryl-4*H*-chromen-4-ones with TBPB, DABCO and potassium persulfate using chlorobenzene as solvent at 115 °C furnished 2-aryl-3-methyl-4*H*-chromen-4-ones, in moderate yields.[447] Microwave-assisted regioselective oxidative radical alkylation of 2-aryl-4*H*-chromen-4-ones with several xanthates in the presence of dilauroyl peroxide in refluxing 1,2-DCE furnished a series of densely functionalized 3-alkyl-2-aryl-4*H*-chromen-4-ones (Scheme 91).[448]



Scheme 91

Kovalevsky et al. established an efficient and highly enantioselective protocol for the functionalization of 3-hydroxy-4*H*-chromen-4-ones at C-2, through conjugate addition with nitroolefins promoted by C_2-symmetric tertiary amine-squaramide catalyst **15**, in ethanol 95% at room temperature (Scheme 92).[449]



R^1 = H, OMe; R^2 = H, Br; R^3 = Ph, 3-OMeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-OMeC_6H_4, 2,4-$Cl_2C_6H_3$, 3,4-OCH_2O-C_6H_3, 3-cyclopentoxyl-4-OMeC_6H_3, furan-2-yl, styryl, ferrocenyl, cymantrenyl

Scheme 92

6. Conclusions

This comprehensive review contains the most recent achievements in the synthesis of diversely substituted 4*H*-chromen-4-ones. From 2012 to 2021, many synthetic strategies have been reported to expand the scope of precursor methodologies and a wide array of novel, creative, selective, efficient, easy-to-handle and eco-friendly approaches have been developed for the preparation of these organic structures. In addition, the huge library of new compounds synthesized highlights the importance of this heterocyclic chemistry and reinforces it as being an interesting research target for further investigations.

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